Canadian Environmental Protection Act, 1999

PRIORITY SUBSTANCES LIST ASSESSMENT REPORT

Formaldehyde
Formaldehyde

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Priority Substances List Assessment Report

Formaldehyde

Environment Canada
Health Canada

February 2001
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<tr>
<th>Acronym</th>
<th>Abbreviation</th>
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<tbody>
<tr>
<td>CAS</td>
<td>Chemical Abstracts Service</td>
</tr>
<tr>
<td>CEPA</td>
<td>Canadian Environmental Protection Act</td>
</tr>
<tr>
<td>CEPA 1999</td>
<td>Canadian Environmental Protection Act, 1999</td>
</tr>
<tr>
<td>CFD</td>
<td>computational fluid dynamics</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CIIT</td>
<td>Chemical Industry Institute of Toxicology</td>
</tr>
<tr>
<td>CTV</td>
<td>Critical Toxicity Value</td>
</tr>
<tr>
<td>DPX</td>
<td>DNA–protein crosslinking</td>
</tr>
<tr>
<td>EEV</td>
<td>Estimated Exposure Value</td>
</tr>
<tr>
<td>ENEV</td>
<td>Estimated No-Effects Value</td>
</tr>
<tr>
<td>EPA</td>
<td>Environmental Protection Agency</td>
</tr>
<tr>
<td>ETS</td>
<td>environmental tobacco smoke</td>
</tr>
<tr>
<td>GWP</td>
<td>Global Warming Potential</td>
</tr>
<tr>
<td>kg-bw</td>
<td>kilogram body weight</td>
</tr>
<tr>
<td>$K_{aw}$</td>
<td>air/water partition coefficient</td>
</tr>
<tr>
<td>$K_{oc}$</td>
<td>organic carbon/water partition coefficient</td>
</tr>
<tr>
<td>$K_{ow}$</td>
<td>octanol/water partition coefficient</td>
</tr>
<tr>
<td>LCL</td>
<td>lower confidence limit</td>
</tr>
<tr>
<td>LOEC</td>
<td>Lowest-Observed-Effect Concentration</td>
</tr>
<tr>
<td>MDF</td>
<td>medium-density fibreboard</td>
</tr>
<tr>
<td>MIR</td>
<td>maximum incremental reactivity</td>
</tr>
<tr>
<td>MS</td>
<td>mainstream</td>
</tr>
<tr>
<td>NAPS</td>
<td>National Air Pollution Surveillance</td>
</tr>
<tr>
<td>NOEC</td>
<td>No-Observed-Effect Concentration</td>
</tr>
<tr>
<td>NOEL</td>
<td>No-Observed-Effect Level</td>
</tr>
<tr>
<td>NOX</td>
<td>nitrogen oxides</td>
</tr>
<tr>
<td>NPRI</td>
<td>National Pollutant Release Inventory</td>
</tr>
<tr>
<td>ODP</td>
<td>Ozone Depletion Potential</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>PEFR</td>
<td>peak expiratory flow rate</td>
</tr>
<tr>
<td>PMR</td>
<td>proportionate mortality ratio</td>
</tr>
<tr>
<td>POCP</td>
<td>Photochemical Ozone Creation Potential</td>
</tr>
<tr>
<td>PSL</td>
<td>Priority Substances List</td>
</tr>
<tr>
<td>RR</td>
<td>relative risk</td>
</tr>
<tr>
<td>SIR</td>
<td>standardized incidence ratio</td>
</tr>
<tr>
<td>SMR</td>
<td>standardized mortality ratio</td>
</tr>
<tr>
<td>SPIR</td>
<td>standardized proportionate incidence ratio</td>
</tr>
<tr>
<td>SS</td>
<td>sidestream</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>TC</td>
<td>Tolerable Concentration</td>
</tr>
<tr>
<td>$TC_{5%}$</td>
<td>Tumorogenic concentration associated with a 5% increase in tumour incidence over background</td>
</tr>
<tr>
<td>UF</td>
<td>Urea-formaldehyde</td>
</tr>
<tr>
<td>UFFI</td>
<td>Urea-formaldehyde foam insulation</td>
</tr>
<tr>
<td>VOC</td>
<td>Volatile organic compound</td>
</tr>
</tbody>
</table>
SYNOPSIS

In Canada, formaldehyde is used primarily in the production of resins and fertilizers and for a variety of minor uses. The Canadian domestic demand for formaldehyde was 191,000 tonnes in 1996.

Formaldehyde enters the Canadian 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. Although there are no quantitative estimates, releases from natural and secondary sources in Canada are likely greater than direct human releases. However, 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, the largest direct human source of formaldehyde in the Canadian environment, released an estimated 11,284 tonnes into the air in 1997. The amount of formaldehyde released into the Canadian environment from industrial processes was 1,424 tonnes in 1997.

When formaldehyde is released to or formed in air, most of it will undergo various degradation processes in air, and a very small amount will move into water. When formaldehyde is released into water, it does not move into other media but is broken down in the water. Formaldehyde does not persist in the environment, but its continuous release and formation can result in chronic exposure of biota near sources of release and formation.

Extensive recent data are available for concentrations of formaldehyde in air at industrial, urban, suburban, rural and remote locations in Canada. Data for concentrations in water are limited to surface water from four rivers, effluents from industrial plants and groundwater from three industrial sites and six cemeteries. 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 Canada, 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.

Formaldehyde is not involved in the depletion of stratospheric ozone or in climate change. Because of its photoreactivity and its relatively high concentrations in Canadian cities, formaldehyde plays a role in the photochemical formation of ground-level ozone.

Critical health effects in mammals associated with exposure to formaldehyde occur primarily at the site of first contact (i.e., the respiratory tract following inhalation and the gastrointestinal tract following ingestion) and are related to concentration in the relevant medium, rather than to total intake. 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.

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.

Following inhalation in laboratory animals, formaldehyde causes degenerative non-neoplastic effects and nasal tumours in rats.
Both sustained cellular proliferation and interaction with genetic material likely contribute to induction of these tumours, and, under similar conditions, formaldehyde is considered to present a carcinogenic hazard to humans.

The majority of the population is exposed to airborne concentrations of formaldehyde less than those associated with sensory irritation. However, in some indoor locations, concentrations may approach those associated with eye and respiratory tract sensory irritation in humans. Based on comparison of risks of cancer estimated on the basis of a biologically motivated case-specific model with calculated exposure in air of the general population in Canada, priority for investigation of options to reduce exposure on the basis of carcinogenicity is considered to be low.

Based on the information available, it is concluded that formaldehyde is not entering the Canadian environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity. Formaldehyde is entering the Canadian environment in a quantity or concentration or under conditions that constitute or may constitute a danger to the environment on which life depends and a danger in Canada to human life or health. Therefore, formaldehyde is considered “toxic” as defined in Section 64 of the Canadian Environmental Protection Act, 1999 (CEPA 1999). Formaldehyde contributes to the photochemical formation of ground-level ozone. It is recommended that key sources of formaldehyde be addressed, therefore, as part of management plans for volatile organic chemicals that contribute to the formation of ground-level ozone. While indications are that concentrations currently in air and water are not causing environmental harm to biota, continued and improved monitoring at sites likely to release formaldehyde is desirable, notably with regards to industrial uses for resins and for fertilizers as well as releases from pulp and paper mills.

It is also recommended that continued investigation of options to reduce exposure to formaldehyde in indoor air be considered under the authority of acts other than CEPA 1999 as part of an overall program to reduce exposure to other aldehydes (e.g., acrolein, acetaldehyde) in indoor air deemed to be “toxic” under Paragraph 64(c) of CEPA 1999.
1.0 INTRODUCTION

The Canadian Environmental Protection Act, 1999 (CEPA 1999) requires the federal Ministers of the Environment and of Health to prepare and publish a Priority Substances List (PSL) that identifies substances, including chemicals, groups of chemicals, effluents and wastes, that may be harmful to the environment or constitute a danger to human health. The Act also requires both Ministers to assess these substances and determine whether they are “toxic” or capable of becoming “toxic” as defined in Section 64 of the Act, which states:

... a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions that
(a) have or may have an immediate or long-term harmful effect on the environment or its biological diversity;
(b) constitute or may constitute a danger to the environment on which life depends; or
(c) constitute or may constitute a danger in Canada to human life or health.

Substances that are assessed as “toxic” as defined in Section 64 may be placed on Schedule I of the Act and considered for possible risk management measures, such as regulations, guidelines, pollution prevention plans or codes of practice to control any aspect of their life cycle, from the research and development stage through manufacture, use, storage, transport and ultimate disposal.

Based on an initial screening of readily accessible information, the rationale for assessing formaldehyde provided by the Ministers’ Expert Advisory Panel on the Second Priority Substances List (Ministers’ Expert Advisory Panel, 1995) was as follows:

Canadians are exposed to formaldehyde through its production; its use in the production of resins; in automobile exhaust and cigarette smoke; and through the “off-gassing” of building materials and consumer products including cosmetics and household cleaning agents. Toxicological effects in animals and humans have been observed at levels similar to the concentrations to which the general population may be exposed. Formaldehyde is genotoxic and carcinogenic in rodents and may be carcinogenic in humans. An assessment is needed to determine the potential risk to human health.

Descriptions of the approaches to assessment of the effects of Priority Substances on the environment and human health are available in published companion documents. The document entitled “Environmental Assessments of Priority Substances under the Canadian Environmental Protection Act. Guidance Manual Version 1.0 — March 1997” (Environment Canada, 1997a) provides guidance for conducting environmental assessments of Priority Substances in Canada. This document may be purchased from:

Environmental Protection Publications
Environmental Technology Advancement Directorate
Environment Canada
Ottawa, Ontario
K1A 0H3

It is also available on the Commercial Chemicals Evaluation Branch web site at www.ec.gc.ca/cceb1/ese/eng/esehome.htm under the heading “Guidance Manual.” It should be noted that the approach outlined therein has evolved to incorporate recent developments in risk assessment methodology that will be addressed in future releases of the guidance manual for environmental assessments of Priority Substances.

The approach to assessment of effects on human health is outlined in the following publication of the Environmental Health Directorate of Health Canada: “Canadian Environmental Protection Act — Human Health Risk Assessment for Priority Substances” (Health Canada, 1994), copies of which are available from:
or on the Environmental Health Directorate publications web site (www.hc-sc.gc.ca/ehp/ehd/catalogue/bch.htm). The approach is also described in an article published in the Journal of Environmental Science and Health — Environmental Carcinogenesis & Ecotoxicology Reviews (Meek et al., 1994). It should be noted that the approach outlined therein has evolved to incorporate recent developments in risk assessment methodology, which are described on the Environmental Substances Division web site (www.hc-sc.gc.ca/ehp/ehd/bch/contaminants/psap/psap.htm) and which will be addressed in future releases of the approach paper for the assessment of effects on human health.

The search strategies employed in the identification of data relevant to assessment of potential effects on the environment (prior to December 1999) and human health (prior to January 1999) are presented in Appendix A. Available Canadian data on sources, use patterns and fate of formaldehyde in the environment have been emphasized. In supporting documentation for this assessment, a report on the health effects of formaldehyde prepared previously by the Bureau of Chemical Hazards, Health Canada (BCH, 1988), was updated. This was based, in part, on a background report compiled by BIBRA Toxicology International (BIBRA, 1994). Review articles were consulted where appropriate. However, all original studies that form the basis for determining whether formaldehyde is “toxic” under CEPA 1999 have been critically evaluated by staff of Environment Canada (entry and environmental exposure and effects) and Health Canada (human exposure and effects on human health).

An Environmental Resource Group was established by Environment Canada to assist in the preparation of the environmental assessment. Members participated in the preparation and review of the environmental sections of the Assessment Report and the environmental supporting document (Environment Canada, 1999a). Members included:

G. Bird, Natural Resources Canada
B. Brownlee, Environment Canada
N. Bunce, University of Guelph
R. Chénier, Environment Canada
T. Currah, OxyChem Durez
T. Dann, Environment Canada
E. Dowdall, Environment Canada
F. Edgecomb, Canadian Plastics Industry Association
M. Eggleton, Environment Canada
G. Granville, Shell Canada Limited
L. Kamboj, Monsanto
R. Keefe, Imperial Oil Limited
G. Rideout, Environment Canada
A. Stelzig, Environment Canada
M. Tushingham, Environment Canada
J. Wittwer, Environment Canada

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

The sections of the Assessment Report relevant to the environmental assessment and the environmental supporting document were reviewed by members of the Environmental Resource Group, as well as by A. Day (Celanese Canada Inc.), D. Mackay (University of Toronto) and P. Makar (Environment Canada).

The content of the health-related sections of this Assessment Report and the supporting documentation (Health Canada, 1999, 2000) was prepared by the following staff of Health Canada:

R. Beauchamp
R.G. Liteplo
M.E. Meek
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 (U.S. Environmental Protection Agency [EPA]), R. Keefe (Imperial Oil Limited), N. Krivanek (Dupont Haskell Laboratory), J. Martin (consultant) and F. Miller (Chemical Industry Institute of Toxicology [CIIT]) (June 1997).

In 1996, a government–private Steering Committee was formed in the United States 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 U.S. 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 U.S. 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, U.S. EPA), was reviewed at an external peer review workshop of the following invitees, convened by Health Canada and the U.S. EPA on March 18–20, 1998, in Ottawa, Ontario (Health Canada, 1998):

B. Allen, RAS Associates
M. Andersen, ICF Kaiser Engineering
(D. Blakey, Health Canada (Chair))
D. Blakey, Health Canada
A. Dahl, Lovelace Respiratory Research Institute
D. Gaylor, U.S. Food and Drug Administration
J. Harkema, Michigan State University
D. Jacobson-Kram, MA BioServices
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 September 28, 1999) (CIIT, 1999) was reviewed by the Chair of the workshop (M. Andersen) to ensure that comments had been adequately addressed (Andersen, 1999).

In this assessment, the outcome of this collaborative exercise and additional data on non-cancer effects and routes of exposure other than ingestion have been considered in the context of the approach to assessment of “toxic” under Paragraph 64(c) of CEPA 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).

The health-related sections of the Assessment Report were reviewed and approved by the Healthy Environments and Consumer Safety Branch Risk Management meeting of Health Canada.

The entire Assessment Report was reviewed and approved by the Environment Canada/Health Canada CEPA Management Committee.

A draft of the Assessment Report was made available for a 60-day public comment period (July 22 to September 20, 2000) (Environment Canada and Health Canada, 2000). Following consideration of comments received, the Assessment Report was revised as appropriate. A summary of the comments and responses is available on the Internet at:

www.ec.gc.ca/cceb1/eng/final/index_e.html

The text of the Assessment Report has been structured to address environmental effects initially (relevant to determination of “toxic” under Paragraphs 64(a) and (b)), followed by effects on human health (relevant to determination of “toxic” under Paragraph 64(c)).

Copies of this Assessment Report are available upon request from:

Inquiry Centre
Environment Canada
Main Floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
K1A 0H3

or on the Internet at:
www.ec.gc.ca/cceb1/eng/final/index_e.html

Unpublished supporting documentation on the environmental assessment (Environment Canada, 1999a) or health assessment (BCH, 1988; Health Canada, 1998, 1999, 2000; Andersen, 1999; CIIT, 1999), which presents additional information, is available upon request from:

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

or

Environmental Health Centre
Room 104
Health Canada
Tunney’s Pasture
Ottawa, Ontario
K1A 0L2
2.1 Identity and physical/chemical properties

Pure formaldehyde is also known as methanal, methylene oxide, oxymethylene, methylaldehyde, oxomethane, formic aldehyde and methylene glycol. Its Chemical Abstracts Service (CAS) number is 50-00-0. The molecular formula is CH₂O.

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 (WHO, 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, when molecules have an increased opportunity to associate with other like species. Partition coefficients of most pure organic substances such as benzene or hexane reflect the properties of the individual monomolecular species at all concentrations — namely, they do not self-associate. This is not the case for formaldehyde, and it is therefore not advisable to use property data at high concentrations to estimate properties under dilute conditions. For example, the common practice of calculating the air/water partition coefficient (Kₐw) from solubility and vapour pressure can be invalid for substances such as formaldehyde. The most environmentally relevant and meaningful properties, such as the octanol/water partition coefficient (Kₐw), Kₐw, the organic carbon/water partition coefficient (Kₐw), etc., should be measured at low concentrations. Extrapolation from concentrations exceeding percent levels should be avoided, and thus any use of structure–property relationships and inter-property correlations (such as Kₐw and solubility) should be examined critically for validity (Bobra and Mackay, 1999).

Values reported for the physical and chemical properties of formaldehyde are given in Table 1.

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 (WHO, 1989; Environment Canada, 1995). In solid form, formaldehyde is marketed as trioxane, (CH₂O)₃, and its polymer paraformaldehyde, with 8–100 units of formaldehyde (WHO, 1989).

2.2 Entry characterization

2.2.1 Production, importation, exportation and use

Formaldehyde is produced commercially by the catalytic air oxidation of methanol (Environment Canada, 1985; Kroschwitz, 1991). In Canada, about 222 000 tonnes of formaldehyde were produced in 1996. In the same year, approximately 7600 tonnes of formaldehyde were imported, and more than 30 000 tonnes of
formaldehyde were exported (Environment Canada, 1997c).

Total Canadian domestic consumption of formaldehyde was reported at about 191 000 tonnes for 1996 (Environment Canada, 1997c). 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 related to fertilizer production, while 2% was used for various other purposes, such as preservatives and disinfectants (Environment Canada, 1997c). Formaldehyde can be used in a variety of industries, including the medical, detergent, cosmetic, food, rubber, fertilizer, metal, wood, leather, petroleum and agricultural industries (WHO, 1989), and as a hydrogen sulfide scavenger in oil operations (Tiemstra, 1989).

In Canada, formaldehyde is acceptable for use in non-aerosol cosmetics provided the concentration does not exceed 0.2% (BND, 1994). Formaldehyde is included in the Cosmetic Notification Hot List maintained by Health Canada’s Product Safety Bureau 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 (Richardson, 1999).

Approximately 80% of the slow-release fertilizer market is based on UF-containing products (ATSDR, 1999; HSDB, 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, there are currently 59 pest control products containing formaldehyde registered under the Pest Control Products Act. Formaldehyde is present as a formulation in 56 of these products, at concentrations ranging from 0.002% 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 (Moore, 2000). Pesticidal uses

### Table 1: Physical and chemical properties of formaldehyde reported in literature

<table>
<thead>
<tr>
<th>Property</th>
<th>Range of reported values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight (g/mol)</td>
<td>30.03</td>
</tr>
<tr>
<td>Melting point (°C)</td>
<td>–118 to –92</td>
</tr>
<tr>
<td>Boiling point (°C, 101.3 kPa)</td>
<td>–21 to –19</td>
</tr>
<tr>
<td>Vapour pressure (calculated) (Pa, at 25°C)</td>
<td>516 000</td>
</tr>
<tr>
<td>Water solubility (mg/L, at 25°C)</td>
<td>400 000 to 550 000</td>
</tr>
<tr>
<td>Henry’s law constant (Pa·m²/mol, 25°C)</td>
<td>2.2 × 10⁻² to 3.4 × 10⁻²</td>
</tr>
<tr>
<td>Log octanol/water partition coefficient (log Kₐ)</td>
<td>–0.75 to 0.35</td>
</tr>
<tr>
<td>Log organic carbon/water partition coefficient (log Kₐ)</td>
<td>0.70 to 1.57</td>
</tr>
</tbody>
</table>

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

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

3 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/L (Dean, 1985) and 1.0 × 10⁸ mg/L (DMER and 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.
are not considered in this assessment because they are regulated by the Pest Control Products Act.

Section 15 of Health Canada’s 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 (Feeley, 1996). However, such use has not been registered in Canada since 1990 (Smith, 2000).

2.2.2 Sources and releases

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 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 below).

2.2.2.1 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 (WHO, 1989; IARC, 1995). Studies have found it to be emitted by bacteria, algae, plankton and vegetation (Hellebust, 1974; Zimmermann et al., 1978; Eberhardt and Sieburth, 1985; Yamada and Matsui, 1992; Nuccio et al., 1995).

2.2.2.2 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. All internal combustion engines have the potential to produce it. 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 (NPRI), on-road motor vehicles are the largest direct source of formaldehyde released into the Canadian environment. 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 emission 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). Data on releases from on-road vehicles were estimated by modelling (Mobile 5C model), using assumptions outlined in Environment Canada (1996). It can be expected that the rates of releases 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 (Jermine et al., 1976; Kitchens et al., 1976; Klus and Kuhn, 1982; Ramdahl et al., 1982; Schriefer et al., 1983; Lipari et al., 1984; WHO, 1989; Walker and Cooper, 1992; Baker, 1994; Guski and Racynski, 1994). Cigarette smoking in Canada is estimated to produce less than 84 tonnes per year, based on estimated emission rates (WHO, 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 U.S. emission factors (Lipari et al., 1984; Sverdrup et al., 1994), the high heating value of fuel and Canadian coal consumption in 1995 (Rose, 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, 1997c,d, 1999a), pulp and paper mills, forestry product plants (U.S. EPA, 1990; Fisher et al., 1991; Environment Canada, 1997c, 1999a; O’Connor and Voss, 1997), tire and rubber plants (Environment Canada, 1997b), petroleum refining and coal processing plants (IARC, 1981; U.S. EPA, 1993), textile mills, automotive manufacturing plants and the metal products industry (Environment Canada, 1999a).

NPRI data for 1997 indicated total environmental releases from 101 facilities of 1423.9 tonnes, 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. Largest emissions to air were reported from Weyerhaeuser Canada Ltd. in Edson, Alberta (121.5 tonnes), and Drayton Valley, Alberta (111.7 tonnes). Only four plants reported releases of formaldehyde to surface water, in quantities of 13.3 tonnes (Abitibi-Consolidated, La Baie, Quebec), 4.1 tonnes (Abitibi Consolidated, Grand-Mère, Quebec), 1.6 tonnes (Tembec Inc., Témiscaming, Quebec) and 0.4 tonnes (Grant Forest Products Corp., Englehart, Ontario). Formaldehyde disposed of through deep-well injection is not considered to interact with biologically active soil strata. From 1979 to 1989, about 76.9 tonnes of formaldehyde were spilled or released to the environment as a result of 35 reported incidents (NATES, 1996).

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).

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).

Regulatory and voluntary initiatives have been directed at the control of emissions from building materials and furnishings, since these are recognized as the major sources of elevated concentrations of formaldehyde in indoor air. Urea-formaldehyde foam insulation (UFFI) was banned from use in Canada in 1980. Voluntary standards have been established to limit the emission of formaldehyde from particleboard (ANSI A208.1-1993) and medium-density fibreboard (MDF) (ANSI A208.2-1994). According to information provided by the Composite Panel Association (formerly the National Particleboard Association and the Canadian Particleboard Association), a dramatic reduction in the emission rates of formaldehyde from composite wood products has been achieved through the use of low-emitting resins, chemical scavengers and improved manufacturing control.
(Tardif, 1998). The Canadian Carpet Institute has established a voluntary carpet emission guideline of 0.05 mg/m² per hour (Piersol, 1995).

2.2.2.3 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 (WHO, 1989; U.S. 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) (U.S. 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 and Schmidt, 1983). In California, Harley and 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 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 with the photochemical oxidation of anthropogenic pollutants occurring there through long-range transport (Satsumabayashi et al., 1995).

2.3 Exposure characterization

2.3.1 Environmental fate

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).

2.3.1.1 Air

Formaldehyde emitted to air primarily reacts with photochemically generated hydroxyl (OH) radicals in the troposphere or undergoes direct photolysis (Howard et al., 1991; U.S. EPA, 1993). Minor fate processes include reactions with nitrate (NO₃) radicals, hydroperoxy (HO₂) radicals, hydrogen peroxide (H₂O₂), ozone (O₃) and chlorine (Cl₂) (U.S. 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; U.S. 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; U.S. 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 (U.S. 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 hours (Atkinson, 1985; Atkinson et al., 1990). Products that can be formed from hydroxyl radical reaction include water (H₂O), formic acid (HCOOH), carbon monoxide (CO) and the hydroperoxyl/formaldehyde adduct (HCO₃) (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 (HCO) 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 formaldehyde photolysis are the most important net source
of smog generation (U.S. 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 hours in the lower troposphere at a solar zenith angle of 40° (Calvert et al., 1972). A half-life of 6 hours 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 (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 and Cohen, 1964; Gay and Bufalini, 1971). 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 (HNO₃) 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 U.S. cities ranged from 0.3 hours under conditions typical of a rainy winter night to 250 hours under conditions typical of a clear summer night (assuming no reaction with hydroperoxy radicals) (U.S. EPA, 1993). During the daytime, under clear-sky conditions, the residence time 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 (ARB, 1993). The washout ratio suggests that 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.

2.3.1.2 Water

In water, formaldehyde is rapidly hydrated to form a glycol (CH₂(OH)₂). Equilibrium almost totally favours the glycol (Dong and 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 undergo biodegradation (U.S. EPA, 1985; Howard, 1989). Incorporated into atmospheric water, formaldehyde or its hydrate can undergo oxidation.

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

2.3.1.3 Sediment

Due to its low 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 the significant environmental fate processes in sediment (U.S. EPA, 1985; Howard, 1989).

2.3.1.4 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 (U.S. EPA, 1985). Howard et al. (1991) estimated a soil half-life of 24–168 hours, based on estimated aqueous aerobic biodegradation half-lives.

2.3.1.5 Biota

In view of the very low bioconcentration factor of 0.19, based on a log K_{ow} of 0.65 (Veith et al., 1980; Hansch and Leo, 1981), formaldehyde is not expected to bioaccumulate. No bioconcentration was observed in fish or shrimp (Stills and Allen, 1979; Hose and Lightner, 1980). No significant aquatic magnification in the food chain is predicted from the model calculations and empirical observations of Thomann (1989).

2.3.1.6 Environmental distribution

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 and Paterson (1991). Assumptions, input parameters and results are presented in Mackay et al. (1995) and Environment Canada (1999a).

Based on its 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 found in that medium (Mackay et al., 1995; DMER and 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 for formaldehyde.

2.3.2 Environmental concentrations

2.3.2.1 Air

2.3.2.1.1 Ambient air

Available sampling and analytical methodologies are sufficiently sensitive to detect formaldehyde in most samples of ambient (outdoor) air in Canada. Formaldehyde was detected (detection limit 0.05 µg/m^3) in 3810 of 3842 24-hour 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 (0.05 µg/m^3) to a maximum of 27.5 µg/m^3 for eight urban sites (Montréal, Quebec [two sites]; Ottawa, Ontario; Windsor, Ontario [two sites]; Toronto, Ontario; Winnipeg, Manitoba; Vancouver, B.C.), to a maximum of
12.03 µg/m³ for two suburban sites (Saint John, New Brunswick; Montréal, Quebec), to a maximum of 9.11 µg/m³ for two rural sites considered to be affected by urban and/or industrial influences (L’Assomption, Quebec; Simcoe, Ontario) and to a maximum of 9.88 µg/m³ for four rural sites considered to be regionally representative (Kejimkujik Park, Nova Scotia; Mount Sutton, Quebec; St. Anicet, Quebec; Egbert, Ontario). Long-term (1 month to 1 year) mean concentrations for these sites ranged from 0.78 to 8.76 µg/m³. The single highest 24-hour concentration measured was 27.5 µg/m³, obtained for an urban sample collected from Toronto, Ontario, on August 8, 1995. The mean concentration for six 24-hour measurements made at this site during the 30-day period from July 14 to August 12 was 22.15 µg/m³. Pooled monthly mean concentrations of formaldehyde determined from data in Canada’s National Air Pollution Surveillance (NAPS) program for suburban and urban sites in Canada between 1990 and 1998 are highest between June and August (Health Canada, 2000).

Concentrations of formaldehyde were measured in 96 air samples (12- to 25-hour) collected from the roofs of buildings at four sites in urban, residential and industrial areas of Prince Rupert, B.C., during 1994 and 1995. Concentrations ranged from 0.08 to 14.7 µg/m³ (detection limit 0.03 µg/m³). Reported averages ranged from 0.73 to 3.94 µg/m³ (SEAM Database, 1996).

Quarterly mean concentrations of formaldehyde in outdoor air during the period from 1990 to 1998 were calculated for two suburban (i.e., in Montréal and Vancouver) and two urban (i.e., in Ottawa and Toronto) NAPS sites and examined for temporal trends. There is no evidence that concentrations of formaldehyde were systematically increasing or decreasing at these sites over this 9-year period (Health Canada, 2000).

Formaldehyde was also measured in 108 6-hour samples collected 4 times daily from August 1 to 28, 1993, at Chebogue Point, Nova Scotia. Concentrations ranged from less than 0.6 µg/m³ to approximately 4.2 µg/m³ (detection limit not specified) (Tanner et al., 1994). This area was assumed to be affected not only by local sources but also by air masses transporting precursors from the northeastern United States.

Atmospheric measurements made in 1992 during the dark winter and sunlit spring of an extremely remote site at Alert, Nunavut, ranged from 0.04 to 0.84 µg/m³ on a 5-minute basis (detection limit 0.04 µg/m³), with a mean of 0.48 µg/m³ (De Serves, 1994).

Concentrations of formaldehyde were determined in air near a forest product plant. The maximum 24-hour average concentrations for March–June 1995, July–September 1995 and October 1995 – March 1996 were 3.01, 1.71 and 4.40 µg/m³, respectively (detection limit not specified) (Environment Canada, 1997c).

2.3.2.2 Indoor air

Few recent data were identified concerning concentrations of formaldehyde in residential indoor air in Canada. In contrast, large numbers of measurements of formaldehyde in the indoor air of Canadian homes were made during the 1970s and 1980s (Government of Canada, 1982) in response to concerns about emissions of formaldehyde from UFFI. These older data, reflecting higher concentrations of formaldehyde in the residential indoor air of “complaint” homes, were not considered to be representative of the concentrations in indoor air to which the general population is currently exposed.

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 hours 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 30, 36, 85 and 116 µg/m³, respectively (Health Canada, 2000). Similar concentrations have been measured in non-workplace indoor air in other countries.

Concurrent 24-hour 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 (WHO, 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 (MS) and sidestream (SS) cigarette smoke. Based on data from the United States 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).

The available Canadian data were inadequate to permit the assessment of the extent of contributions from other combustion sources (e.g., woodstoves, vehicles in attached garages, etc.) or other potential sources (e.g., furniture, building materials) to the measured concentrations of formaldehyde in indoor air.

2.3.2.2 Water

2.3.2.2.1 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 utilized (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 U.S. 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/L. In general, concentrations of formaldehyde in drinking water are expected to be less than 100 µg/L (WHO, 1989; IARC, 1995).

2.3.2.2.2 Surface water

Concentrations of formaldehyde in raw water from the North Saskatchewan River were measured at the Rossdale drinking water treatment plant in Edmonton, Alberta. Concentrations between March 1989 and January 1990 averaged 1.2 µg/L, with a peak value of 9.0 µg/L. 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/L) 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. 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/L) and 8.4 µg/L in raw water samples collected on December 2, 1993, and February 15, 1994, respectively, from the Detroit River. In the Ottawa River, concentrations were below the detection limit (1.0 µg/L) in three profiles taken between April 12 and June 7, 1994. In the Grand River, a mean concentration of 1.1 µg/L was obtained for seven sampling dates between May 11 and June 21, 1994.

2.3.2.2.3 Effluent

Formaldehyde is not routinely measured as part of most industrial permitting or monitoring of effluent releases. Recent follow-up with individual plants reporting releases indicated that plants that had previously released effluents to surface waters now release to municipal wastewater systems or divert their effluents to activated sludge treatment prior to release into the environment, thereby reducing or eliminating releases of formaldehyde. 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/L, with a 4-day mean of 240 µg/L (Environment Canada, 1999a).

2.3.2.2.4 Groundwater

Extensive monitoring of groundwater from a site of production and use of formaldehyde included 10 samples in which formaldehyde concentrations were below the detection limit (50 µg/L) and 43 samples with concentrations ranging from 65 to 690 000 µg/L (mean of two duplicates) from November 1991 to February 1992 (Environment Canada, 1997c). Data had been collected as part of a monitoring program 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. Waste ponds associated with the formaldehyde releases are no longer in service and have been capped, and the wastewater is now treated in an effluent treatment unit (Environment Canada, 1999a).

Quarterly analyses of five monitoring wells on the property of a plant that produces UF resins were carried out during 1996–1997. Concentrations ranged from below the detection limit (50 µg/L) to 8200 µg/L, with an overall median of 100 µg/L. Concentrations for different wells indicated little dispersion from wells close to the source of contamination (Environment Canada, 1997c).

Samples from eight monitoring wells at a fibreglass insulation plant were reported to have concentrations ranging from below detection (5 µg/L) to 190 µg/L on March 24, 1997. Groundwater data from 1996 indicate concentrations from below the detection limit (0.5–5.4 µg/L) up to 120 µg/L. However, review of the analytical methods used indicates that these results may be unreliable (Environment Canada, 1997c).

Groundwater samples were collected from wells downstream from six cemeteries in Ontario. They contained formaldehyde concentrations of 1–30 µg/L (detection limit not specified). These values could be overestimates, as a blank sample was found to contain 7.3 µg/L (Chan et al., 1992).

2.3.2.2.5 Atmospheric water

While no data are available in Canada, concentrations of formaldehyde in rain, snow, fog and cloud water have been measured in other countries. Rain concentrations ranged from 0.44 µg/L (near Mexico City) to 3003 µg/L (during the burning season in Venezuela). Mean concentrations ranged from 77 µg/L (in Germany) to 321 µg/L (during the non-burning season in Venezuela). In snow, formaldehyde concentrations ranged from 18 to 901 µg/L in California. A mean snow concentration of 4.9 µg/L is reported for Germany. In fog water, concentrations of 480–17 027 µg/L have been measured in the Po valley, Italy, with a mean of 3904 µg/L (see Environment Canada, 1999a).
2.3.2.3 Sediment

No data were identified on concentrations of formaldehyde in sediments in Canada.

2.3.2.4 Soil

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) (Alberta Environmental Protection, 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.

2.3.2.5 Biota

No data were identified on concentrations of formaldehyde in Canadian biota.

2.3.2.6 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 (WHO, 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 and Denbsky, 1970; Tsuchiya et al., 1975) and marine fish (Rehbein, 1986; Tsuda et al., 1988).

Formaldehyde develops post-mortem 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 (Yasuara and 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. No data regarding the formaldehyde content of freshwater fish, marine fish or shellfish in Canada were identified.

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 have been reported in the outer layer of smoked ham (Brunn and 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/L in Japan (Tsuchiya et al., 1994) and from 0.02 to 3.8 mg/L in Brazil (de Andrade...
et al., 1996). In earlier work conducted in Canada, Lawrence and 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 United States (Hayashi et al., 1986). These concentrations reflect the levels in the beverages as consumed.

Data from several studies indicate that low concentrations of formaldehyde may be present in various prepared foods and 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 United States, 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).

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 and 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.

2.3.2.7 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. (WHO, 1989). Levels of formaldehyde in hand dishwashing liquids and liquid personal cleansing products available in Canada are less than 0.1% (w/w) (McDonald, 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 (WHO, 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 and 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 and Andersen, 1993).

Formaldehyde is present in the smoke resulting from the combustion of tobacco products. Estimates of emission factors for formaldehyde (e.g., µg/cigarette) from MS and SS smoke and from ETS have been determined by a number of different protocols for cigarettes in several countries, including Canada.

A range of MS smoke emission factors from 73.8 to 283.8 µg/cigarette was reported for 26 U.S. brands, which included non-filter, filter and menthol cigarettes of various lengths (Miyake and 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. MS smoke emission factors ranged from 8 to 50 µg/cigarette when tested under standard conditions (British Columbia Ministry of Health, 1998).

Levels of formaldehyde are higher in SS smoke than in MS smoke. Guerin et al. (1992) reported that popular commercial U.S. cigarettes deliver approximately 1000–2000 µg formaldehyde per cigarette in their SS smoke. Schlitt and Knöppel (1989) reported a mean (n = 5) formaldehyde content of 2360 µg/cigarette in the SS smoke from a single brand in Italy. Information from the British Columbia Ministry of Health from tests conducted on 11 brands of Canadian cigarettes indicates that emission factors from SS smoke ranged from 368 to 448 µg/cigarette (British Columbia Ministry of Health, 1998).

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

2.3.2.8 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 and 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 crosslinking 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 United States finished with resins rated as having high formaldehyde release was 27%, about one-half the percentage in 1980, according to Hatch and Maibach (1995). It has been reported that the average level contained by textiles made in the United States is approximately 100–200 ppm free formaldehyde (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 ppm (i.e., µg/g), five products contained between 30 and 100 ppm, and the remaining four products contained less than 30 ppm formaldehyde.

2.3.2.9 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 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 United States in 1982, although the U.S. ban was subsequently overturned.

Pressed wood products (i.e., particleboard, MDF 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 source factors that include source strength, loading factors and the presence of source combinations (Godish, 1988). The best currently available approach to evaluating the source strength of indoor materials and products is to test their emission rates (Tucker, 1990). Emission rates of formaldehyde from pressed wood products determined by emission chamber testing in Canada (Figley and Makohon, 1993; Piersol, 1995), the United Kingdom (Crump et al., 1996) and the United States (Kelly et al., 1999) are now typically less than 0.3 mg/m² per hour (Health Canada, 2000).

Formaldehyde release from pressed wood materials is greater in mobile homes than in conventional housing, since mobile homes typically have higher loading ratios (e.g., exceeding 1 m²/m³) of these materials. In addition, mobile homes have minimal ventilation, are minimally insulated and are often situated in exposed sites subject to temperature extremes (Meyer and 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. Work has also been done on resin sealants to effectively seal the resin and prevent the residual formaldehyde from escaping (Taber, 1988). Surface coatings and treatments (e.g., paper and vinyl decorative laminates) can significantly affect an original material’s off-gassing characteristics and in some cases can result in an order of magnitude reduction in the emission rates of formaldehyde from pressed wood products (Figley and 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 formaldehyde emission rate of 29 mg/m² per hour was determined for one product (McCrillis et al., 1999).

Emission rates of formaldehyde from carpets and carpet backings, vinyl floorings and wall coverings are now generally less than 0.1 mg/m² per hour (Health Canada, 2000).
2.4 Effects characterization

2.4.1 Ecotoxicology

Below, a brief summary is presented of the most sensitive organisms for the terrestrial and aquatic endpoints. More extensive description of available data on environmental effects is provided in several reviews (NRC, 1982; WHO, 1989; RIVM, 1992) and in the databases given in Appendix A.

2.4.1.1 Terrestrial organisms

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 78, 128, 239 and 438 µg/m³ in air (day: 25°C, 40% humidity; night: 14°C, 60% humidity) for 7 hours per day, 3 days per 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 a plant’s vulnerability 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 and Shimabuku, 1992). Other sensitive effects on terrestrial vegetation include a significant reduction of the pollen tube length of lily (*Lilium longiflorum*) following a 5-hour exposure to 440 µg/m³ in air; total inhibition of pollen tube elongation occurred at 1680 µg/m³ (Masaru *et al.*, 1976). A 5-hour exposure to 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 studied following exposure to formaldehyde in fog water. Seedlings of winter wheat (*Triticum aestivum*), aspen (*Populus tremuloides*), rapeseed (*Brassica rapa*) and slash pine (*Pinus elliottii*) were exposed to formaldehyde concentrations of 0, 9000 or 27 000 µg/L in fog for 4.5 hours per night, 3 nights per week, for 40 days. Based on an unspecified Henry’s law constant, calculated corresponding atmospheric gas-phase formaldehyde concentrations were 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 and Shimabuku, 1992).

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

For terrestrial invertebrates, nematodes in peat were killed by fumigation applications of 370 g/L 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 2.4.3.
2.4.1.2 Aquatic organisms

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/L in water caused 40–50% mortality after 96 hours in day-old zygotes of Phyllospora comosa, a brown marine macroalga endemic to southeastern Australia. Total (100%) mortality resulted from exposures to 100 mg/L for 24 hours and 10 mg/L for 96 hours. The 96-hour No-Observed-Effect Concentration (NOEC) and Lowest-Observed-Effect Concentration (LOEC) (percent mortality not specified) of 7-day-old embryos of the same species were reported as 1 and 10 mg/L, respectively, indicating that older organisms are more tolerant (Burridge et al., 1995a). Concentrations of 0.1, 1 and 10 mg/L also reduced germination and growth rates of the zygotes and embryos (Burridge et al., 1995b).

Freshwater algae may be slightly more tolerant of formaldehyde, based on a cell multiplication inhibition test (Bringmann and Kühn, 1980a). The premise of this test is that the number of cells in a test culture free from dissolved toxic substances will exceed that of a contaminated culture after a certain period with otherwise identical conditions and nutrient supplies. The number of cells in suspension can be measured turbidimetrically and is expressed as the extinction of primary light at 578 nm for a 10-mm layer of cells. A mean extinction of ≥3% lower than that of controls is described as the toxicity threshold. In this study, the green alga, Scenedesmus quadricauda, was exposed to various dilutions of formalin (35% CH₂O w/w) for 7 days (shaken once a day). The toxicity threshold was 0.9 mg formaldehyde/L (2.5 mg formalin/L) (Bringmann and Kühn, 1980a).

Other freshwater microorganisms were similarly sensitive in analogous cell multiplication studies. A 48-hour toxicity threshold (5% below average cell counts of controls) of 1.6 mg formaldehyde/L (4.5 mg formalin/L, 35% CH₂O w/w) was determined for the saprozoic flagellate protozoan, Chilomonas paramecium (Bringmann et al., 1980), and a 72-hour toxicity threshold (≥3% inhibition of cell multiplication, 25°C) of 7.7 mg/L (22 mg formalin/L, 35% CH₂O w/w) was reported for the protozoan, Entosiphon sulcatum (Bringmann and Kühn, 1980b). For bacteria, the 16-hour toxicity threshold (≥3% inhibition of cell multiplication) was 4.9 mg formaldehyde/L (14 mg formalin/L, 35% CH₂O w/w) for Pseudomonas putida (Bringmann and Kühn, 1980a), and a 25-minute EC₅₀ (light emission inhibition) of 2.5 mg formaldehyde/L (242 µM formalin, 37% CH₂O w/w) was observed in the Photobacterium phosphoreum Microtox test (Chou and 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-hour EC₅₀ (immobility) of 0.36 mg formaldehyde/L (1.05 µL formalin/L, 37% CH₂O w/w). The snail, Helisoma sp., bivalve, Corbicula sp., freshwater prawn, Palaeomonetes hadiakensis, and backswimmer, Notonecta sp., have 96-hour EC₅₀ values (immobility, delayed response to tactile stimuli) of 32, 43, 160 and 287 µg/L (93, 126, 465 and 835 µL formalin/L, 37% CH₂O w/w), respectively, assuming 1 µL formalin/L = 0.34 mg formaldehyde/L (Bills et al., 1977). Reported 24-hour LC₅₀ values for Daphnia magna range from 2 to 1000 mg/L (WHO, 1989).

Formaldehyde toxicity is variable for fish as well. The most sensitive freshwater fish were fingerlings of striped bass (Roccus saxatilis). Reardon and Harrell (1990) found 96-hour LC₅₀ values of 1.8, 5.0, 5.7 and 4.0 mg/L (4.96, 13.52, 15.48 and 10.84 mg formalin/L, 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 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-hour LC50 of 6.7 mg/L for striped bass under static conditions. Other short-term (3- to 96-hour) LC50s of between 10 and 10 000 mg/L were reported for 19 species and three life stages of freshwater fish (U.S. EPA, 1985; WHO, 1989). In some studies, formaldehyde caused disruption of normal gill function (Reardon and Harrell, 1990).

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

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

2.4.2 Abiotic atmospheric effects

The potential for formaldehyde to contribute to the depletion of stratospheric ozone, to climate change or to formation of ground-level ozone was examined.

Since formaldehyde is not a halogenated compound, its Ozone Depletion Potential (ODP) is 0, and it will therefore not contribute to the depletion of stratospheric ozone (Bunce, 1996).

Gases involved in climate change strongly absorb infrared radiation of wavelengths between 7 and 13 µm, enabling them to trap and re-radiate the Earth’s thermal radiation (Wang et al., 1976; Ramanathan et al., 1985). Worst-case calculations were made to determine if formaldehyde has the potential to contribute to climate change (Bunce, 1996), assuming it has the same infrared absorption strength as the reference compound, CFC-11. The Global Warming Potential (GWP) was calculated to be 3.2 × 10⁻⁴ (relative to the reference compound CFC-11, which has a GWP of 1), based on the following formula:

\[
GWP = \left( \frac{t_{\text{formaldehyde}}}{t_{\text{CFC-11}}} \right) \times \left( \frac{M_{\text{CFC-11}}}{M_{\text{formaldehyde}}} \right) \times \left( \frac{S_{\text{formaldehyde}}}{S_{\text{CFC-11}}} \right)
\]

where:

- \( t_{\text{formaldehyde}} \) is the lifetime of formaldehyde (4.1 × 10⁻³ years),
- \( t_{\text{CFC-11}} \) is the lifetime of CFC-11 (60 years),
- \( M_{\text{CFC-11}} \) is the molecular weight of CFC-11 (137.5 g/mol),
- \( M_{\text{formaldehyde}} \) is the molecular weight of formaldehyde (30 g/mol),
- \( S_{\text{formaldehyde}} \) is the infrared absorption strength of formaldehyde (2389/cm² per atmosphere, default), and
- \( S_{\text{CFC-11}} \) is the infrared absorption strength of CFC-11 (2389/cm² per atmosphere).

Since this estimate for the GWP is much less than 1% of that of the reference compound, it is unlikely that formaldehyde could contribute significantly to climate change (Bunce, 1996).

The contribution of VOCs to the formation of ground-level ozone, and the resulting contribution to smog formation, is a complex process and has been studied extensively. The terms reactivity, incremental reactivity and photochemical ozone formation potential denote the ability of an organic compound in the atmosphere to influence the formation of ozone.
Estimates of reactivity of a substance depend on the definition and method of calculation of the reactivity, the VOC/NOx ratio, the age of the air mass, the chemical mechanisms in the model, the chemical composition of the hydrocarbon mixture into which the VOC is emitted, the geographical and meteorological conditions of the airshed of interest (including temperature and intensity and quality of light) and the extent of dilution (Paraskevopoulos et al., 1995).

The Photochemical Ozone Creation Potential (POCP) is one of the simpler indices of the potential contribution of an organic compound to the formation of ground-level ozone, based on the rate of reaction of the substance with the hydroxyl radical relative to ethene (CEU, 1995). Ethene, a chemical that is considered to be important in ozone formation, has an assigned POCP value of 100. The POCP for formaldehyde was estimated to be 105 relative to ethene, using the following formula (Bunce, 1996):

$$\text{POCP} = \left( \frac{k_{\text{formaldehyde}}}{k_{\text{ethene}}} \right) \times \left( \frac{M_{\text{ethene}}}{M_{\text{formaldehyde}}} \right) \times 100$$

where:
- \(k_{\text{formaldehyde}}\) is the rate constant for the reaction of formaldehyde with OH radicals \((9.6 \times 10^{-12} \text{ cm}^3/\text{mol per second})\),
- \(k_{\text{ethene}}\) is the rate constant for the reaction of ethene with OH radicals \((8.5 \times 10^{-12} \text{ cm}^3/\text{mol per second})\),
- \(M_{\text{ethene}}\) is the molecular weight of ethene \((28.1 \text{ g/mol})\), and
- \(M_{\text{formaldehyde}}\) is the molecular weight of formaldehyde \((30 \text{ g/mol})\).

Various published reactivity values for formaldehyde and other selected VOCs are presented by Paraskevopoulos et al. (1995). The use of a maximum incremental reactivity (MIR) scale has been recommended by Carter (1994) as optimal when applied to the wide variety of conditions where ozone is sensitive to VOCs, being fairly robust to the choices of scenarios used to derive it. Experimental data indicate that its photolysis is the key factor leading to net contribution to ozone formation under conditions of low reactive organic gas to NOx ratios (Carter et al., 1995).

Recently, formaldehyde was one of the VOCs identified in the Canadian 1996 NOx/VOC Science Assessment as part of the Multi-Stakeholder NOx/VOC Science Program (Dann and Summers, 1997). Based on air measurements taken at nine urban and suburban sites in Canada from June to August from 1989 to 1993, formaldehyde was ranked 16th of the most abundant non-methane hydrocarbon and carbonyl species. Based on these measurements and on an MIR value of 4.39 mol ozone/mol carbon, formaldehyde represented approximately 7.8% of the total volatile organic carbon reactivity and was ranked 4th when sorted by the total volatile organic carbon reactivities. Total volatile organic carbon reactivity denotes the ability of organic compounds to contribute to the formation of ozone.

Therefore, based on its reactivity and the concentrations encountered in Canada, formaldehyde is likely to play a role in the photochemical formation of ground-level ozone in urban areas in Canada.

### 2.4.3 Experimental animals and in vitro

Information on non-neoplastic effects associated with the repeated inhalation or oral exposure of laboratory animals to formaldehyde is summarized in Tables 2 and 3, respectively.

#### 2.4.3.1 Acute toxicity

Reported LC50s in rodents for the inhalation of formaldehyde range from 493 to 984 mg/m3 (WHO, 1989). For rats and guinea pigs, oral LD50s of 800 and 260 mg/kg-bw have been reported (WHO, 1989). Acute exposure of animals to elevated concentrations of formaldehyde (e.g., >120 mg/m3) produces dyspnea, vomiting, hypersalivation, muscle spasms and death (WHO, 1989). Alterations in
<table>
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<tr>
<th>Protocol</th>
<th>Results</th>
<th>Critical effect [comments]</th>
<th>Reference</th>
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<tr>
<td><strong>Short-term toxicity</strong></td>
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<tr>
<td>F344 rats and B6C3F, mice exposed to 0, 0.5, 2, 6 or 15 ppm (0, 0.6, 2.4, 7.2 or 18 mg/m³) formaldehyde for 6 hours/day for 3 days.</td>
<td>NO(A)EL: 2.4 mg/m³ (rats) 7.2 mg/m³ (mice) LO(A)EL: 7.2 mg/m³ (rats) 18 mg/m³ (mice)</td>
<td>Increased cell proliferation in nasal cavity. In rats, a small transient increase in cell proliferation was observed following exposure to 0.6 mg/m³ (and to a lesser extent to 2.4 mg/m³) after 1 day of exposure only. [number and sex of animals not specified]</td>
<td>Swenberg et al., 1983, 1986</td>
</tr>
<tr>
<td>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/m³) formaldehyde for 6 hours/day, 5 days/week, for 1, 2, 4, 9 or 14 days.</td>
<td>NO(A)EL: 2.4 mg/m³ LO(A)EL: 7.1 mg/m³</td>
<td>Histopathological effects in nasal cavity. Inhibition of mucociliary clearance.</td>
<td>Morgan et al., 1986a</td>
</tr>
<tr>
<td>Groups of 10 male Wistar rats exposed to 0, 5 or 10 ppm (0, 6 or 12 mg/m³) formaldehyde for 8 hours/day (“continuous exposure”) or to 10 or 20 ppm (12 or 24 mg/m³) formaldehyde for eight 30-minute exposure periods separated by 30-minute intervals (“intermittent exposure”), 5 days/week for 4 weeks.</td>
<td>NO(A)EL: 6 mg/m³</td>
<td>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.</td>
<td>Wilmer et al., 1987</td>
</tr>
<tr>
<td>Groups of three male rhesus monkeys exposed to 0 or 6 ppm (0 or 7.2 mg/m³) formaldehyde for 6 hours/day, 5 days/week, for either 1 or 6 weeks.</td>
<td>NO(A)EL: 7.2 mg/m³</td>
<td>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]</td>
<td>Monticello et al., 1989</td>
</tr>
<tr>
<td>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/m³) formaldehyde for 22 hours/day for 3 consecutive days.</td>
<td>NO(A)EL: 1.3 mg/m³ LO(A)EL: 3.7 mg/m³</td>
<td>Histopathological effects and increased cell proliferation in nasal cavity.</td>
<td>Reuzel et al., 1990</td>
</tr>
<tr>
<td>Groups of 36 male F344 rats exposed to 0, 0.7, 2, 6.2, 9.9 or 14.8 ppm (0, 0.8, 2.4, 7.4, 11.9 or 17.8 mg/m³) formaldehyde for 6 hours/day, 5 days/week, for 1, 4 or 9 days or 6 weeks.</td>
<td>NO(A)EL: 2.4 mg/m³ LO(A)EL: 7.4 mg/m³</td>
<td>Histopathological effects and increased cell proliferation in nasal cavity. [exposure to formaldehyde had no histopathological effect on the lungs, trachea or carina]</td>
<td>Monticello et al., 1991</td>
</tr>
<tr>
<td>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/m³) formaldehyde, 6 hours/day for 3 consecutive days.</td>
<td>NO(A)EL: 1.2 mg/m³ LO(A)EL: 3.8 mg/m³</td>
<td>Histopathological effects and increased cell proliferation in nasal cavity.</td>
<td>Cassee et al., 1996</td>
</tr>
<tr>
<td><strong>Subchronic toxicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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/m³) formaldehyde for 6 hours/day, 5 days/week, for 13 weeks.</td>
<td>NO(A)EL: 1.2 mg/m³ LO(A)EL: 11.6 mg/m³</td>
<td>Histopathological effects in nasal cavity. [exposure of males to 23.8 mg/m³ 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/m³]</td>
<td>Woutersen et al., 1987</td>
</tr>
<tr>
<td>Protocol</td>
<td>Results</td>
<td>Critical effect [comments]</td>
<td>Reference</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>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/m³) formaldehyde for 6 hours/day, 5 days/week, for 13 weeks.</td>
<td>1.2 mg/m³</td>
<td>Histopathological effects in nasal cavity. [exposure to formaldehyde had no effect upon hepatic protein or glutathione levels]</td>
<td>Appelman et al., 1988</td>
</tr>
<tr>
<td>Groups of 50 male and female Wistar rats exposed to 0, 0.3, 1 or 3 ppm (0, 0.4, 1.2 or 3.6 mg/m³) formaldehyde for 6 hours/day, 5 days/week, for 13 weeks.</td>
<td>1.2 mg/m³ 3.6 mg/m³</td>
<td>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]</td>
<td>Zwart et al., 1988</td>
</tr>
<tr>
<td>Groups of 25 male Wistar rats exposed to 0, 1 or 2 ppm (0, 1.2 or 2.4 mg/m³) formaldehyde for 8 hours/day (continuous exposure) or to 2 or 4 ppm (2.4 or 4.8 mg/m³) formaldehyde in eight 30-minute exposure periods separated by 30-minute intervals (intermittent exposure), 5 days/week for 13 weeks.</td>
<td>2.4 mg/m³ 4.8 mg/m³</td>
<td>Histopathological effects in nasal cavity. In animals with the same cumulative exposure to formaldehyde (i.e., 19.2 mg/m³-hours 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]</td>
<td>Wilmer et al., 1989</td>
</tr>
<tr>
<td>Groups of 10 male F344 rats exposed to 0, 0.7, 2.0, 5.9, 10.5 or 14.5 ppm (0, 0.8, 2.4, 7.1, 12.6 or 17.4 mg/m³) formaldehyde for 6 hours/day, 5 days/week, for 11 weeks and 4 days.</td>
<td>2.4 mg/m³ 7.1 mg/m³</td>
<td>Histopathological effects and increased cell proliferation in nasal cavity.</td>
<td>Casanova et al., 1994</td>
</tr>
</tbody>
</table>

**Chronic toxicity**

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Results</th>
<th>Critical effect [comments]</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>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/m³) formaldehyde for 22 hours/day, 7 days/week, for 26 weeks.</td>
<td>1.2 mg/m³ 3.6 mg/m³</td>
<td>Monkeys and rats (histopathological effects in nasal cavity). Comparable effects observed in both species.</td>
<td>Rusch et al., 1983</td>
</tr>
<tr>
<td>Groups of approximately 120 male and female F344 rats and B6C3F, mice exposed to 0, 2.0, 5.6 or 14.3 ppm (0, 2.4, 6.7 or 17.2 mg/m³) formaldehyde for 6 hours/day, 5 days/week, for up to 24 months, followed by an observation period of 6 months.</td>
<td>2.4 mg/m³ (mice) 2.4 mg/m³ (rats)</td>
<td>Rats and mice (histopathological effects in nasal cavity).</td>
<td>Swenberg et al., 1980; Kerns et al., 1983</td>
</tr>
<tr>
<td>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/m³) formaldehyde for 6 hours/day, 5 days/week, for 52 weeks.</td>
<td>1.2 mg/m³ 11.3 mg/m³</td>
<td>Histopathological effects in nasal cavity.</td>
<td>Appelman et al., 1988</td>
</tr>
</tbody>
</table>
### Table 2 (continued)

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Results</th>
<th>Critical effect [comments]</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronic toxicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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/m³) formaldehyde for 6 hours/day, 5 days/week, for 28 months.</td>
<td>1.2 mg/m³</td>
<td>11.8 mg/m³</td>
<td>Histopathological effects in nasal cavity.</td>
</tr>
<tr>
<td>Groups of 30 Wistar rats exposed to 0, 0.1, 1 or 9.2 ppm (0, 0.12, 1.2 or 11 mg/m³) formaldehyde for 6 hours/day, 5 days/week, for 3 months and then observed for a further 25-month period.</td>
<td>1.2 mg/m³</td>
<td>11 mg/m³</td>
<td>Histopathological effects in nasal cavity. [relatively short period of exposure to formaldehyde]</td>
</tr>
<tr>
<td>Groups of approximately 90–150 male F344 rats exposed to 0, 0.7, 2, 6, 10 or 15 ppm (0, 0.8, 2.4, 7.2, 12 or 18 mg/m³) formaldehyde for 6 hours/day, 5 days/week, for up to 24 months.</td>
<td>2.4 mg/m³</td>
<td>7.2 mg/m³</td>
<td>Histopathological effects and increased cell proliferation in nasal cavity.</td>
</tr>
<tr>
<td>Groups of 32 male F344 rats exposed to 0, 0.3, 2.17 or 14.85 ppm (0, 0.4, 2.6 or 17.8 mg/m³) formaldehyde for 6 hours/day, 5 days/week, for up to 28 months.</td>
<td>0.4 mg/m³</td>
<td>2.6 mg/m³</td>
<td>Histopathological effects in nasal cavity. [incidence summed for all animals examined during interim and terminal sacrifices]</td>
</tr>
</tbody>
</table>
## TABLE 3  Summary of non-neoplastic effect levels (oral exposure) for formaldehyde

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Results</th>
<th>Critical effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-term toxicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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-bw per day for 4 weeks.</td>
<td>25 mg/kg-bw per day</td>
<td>125 mg/kg-bw per day</td>
<td>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]</td>
</tr>
<tr>
<td><strong>Subchronic toxicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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-bw per day for 13 weeks.</td>
<td>50 mg/kg-bw per day</td>
<td>100 mg/kg-bw per day</td>
<td>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 endpoints examined; target intakes may not have been achieved]</td>
</tr>
<tr>
<td>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-bw per day for 90 days.</td>
<td>75 mg/kg-bw per day</td>
<td>100 mg/kg-bw per day</td>
<td>Reduction in weight gain. [exposure to formaldehyde had no effect upon hematological or clinical parameters or organ histopathology (including the gastrointestinal mucosa); limited number of endpoints examined; target intakes may not have been achieved]</td>
</tr>
<tr>
<td><strong>Chronic toxicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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-bw per day for up to 2 years. [The average concentration of formaldehyde in the drinking water was 0, 20, 260 or 1900 mg/L in the control, low-, mid- and high-dose groups, respectively.]</td>
<td>15 mg/kg-bw per day</td>
<td>82 mg/kg-bw per day</td>
<td>Histopathological effects in the forestomach and glandular stomach. Reduced weight gain. [exposure to formaldehyde had no effect upon hematological parameters]</td>
</tr>
<tr>
<td>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/L) formaldehyde for 24 months (for approximate intakes of 0, 10, 50 and 300 mg/kg-bw per day, respectively).</td>
<td>10 mg/kg-bw per day</td>
<td>300 mg/kg-bw per day</td>
<td>Reduced weight gain, altered clinical chemistries and histopathological effects in the forestomach and glandular stomach. [small group sizes]</td>
</tr>
</tbody>
</table>
mucociliary clearance and histopathological changes within the nasal cavity have been observed in rats exposed acutely to formaldehyde at concentrations of $\geq 2.6 \text{ mg/m}^3$ (Monteiro-Riviere and Popp, 1986; Morgan et al., 1986a; Bhalla et al., 1991).

2.4.3.2 Short-term and subchronic toxicity

2.4.3.2.1 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-term and subchronic 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 3.7 mg/m$^3$ and above. Effects were generally not observed at 1.2 or 2.4 mg/m$^3$, 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 in primates effects 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 appears 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).

2.4.3.2.2 Oral exposure

Data on toxicological effects arising from the short-term oral exposure of laboratory animals to formaldehyde are limited to one study in which histopathological effects in the forestomach were not observed in Wistar rats receiving 25 mg/kg-bw per day in drinking water over a period of 4 weeks (Til et al., 1988). Information on toxicological effects of the subchronic 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 (Johannsen et al., 1986). Reduction of weight gain in both species was observed at 100 mg/kg-bw per day; No-Observed-Effect Levels (NOELs) were 50 and 75 mg/kg-bw per day, respectively.

2.4.3.3 Chronic toxicity and carcinogenicity

2.4.3.3.1 Chronic toxicity

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 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 formaldehyde concentrations of 2.4 mg/m$^3$ 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-bw per day and above (Til et al., 1989; Tobe et al., 1989).

2.4.3.3.2 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 7.2 mg/m$^3$. Currently, there is no definitive evidence indicating that formaldehyde is carcinogenic when administered orally to laboratory animals. Limited chronic dermal toxicity studies (Krivaneck et al., 1983; Iversen, 1988) and older investigations in which animals were injected with formaldehyde (WHO, 1989) add little additional weight to the evidence for the carcinogenicity of formaldehyde in animals.
Figure 1  Formaldehyde carcinogenicity

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 hours per day, 5 days per 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, 0.8, 2.4, 7.2, 12 or 18 mg/m³) formaldehyde for 6 hours per day, 5 days per week, for up to 24 months and assessed tumour incidence within the nasal cavity. 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 also determined after 3, 6, 12 and 18 months of exposure. The overall incidence of nasal squamous cell carcinoma in animals exposed to 0, 0.8, 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 as well as 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 hours per day, 5 days per 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 naso-maxillary 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, 0.36, 2.4 or 17 mg/m³ for 6 hours per day, 5 days per 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, 2.17 or 14.85 ppm (0, 0.36, 2.6 or 17.8 mg/m³) formaldehyde for 6 hours per day, 5 days per 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.

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 hours per day, 5 days per 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 absence of a significant increase in the incidence of nasal tumours in mice 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., 1989).
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, 50, 100 or 200 mg/m$^3$ for three 1-hour 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 12 mg formaldehyde/m$^3$ for their entire lives (Dalbey, 1982).

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-bw 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/L (i.e., providing intakes up to 300 mg/kg-bw per day).

In contrast, increases in tumours of the hematopoietic 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/L for 104 weeks and the animals observed until death (estimated intakes up to approximately 200 mg/kg-bw per day). The proportion of males and females with leukemias (all “hemolymphoreticular neoplasias,” e.g., lymphoblastic leukemias and lymphosarcomas, immunoblastic lymphosarcomas and “other” leukemias) increased from 4% and 3%, respectively, in the controls to 22% and 14%, respectively, in the animals receiving drinking water containing 1500 mg formaldehyde/L.

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 endpoints. Parenthetically, it should be noted that the incidence of hematopoietic tumours (e.g., myeloid leukemia, generalized histiocytic sarcoma) was not increased in Wistar rats receiving up to 109 mg formaldehyde/kg-bw per day in drinking water for up to 2 years (Til et al., 1989).

Using a rodent model for gastric carcinogenesis in which Wistar rats were “initiated” with N-methyl-N'-nitro-N-nitrosoguanidine, Takahashi et al. (1986) provided limited evidence for the tumour-promoting activity of formaldehyde following oral exposure.

2.4.3.4 Genotoxicity and related endpoints

A wide variety of endpoints 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 at high concentrations (i.e., weakly genotoxic) in both bacterial and mammalian cells in vitro (inducing both point and large-scale mutations). 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, as well as 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 nasoturbinate and maxilloturbinate cells.

Exposure of male Sprague-Dawley rats to 0.5, 3 or 15 ppm (0.6, 3.6 or 18 mg/m$^3$) formaldehyde for 6 hours per day, 5 days per 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 hours per day for 4 months — approximately 0.7%, 2.4% and 4% in animals exposed to 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 hours per 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 hours of administration (by gavage) of 200 mg formaldehyde/kg-bw 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 spermatoocytes 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 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-hour exposure to 4 mmol formaldehyde/L 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/L 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.

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 (DPX) has been observed in the nasal epithelium of rats (Casanova and Heck, 1987; Heck and 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 DPX at concentrations above 4 ppm (4.8 mg/m³) formaldehyde (see also Table 4) 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 and Delehanty, 1986; Snyder and van Houten, 1986; Craft et al., 1987; Heck and 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).
### Table 4  Comparative effects of formaldehyde exposure upon cell proliferation, DNA–protein crosslinking and tumour incidence

<table>
<thead>
<tr>
<th>Formaldehyde concentration, mg/m³ (ppm)</th>
<th>Cell proliferation ([³H]thymidine-labelled cells/mm basement membrane)¹</th>
<th>DNA–protein crosslink formation (pmol [¹⁴C]formaldehyde bound/mg DNA)²</th>
<th>Incidence of nasal carcinoma³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anterior lateral meatus</td>
<td>Posterior lateral meatus</td>
<td>Anterior mid-septum</td>
</tr>
<tr>
<td></td>
<td>Anterior lateral meatus</td>
<td>Posterior lateral meatus</td>
<td>Anterior mid-septum</td>
</tr>
<tr>
<td></td>
<td>All sites</td>
<td>Anterior lateral meatus</td>
<td>Posterior lateral meatus</td>
</tr>
<tr>
<td>0 (0)</td>
<td>10.11</td>
<td>7.69</td>
<td>6.58</td>
</tr>
<tr>
<td>0.8 (0.7)</td>
<td>10.53</td>
<td>7.82</td>
<td>8.04</td>
</tr>
<tr>
<td>2.4 (2)</td>
<td>9.83</td>
<td>11.24</td>
<td>12.74</td>
</tr>
<tr>
<td>7.2 (6)</td>
<td>15.68</td>
<td>9.96</td>
<td>4.15</td>
</tr>
<tr>
<td>12 (10)</td>
<td>76.79</td>
<td>15.29</td>
<td>30.01</td>
</tr>
<tr>
<td>18 (15)</td>
<td>93.22</td>
<td>59.52</td>
<td>75.71</td>
</tr>
</tbody>
</table>

¹ Cell proliferation measured in three locations of the nasal epithelium in male F344 rats exposed to the indicated concentrations of formaldehyde, 6 hours per day, 5 days per week, for 3 months (Monticello et al., 1996).

² 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 hours per day, 5 days per 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.

³ 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 hours per day, 5 days per week, for 24 months (Monticello et al., 1996).
2.4.3.5 Reproductive and developmental 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 or 46.8 mg/m$^3$) formaldehyde for 6 hours per 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 was 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/m$^3$) formaldehyde for 6 hours per 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).

2.4.3.6 Immunological and neurological effects

Other than a significant ($p < 0.05$) 9% increase in bacterial pulmonary survival in one study of mice exposed to 15 ppm (18 mg/m$^3$) (Jakab, 1992), as well as a statistically significant ($p < 0.05$ or 0.01) reduction in serum IgM titres in animals administered 40 or 80 mg/kg-bw per day orally, 5 days per 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; Holmstrom et al., 1989b). Endpoints examined in these studies (Dean et al., 1984; Adams et al., 1987; Holmstrom 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/m$^3$) 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/m$^3$ for 6 hours per day on 10 consecutive days (Tarkowski and Gorski, 1995). Similarly, exposure of female Dunkin-Hartley guinea pigs, sensitized to airborne ovalbumin, to 0.3 mg formaldehyde/m$^3$ 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).

2.4.3.7 Toxicokinetics/metabolism and mode of carcinogenesis

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 absorption occur primarily in the nasal passages, while in oronasal breathers (such as monkeys and humans), they likely occur primarily in the nasal passages and oral cavity 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, brain) in the rat.

Due to its deposition principally within the respiratory tract and rapid metabolism, exposure to high atmospheric concentrations of formaldehyde does not result in an increase in blood concentrations in humans (Heck et al., 1985).

In animal species, the half-life of formaldehyde in the circulation ranges from approximately 1 to 1.5 minutes (Rietbrock, 1969; McMartin et al., 1979). Formaldehyde and formate are incorporated into the one-carbon pathways involved with 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 and Tjälve, 1978; Heck et al., 1983; Billings et al., 1984; Keefer et al., 1987; Upreti et al., 1987; Bhatt et al., 1988).

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 2.4 mg/m$^3$ (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/m$^3$) (Casanova and 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 endpoints (DPX, sustained increases in proliferation and tumours) and concordance of incidence of these effects across regions of the nasal passages (see Table 4).

Increased cellular proliferation as a consequence of epithelial cell toxicity is the most significant determinant of neoplastic progression. The effect of formaldehyde exposure on cell proliferation within the respiratory epithelium of rats has been examined in a number of short-term, subchronic and chronic studies (Swenberg et al., 1983; Wilmer et al., 1987, 1989; Zwart et al., 1988; Reuzel et al., 1990; Monticello et al., 1991, 1996; Casanova et al., 1994). A sustained increase in proliferation of nasal epithelial cells has not been observed following the exposure of rats to concentrations of formaldehyde of ≤2.4 mg/m$^3$ (2 ppm) irrespective of the exposure period. In rats exposed to formaldehyde, increased respiratory epithelial cell proliferation in the nasal cavity was more closely related to the concentration to which the animals were exposed than to the total cumulative dose (Swenberg et al., 1983). The relative magnitude of increase in proliferative response is dependent upon the specific site within the nasal cavity and not always directly related to the length of exposure.
(Swenberg et al., 1986; Monticello et al., 1991, 1996; Monticello and Morgan, 1994). The extent of the carcinogenic response following exposure to formaldehyde is also dependent upon the size of the target cell population within specific regions of the nasal cavity (Monticello et al., 1996).

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

2.4.4 Humans

2.4.4.1 Case reports and clinical studies

Reports of death following acute inhalation exposure to formaldehyde were not identified. Ulceration and damage along the gastrointestinal tract have been observed in cases where formaldehyde had been ingested (Kochhar et al., 1986; Nishi et al., 1988; WHO, 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 and Kraft, 1991; Norton, 1991; Flyvholm and Menne, 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, eye, nose and throat irritation were experienced by volunteers exposed for short periods to levels of formaldehyde ranging from 0.3 to 3.6 mg/m³ (Andersen and Mølhave, 1983; Sauder et al., 1986, 1987; Schachter et al., 1986; Green et al., 1987, 1989; Witek et al., 1987; Kulle, 1993; Pazdruk et al., 1993). Mucociliary clearance in the anterior portion of the nasal cavity was reduced following exposure of volunteers to 0.3 mg formaldehyde/m³ (Andersen and Mølhave, 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 hours) to concentrations of formaldehyde up to 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).

2.4.4.2 Epidemiological studies

2.4.4.2.1 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 5 and 6, respectively.

In most epidemiological studies, the potential association between exposure to formaldehyde and cancer of the respiratory tract has been examined. However, in some
### Table 5  Summary of risk measures from case–control studies

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Formaldehyde exposure</th>
<th>Risk measure (95% CI)</th>
<th>Reference (comments)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oropharynx or hypopharynx SEER population based – Washington State</td>
<td>≥10 years occupational exposure</td>
<td>OR = 1.3 (0.7–2.5) OR = 1.5 (0.7–3.0)</td>
<td>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)</td>
</tr>
<tr>
<td>Nasopharynx SEER population based– Washington State</td>
<td>exposure score of ≥20</td>
<td>OR = 2.1 (0.6–7.8)</td>
<td>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)</td>
</tr>
<tr>
<td>Nasopharynx SEER population based – Washington State</td>
<td>residential exposure of ≥10 years residential exposure of &lt;10 years</td>
<td>OR = 5.5 (1.6–19.4) OR = 2.1 (0.7–6.6)</td>
<td>Vaughan et al., 1986b (IARC Working Group considered living in a mobile home a poor proxy for exposure)</td>
</tr>
<tr>
<td>Nasal squamous cell carcinoma Hospital based – Netherlands</td>
<td>occupational exposure assessment A occupational exposure assessment B</td>
<td>OR = 3.0 (1.3–6.4) OR = 1.9 (1.0–3.6)</td>
<td>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 assessments A &amp; B were both positive)</td>
</tr>
<tr>
<td>Squamous cell carcinoma of nasal cavity/paranasal sinus Danish Cancer Registry</td>
<td>occupational exposure without exposure to wood dust</td>
<td>OR = 2.0 (0.7–5.9)</td>
<td>Olsen and 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)</td>
</tr>
<tr>
<td>Nasopharynx Connecticut Tumour Registry</td>
<td>highest potential exposure category highest potential exposure category and dying at 68+ years of age</td>
<td>OR = 2.3 (0.9–6.0) OR = 4.0 (1.3–12)</td>
<td>Roush et al., 1987</td>
</tr>
<tr>
<td>Oral/oropharynx Population based – Turin, Italy</td>
<td>“any” occupational exposure “probable or definite” occupational exposure</td>
<td>OR = 1.6 (0.9–2.8) OR = 1.8 (0.6–5.5)</td>
<td>Merletti et al., 1991 (Small number of cases with “definite” exposure to formaldehyde)</td>
</tr>
<tr>
<td>Larynx SEER population based – Washington State</td>
<td>“high” occupational exposure occupational exposure of ≥10 years occupational exposure score of ≥20</td>
<td>OR = 2.0 (0.2–19.5) OR = 1.3 (0.6–3.1) OR = 1.3 (0.5–3.3)</td>
<td>Wortley et al., 1992</td>
</tr>
<tr>
<td>Nasal cavity/paranasal sinus (adenocarcinoma) Population based – France</td>
<td>“any” exposure without exposure to wood dust “any” exposure with medium to high exposure to wood dust “no” exposure but medium to high exposure to wood dust</td>
<td>OR = 8.1 (0.9–72.9) OR = 692 (91.9–5210) OR = 130 (14.1–1191)</td>
<td>Luce et al., 1993 (IARC Working Group noted possible residual confounding by exposure to wood dust)</td>
</tr>
<tr>
<td>Cancer</td>
<td>Formaldehyde exposure</td>
<td>Risk measure (95% CI)</td>
<td>Reference (comments)</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------</td>
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<td>----------------------</td>
</tr>
<tr>
<td>Nasopharynx Hospital based – Philippines</td>
<td>&lt;15 years of exposure</td>
<td>OR = 2.7 (1.1–6.6)</td>
<td>West et al., 1993</td>
</tr>
<tr>
<td></td>
<td>&gt;25 years since first exposure</td>
<td>OR = 2.9 (1.1–7.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;25 years of age at first exposure</td>
<td>OR = 2.7 (1.1–6.6)</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>likely occupational exposure</td>
<td>OR = 0.62 (0.29–1.36)</td>
<td>Bond et al., 1986</td>
</tr>
<tr>
<td>Lung Nested – cohort of chemical workers – Texas</td>
<td>“long–high” occupational exposure/ (cancer controls/population controls)</td>
<td>OR = 1.5 (0.8–2.8)</td>
<td>Gérin et al., 1989</td>
</tr>
<tr>
<td>Lung (adenocarcinoma) Population based – Montréal, Quebec</td>
<td>“long–high” occupational exposure/ (cancer controls/population controls)</td>
<td>OR = 2.3 (0.9–6.0)</td>
<td></td>
</tr>
<tr>
<td>Respiratory cancer Nested – cohort of Finnish woodworkers</td>
<td>cumulative exposure of ≥3.6 mg/m³-months, with minimum 10-year induction period</td>
<td>OR = 0.69 (0.21–2.24)</td>
<td>Partanen et al., 1990</td>
</tr>
<tr>
<td></td>
<td>cumulative exposure of ≥3.6 mg/m³-months, with minimum 10-year induction period exposure to formaldehyde in wood dust</td>
<td>OR = 0.89 (0.26–3.0)</td>
<td>(IARC Working Group noted that there were too few cancers at sites other than the lung for meaningful analysis)</td>
</tr>
<tr>
<td>Lung Population based – Missouri</td>
<td>potentially exposed non-smokers</td>
<td>OR = 0.9 (0.2–3.3)</td>
<td>Brownson et al., 1993</td>
</tr>
<tr>
<td>Lung Nested – cohort of U.S. automotive foundry workers</td>
<td>occupational exposure with latency period of:</td>
<td>OR = 1.31 (0.93–1.85)</td>
<td>Andjelkovich et al., 1994</td>
</tr>
<tr>
<td></td>
<td>0 years</td>
<td>OR = 1.04 (0.71–1.52)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 years</td>
<td>OR = 0.98 (0.65–1.47)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15 years</td>
<td>OR = 0.99 (0.60–1.62)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20 years</td>
<td>OR = 1.8 (0.6–5.7)</td>
<td>Brownson et al., 1993</td>
</tr>
<tr>
<td>Multiple myeloma Incident cases in follow-up of cancer prevention study in United States</td>
<td>probably exposed</td>
<td>OR = 1.1 (0.7–1.6)</td>
<td>Heineman et al., 1992</td>
</tr>
<tr>
<td>Multiple myeloma Danish Cancer Registry</td>
<td>males with probable occupational exposure</td>
<td>OR = 1.1 (0.7–1.6)</td>
<td>Heineman et al., 1992</td>
</tr>
<tr>
<td></td>
<td>females with probable occupational exposure</td>
<td>OR = 1.6 (0.4–5.3)</td>
<td>Pottern et al., 1992</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma Iowa State Health Registry</td>
<td>potential “lower intensity” of exposure</td>
<td>OR = 1.2 (0.9–1.7)</td>
<td>Blair et al., 1993</td>
</tr>
<tr>
<td></td>
<td>potential “higher intensity” of exposure</td>
<td>OR = 1.3 (0.5–3.8)</td>
<td></td>
</tr>
<tr>
<td>Ocular melanoma Cases diagnosed or treated at UCSF Ocular Oncology Unit</td>
<td>“ever” exposed to formaldehyde</td>
<td>OR = 2.9 (1.2–7.0)</td>
<td>Holly et al., 1996</td>
</tr>
</tbody>
</table>

1 SEER = Surveillance, Epidemiology and End Results program of the National Cancer Institute; UCSF = University of California at San Francisco.

2 Data in parentheses represent 90% confidence interval.
<table>
<thead>
<tr>
<th>Cancer</th>
<th>Cohort exposed</th>
<th>Risk measure¹</th>
<th>Reference (comments)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>male anatomists</td>
<td>SMR = 2.7 (1.3–5.0): 10</td>
<td>Stroup et al., 1986</td>
</tr>
<tr>
<td>Leukemia</td>
<td></td>
<td>SMR = 1.5 (0.7–2.7): 10</td>
<td>(Likely exposure to other substances; no quantitative data on exposure)</td>
</tr>
<tr>
<td>“Other lymphatic tissues”</td>
<td></td>
<td>SMR = 2.0 (0.7–4.4): 6</td>
<td></td>
</tr>
<tr>
<td>Nasal cavity and sinus</td>
<td></td>
<td>SMR = 0 (0.7–7.2): 0</td>
<td></td>
</tr>
<tr>
<td>Larynx</td>
<td></td>
<td>SMR = 0.3 (0–2): 1</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td>SMR = 0.3 (0.1–0.5): 12</td>
<td></td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>male abrasives production workers</td>
<td>SIR = 4 (0.5–14): 2</td>
<td>Edling et al., 1987</td>
</tr>
<tr>
<td>Lymphoma</td>
<td></td>
<td>SIR = 2 (0.2–7.2): 2</td>
<td>(Increases based on only two cases each)</td>
</tr>
<tr>
<td>Pancreas</td>
<td></td>
<td>SIR = 1.8 (0.2–6.6): 2</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td>SIR = 0.57 (0.1–2.1): 2</td>
<td></td>
</tr>
<tr>
<td>Buccal cavity</td>
<td>garment manufacturing workers</td>
<td>SMR = 343 (118–786): 4</td>
<td>Stayner et al., 1988</td>
</tr>
<tr>
<td>Connective tissue</td>
<td></td>
<td>SMR = 364 (123–825): 4</td>
<td></td>
</tr>
<tr>
<td>Trachea, bronchus and lung</td>
<td></td>
<td>SMR = 114 (86–149): 39</td>
<td></td>
</tr>
<tr>
<td>Pharynx</td>
<td></td>
<td>SMR = 111 (20–359): 2</td>
<td></td>
</tr>
<tr>
<td>Alimentary tract</td>
<td>resin manufacturing workers</td>
<td>SMR = 134 (p &gt; 0.05): 11</td>
<td>Bertazzi et al., 1989</td>
</tr>
<tr>
<td>Stomach</td>
<td></td>
<td>SMR = 164 (p &gt; 0.05): 5</td>
<td>(Small cohort exposed primarily to low concentrations; few deaths during observation period)</td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td>SMR = 244 (p &gt; 0.05): 2</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td>SMR = 69: 6</td>
<td></td>
</tr>
<tr>
<td>Buccal cavity and pharynx</td>
<td>male pathologists</td>
<td>SMR = 0.52 (0.28–0.89): 13</td>
<td>Matanoski, 1989</td>
</tr>
<tr>
<td>Respiratory system</td>
<td></td>
<td>SMR = 0.56 (0.44–0.77): 77</td>
<td></td>
</tr>
<tr>
<td>Hypopharynx</td>
<td></td>
<td>SMR = 4.7 (0.97–13.4): 3</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td></td>
<td>SMR = 1.4 (1.04–1.88): 47</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td></td>
<td>SMR = 1.68 (1.14–2.38): 31</td>
<td></td>
</tr>
<tr>
<td>Buccal cavity and pharynx</td>
<td>male mortuary workers</td>
<td>PMR = 120 (81–171): 30</td>
<td>Hayes et al., 1990</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td></td>
<td>PMR = 216 (59–554): 4</td>
<td></td>
</tr>
<tr>
<td>Lymphatic and hematopoietic</td>
<td></td>
<td>PMR = 139 (115–167): 115</td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td></td>
<td>PMR = 127 (104–153): 111</td>
<td></td>
</tr>
<tr>
<td>Trachea, bronchus and lung</td>
<td></td>
<td>PMR = 94.9; 308</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>male chemical workers employed before 1965</td>
<td>SMR = 123 (110–136): 348</td>
<td>Gardner et al., 1993</td>
</tr>
<tr>
<td>Buccal cavity</td>
<td>1965</td>
<td>SMR = 137 (28–141): 3</td>
<td>(35% of cohort exposed to &gt;2 ppm [2.4 mg/m³])</td>
</tr>
<tr>
<td>Pharynx</td>
<td></td>
<td>SMR = 147 (59–303): 7</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>workers exposed to &gt;2.4 mg formaldehyde/m³ at one specific plant</td>
<td>SMR = 126 (107–147): 165</td>
<td>Hansen and Olsen, 1995</td>
</tr>
<tr>
<td>Nasal cavity</td>
<td>male industrial workers</td>
<td>SPIR = 2.3 (1.3–4.0): 13</td>
<td></td>
</tr>
<tr>
<td>Nasopharynx</td>
<td></td>
<td>SPIR = 1.3 (0.3–3.2): 4</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td>SPIR = 1.0 (0.9–1.1): 410</td>
<td></td>
</tr>
<tr>
<td>Larynx</td>
<td></td>
<td>SPIR = 0.9 (0.6–1.2): 32</td>
<td></td>
</tr>
<tr>
<td>Oral cavity and pharynx</td>
<td></td>
<td>SPIR = 1.1 (0.7–1.7): 23</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>Cohort exposed</td>
<td>Risk measure $^1$</td>
<td>Reference (comments)</td>
</tr>
<tr>
<td>------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>-----------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Nasal cavity</td>
<td>male industrial workers exposed above baseline levels</td>
<td>SPIR = 3.0 (1.4–5.7): 9</td>
<td></td>
</tr>
<tr>
<td>Buccal cavity and pharynx</td>
<td>male automotive foundry workers</td>
<td>SMR = 131 (48–266): 6</td>
<td>Andjelkovich et al., 1995</td>
</tr>
<tr>
<td>Trachea, bronchus and lung</td>
<td>white male industrial workers with ≥0.1 ppm formaldehyde</td>
<td>SMR = 120 (89–158): 51</td>
<td>(25% of cohort exposed to &gt;1.5 ppm [1.8 mg/m³])</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>white male industrial workers exposed to ≥0.1 ppm formaldehyde</td>
<td>SMR = 2.7 (p &lt; 0.05): 6</td>
<td>Blair et al., 1986</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>white male industrial workers with cumulative exposures of:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 ppm-years</td>
<td>SMR = 530: 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤0.5 ppm-years</td>
<td>SMR = 271 (p &gt; 0.05): 2</td>
<td>(4% of cohort exposed to ≥2 ppm [2.4 mg/m³])</td>
</tr>
<tr>
<td></td>
<td>0.5–5.5 ppm-years</td>
<td>SMR = 256 (p &gt; 0.05): 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥5.5 ppm-years</td>
<td>SMR = 433 (p &gt; 0.05): 2</td>
<td></td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>white male industrial workers co-exposed to particulates with cumulative formaldehyde exposures of:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 ppm-years</td>
<td>SMR = 0: 0</td>
<td>Blair et al., 1987</td>
</tr>
<tr>
<td></td>
<td>&lt;0.5 ppm-years</td>
<td>SMR = 192: 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.5–&lt;5.5 ppm-years</td>
<td>SMR = 403: 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥5.5 ppm-years</td>
<td>SMR = 746: 2</td>
<td></td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>white male industrial workers:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>exposed for &lt;1 year</td>
<td>SMR = 517 (p ≤ 0.05): 3</td>
<td>Collins et al., 1988</td>
</tr>
<tr>
<td></td>
<td>exposed for ≥1 year</td>
<td>SMR = 218 (p &gt; 0.05): 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>exposed at one plant with particulates</td>
<td>SMR = 1031 (p ≤ 0.01): 4</td>
<td></td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>white male workers, hired between 1947 and 1956, employed at one specific plant for:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;1 year</td>
<td>SMR = 768 (p &gt; 0.05): 2</td>
<td>Marsh et al., 1996</td>
</tr>
<tr>
<td></td>
<td>≥1 year</td>
<td>SMR = 1049 (p &lt; 0.05): 2</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>white male industrial workers exposed to ≥0.1 ppm formaldehyde</td>
<td>SMR = 111 (96–127): 210</td>
<td>Blair et al., 1986</td>
</tr>
<tr>
<td></td>
<td>white male industrial workers with ≥20 years since first exposure</td>
<td>SMR = 132 (p ≤ 0.05): 151</td>
<td>(4% of cohort exposed to ≥2 ppm [2.4 mg/m³])</td>
</tr>
<tr>
<td>Cancer</td>
<td>Cohort exposed</td>
<td>Risk measure</td>
<td>Reference (comments)</td>
</tr>
<tr>
<td>--------</td>
<td>----------------</td>
<td>--------------</td>
<td>----------------------</td>
</tr>
<tr>
<td></td>
<td>white male industrial workers with cumulative exposures of:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 ppm-years</td>
<td>SMR = 68 (37–113); 14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤0.5 ppm-years</td>
<td>SMR = 122 (98–150); 88</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.51–5.5 ppm-years</td>
<td>SMR = 100 (80–124); 86</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;5.5 ppm-years</td>
<td>SMR = 111 (85–143); 62</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>wage-earning white males in industrial cohort exposed to formaldehyde and other substances</td>
<td>SMR = 1.4 (p ≤ 0.05); 124</td>
<td>Blair <em>et al.</em>, 1990a</td>
</tr>
<tr>
<td></td>
<td>wage-earning white males in industrial cohort exposed to formaldehyde</td>
<td>SMR = 1.0 (p &gt; 0.05); 88</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>subjects in industrial cohort less than 65 years of age with cumulative exposures of:</td>
<td>RR = 1.0</td>
<td>Sterling and Weinkam, 1994</td>
</tr>
<tr>
<td></td>
<td>&lt;0.1 ppm-years</td>
<td>RR = 1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.1–0.5 ppm-years</td>
<td>RR = 1.47 (1.03–2.12)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>0.5–2.0 ppm-years</td>
<td>RR = 1.08 (0.67–1.70)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&gt;2.0 ppm-years</td>
<td>RR = 1.83 (1.09–3.08)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>males in industrial cohort less than 65 years of age with cumulative exposures of:</td>
<td>RR = 1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;0.1 ppm-years</td>
<td>RR = 1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.1–0.5 ppm-years</td>
<td>RR = 1.50 (1.03–2.19)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>0.5–2.0 ppm-years</td>
<td>RR = 1.18 (0.73–1.90)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&gt;2.0 ppm-years</td>
<td>RR = 1.94 (1.13–3.34)</td>
<td>2</td>
</tr>
<tr>
<td>Lung</td>
<td>white wage-earning males in industrial cohort with &gt;2 ppm-years of cumulative exposure and exposure durations of:</td>
<td>(no observed deaths)</td>
<td>Blair and Stewart, 1994</td>
</tr>
<tr>
<td></td>
<td>&lt;1 year</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1–&lt;5 years</td>
<td>SMR = 1.1 (p &gt; 0.05); 9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5–&lt;10 years</td>
<td>SMR = 2.8 (p &lt; 0.05); 17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;10 years</td>
<td>SMR = 1.0 (p &gt; 0.05); 10</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>white male workers employed at one specific plant for:</td>
<td></td>
<td>Marsh <em>et al.</em>, 1996</td>
</tr>
<tr>
<td></td>
<td>&lt;1 year</td>
<td>SMR = 134 (p &lt; 0.05); 63</td>
<td>(25% exposed to &gt;0.7 ppm [0.9 mg/m³])</td>
</tr>
<tr>
<td></td>
<td>≥1 year</td>
<td>SMR = 119 (p &gt; 0.05); 50</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>white males in industrial cohort with cumulative exposures of:</td>
<td></td>
<td>Callas <em>et al.</em>, 1996</td>
</tr>
<tr>
<td></td>
<td>0 ppm-years</td>
<td>RR = 1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.05–0.5 ppm-years</td>
<td>RR = 1.46 (0.81–2.61)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.51–5.5 ppm-years</td>
<td>RR = 1.27 (0.72–2.26)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;5.5 ppm-years</td>
<td>RR = 1.38 (0.77–2.48)</td>
<td></td>
</tr>
</tbody>
</table>

1. Unless otherwise noted, values in parentheses are 95% confidence interval or level of statistical significance. Risk measures are presented here 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.

2. Values in parentheses represent 90% confidence interval.
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, leukemic, lymphoid and hematopoietic, 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 (Table 5), 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 5. There was no increase in an additional investigation that is also considered to be limited (Olsen and 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 and Asnaes, 1986; Hayes et al., 1990) and no increase in another (Luce et al., 1993), although there were limitations (as noted in Table 5) 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 (Table 5).

There is little convincing evidence of increased risks of nasopharyngeal cancer in cohort studies of populations of professionals or industrial workers occupationally 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 6, 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 and Olsen, 1995); in the latter study, however, the standardized proportionate incidence ratio (SPIR) 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 United States (4% of cohort exposed to ≥2 ppm [2.4 mg/m³]) 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 (OR) was greater than for “lung cancer,” the number of cases on which this observation was based was small (Gerin 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 duration of exposure to dust-borne formaldehyde, except in one category (Partanen et al., 1990).

In smaller cohort studies of professional and industrial workers (Table 6), there have been no significant excesses of cancers of the trachea, bronchus or lung (Hayes et al., 1990; Andjelkovich et al., 1995), the buccal cavity or pharynx (Matanoski, 1989; Hayes et al., 1990; Andjelkovich et al., 1995), the lung (Stroup et al., 1986; Bertazzi et al., 1989; Hansen and 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 or lung, buccal cavity or pharynx (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), 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 (SMR) 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 excess of cancers of the buccal cavity 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 United States (4% of cohort exposed to ≧2 ppm [2.4 mg/m³]), Blair et al. (1986) observed a slight but significant (1.3-fold) excess of deaths due to lung cancer among the sub-cohort 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 and 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). These analyses revealed no increased risk of cancer of the oral cavity associated with exposure to formaldehyde (Blair et al., 1990b; 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 \( \text{RR} = 1.2 \)) exposure to formaldehyde, compared with those with higher (\( \text{RR} = 1.0 \)) or substantial (\( \text{RR} = 1.1 \)) 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).

### 2.4.4.2.2 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). 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 and Sazonova, 1982; Bauchinger and Schmid, 1985; Yager et al., 1986; Dobiás et al., 1988, 1989; Kitaeva et al., 1996), but not others (Fleig et al., 1982; Thomson et al., 1984; Vasudeva and 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 the contribution of co-exposures cannot be precluded.

### 2.4.4.2.3 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), chemicals, and furniture and wood products (Alexandersson and Hedenstierna, 1988, 1989; Holmström and Wilhelmsson, 1988; Malaka and Kodama, 1990) or through employment in the funeral services industry (Holness and 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 (0.2 mg/m$^3$) 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 and Hedenstierna, 1988, 1989; Holmström and Wilhelmssson, 1988; Malaka and 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 and Hedenstierna, 1989). In the subset of these investigations in which exposure was monitored for individuals (i.e., excluding only that of Malaka and Kodama, 1990), workers were exposed to mean concentrations of formaldehyde of 0.4 mg/m$^3$ (0.3 ppm) 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 and 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 and Nethercott, 1989). These groups of workers were exposed to mean concentrations of formaldehyde of up to 2 ppm (2.4 mg/m$^3$).

In a survey of residences in Minnesota, prevalences of nose and throat irritation among residents were low for exposures to concentrations of formaldehyde less than 0.12 mg/m$^3$ (0.1 ppm) but considerable at levels greater than 0.4 mg/m$^3$ (0.3 ppm) (Ritchie and 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/m$^3$]), “medium” (0.1–0.3 ppm [0.12–0.4 mg/m$^3$]) and “high” (>0.3 ppm [0.4 mg/m$^3$]), 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 (0.4 mg/m$^3$) than for levels below 0.3 ppm (0.4 mg/m$^3$). 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 (0.4 mg/m$^3$) were high (71–99%), those reporting effects at below 0.1 ppm (0.12 mg/m$^3$) were small (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 (0.4 mg/m$^3$) and between 0% and 3% for <0.1 ppm (0.12 mg/m$^3$).

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, respectively; only the questionnaire was completed for children under the age of 10. Monitoring for formaldehyde was conducted in 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.

### 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 and Montanaro, 1991; Stenton and 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 ppm. 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.
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 0.3 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 recent 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.

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 and 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.
3.0 ASSESSMENT OF “TOXIC” UNDER CEPA 1999

3.1 CEPA 1999 64(a): Environment

The environmental risk assessment of a PSL substance is based on the procedures outlined in Environment Canada (1997a). Analysis of exposure pathways and subsequent identification of sensitive receptors are used to select environmental assessment endpoints (e.g., adverse reproductive effects on sensitive fish species in a community). For each endpoint, a conservative Estimated Exposure Value (EEV) is selected and an Estimated No-Effects Value (ENEV) is determined by dividing a Critical Toxicity Value (CTV) by an application factor. A conservative (or hyperconservative) quotient (EEV/ENEV) is calculated for each of the assessment endpoints in order to determine whether there is potential ecological risk in Canada. If these quotients are less than one, it can be concluded that the substance poses no significant risk to the environment, and the risk assessment is completed. If, however, the quotient is greater than one for a particular assessment endpoint, then the risk assessment for that endpoint proceeds to an analysis where more realistic assumptions are used and the probability and magnitude of effects are considered. This latter approach involves a more thorough consideration of sources of variability and uncertainty in the risk analysis.

3.1.1 Assessment endpoints

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.

3.1.1.1 Terrestrial

Data on terrestrial toxicity are available for a variety of microorganisms, plants and invertebrates (Section 2.4.1.1), as well as from mammalian toxicology studies (Section 2.4.3). The most sensitive identified endpoints include primarily effects on the growth and development of plants (Haagen-Smit et al., 1952; Barker and 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 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 endpoints will be used as the CTV for the risk characterization for terrestrial effects.

3.1.1.2 Aquatic

Aquatic toxicity data are available for a variety of algae, microorganisms, invertebrates, fish and amphibians (Section 2.4.1.2). Identified sensitive endpoints include effects on the development and survival of algae and invertebrates (Bills et al., 1977; Bringmann and Kühn, 1980a; Burridge et al., 1995a,b), inhibition of cell multiplication in protozoa (Bringmann and Kühn, 1980a), immobilization of crustaceans (Bills et al., 1977) and mortality in fish (Reardon and 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.

Therefore, although limited, the available studies cover an array of organisms from different taxa and ecological niches and are considered adequate for an assessment of risks to aquatic biota. The response for all of these endpoints that occurs at lowest concentration is the CTV for the risk characterization for aquatic effects.

3.1.2 Environmental risk characterization

3.1.2.1 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.

3.1.2.1.1 Hyperconservative analysis

The highest reported concentration of formaldehyde in ambient air in Canada is 27.5 µg/m³. This value was obtained for a 24-hour urban sample collected in Toronto, Ontario, on August 8, 1995. The mean concentration for six measurements made at this site during a 30-day period encompassing this date (July 14 to August 12, 1995) is 22.15 µg/m³. This mean concentration will be used as the EEV in the hyperconservative analysis of the chronic exposure scenario for terrestrial organisms. A 1-month mean is selected for the EEV because it corresponds to a longer exposure period relative to the life span of test organisms for which data are available.

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/L) that affects the growth and reproduction potential of rapeseed (Brassica rapa) exposed 4.5 hours per night, 3 nights per week, for 40 days (Barker and 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.

The 40-day intermittent exposure of Brassica rapa can be considered as chronic exposure (covering a significant portion of a life
stage of the organism). For the hyperconservative analysis, the ENEV for terrestrial organisms is derived by dividing the CTV by a factor of 10. This factor accounts 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. As a result, the ENEV is 1.8 µg/m³.

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

\[
\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}} = \frac{22.15 \, \mu g/m³}{1.8 \, \mu g/m³} = 12.3
\]

Since the hyperconservative quotient is more than 1, there is a need to proceed to a more realistic analysis of whether formaldehyde emissions cause adverse effects on terrestrial organisms in Canada.

3.1.2.1.2 Conservative analysis

For a conservative analysis, a more 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 December 6, 1989 and December 18, 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 NAPS 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 a conservative analysis, a more realistic ENEV could be calculated by dividing the hyperconservative CTV of 18 µg/m³ (rapeseed) by a more refined application factor. 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 and 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 µg/m³). 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 and 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, keeping a CTV of 18 µg/m³, the application factor of 10 used in the hyperconservative scenario can be reduced to 2 for the conservative assessment. As a result, the ENEV for the conservative analysis of the exposure scenario for terrestrial organisms will be 9 µg/m³.

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

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}$$

$$= \frac{7.48 \ \mu g/m^3}{9 \ \mu g/m^3}$$

$$= 0.83$$

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 and 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 and Shimabuku (1992). In addition, no data were found on concentrations of formaldehyde in fog in Canada or frequency of fog incidence in urban areas 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 chronic 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 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 hours per day, 3 days per 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.

The 28-day intermittent exposure of the bean plant can be considered as chronic 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 µg/m³. This yields the following conservative quotient:
This quotient is very close to one.

Given the arguments for reducing the application factor of the hyperconservative rapeseed CTV 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 µg/m³. This results in a lower conservative quotient:

\[
\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}} = \frac{7.48 \text{ µg/m}^3}{39 \text{ µg/m}^3} = 0.19
\]

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

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 µg/m³ for alfalfa; Haagen-Smit et al., 1952), with no effects on plants at concentrations of 44 mg/m³ (Wolverton et al., 1984).

A summary of the values used in the environmental risk analysis of formaldehyde in the terrestrial environment is presented in Table 7.

### Table 7  Summary of the environmental risk analysis for terrestrial organisms

<table>
<thead>
<tr>
<th>Terrestrial organisms</th>
<th>EEV (µg/m³)</th>
<th>CTV (µg/m³)</th>
<th>Application factor</th>
<th>ENEV (µg/m³)</th>
<th>Quotient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tier 1: Hyperconservative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest urban mean, rapeseed in fog</td>
<td>22.15</td>
<td>18</td>
<td>10</td>
<td>1.8</td>
<td>12.3</td>
</tr>
<tr>
<td><strong>Tier 2: Conservative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest 90th percentile, rapeseed in fog</td>
<td>7.48</td>
<td>18</td>
<td>2</td>
<td>9</td>
<td>0.83</td>
</tr>
<tr>
<td>Highest 90th percentile, bean plant in air</td>
<td>7.48</td>
<td>78</td>
<td>10</td>
<td>7.8</td>
<td>0.96</td>
</tr>
<tr>
<td>Highest 90th percentile, bean plant in air</td>
<td>7.48</td>
<td>78</td>
<td>2</td>
<td>39</td>
<td>0.19</td>
</tr>
</tbody>
</table>
3.1.2.2 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.

3.1.2.2.1 Hyperconservative analysis

A hyperconservative analysis has been conducted for aquatic organisms exposed to concentrations measured in surface water, effluents and groundwater.

The highest concentration of formaldehyde reported in surface water is 9.0 µg/L, 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/L (Environment Canada, 1999a). In various groundwater samples, the highest concentration of formaldehyde was 690 000 µg/L at an industrial site (Environment Canada, 1997c). These values will be used as the EEVs in the hyperconservative analysis of aquatic organisms in surface water, effluent and groundwater. The effluent EEV is based on the conservative assumption that organisms could be living at the point of discharge. The groundwater EEV is based on the conservative assumption that the groundwater could recharge directly to surface water at its full concentration.

For exposure of aquatic animals to formaldehyde in water, the CTV is 100 µg/L, based on the concentration that causes 40–50% mortality after 96 hours in day-old zygotes of the marine alga, *Phyllospora comosa* (Burridge et al., 1995a). This value was selected as the most sensitive endpoint from a large data set composed of toxicity studies conducted on at least 36 species of freshwater and marine aquatic algae, microorganisms, invertebrates, fish and amphibians.

The 96-hour exposure for *Phyllospora comosa* zygotes can be considered as chronic exposure (covering a significant portion of the lifetime of the organism). For a hyperconservative analysis, the ENEV is derived by dividing the CTV by a factor of 10. This factor accounts for the uncertainty in the extrapolation from a chronic 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 10 µg/L.

The hyperconservative quotients are calculated by dividing the EEV by the ENEV as follows:

**Surface water analysis**

\[
\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}
\]

\[
= \frac{9.0 \, \mu\text{g/L}}{10 \, \mu\text{g/L}}
\]

\[
= 0.9
\]

Since the hyperconservative quotient is less than 1, it is unlikely that formaldehyde causes adverse effects on aquatic organisms in ambient surface water in Canada, and more realistic exposure scenarios need not be considered.
**Effluent analysis**

Quotient = \( \frac{\text{EEV}}{\text{ENEV}} \)

= \( \frac{325 \, \mu g/L}{10 \, \mu g/L} \)

= 32.5

Since the hyperconservative quotient is greater than 1, it is necessary to consider further the likelihood of biota being exposed to such concentrations in surface water near point sources in Canada.

**Groundwater analysis**

Quotient = \( \frac{\text{EEV}}{\text{ENEV}} \)

= \( \frac{690 \, 000 \, \mu g/L}{10 \, \mu g/L} \)

= 69 000

Since the hyperconservative quotient is greater than 1, it is necessary to consider further the likelihood of biota being exposed to such concentrations in Canada.

### 3.1.2.2.2 Conservative analysis

For a conservative analysis, more realistic estimates of aquatic exposure must be used. In the case of effluent, dilution can be considered. For a conservative analysis, the hyperconservative EEV of 325 µg/L 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/L.

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/L). 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/L for measurements taken at five wells at the contaminated site during 1996–1997. Assuming some degree of dilution similar to that of effluent in receiving water bodies, the median value can also 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/L.

For a conservative analysis, an endpoint 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/L, based on the 96-hour EC50 (immobility) for this organism (Bills *et al.*, 1977). This value was selected as the most sensitive endpoint 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/L.
The conservative quotients are calculated by dividing the EEV by the ENEV as follows:

**Effluent analysis**

Quotient = \( \frac{\text{EEV}}{\text{ENEV}} \)

\[
= \frac{32.5 \, \mu\text{g/L}}{36 \, \mu\text{g/L}} 
= 0.9 
\]

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.

**Groundwater analysis**

Quotient = \( \frac{\text{EEV}}{\text{ENEV}} \)

\[
= \frac{10 \, \mu\text{g/L}}{36 \, \mu\text{g/L}} 
= 0.28 
\]

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.

A summary of the values used in the environmental risk analysis of formaldehyde in the aquatic environment is presented in Table 8.

### 3.1.2.3 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 chronic studies available. To account for these uncertainties, application factors were used in the environmental risk analysis to derive ENEVs.

Regarding environmental exposure, there could be concentrations of formaldehyde in Canada that are higher than those identified and used in this assessment.

**Table 8** Summary of the environmental risk analysis for aquatic organisms

<table>
<thead>
<tr>
<th>Aquatic organisms</th>
<th>EEV (µg/L)</th>
<th>CTV (µg/L)</th>
<th>Application factor</th>
<th>ENEV (µg/L)</th>
<th>Quotient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tier 1: Hyperconservative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surface water – marine algae</td>
<td>9.0</td>
<td>100</td>
<td>10</td>
<td>10</td>
<td>0.9</td>
</tr>
<tr>
<td>Effluent – marine algae</td>
<td>325</td>
<td>100</td>
<td>10</td>
<td>10</td>
<td>32.5</td>
</tr>
<tr>
<td>Groundwater – marine algae</td>
<td>690 000</td>
<td>100</td>
<td>10</td>
<td>10</td>
<td>69 000</td>
</tr>
<tr>
<td><strong>Tier 2: Conservative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effluent – seed shrimp</td>
<td>32.5</td>
<td>360</td>
<td>10</td>
<td>36</td>
<td>0.9</td>
</tr>
<tr>
<td>Groundwater – seed shrimp</td>
<td>10</td>
<td>360</td>
<td>10</td>
<td>36</td>
<td>0.28</td>
</tr>
</tbody>
</table>
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.

Despite some data gaps regarding the environmental effects and exposure of formaldehyde, the data available at this time are considered adequate for making a conclusion on the environmental risk of formaldehyde in Canada.

3.2 CEPA 1999 64(b): Environment upon which life depends

Formaldehyde does not deplete stratospheric ozone, and its potential for climate change is negligible. The photolysis of formaldehyde leads to the direct formation of radicals that are active in the formation of ground-level ozone (Carter et al., 1995). In addition, formaldehyde is more reactive with hydroxyl radicals (POCP of 105) than compounds such as ethene that are recognized as important in the formation of ground-level ozone (Bunce, 1996). Given its reactivity and concentrations measured in air in Canada, formaldehyde represented approximately 7.8% of the total volatile organic carbon reactivity, ranking it 4th among non-methane hydrocarbons and carbonyl compounds contributing to the formation of ground-level ozone (Dann and Summers, 1997). Formaldehyde is therefore important in the photochemical formation of ground-level ozone.

3.3 CEPA 1999 64(c): Human health

3.3.1 Estimated population exposure

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 gastrointestinal tract following ingestion) and are related to the concentration of formaldehyde in media to which humans are exposed, rather than 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).

The general population in Canada is exposed to low concentrations of formaldehyde in outdoor air and to generally higher concentrations in indoor air. A subset of data from the NAPS program 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. The selected data are from sites classified as suburban (n = 4) or urban (n = 4) and include all 24-hour concentrations of formaldehyde (n = 2818) measured at these sites between January 1990 and December 1998 (Health Canada, 2000). The distribution of concentrations is positively skewed, with median, arithmetic mean and upper-percentile concentrations as summarized in Table 9. The distribution of concentrations at one of the four urban sites (i.e., in Toronto) was selected as a reasonable worst case. The distribution of concentrations of formaldehyde at this site is also positively skewed, and statistical parameters of this distribution are summarized in Table 9.

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). Sampling duration was 24 hours in two of the studies selected (n = 47 samples). These samples were collected and analyzed by the same methodologies and by the same laboratory as for the NAPS data referred to above. Passive sampling for 7-day periods and different analytical methodology were employed in the remaining three studies (n = 104). The distributions of concentrations of formaldehyde from the 24-hour active and the 7-day passive samples were compared. These distributions were judged to be sufficiently similar to justify pooling the data from the five studies. Median, arithmetic mean and upper-percentile concentrations of this distribution are summarized in Table 9.

The distribution of pooled concentrations is positively skewed. When plotted in 10 µg/m³ bins, there is a good fit to a lognormal distribution.

Table 9  Concentrations of formaldehyde in outdoor air and residential indoor air in Canada

<table>
<thead>
<tr>
<th>Medium of exposure</th>
<th>Number of samples</th>
<th>Mid-points of distributions (µg/m³)</th>
<th>Upper percentiles of distributions of concentrations (µg/m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Median</td>
<td>Mean ¹</td>
</tr>
<tr>
<td>Outdoor air – NAPS data¹</td>
<td>2818</td>
<td>2.8</td>
<td>3.3</td>
</tr>
<tr>
<td>Outdoor air – reasonable worst-case site²</td>
<td>371</td>
<td>2.9</td>
<td>4.0</td>
</tr>
<tr>
<td>Indoor air – five studies³</td>
<td>151</td>
<td>29.8</td>
<td>35.9</td>
</tr>
<tr>
<td>Indoor air – lognormal distribution⁴</td>
<td>–</td>
<td>28.7</td>
<td>–</td>
</tr>
</tbody>
</table>

¹ Data are for selected suburban (n = 4) and urban (n = 4) sites of the NAPS Program (Dann, 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.

² One of the four urban sites (i.e., NAPS site 060418 in Toronto) was selected for the reasonable worst-case purpose.

³ 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.

⁴ 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.

⁵ 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.
characterized by the same geometric mean (i.e., 28.7 µg/m³) and standard deviation (2.92). Upper percentiles of this lognormal distribution were calculated and are shown for comparison in Table 9. The values of these percentiles are higher for the lognormal distribution than for the more limited data set. This is to be expected, since the lognormal distribution approaches the x-axis asymptotically.

These data are used to estimate the distribution of time-weighted 24-hour concentrations of formaldehyde to which the general population is exposed (Health Canada, 2000). This requires consideration of the proportion of the 24-hour day that is spent indoors versus the time spent outdoors. Recent deterministic (i.e., point) estimates (EHD, 1998) indicate that, in general, all age groups spend a daily average of 21 hours in indoor environments and 3 hours outdoors in Canada. Probabilistic estimates of the proportion of time spent indoors versus outdoors are more desirable, as these would provide an indication of the distributions of these average estimates, but these estimates were not available. Instead, a mean time spent outdoors of 3 hours is assumed based on the point estimates of time spent indoors and outdoors (EHD, 1998). The distribution of the time spent outdoors is arbitrarily assumed to be normal in shape with an arithmetic standard deviation of 2 hours. In the probabilistic simulation, this distribution is truncated at 0 hours and 9 hours. The time spent indoors is calculated as 24 hours minus the time spent outdoors.

Estimates of the distribution of time-weighted 24-hour concentrations of formaldehyde to which the general population is exposed were developed using simple random sampling with Crystal Ball™ Version 4.0 (Decisioneering, Inc., 1996) and simulations of 10 000 trials. Each trial involves random sampling of the distribution of concentrations in outdoor air and multiplying this by a random sample of the time spent outdoors. This results in an estimate of the concentration-time product for formaldehyde (C₀, in µg-hour/m³) resulting from exposure to outdoor air. The “time spent indoors” is then calculated as 24 hours minus “time spent outdoors.” This “time spent indoors” is then multiplied by a random sample from the distribution of concentrations in indoor air and results in an estimate of the concentration-time product for formaldehyde (C₁, in µg-hour/m³) resulting from exposure to indoor air. The average 24-hour time-weighted concentration of formaldehyde for each trial is then calculated as \((1/24) \times (C₀ + C₁)\) for exposure to outdoor and indoor air.

Two simulations were run. In both simulations, the distribution of concentrations of formaldehyde in outdoor air is represented by a frequency histogram of the data from the eight selected NAPS sites \((n = 2818\) samples). In the first simulation, the distribution of concentrations of formaldehyde in residential indoor air is represented by a frequency histogram of the pooled data from the five selected studies \((n = 151\) samples). In the second simulation, the distribution of concentrations of formaldehyde in residential indoor air is represented by an assumed lognormal distribution with the same geometric mean (28.7 µg/m³) and standard deviation (2.92) as for the pooled data. This assumed lognormal distribution is truncated at 150 µg/m³, the highest concentration measured among the five studies. It is assumed that the general population is exposed to similar distributions of concentrations in the indoor air of public places. Exposure to formaldehyde in the indoor air of workplaces is not addressed specifically; therefore, the general population is assumed to be exposed to similar concentrations of formaldehyde in the indoor air of all workplaces. Estimates of the median, arithmetic mean and upper percentiles of the distributions of 24-hour time-weighted average concentrations of formaldehyde determined from these probabilistic simulations are summarized in Table 10. The two simulations were each run five times. The relative standard deviations of the upper-percentile estimates of time-weighted average concentrations were calculated to determine the stability of these upper-percentile estimates. These relative standard deviations are also summarized in Table 10. Examples of the shapes of the distributions resulting from the two simulations are available in
Health Canada (2000). Based on the assumptions underlying these probabilistic simulations, the estimates summarized in Table 10 indicate that one of every two persons would be exposed to 24-hour average concentrations of formaldehyde in air of 24–29 µg/m³ or greater (i.e., median concentrations). Similarly, 1 in 20 persons (i.e., 95th percentile) would be exposed to 24-hour average concentrations of formaldehyde in air of 80–94 µg/m³ or greater.

Based on limited data from the United States, concentrations in drinking water may range up to approximately 10 µg/L, 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/L) 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/L were observed in a U.S. 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 from less than 0.03 to 14 mg/kg (Health Canada, 2000). However, the proportion of formaldehyde in foods that is bioavailable is unknown.

### 3.3.2 Hazard characterization

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 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 gastrointestinal tracts following inhalation and ingestion, respectively).

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

### Table 10: Probabilistic estimates of 24-hour time-weighted average concentrations of formaldehyde in air

<table>
<thead>
<tr>
<th></th>
<th>Mid-points of distributions (µg/m³)</th>
<th>Upper percentiles of distributions of concentrations (µg/m³) and relative standard deviations (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Mean³</td>
</tr>
<tr>
<td>Simulation 1¹</td>
<td>29</td>
<td>36</td>
</tr>
<tr>
<td>Simulation 2²</td>
<td>24</td>
<td>33</td>
</tr>
</tbody>
</table>

¹ 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).

² For simulation 2, a lognormal distribution of concentrations, truncated at 150 µg/m³, is assumed. This lognormal distribution has the same geometric mean (28.7 µg/m³) and standard deviation (2.92) as the distribution of concentrations for the pooled data from the five selected studies.

³ This is the arithmetic mean concentration.
3.3.2.1 Genotoxicity and carcinogenicity

3.3.2.1.1 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 endpoints indicate that formaldehyde is weakly genotoxic 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. The results of in vivo studies in animals are similar to those in humans, with effects at site of contact being observed (e.g., modest increase in the proportion of pulmonary macrophages with chromosomal aberrations in rats following inhalation and cytogenetic alterations in the gastrointestinal epithelium of rats following oral exposure). 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 weakly genotoxic, with effects most likely to be observed in vivo in cells from tissues or organs with which the aldehyde comes into first contact.

3.3.2.1.2 Carcinogenicity

Inhalation

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. The data for nasal and nasopharyngeal cancer are less clear. In case–control studies, there have been increases in cancers of the nasal or nasopharyngeal cavities that fulfil, at least in part, traditional criteria of causality, with tumours having been observed in workers with highest levels 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.

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 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 blood concentrations.

As described in Section 2.4.3.7, 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 endpoints (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 and Heck, 1987; Heck and 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 endpoints 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 DPX) and tumours is limited to that presented in Table 4.

In all cases where examined, without exception, sustained cytotoxicity and cellular proliferation were observed in the nasal cavities of the same strain of rats exposed in a similar manner in short-term studies to concentrations or doses that induced nasal tumours in the cancer bioassays (Monticello et al., 1991, 1996). However, the converse is not always true. 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 and Heck, 1987; Heck and Casanova, 1987; Casanova et al., 1989, 1994).

In addition, where proliferative response (Monticello et al., 1991, 1996) and DPX (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 DPX, cytotoxicity, proliferative response and tumours are highly non-linear, with significant increases in all endpoints being observed at concentrations of 4 ppm (4.8 mg/m³) and above (Table 4). 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 proliferation and DPX 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 DPX, 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 and
Casanova, 1994) and point mutations in the p53 tumour suppressor gene in tumours from the noses of rats exposed to formaldehyde (Recio et al., 1992).

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 endpoints 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 wider area deeper within the respiratory tract. Indeed, in rats exposed to moderate levels of formaldehyde, histopathological changes, increased epithelial cell proliferation as well as 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.

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 gastrointestinal tract 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.

3.3.2.2 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; WHO, 1989), studies on potential changes within the gastrointestinal tract in humans following the long-term ingestion of this substance were not identified. However, histological changes within the surface epithelium of the gastrointestinal tract of rats (e.g., erosions and/or ulcers, hyperkeratosis, hyperplasia, gastritis) have been observed following chronic 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 (Hemminiki 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 and 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 and 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 ppm) 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 ppm). In North America, less than 10% of patients presenting with contact dermatitis may be immunologically hypersensitive to formaldehyde.

### 3.3.3 Exposure–response analysis

Cancer and non-neoplastic effects are addressed separately here. However, 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.

Emphasis in the dose–response analyses for cancer presented below is on a biologically motivated case-specific model that incorporates a two-stage clonal growth model. This model is supported by dosimetry calculations from computational fluid dynamics (CFD) modelling of formaldehyde flux in various regions of the nose and a single-path model for the lower respiratory tract. 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.

There has been no 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. However, output of the model is considered adequate as a basis to ensure that measures taken to prevent sensory irritation\(^1\) in human populations are sufficiently protective with respect to carcinogenic potential.

3.3.3.1 Inhalation

3.3.3.1.1 Carcinogenicity

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 DPX, likely also contributes, although the probability of mutation resulting from DPX is unknown.

Available data are also consistent with the hypothesis that humans would respond qualitatively similarly to experimental animals in this regard. However, since formaldehyde is highly reactive at the site of contact, dosimetry is of critical importance in 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 approach to dose–response modelling emphasized here, therefore, is biologically based, reflecting the non-linearity in concentration–response relationships for formaldehyde-induced nasal cancer and associated intermediate endpoints and incorporating, to the extent possible, mechanistic data and state-of-the-art analyses for species-specific dosimetry. It incorporates regenerative cell proliferation as a required step in the induction of tumours by formaldehyde and a contribution from mutagenicity (not defined specifically by DPX) 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. Species variations in dosimetry are taken into account by CFD modelling of formaldehyde flux in various regions of the nose and a single-path model for the lower respiratory tract of humans.

The outcome is compared with that derived based on empirical default methodology for estimation of tumorigenic concentrations in the experimental range for Priority Substances (Health Canada, 1994). However, it is the biologically motivated case-specific model that is considered to provide the most defensible estimates of cancer risk, on the basis that it

\(^1\) Occurs at lower concentrations than effects on mucociliary clearance or histopathological damage to the nose of humans.
encompasses more of the available biological data, thereby offering considerable improvement over default (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).

Biologically motivated case-specific model

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 biologically based, two-stage clonal growth model developed (Figure 2) is identical in biological structure to other such 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).

Formaldehyde is assumed to act as a direct mutagen, with the effect considered proportional to the estimated tissue concentration of DNA–protein crosslinks. The dose–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. The second mode of carcinogenic action considers cytotoxicity and the subsequent regenerative cellular proliferation associated with exposure to formaldehyde, incorporating a “hockey stick” dose–response curve (i.e., dose threshold curve) within the model. 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 3), 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.

**Figure 2** Two-stage clonal growth model (reproduced from CIIT, 1999)
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 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 biologically based, two-stage clonal growth model 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 exposure–response model developed for humans (see Figure 4) 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. The parameter representing the time for a malignant cell to expand clonally into a clinically detectable tumour was set at 3.5 years.

2 Data on predicted risks of upper respiratory tract cancers for smokers are also presented in CIIT (1999).
In addition to the human nasal CFD model, a typical-path, one-dimensional model of formaldehyde uptake was developed for the lower respiratory tract. The 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 L/minute. 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 for 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 DPX 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 two-stage 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 predicted non-zero additional risks throughout the exposure ranges examined. The two-stage model
describes a low-dose, linear carcinogenic response for humans exposed to levels of formaldehyde of \( \leq 0.1 \text{ ppm (0.12 mg/m}^3) \), 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/m\(^3\)). Based upon the two-stage clonal growth model, 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 µg/m\(^3\)), range from \( 2.3 \times 10^{-10} \) to \( 2.7 \times 10^{-8} \), respectively (CIIT, 1999).

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.

Default modelling

For comparison, based upon the approach typically employed in the assessment of Priority Substances, a Tumorigenic Concentration\(_{05}\) (TC\(_{05}\)) (i.e., the concentration associated with a 5% increase in tumour incidence over background) of 7.9 ppm (9.5 mg/m\(^3\)) (95% lower confidence limit [LCL] = 6.6 ppm [7.9 mg/m\(^3\)]) 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.\(^3\) The TC\(_{05}\) is calculated by first fitting a multistage model to the exposure–response data. The multistage model is given by

\[
P(d) = 1 - e^{-q_0 - q_1d - ... - q_kd^k}
\]

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 \( q_i > 0 \), \( i = 1, ..., k \) are parameters to be estimated.

The model was fit using GLOBAL82 (Howe and Crump, 1982), and the TC\(_{05}\) 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 \( p = 0.45 \).

3.3.3.1.2 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 \( \leq 0.1 \text{ ppm (0.12 mg/m}^3) \) 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 (0.3 mg/m\(^3\)) and induce histopathological effects in the nasal epithelium in

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\(^3\) 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/m\(^3\)) (CIIT, 1999).
cross-sectional studies of formaldehyde-exposed workers (0.3 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.

3.3.3.2 Oral exposure

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 gastrointestinal tract) 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 gastrointestinal tract of rats as follows:

\[
TC = \frac{260 \text{ mg/L}}{100} = 2.6 \text{ mg/L}
\]

where:
- 260 mg/L is the NOEL for effects (i.e., histopathological changes) in the gastrointestinal tract 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).

3.3.4 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 Canada is on 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 humans (as well as laboratory animals), signs of ocular and upper respiratory tract sensory irritation have been observed at exposures typically greater than 0.1 ppm [120 µg/m³]). The estimated median and mean 24-hour 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 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.

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 × 10⁻⁸). Based on this estimate of risk, priority for investigation of options to reduce exposure in relation to the carcinogenicity of formaldehyde is low.
Available information is considered insufficient to fully characterize the exposure of individuals in Canada to formaldehyde in foodstuffs. However, based upon limited information, the levels of formaldehyde in drinking water appear to be more than 2 orders of magnitude less than the Tolerable Concentration (2.6 mg/L). Although the concentration of formaldehyde in some food products would appear to exceed the Tolerable Concentration, the extent of its bioavailability therein is unknown.

3.3.5 Uncertainties and degree of confidence in human health risk characterization

There is a moderate degree of confidence in the characterization of the principal source of exposure of the general population (i.e., residential indoor air). In the two studies where there was active sampling for a 24-hour duration, the analytical and sampling methodologies were optimum, all of the samples were analyzed by a single specialized laboratory, and the effects of diurnal variation were minimized by the 24-hour sampling duration. The data are also reasonably current (i.e., 1991–1993) and the measured values consistent with those determined in surveys in other countries. While some uncertainty is introduced by pooling of these data with those from the remaining three studies, which involved passive sampling, the ranges and distributions of concentrations in these subsets of data were similar. Some uncertainty is introduced by the limited size and representation of the data set (n = 151 homes in Windsor, Hamilton, Trois-Rivières, Québec, Saskatoon and various locations in the Northwest Territories), lack of random sampling of the homes and involvement of volunteers.

Although it contributes less to total exposure, there is a high degree of confidence in the characterization of the concentrations of formaldehyde in ambient air in Canada, due to the magnitude and sensitivity of the relevant monitoring data. Analytical and sampling methodologies were optimum, all of the samples were analyzed by a single specialized laboratory, and the effects of diurnal variation were minimized by the 24-hour sampling duration. The data set is large (n = 2819) and reasonably current (i.e., 1990–1998), and the concentrations of formaldehyde are consistent with those reported for outdoor air in other Canadian and international studies. However, the locations of NAPS sites were not determined by a random sampling scheme, and a subset of only eight NAPS sites was selected. The data may also not be strictly representative of population exposure, since the air is sampled at elevations higher than the breathing zone at some sites and may be remote from populated areas. However, samples from Canada’s three major urban centres (i.e., Montréal with two sites, Toronto and Vancouver) account for 54% of the 2819 samples, and samples from two sites in Windsor, Ontario, account for an additional 21% of the samples in this data set.

Uncertainty concerning the time spent indoors by Canadians is judged to be low, since the estimate is based on the most current Canadian data, the time–activity data were obtained based on a random sampling scheme, and analysis of the data involved population weighting. However, the same mean time spent outdoors is assumed for Canadians of all age groups and in all regions of the country, a normal distribution is assumed for the hours per day spent outdoors, and the variance of the assumed normal distribution is also assumed (i.e., standard deviation of 2).

The degree of uncertainty concerning the formaldehyde content of food currently consumed by Canadians is sufficiently high so as to preclude meaningful estimation of exposure from this source, except as a basis for determining potential relative proportions of total intake from various media. Identified data on concentrations in this medium are restricted to a small number of food samples collected in other countries, sometimes in early studies for which there is some suspicion of production of formaldehyde due to the relatively high temperatures and acidic reagents employed.
There are no indications that food items were selected on a random basis and often no indication whether the reported concentrations reflect formaldehyde content in the food as consumed. Due to its high volatility, the formaldehyde content would be expected to be reduced during processing and cooking. Formaldehyde is not expected to partition into the fatty compartments of foods, and direct contact of formaldehyde in food applications is very limited. Also, while there is some suggestion that formaldehyde is present in food in bound (unavailable) form, data to substantiate this contention were not identified.

There is a moderate degree of certainty that consumption of drinking water does not contribute significantly to the daily intake of formaldehyde by Canadians, since formaldehyde is relatively unstable in water. However, no data concerning the range and distribution of concentrations of formaldehyde in Canadian drinking water were identified.

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 model accounts for much of its uncertainty.

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

For Priority Substances where the induction of cancer through direct interaction with genetic material cannot be ruled out and available data are inadequate as a basis for development of biologically motivated case-specific models, cancer potency is estimated based on empirical modelling of experimental data within or close to the experimental range, as described above (Section 3.3.3). Estimates of exposure are then compared with these quantitative estimates of carcinogenic potency (Exposure Potency Index) to characterize risk and provide guidance in establishing priorities for further action (i.e., analysis of options to reduce exposure) (Health Canada, 1994) under CEPA 1999. While the biologically motivated case-specific model is clearly preferred as a basis for characterization of exposure–response for cancer for formaldehyde due to its incorporation of as many of the biological data as possible, the priority for investigation of options to reduce exposure...
Utilization of this default approach in the case of formaldehyde would indicate that probabilistic estimates of the 24-hour median, mean and 97.5th percentile concentrations of formaldehyde in air in Canada (generally and for a worst-case site) would be approximately 327-, 263- and 98-fold lower, respectively, than the maximum likelihood estimate of the carcinogenic potency (i.e., TC_{50} = 9.5 mg/m^3)\(^4\) derived from a carcinogenesis bioassay in rats (Monticello et al., 1996). Overall, based upon these Exposure Potency Indices (ranging from 3 \times 10^{-3} to 1.0 \times 10^{-2}), the priority for the investigation of options to reduce exposure to formaldehyde in air would have been considered to be high.

### 3.4 Conclusions

**CEPA 1999 64(a):** Based on analyses of worst-case situations that are likely to be encountered in Canada, risk quotients for water and air are less than 1. The environmental risks associated with concentrations of formaldehyde likely to be found in Canada therefore appear to be low. Therefore, available data indicate that it is unlikely that formaldehyde is entering or may enter the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity, and it is not considered to be “toxic” as defined in CEPA 1999 Paragraph 64(a).

**CEPA 1999 64(b):** Formaldehyde is not involved in depletion of stratospheric ozone and likely does not contribute significantly to climate change. Because of its reactivity and abundance in air, formaldehyde contributes, along with other reactive volatile organic chemicals, to the formation of tropospheric ozone. Therefore, based on available data, formaldehyde is entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger to the environment on which life depends, and it is considered to be “toxic” as defined in CEPA 1999 Paragraph 64(b).

**CEPA 1999 64(c):** Although other factors (such as sustained cellular proliferation) play an important role, there is likely a genetic component (i.e., mutation, for which DNA–protein crosslinks serve as a marker for potential) in the induction of tumours following the inhalation of formaldehyde. Therefore, formaldehyde is considered to be “toxic” as defined in Paragraph 64(c) of CEPA 1999. For compounds where the induction of cancer through direct interaction with genetic material cannot be ruled out, this approach is consistent with the objective that exposure be reduced wherever possible and obviates the need to establish an arbitrary “de minimis”

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\(^4\) Concentration of formaldehyde causing a 5% increase in tumour incidence over background.
level of risk for the
determination of “toxic” under
CEPA 1999. However, based
on comparison of risks of
cancer estimated on the basis
of a biologically motivated
case-specific model with
calculated exposure in air
of the general population
in Canada, the priority for
investigation of options to
reduce exposure on the
basis of carcinogenicity is
considered to be low. While
the majority of the population
is exposed to concentrations
of formaldehyde less than
those associated with
sensory irritation, continued
investigation of options
to reduce exposure to
formaldehyde in indoor air
is recommended as part of an
overall program to reduce
exposure to other aldehydes
considered to be “toxic”
under Paragraph 64(c) of
CEPA 1999.

Overall conclusion: Based on critical assessment
of relevant information, formaldehyde is considered
to be “toxic” as defined in Section 64 of CEPA 1999.

3.5 Considerations for follow-up
(further action)

Formaldehyde contributes to the photochemical
formation of ground-level ozone. It is
recommended that key sources of formaldehyde
be addressed, therefore, as part of management
plans for volatile organic chemicals that
contribute to the formation of ground-level
ozone. While indications are that concentrations
currently in air and water are not causing
environmental harm to biota, continued and
improved monitoring at sites likely to release
formaldehyde are desirable, notably with regards
to industrial uses for resins and for fertilizers as
well as releases from pulp and paper mills.

Although the priority for investigation
of options to reduce exposure in the general
environment is generally considered to be low, in
relation to carcinogenic potential, in some indoor
locations, concentrations are only slightly lower
than, and may even approach, the level associated
with signs of eye and respiratory tract sensory
irritation in humans. Therefore, it is recommended
that continued investigation of options to reduce
exposure to formaldehyde in indoor air be
considered under the authority of acts other than
CEPA 1999 as part of an overall program to
reduce exposure to other aldehydes (e.g., acrolein,
acetaldehyde) in indoor air deemed to be “toxic”
under Paragraph 64(c) of CEPA 1999. Where the
control of any identified sources falls within the
authority of an Act other than CEPA 1999, the
results of these investigations should be forwarded
to the appropriate authority for further
consideration.
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APPENDIX A  SEARCH STRATEGIES EMPLOYED FOR IDENTIFICATION OF RELEVANT DATA

Environmental assessment


Health assessment

Data relevant to the assessment of the potential risks of formaldehyde to human health were identified through evaluation of existing review
documents of the Department of National Health and Welfare (BCH, 1988), the Agency for Toxic Substances and Disease Registry (ATSDR, 1997), the World Health Organization (WHO, 1989), the International Agency for Research on Cancer (IARC, 1995), as well as a review prepared under contract by BIBRA Toxicology International (BIBRA, 1994). To identify additional relevant toxicological data, literature searches on formaldehyde were conducted using the strategy of searching by its name or CAS registry number in the following databases: CCRIS (Chemical Carcinogenesis Research Information System, U.S. National Cancer Institute), DART (Developmental and Reproductive Toxicology, U.S. National Library of Medicine), EMIC (Environmental Mutagen Information Center database, Oak Ridge National Laboratory) and EMICBACK (backfile of EMIC), ETICBACK (backfile of Environmental Teratology Information Center database, U.S. Environmental Protection Agency and U.S. National Institute of Environmental Health Sciences), GENE-TOX (Genetic Toxicology, U.S. Environmental Protection Agency), HSDB, IRIS (Integrated Risk Information System, U.S. Environmental Protection Agency) and RTECS. Its name, registry number and major synonyms were searched in the ToxlinePlus (1985–1999) and Toxline (before 1985) databases. The CAS registry number was searched in the Toxlit (1981–1999) database. The EMBASE (on-line version of Excerpta Medica) database, for 1981–1999, was searched using the name, registry number and major synonyms, combined with a link to toxicological information. In addition to the above sources of information, numerous provincial and federal government officials and representatives of various industrial sectors were contacted between February and August of 1996 for data relevant to exposure and/or effects.