

*Canadian Environmental  
Protection Act, 1999*



**PRIORITY SUBSTANCES LIST ASSESSMENT REPORT**



**2-Methoxyethanol**

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*Canadian Environmental Protection Act, 1999*

## **PRIORITY SUBSTANCES LIST ASSESSMENT REPORT**

### **2-Methoxyethanol**

Environment Canada  
Health Canada

August 2002

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# LIST OF ACRONYMS AND ABBREVIATIONS

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|                  |  |
|------------------|--|
| BCF              | bioconcentration factor                            |
| CAS              | Chemical Abstracts Service                         |
| CEPA             | <i>Canadian Environmental Protection Act</i>       |
| CEPA 1999        | <i>Canadian Environmental Protection Act, 1999</i> |
| CFC              | chlorofluorocarbon                                 |
| CI               | confidence interval                                |
| CTV              | Critical Toxicity Value                            |
| EEV              | Estimated Exposure Value                           |
| ENEV             | Estimated No-Effects Value                         |
| GWP              | Global Warming Potential                           |
| HC <sub>5</sub>  | hazardous concentration to 5% of test species      |
| K <sub>ow</sub>  | octanol/water partition coefficient                |
| kg-bw            | kilogram body weight                               |
| LC <sub>50</sub> | median lethal concentration                        |
| LD <sub>50</sub> | median lethal dose                                 |
| LOEL             | Lowest-Observed-Effect Level                       |
| MAA              | 2-methoxyacetic acid                               |
| MALD             | 2-methoxyacetaldehyde                              |
| NOEL             | No-Observed-Effect Level                           |
| ODP              | Ozone Depletion Potential                          |
| POCP             | Photochemical Ozone Creation Potential             |
| PSL              | Priority Substances List                           |
| RR               | relative risk                                      |

# SYNOPSIS

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2-Methoxyethanol is not commercially produced in Canada. It is imported for use mainly as a chemical processing aid and as a component of formulated products. The use of 2-methoxyethanol has declined over the past few years because it has been partially replaced in some countries by other substances. All reported environmental releases are to the atmosphere.

2-Methoxyethanol reacts with hydroxyl radicals in the air with a half-life of about 18 hours. Much of the 2-methoxyethanol released to the atmosphere is predicted to remain in air, but a substantial proportion would partition to water and to soil. 2-Methoxyethanol is biodegraded in surface water and aerobic soil with an estimated half-life of 1–4 weeks. It is somewhat more persistent under anaerobic conditions. 2-Methoxyethanol has a very low octanol/water partition coefficient and is therefore not expected to bioaccumulate to any significant degree. There are very few available data on concentrations of 2-methoxyethanol in the environment in Canada or elsewhere.

Data on toxicity exist for aquatic organisms, including microorganisms, invertebrates and fish. 2-Methoxyethanol is not very toxic to these organisms; in a number of studies, the LC<sub>50</sub> was above the highest concentration tested.

Because of the paucity of environmental monitoring data, exposure values for the environmental assessment were estimated based on modelling. Estimated environmental concentrations of 2-methoxyethanol are several orders of magnitude lower than the adverse effects thresholds calculated for sensitive organisms.

2-Methoxyethanol is not involved in stratospheric ozone depletion and is not an important contributor to climate change or ground-level ozone formation.

Based on a relatively extensive database in experimental animals, 2-methoxyethanol has consistently been associated with a wide range of adverse effects on health, including those considered to be severe and irreversible (e.g., teratogenicity), with some occurring at relatively low levels of exposure. However, although relevant data are limited, exposure of the general population through environmental media is expected to be low, due to reported declining use of the compound in recent years as it is replaced with less hazardous compounds. Margins between worst-case estimates of exposure from environmental media and lowest effect levels for developmental toxicity obtained in toxicological investigations in experimental animals are large. However, available data are insufficient to conclude that margins between worst-case estimates of exposure in consumer products and lowest effect levels are adequate.

**Based on these considerations, it is concluded that 2-methoxyethanol is not entering 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 or that constitute or may constitute a danger to the environment on which life depends. On the basis principally of its high health hazard potential, 2-methoxyethanol may be entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health. Therefore, 2-methoxyethanol is considered to be “toxic” under Section 64 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999).**





It is recommended that additional information be acquired on patterns of use of 2-methoxyethanol in Canada, particularly in relation to its presence in consumer products. It is further recommended that, in view of the profile of toxicity of 2-methoxyethanol, potential for exposure of the general population to this compound be eliminated or reduced to the extent possible.



# 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
- have or may have an immediate or long-term harmful effect on the environment or its biological diversity;
  - constitute or may constitute a danger to the environment on which life depends; or
  - 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 initial screening of readily accessible information, the rationale for assessing 2-methoxyethanol (along with 2-ethoxyethanol and 2-butoxyethanol) provided by the Ministers’ Expert Advisory Panel on the Second Priority Substances List (Ministers’ Expert Advisory Panel, 1995) was as follows:

Potential sources of exposure to these compounds include releases from various industrial and consumer uses. These compounds are widely used as solvents in paints and protective coatings; in printing inks, industrial solvents and cleaners; in the production of plasticizers; as a de-icer in fuels and

automotive brake fluids; and in electronics manufacturing. Effects due to exposure include disorders of the central nervous system, blood system, kidneys and liver in both humans and animals. An assessment is required to determine the presence of these substances in the Canadian environment, exposure and the potential risks 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

An electronic version (PDF file), may be requested from: PSL.LSIP@ec.gc.ca. It should also be noted that the approach outlined therein has evolved to incorporate recent developments in risk assessment methodology, which will be addressed in future releases of the guidance manual for environmental assessments of Priority Substances.

The search strategies employed in the identification of data relevant to the assessment of entry, environmental fate and exposure and potential effects on the environment (prior to October 1999) are presented in Appendix A. Review articles were consulted where appropriate. However, all original studies that form the basis for determining whether 2-methoxyethanol is “toxic” under Paragraph 64(a) or 64(b) of CEPA 1999 have been critically evaluated by staff of Environment Canada.



The approach to assessment of effects on human health is outlined in the following publication of the Safe Environments Program (formerly 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:

Existing Substances Division  
Health Canada  
Environmental Health Centre  
Tunney’s Pasture  
Address Locator 0801C2  
Ottawa, Ontario  
K1A 0L2

or on the Safe Environments Program (formerly the Environmental Health Directorate) publications web site ([www.hc-sc.gc.ca/hecs-sesc/exsd/psap.htm](http://www.hc-sc.gc.ca/hecs-sesc/exsd/psap.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 Existing Substances Division web site ([www.hc-sc.gc.ca/exsd-dse](http://www.hc-sc.gc.ca/exsd-dse)) and which will be addressed in future releases of the approach paper for the assessment of effects on human health.

The approach to assessment of 2-methoxyethanol is necessarily restricted because of the extremely limited data upon which to base estimates of population exposure. Moreover, use of this substance has declined substantially worldwide in recent years, as it has been replaced with less hazardous substances. Indeed, available information indicates that 2-methoxyethanol has not been produced in Canada in the last several years. Therefore, in view of the fact that measures have been introduced to reduce population exposure, a screening approach has been adopted for assessment of whether or not the substance would be considered “toxic” under Paragraph 64(c) of CEPA 1999 primarily as a basis for determining whether current measures are sufficiently protective of human health.

In view of the limited objectives of this screening assessment, therefore, lowest effect levels identified primarily from secondary sources are compared with worst-case or bounding estimates of exposure. The adequacy of these rather crude margins of exposure is considered in relation to intake from various sources estimated on the basis of primary review of the limited available Canadian data on exposure from various sources, including environmental media and consumer products. On this basis, areas where additional information may be required to ensure that current measures for reduction of population exposure are sufficiently protective have been identified.

Data on the health effects of 2-methoxyethanol were identified primarily from a review prepared in 1996 by BIBRA International, which was updated and modified in 1998 (BIBRA International, 1996/Health Canada, 1998). Relevant data identified subsequent to this update are summarized in Health Canada (1999). The search strategies used in the identification of relevant data on health effects from 1996 to October 1999 are outlined in Appendix A.

Sections of the Assessment Report related to the environmental assessment of 2-methoxyethanol and the environmental Supporting Document (Environment Canada, 1999) were prepared or reviewed by the members of the Environmental Resource Group, established by Environment Canada to support the environmental assessment:

D. Boersma, Environment Canada  
R. Breton, Environment Canada  
P. Cureton, Environment Canada  
N. Davidson, Environment Canada  
R. Desjardins, Environment Canada  
L. Hamel, Union Carbide Canada Inc.  
B. Lee, Environment Canada  
S. Lewis, Chemical Manufacturers’  
Association  
B. Sebastien, Environment Canada  
K. Taylor, Environment Canada (lead for  
the environmental assessment)

Sections of the Assessment Report relevant to the environmental assessment and the environmental Supporting Document (Environment Canada, 1999) were also reviewed by:

S. Dobson, Institute of Terrestrial Ecology  
C. Staples, Assessment Technologies Inc.

The health-related sections of the Assessment Report were prepared and the background Supporting Document was updated by the following staff of Health Canada:

H. Hirtle  
K. Hughes  
M.E. Meek  
L. Turner

Adequacy of data coverage and defensibility of the conclusions presented in the health assessment were considered in a written review by:

M. Dourson, Toxicology Excellence in Risk Assessment  
J.B. Knaak, Oxychem (retired)  
R.A. Rudel, Silent Spring Institute

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 (August 19 to October 18, 2000) (Environment Canada and Health Canada, 2000). Following consideration of the comments received, the Assessment Report was revised as appropriate. A summary of the comments and their responses is available on the Internet at:  
[www.ec.gc.ca/substances/ese/eng/psap/final/main.cfm](http://www.ec.gc.ca/substances/ese/eng/psap/final/main.cfm)

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 by emailing:

[PSL.LSIP@ec.gc.ca](mailto:PSL.LSIP@ec.gc.ca)

Unpublished supporting documentation, 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*

Existing Substances Division  
Health Canada  
Environmental Health Centre  
Tunney's Pasture  
Address Locator 0801C2  
Ottawa, Ontario  
K1A 0L2



## 2.0 SUMMARY OF INFORMATION CRITICAL TO ASSESSMENT OF “TOXIC” UNDER CEPA 1999

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### 2.1 Identity and physical/chemical properties<sup>1</sup>

2-Methoxyethanol has the empirical molecular formula  $C_3H_8O_2$ , the structural formula  $CH_3OCH_2CH_2OH$  and a molecular weight of 76.1 g/mol. Its Chemical Abstracts Service (CAS) registry number is 109-86-4. 2-Methoxyethanol is a colourless viscous liquid with a water solubility of 500 000 mg/L (DMER and AEL, 1996), an octanol/water partition coefficient ( $\log K_{ow}$ ) of  $-0.77$  (Hansch and Leo, 1985), a vapour pressure of 1300 Pa at 25°C (Riddick *et al.*, 1986) and a Henry's law constant of 0.198 Pa·m<sup>3</sup>/mol (calculated value) (DMER and AEL, 1996). The conversion factor for 2-methoxyethanol in air is 1 ppm = 3.11 mg/m<sup>3</sup>.

2-Methoxyethanol is a substance in the class of chemicals sometimes referred to as “glycol ethers.”

Synonyms for 2-methoxyethanol include 2-methoxy-1-ethanol, ethylene glycol monomethyl ether and methyl Cellosolve.

### 2.2 Entry characterization

#### 2.2.1 Production, importation and uses

2-Methoxyethanol was not produced in or exported from Canada in 1995 and 1996, according to data submitted to Environment Canada by 10 companies in a survey conducted under the authority of Section 16 of the *Canadian Environmental Protection Act (CEPA)* (Environment Canada, 1997b). According to

data reported through this survey, importation of 2-methoxyethanol totalled less than 100 tonnes in 1995 and 80 tonnes in 1996.

2-Methoxyethanol has been reported to be used in paints, coatings, inks, cleaners, polishes, brake fluids and jet fuels and to find wide application as a solvent, chemical intermediate and solvent coupler of mixtures and water-based formulations (Stemmler *et al.*, 1997). Data submitted to Environment Canada in the survey conducted under the authority of Section 16 of CEPA indicated that less than 200 and 75 tonnes of 2-methoxyethanol were used in Canada in 1995 and 1996, respectively, mainly as a chemical processing aid and as a component of formulated products (Environment Canada, 1997b). The use of 2-methoxyethanol has declined over the past few years because it has been partially replaced in some countries by other substances.

According to monitoring data on concentrations in occupational air collected between 1983 and 1994 by the Ontario Ministry of Labour (Rachamin *et al.*, 1996), the majority of industries with concentrations of 2-methoxyethanol above the limit of detection were commercial printing and small electrical appliances, machinery and equipment manufacturing.

#### 2.2.2 Sources and releases

##### 2.2.2.1 Natural sources

2-Methoxyethanol has not been reported to occur as a natural product (U.S. EPA, 1986; WHO, 1990). There are no known reactions

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<sup>1</sup> See the environmental Supporting Document (Environment Canada, 1999) for a more complete listing of ranges of values reported and criteria for selection of physical and chemical properties.



that would lead to the *in situ* production of 2-methoxyethanol or other glycol ethers in the atmosphere (Rogozen *et al.*, 1987).

#### 2.2.2.2 Anthropogenic sources

Total on-site environmental releases of 2-methoxyethanol reported to the National Pollutant Release Inventory in 1994 amounted to 17.0 tonnes (NPRI, 1996). All of this was released into the atmosphere from one facility in southern Ontario. Total transfers of 2-methoxyethanol for off-site disposal amounted to 2.12 tonnes in 1994, with all going to incinerators. A reported total of 0.07 tonnes of 2-methoxyethanol was sent for energy recovery in 1994 (NPRI, 1996).

In 1995, total on-site environmental releases of 2-methoxyethanol reported to the National Pollutant Release Inventory amounted to 6.3 tonnes (NPRI, 1998). All of this was released to the atmosphere from stack emissions at one facility in southern Ontario. Total transfers of 2-methoxyethanol for off-site disposal amounted to 33.9 tonnes in 1995 (NPRI, 1998). No releases of 2-methoxyethanol were reported to the National Pollutant Release Inventory in 1996 (NPRI, 1998).

According to data submitted in the CEPA Section 16 survey (with different reporting requirements from the National Pollutant Release Inventory), environmental releases of 2-methoxyethanol in Canada totalled 8.7 tonnes in 1996, all to the air (Environment Canada, 1997b).

The Canadian Chemical Producers' Association (1997) reported total emissions of 2-methoxyethanol of 3.0, 0.036, 0.02 and 0.009 tonnes from member companies in 1992, 1993, 1994 and 1995, respectively, all of which were released to air by a single company. Reported releases totalled 0.006 tonnes in 1996, 0 tonnes in 1997 (Canadian Chemical Producers' Association, 1999a) and 0 tonnes in 1998 (Canadian Chemical Producers' Association, 1999b).

## 2.3 Exposure characterization

### 2.3.1 Environmental fate

#### 2.3.1.1 Air

Due to its high volatility (vapour pressure 1300 Pa at 25°C), 2-methoxyethanol is expected to be present principally in air. Howard *et al.* (1991) calculated a half-life in the range of 5.7–57 hours for 2-methoxyethanol in the atmosphere, based on the rate constant for its reaction with hydroxyl radicals. The U.S. Environmental Protection Agency (U.S. EPA, 1986) calculated a half-life of 17.5 hours for the reaction of 2-methoxyethanol with atmospheric hydroxyl radicals, assuming an ambient concentration of hydroxyl radicals of  $8.0 \times 10^5$  molecules/cm<sup>3</sup>.

#### 2.3.1.2 Surface water

2-Methoxyethanol volatilizes rapidly from the water surface, with an estimated half-life of 2.8 hours (Lyman *et al.*, 1982).

Biodegradation of 2-methoxyethanol in natural water would also be significant (U.S. EPA, 1986). Howard *et al.* (1991) estimated a half-life in water of 1–4 weeks, based on unacclimated aerobic biodegradation.

#### 2.3.1.3 Groundwater

Howard *et al.* (1991) estimated a half-life in groundwater of 2–8 weeks, based on unacclimated aerobic biodegradation.

#### 2.3.1.4 Soils

2-Methoxyethanol would be expected to be highly mobile in soil because of its high water solubility and low  $K_{ow}$  (U.S. EPA, 1986), but much of the substance would volatilize from the soil surface.

Howard *et al.* (1991) estimated a half-life in aerobic soils of 1–4 weeks, based on unacclimated aerobic biodegradation.

2-Methoxyethanol underwent biooxidation to 2-methoxyacetic acid (MAA) by the soil bacterium *Alcaligenes* MC11, which was able to use 2-methoxyethanol as a source of carbon (Harada and Nagashima, 1975). *Pseudomonas* sp. 4-5-3, *Xanthobacter autotrophicus* EC1-2-1 and a bacterium identified only as “strain MC2-2-1” could also use 2-methoxyethanol as a source of carbon for aerobic growth (Kawai, 1995).

For anaerobic soils, Howard *et al.* (1991) estimated an anaerobic half-life in soil of 4–16 weeks for 2-methoxyethanol, based on its unacclimated aqueous aerobic biodegradation half-life.

#### 2.3.1.5 Biota

A bioconcentration factor (BCF) of 0.15 was estimated for 2-methoxyethanol, based on its  $\log K_{ow}$  of  $-0.77$  and using the equation proposed by Lyman *et al.* (1982):  $\log BCF = 0.76 \log K_{ow} - 0.23$  (U.S. EPA, 1986). Bioaccumulation of 2-methoxyethanol in aquatic organisms would therefore not be significant.

#### 2.3.1.6 Environmental distribution

Because of the high water solubility and low  $\log K_{ow}$  of 2-methoxyethanol, physical adsorption to suspended solids and sediments should not be significant (U.S. EPA, 1986). Based on its physical/chemical properties, 2-methoxyethanol is expected to volatilize from soil or leach rapidly into the ground (Howard, 1990).

The environmental partitioning of 2-methoxyethanol when released into air, water or soil was estimated by a Level III fugacity model (DMER and AEL, 1996). Values for input parameters were as follows: molecular weight, 76.1 g/mol; vapour pressure, 1300 Pa; water

solubility, 500 000 mg/L;  $\log K_{ow}$ ,  $-0.77$ ; Henry's law constant, 0.198 Pa·m<sup>3</sup>/mol; half-life<sup>2</sup> in air, 55 hours; half-life in water, 550 hours; half-life in soil, 550 hours; and half-life in sediment, 1700 hours. Modelling was based upon an assumed emission rate of 1000 kg/hour, although the emission rate used would not affect the estimated percent distribution. If 2-methoxyethanol is emitted into air, EQC (Equilibrium Criterion) fugacity Level III modelling predicts that about 50% would be present in air, while approximately 25% would be present in soil and about 25% in water. If 2-methoxyethanol is emitted into water, more than 99% would be present in water. If 2-methoxyethanol is released to soil, about 75% would be present in the soil, while approximately 25% would be present in water (DMER and AEL, 1996).

#### 2.3.2 Environmental concentrations

Very few data on levels of 2-methoxyethanol in the environment have been identified for Canada or elsewhere (U.S. EPA, 1986; WHO, 1990). One study was conducted to determine concentrations of 2-methoxyethanol in multiple Canadian media to which humans are exposed, including drinking water and indoor and outdoor air (Conor Pacific Environmental Technologies, 1998), as outlined below in Section 2.3.2.1. Additional data on levels of 2-methoxyethanol in specific media are presented in the subsequent sections.

##### 2.3.2.1 Multimedia exposure study

In a Canadian multimedia study, exposure to a number of volatile organic chemicals was measured for 50 participants across Canada (Conor Pacific Environmental Technologies, 1998). Thirty-five participants were randomly selected from the Greater Toronto area in Ontario,

<sup>2</sup> For each environmental compartment, DMER and AEL (1996) use a series of ranges of half-life times (<10 hours, 10–30 hours, 30–100 hours, etc.), and the half-life of the particular substance is assigned to the appropriate range, based on a consideration of available persistence data. The geometric mean of this range is then used as an input parameter for the fugacity model. For example, the atmospheric half-life of 2-methoxyethanol in air is judged to be between 30 and 100 hours. The geometric mean of this range, 55 hours, is used as an input parameter in the model. Conservative values for persistence were selected (i.e., longer rather than shorter half-lives) to ensure that persistence is not underestimated.



six participants from Queens Subdivision in Nova Scotia and nine from Edmonton, Alberta. For each participant, samples of drinking water and indoor, outdoor and personal air were collected over a 24-hour period. Samples of foods and beverages were not analysed for the determination of 2-methoxyethanol. The concentration of 2-methoxyethanol was below the method detection limit (0.6 µg/L) in all samples of drinking water. Similarly, it was not detected (<5 µg/m<sup>3</sup>) in all samples of indoor, outdoor and personal air.

#### 2.3.2.2 Ambient air

Other than the multimedia exposure study discussed in Section 2.3.2.1, no data were identified on the concentration of 2-methoxyethanol in ambient air in Canada.

#### 2.3.2.3 Indoor air

In northern Italy, six indoor air samples were collected from homes in 1983–1984 and analysed for several organic pollutants by gas chromatography with mass spectrometric detection. The concentration of 2-methoxyethanol in one of the samples was 70 µg/m<sup>3</sup>; in the remaining five samples, however, the concentration was below the limit of detection (not specified) (De Bortoli *et al.*, 1986).

In a study conducted in Germany, indoor air samples were collected following the sealing of wooden parqueted flooring in a school room with a product containing 2-methoxyethanol. The concentrations of 2-methoxyethanol in samples collected 10, 18, 25, 35, 52 and 90 days after sealing were 220, 150, 180, 160, 59 and 26 µg/m<sup>3</sup>, respectively (Schriever and Marutzky, 1990).

#### 2.3.2.4 Surface water

No data were identified on the concentration of 2-methoxyethanol in surface water in Canada or elsewhere.

#### 2.3.2.5 Drinking water

2-Methoxyethanol was listed as a contaminant in drinking water samples analysed between June 1977 and November 1980 in a survey of 12 U.S. cities (Lucas, 1984). The concentration of the substance was not quantified but was less than 1 µg/L.

#### 2.3.2.6 Soil

No data were identified on the concentration of 2-methoxyethanol in soil in Canada or elsewhere.

#### 2.3.2.7 Food

No data on concentrations of 2-methoxyethanol in food were identified.

#### 2.3.2.8 Consumer products

Glycol ethers are used as solvents in a number of consumer products, including paints, paint thinners and cleaning products. In Canada, there are no regulations concerning permissible levels of glycol ethers, including 2-methoxyethanol, in consumer products (Health Canada, 1998a). 2-Methoxyethanol was not detected in the emissions of 13 consumer products, including window cleaners, all-purpose cleaners, paints, nail polish removers and hair dye (classes of products reported to contain glycol ethers, based on available information), purchased in the Ottawa, Ontario, area (Cao, 1999). Glycol ethers, including 2-methoxyethanol, are not registered for use as an active ingredient in therapeutic products in Canada (Health Canada, 1998b). Of the cosmetic products registered for use in Canada, one nail polish remover was reported to contain 2-methoxyethanol in the range of 30–100% (Health Canada, 1998c); 2-methoxyethanol is also a component in an insecticidal formulation used on ornamental plants (Health Canada, 1998d).

In the United States, all-purpose cleaning products may contain concentrations of up to 2% 2-methoxyethanol, and metal cleaners may contain up to 6% (Flick, 1986, 1989). Versar Inc. (1986) reported varnish to contain 1.1%



2-methoxyethanol. In the Clinical Toxicology of Commercial Products database, one consumer product in the category of “coatings/inks” (which includes paints, varnishes, sealants, other coatings, marking pens and other similar items) and two products in the category of “coating thinners/strippers” were reported to emit 2-methoxyethanol (CARB, 1991). In a summary of the emissions of 2-methoxyethanol from materials listed in the NASA/McDonnell Douglas Materials Testing Data Base, emissions of 2-methoxyethanol from five adhesives were in the range of 1.2–30 µg/g product (median 2.1 µg/g product), those from one fabric were 0.33 µg/g product, and those from seven products in the category of “pens/inks” were in the range of 1.6–960 µg/g product (median 38 µg/g product) (CARB, 1991).

In a study conducted in Italy, 2-methoxyethanol was measured in the headspace analysis of a liquid wax for marble, ceramic and linoleum (Knöppel and Schauenburg, 1989). According to the 1993 Products Register in Sweden, 2-methoxyethanol was used in 23 products, totalling 260–262 tonnes of 2-methoxyethanol per year in these products (Johanson and Rick, 1996).

#### 2.3.2.9 Fugacity modelling

Environmental concentrations of 2-methoxyethanol were estimated by ChemCan v. 4.0 modelling. This model is a Level III fugacity-based regional model developed to estimate the environmental fate of chemicals in Canada. ChemCan calculates the distribution of chemicals in the environmental media, the transport and transformation process rates, and average concentrations in any of 24 regions or ecozones of Canada. The highest reported recent release of 2-methoxyethanol in Canada is 17 tonnes, released into the air by one facility in southern Ontario in 1994 (NPRI, 1996). “Ontario – Mixed Wood Plain” was therefore selected as the geographic region for ChemCan modelling of 2-methoxyethanol. The input rate was 1.941 kg

2-methoxyethanol per hour, all to the atmosphere. Chemical input values were as follows: molecular weight, 76.1 g/mol; vapour pressure, 1300 Pa; water solubility, 500 000 mg/L; log  $K_{ow}$ , -0.77; Henry’s law constant, 0.198 Pa·m<sup>3</sup>/mol; half-life in air, 55 hours; half-life in water, 550 hours; half-life in soil, 550 hours; and half-life in sediment, 1700 hours. For Ontario – Mixed Wood Plain, environmental characteristics were as follows: total surface area, 169 000 km<sup>2</sup>; proportion of area covered by water, 43.8%; average air height, 2 km; average water depth, 20 m; average soil depth, 10 cm; residence time in air, 1.71 days; residence time in water, 618 days; environmental temperature, 7.4°C.

Environmental concentrations of 2-methoxyethanol in southern Ontario predicted by ChemCan v. 4.0 modelling are as follows: 0.146 ng/m<sup>3</sup> in air;  $4.8 \times 10^{-5}$  µg/L in water;  $9.4 \times 10^{-4}$  ng/g dry weight in soil; and  $2.34 \times 10^{-5}$  ng/g dry weight in sediments. The ChemCan model estimates average concentrations throughout the region; therefore, actual concentrations in the vicinity of releases will be higher than those estimated by the model.

## 2.4 Effects characterization

### 2.4.1 Ecotoxicology

#### 2.4.1.1 Terrestrial organisms

No information on the effects of 2-methoxyethanol on wildlife was identified. Data for experimental animals pertinent to the human health assessment are presented in Section 2.4.2. From the results of inhalation studies presented in that section, the animals that were most sensitive to airborne 2-methoxyethanol were New Zealand white rabbits. The Lowest-Observed-Effect Level (LOEL) for fetal toxicity (reduced weight, minor skeletal variations or testicular hypoplasia) was reported to be 10 ppm (31 mg/m<sup>3</sup>, or  $3.1 \times 10^7$  ng/m<sup>3</sup>) (Hanley *et al.*, 1984a,b; see Section 2.4.2.7.2).



#### 2.4.1.2 Aquatic organisms

Data on chronic toxicity have been identified only for protozoans and algae. The most sensitive organism reported was the flagellate protozoan, *Chilomonas paramecium*, with a 2-day toxicity threshold of 2200 µg/L, based on inhibition of cell multiplication (Bringmann and Kuehn, 1981). The most sensitive algal species reported was the blue-green alga, *Microcystis aeruginosa*, with an 8-day toxicity threshold of 100 000 µg/L, based on inhibition of cell multiplication (Bringmann and Kuehn, 1978). Data on acute toxicity have been reported for microorganisms, invertebrates and fish, although in many studies the LC<sub>50</sub> for 2-methoxyethanol was above the highest concentration tested. For example, the 24-hour LC<sub>50</sub> for goldfish (*Carassius auratus*) was >5 000 000 µg/L (Bridie *et al.*, 1979). The 96-hour LC<sub>50</sub> for rainbow trout (*Oncorhynchus mykiss*) was 15 520 000 µg/L (Benville, 1974).

#### 2.4.2 Experimental animals and in vitro

Identified information on the effects of 2-methoxyethanol in experimental animals is summarized in this section. As outlined in Section 1.0, this summary is based primarily on the review of relevant data prepared by BIBRA International, updated to include recent information identified in searches of on-line databases (BIBRA International, 1996/Health Canada, 1998). Original accounts were consulted as necessary for clarification.

In view of the limited objective of this screening assessment, presentation of data on health effects associated with 2-methoxyethanol is limited to an overview of the nature of the effects with emphasis on the lowest identified effect levels from repeated-exposure studies relevant to characterization of margins between estimates of population exposure and levels causing toxic effects; detailed descriptions of study protocols and results are included in the supporting documentation (BIBRA International, 1996/Health Canada, 1998; Health Canada, 1999).

#### 2.4.2.1 Kinetics and metabolism

2-Methoxyethanol is extensively absorbed following oral, inhalation or dermal exposure and distributed extensively throughout the body, including the developing fetus, in which levels of metabolites may be greater than in the dams (Welsch and Sleet, 1987; Sleet *et al.*, 1988; Scott *et al.*, 1989). The major metabolic pathways of 2-methoxyethanol involve oxidation. In the first pathway, 2-methoxyethanol is rapidly metabolized via alcohol and aldehyde dehydrogenases to 2-methoxyacetaldehyde (MALD), then MAA (the likely active metabolites). The MAA is subsequently conjugated with glycine or *O*-demethylated, then oxidized to produce carbon dioxide; some MAA may also undergo Krebs cycle transformation. Alternatively, 2-methoxyethanol may be oxidized via microsomal P-450 mixed-function oxidases and *O*-demethylated to form formaldehyde and ethylene glycol. 2-Methoxyethanol may also be directly conjugated with sulphate or glucuronic acid.

In general, MAA (in free or conjugated form) was the principal metabolite detected in the urine of rats, mice and humans exposed by ingestion or inhalation; other urinary metabolites included ethylene glycol (particularly in rats following repeated exposure in drinking water) (Medinsky *et al.*, 1990) and products of Krebs cycle metabolism. The putatively toxic metabolite, MAA, is eliminated much more slowly in humans than in rats, with half-lives in the blood of 77 and 19 hours, respectively (Groeseneken *et al.*, 1989).

The acetate moiety of 2-methoxyethanol (2-methoxyethyl acetate), which is commonly encountered in the occupational environment, is rapidly hydrolysed to 2-methoxyethanol via esterases in several tissues in the body (WHO, 1990). For this reason, data on the toxicity of 2-methoxyethyl acetate have been included in this assessment.

#### 2.4.2.2 Acute toxicity

2-Methoxyethanol is of low to moderate acute toxicity in experimental animals following oral, inhalation or dermal exposure, with oral LD<sub>50</sub>s generally in the range of 1000 mg/kg-bw or more (Smyth *et al.*, 1941; Carpenter *et al.*, 1956; ECETOC, 1995). Sublethal effects following acute exposure to lower doses include reproductive toxicity in males ( $\geq 50$  mg/kg-bw), alterations in hematological parameters ( $\geq 200$  mg/kg-bw) and effects in the liver, thymus and spleen (300 mg/kg-bw) (Chapin and Lamb, 1984; Anderson *et al.*, 1987; Holloway *et al.*, 1990; Kawamoto *et al.*, 1990; Ku *et al.*, 1994). 2-Methoxyethanol did not induce skin sensitization and has low potential for causing skin or eye irritation (Carpenter and Smyth, 1946; Jacobs *et al.*, 1987, 1989; Jacobs, 1992; Devillers and Chessel, 1995; Zissu, 1995).

#### 2.4.2.3 Short-term toxicity

The thymus, testes and blood have consistently been the most sensitive targets for adverse effects in rats repeatedly exposed over the short term to 2-methoxyethanol or 2-methoxyethyl acetate via ingestion, inhalation or dermal application (Miller *et al.*, 1981; Grant *et al.*, 1985; Fairhurst *et al.*, 1989; Feuston *et al.*, 1989; Kawamoto *et al.*, 1990; Exon *et al.*, 1991; Smialowicz *et al.*, 1991a; NTP, 1993; Butterworth *et al.*, 1995; Williams *et al.*, 1995). Reduced relative weight of the thymus was observed in rats orally administered 50 mg/kg-bw per day or more (4 days) or exposed to airborne concentrations of 300 ppm (933 mg/m<sup>3</sup>) or greater (9 days), while histopathological changes were noted at higher exposure levels. Histopathological effects or reduced weights were also observed in the testes of rats exposed to around 88 mg/kg-bw per day or 300 ppm (933 mg/m<sup>3</sup>) or greater for 9 or 10 days, while alterations in hematological parameters were reported in rats administered 70 mg/kg-bw per day or 300 ppm (933 mg/m<sup>3</sup>) or more for 5 days or longer.

Although the database in mice is more limited, mice appear to be less sensitive than rats

to induction of effects on these organs, as effects on the thymus, blood and testes were noted only at oral doses of 1000, 500 and 250 mg/kg-bw per day ( $\geq 4$  days) (Nagano *et al.*, 1979, 1984; Miller *et al.*, 1981; Hong *et al.*, 1988) and airborne concentrations of 300, 300 and 1000 ppm (933, 933 and 3110 mg/m<sup>3</sup>) (9 days), respectively (NTP, 1993). Available data on short-term toxicity in other experimental species are too limited for meaningful comparison.

#### 2.4.2.4 Subchronic toxicity

##### 2.4.2.4.1 Oral

The thymus, testes and blood were also the primary targets of 2-methoxyethanol-induced toxicity in rats exposed subchronically by gavage or in drinking water. Atrophy or decreased weight of the thymus and testes and alterations in hematological parameters (including mean hemoglobin concentration, packed cell volume, and red and white blood cell counts) were observed in rats administered oral doses of 285 mg/kg-bw per day (the lowest dose tested) or more for 6 weeks (U.S. EPA, 1992). Testicular degeneration and decreased thymus weights, along with effects on the blood (including anemia and reduced white blood cell and platelet counts), were also reported in F344/N rats exposed to 2-methoxyethanol in drinking water for 13 weeks at concentrations equivalent to doses of 71 mg/kg-bw per day or more (NTP, 1993). Similar to the results in short-term studies, B6C3F<sub>1</sub> mice were less sensitive than rats to effects induced by 2-methoxyethanol, as effects on the testes and thymus were noted only at doses of 530 and 990 mg/kg-bw per day and above, respectively, in drinking water for 13 weeks (hematological parameters were not examined); histopathological changes in the adrenal gland and splenic hematopoiesis were observed at doses as low as 492 mg/kg-bw per day (NTP, 1993).

##### 2.4.2.4.2 Inhalation

Decreased thymus and testes weights, accompanied by histopathological changes in testes and alterations in several hematological



(white blood cells, platelets and hemoglobin concentration) and clinical chemistry (total protein, albumin and globulin) parameters, were also observed in Sprague-Dawley rats exposed to 300 ppm (933 mg/m<sup>3</sup>) 2-methoxyethanol by inhalation for 13 weeks. The only effect noted at lower concentrations was a decrease in body weight in females at 100 ppm (311 mg/m<sup>3</sup>) (Miller *et al.*, 1983; Rao *et al.*, 1983; Hanley *et al.*, 1984a). These investigators observed New Zealand white rabbits to be more sensitive to the testicular toxicity of exposure to 2-methoxyethanol for 13 weeks, as degeneration was noted at concentrations as low as 30 ppm (93 mg/m<sup>3</sup>), while lymphoid atrophy of the thymus occurred at 100 ppm (311 mg/m<sup>3</sup>) and above. Effects on the blood (decreased counts of red and white blood cells and platelets and reduced hemoglobin concentration) were observed at 300 ppm (933 mg/m<sup>3</sup>) (Miller *et al.*, 1983).

#### 2.4.2.4.3 Dermal

Dermal exposure to 1000 mg/kg-bw per day for 13 weeks resulted in histopathological effects on the testes in guinea pigs, along with reduced organ and body weights and changes in hematological (mild anemia and reduced white blood cells) and clinical chemistry (blood enzymes and urinary calcium) parameters (Hobson *et al.*, 1986).

#### 2.4.2.5 Chronic toxicity and carcinogenicity

No studies on the effects of chronic exposure to 2-methoxyethanol have been identified.

#### 2.4.2.6 Genotoxicity

Although 2-methoxyethanol is not mutagenic in *in vitro* investigations, there is some indication that it induces clastogenic damage, and there is consistent evidence that the initial metabolite, MALD, is genotoxic in several cell lines. While the results of available *in vivo* studies suggest that 2-methoxyethanol is not genotoxic in somatic cells, there is some indication that it induces genetic effects in male germ cells.

#### 2.4.2.6.1 In vitro studies

2-Methoxyethanol was not mutagenic in several strains of *Salmonella* (McGregor *et al.*, 1983; McGregor, 1984; Zeiger *et al.*, 1992; Hoflack *et al.*, 1995); although its primary metabolite, MAA, was also not mutagenic (McGregor *et al.*, 1983; Hoflack *et al.*, 1995), the acetaldehyde intermediate (MALD) was active in one strain, both with and without exogenous metabolic activation (Hoflack *et al.*, 1995). 2-Methoxyethyl acetate was not mutagenic in yeast (Abbondandolo *et al.*, 1980), although it caused chromosome malsegregation and aneuploidy (Zimmermann *et al.*, 1985; Whittaker *et al.*, 1989). 2-Methoxyethanol did not induce point mutations in mammalian cells *in vitro* (McGregor, 1984; Ma *et al.*, 1993; Chiewchanwit *et al.*, 1995), although the acetaldehyde metabolite induced an increase in HPRT and GPT mutations in Chinese hamster cells (Elias *et al.*, 1996).

There is some evidence that 2-methoxyethanol and its acetate cause increases in chromosomal aberrations in cultured mammalian (including human) cells; while the intermediate MALD was a potent inducer of chromosomal aberrations in various cell lines, MAA was inactive (Villalobos-Pietrini *et al.*, 1989; Loveday *et al.*, 1990; Chiewchanwit and Au, 1994; Elias *et al.*, 1996). Positive results were obtained for induction of micronuclei in mammalian cells for the parent compound as well as both metabolites, with the acetaldehyde being much more potent than either 2-methoxyethanol or MAA (Elias *et al.*, 1996). There was no convincing evidence that 2-methoxyethanol induced sister chromatid exchanges *in vitro*, although both MALD and MAA were active in this assay (Villalobos-Pietrini *et al.*, 1989; Loveday *et al.*, 1990; Chiewchanwit and Au, 1994; Elias *et al.*, 1996). Both 2-methoxyethanol and MALD induced aneuploidy or other mitotic aberrations *in vitro* (Zimmermann *et al.*, 1985; Whittaker *et al.*, 1989; Elias *et al.*, 1996).



#### 2.4.2.6.2 In vivo studies

2-Methoxyethanol did not induce chromosomal aberrations in rats or mice following single or repeated exposure via inhalation, ingestion or intravenous injection (McGregor *et al.*, 1983; Au *et al.*, 1993), nor did 2-methoxyethyl acetate induce micronuclei in the bone marrow of hamsters administered a single dose via intraperitoneal injection (Basler, 1986). In the COMET assay, a single gavage dose of 500 mg 2-methoxyethanol/kg-bw per day or more caused DNA damage in bone marrow and haploid testicular cells of rats, along with a decrease in percentage head DNA content; however, the damage was transient, as it was not present 5 weeks after exposure (Anderson *et al.*, 1996). Results of dominant lethal assays in rodents have been mixed (McGregor *et al.*, 1983; Rao *et al.*, 1983; Anderson *et al.*, 1987).

#### 2.4.2.7 Developmental toxicity

##### 2.4.2.7.1 Oral

2-Methoxyethanol and its principal metabolite, MAA, have consistently induced developmental toxicity in numerous oral studies in several species of experimental animals (although data are insufficient to evaluate variations in sensitivity across species), generally at doses or concentrations lower than those that are maternally toxic, and often at the lowest exposure level tested. For example, decreased fetal body weights were noted in rats repeatedly exposed to 2-methoxyethanol doses of 16 mg/kg-bw per day (the lowest dose) or more in the diet during gestation, with malformations being observed at doses of 31 mg/kg-bw per day or greater, while maternal toxicity was present only at higher doses (i.e.,  $\geq 140$  mg/kg-bw per day) (Nelson *et al.*, 1989). Similar results were obtained in several other studies in rats exposed to 2-methoxyethanol in the diet or by gavage (single or repeated doses) (Ritter *et al.*, 1985; Toraason *et al.*, 1985, 1986a,b,c; Toraason and Breitenstein, 1988; Nelson *et al.*, 1991; Sleet *et al.*, 1996). In many of these studies, the

cardiovascular system, kidney and skeletal system were the principal targets for 2-methoxyethanol-induced malformations; functional defects of the heart were also noted. Skeletal variations and delayed ossification were also reported in one study in mice repeatedly administered relatively low oral doses of 2-methoxyethanol (i.e.,  $\geq 31.25$  mg/kg-bw per day), with more severe effects occurring at higher doses, which were also maternally toxic (Nagano *et al.*, 1981, 1984). Although the heart appeared to be a sensitive target organ in rats, this was not observed in mice, although fewer studies in mice were identified. However, the developing immune system was a target in one study in mice, based on effects on thymic cellularity, thymocyte antigen expression and liver prolymphoid cells (Holladay *et al.*, 1994). Oral administration of 12 mg 2-methoxyethanol/kg-bw per day or more for 25 days during pregnancy was maternally toxic and embryotoxic in cynomolgus monkeys; however, there was no definitive evidence of malformations at doses of up to 36 mg/kg-bw per day (Scott *et al.*, 1989).

##### 2.4.2.7.2 Inhalation

In inhalation studies in rats, developmental effects, including increased resorptions, decreased pup or fetal weights and minor skeletal variations, were observed following repeated maternal exposure to 2-methoxyethanol concentrations of 50 ppm (156 mg/m<sup>3</sup>) and above (Doe *et al.*, 1983; Hanley *et al.*, 1984a,b; Nelson *et al.*, 1984a), while more severe malformations, such as heart defects, were noted at 100 ppm (311 mg/m<sup>3</sup>) or more (Nelson *et al.*, 1984a). Neurochemical changes and behavioural effects were observed in offspring of rats exposed to 25 ppm (78 mg/m<sup>3</sup>) (Nelson *et al.*, 1984b). In single studies in mice and rabbits, LOELs for fetal toxicity (reduced weight, minor skeletal variations or testicular hypoplasia) were reported to be 50 and 10 ppm (156 and 31 mg/m<sup>3</sup>), respectively, with No-Observed-Effect Levels (NOELs) of 10 and 3 ppm (31 and 9 mg/m<sup>3</sup>) (Hanley *et al.*, 1984a,b).



#### 2.4.2.7.3 Dermal

Repeated dermal exposure of dams to doses of about 48 mg/kg-bw per day or more induced developmental toxicity (including malformations) in rats (Wickramaratne, 1986; Feuston *et al.*, 1990; Hellwig, 1993). 2-Methoxyethanol was also teratogenic in rats and mice when administered by other routes of exposure (i.e., intravenous, subcutaneous or intraperitoneal injection).

#### 2.4.2.8 Reproductive toxicity

##### 2.4.2.8.1 Reproductive effects in males

In the large number of relevant studies identified, 2-methoxyethanol was consistently toxic to the male reproductive system in multiple species exposed by all routes of administration. Effects on reproductive ability as well as reproductive organs have been observed, often at the lowest dose or concentration tested.

##### Oral

Single or repeated oral administration of 2-methoxyethanol induced adverse effects on the testes (including weight and histopathological changes or biochemical indicators of testicular damage, such as urinary creatine) and/or various sperm parameters in every identified study in which these endpoints were examined, generally at doses of about 50 mg/kg-bw per day or more (Foster *et al.*, 1983, 1984; Chapin and Lamb, 1984; Chapin *et al.*, 1985a,b; Creasy *et al.*, 1985; Anderson *et al.*, 1987; Ghanayem and Chapin, 1990; Holloway *et al.*, 1990; Reader *et al.*, 1991; Smialowicz *et al.*, 1991a; Vachhrajani and Dutta, 1992; NTP, 1993; Ku *et al.*, 1994; Butterworth *et al.*, 1995; Aich and Manna, 1996; Timbrell *et al.*, 1996), although testicular effects were reportedly induced at 30 mg/kg-bw per day, based on a secondary account of a multi-generation study in which rats were exposed to 2-methoxyethanol in drinking water (Gulati *et al.*, 1990a,b). Alterations in sperm morphology were observed in mice or rats following acute oral administration of 500 mg/kg-bw or more

(Anderson *et al.*, 1987). Reduced male fertility was also observed in several acute and short-term studies (in one study at a dose lower than those that induced histopathological changes in the testes [i.e., 50 mg/kg-bw per day]) (Chapin *et al.*, 1985a; Anderson *et al.*, 1987; Holloway *et al.*, 1990). In mice, effects on male fertility and reproductive organs were reported following short- and long-term administration of oral doses of 60 and 170 mg/kg-bw per day or more, respectively, although fewer studies in mice were identified (Nagano *et al.*, 1979, 1984; Anderson *et al.*, 1987; Chapin *et al.*, 1993; NTP, 1993). Similar effects on the testes or male reproductive ability were observed in short-term and subchronic studies in guinea pigs, rabbits and hamsters, with the lowest LOEL being 25 mg/kg-bw per day in rabbits (Nagano *et al.*, 1984; Ku *et al.*, 1994, 1995; Foote *et al.*, 1995; Berndtson and Foote, 1997).

##### Inhalation

Male reproductive toxicity (effects on organs, sperm parameters and/or fertility) was also induced in rats acutely or repeatedly exposed to 2-methoxyethanol by inhalation at 300 ppm (933 mg/m<sup>3</sup>) or more (Doe *et al.*, 1983; McGregor *et al.*, 1983; Miller *et al.*, 1983; Rao *et al.*, 1983; Hanley *et al.*, 1984a; Samuels *et al.*, 1984; Lee and Kinney, 1989; Lee *et al.*, 1989). Reproductive effects were also observed in male mice exposed to 500 ppm (1555 mg/m<sup>3</sup>) 2-methoxyethanol (the only concentration tested) for 5 days (McGregor *et al.*, 1983) and in male rabbits at 30 ppm (93 mg/m<sup>3</sup>) (the lowest concentration tested) or more for 13 weeks (Miller *et al.*, 1983).

##### Dermal

Repeated dermal exposure to 2-methoxyethanol for 7 days also induced effects on the testes, sperm parameters and fertility in rats; effects were noted at all doses tested when the site of administration was occluded (i.e.,  $\geq 625$  mg/kg-bw per day) (Feuston *et al.*, 1989).

#### 2.4.2.8.2 Reproductive effects in females

Although not as extensively investigated, effects on the female reproductive system have also been associated with exposure to 2-methoxyethanol.

##### Oral

Changes in estrous cyclicity and hormone levels as well as histopathological changes in the ovaries were observed in rats administered 100 and 300 mg/kg-bw per day or more, respectively, for several days, with a NOEL of 10 mg/kg-bw per day (Davis *et al.*, 1997). Atrophy of female reproductive organs was also noted in rats exposed to oral doses of 297 mg/kg-bw per day or more for 13 weeks, although reduced body weight also occurred at these doses (NTP, 1993). Similarly, in mice, atrophy of the ovaries and altered estrous cycle were noted following subchronic oral administration of 2-methoxyethanol, but only at doses greater than those that induced these effects in rats (i.e.,  $\geq 1839$  and  $\geq 1194$  mg/kg-bw per day, respectively; no effects were observed at lower exposure levels) (NTP, 1993). Conversely, however, Chapin *et al.* (1993) reported an increase in ovary weights in female mice at 636 mg/kg-bw per day in a multigeneration study.

##### Inhalation

No effects on female reproductive success or organs were observed in rats or rabbits exposed to 2-methoxyethanol by inhalation at concentrations of up to 300 ppm (933 mg/m<sup>3</sup>) for 13 weeks (Miller *et al.*, 1983; Rao *et al.*, 1983; Hanley *et al.*, 1984a).

#### 2.4.2.9 Immunotoxicity

Exposure to 2-methoxyethanol or 2-methoxyethyl acetate significantly altered immune function in rats exposed orally or dermally. Although fewer studies are available, mice appear to be much less sensitive to the immunotoxicity of 2-methoxyethanol. Immunosuppression was observed in several studies in male and/or female

rats (several strains) repeatedly administered oral doses of 50 mg 2-methoxyethanol/kg-bw per day or more over periods of 2–21 days, based on alterations in lymphoproliferative response of splenic lymphocytes to various mitogens, antibody plaque-forming cell response to antigens and other immune function parameters (Exon *et al.*, 1991; Smialowicz *et al.*, 1991a,b, 1992a,b, 1993; Riddle *et al.*, 1992, 1996; Williams *et al.*, 1995). In addition, thymus weights were decreased in most studies (at doses as low as 25 mg/kg-bw per day); occasionally, reductions in spleen weights or cellularity were also observed. In mice, however, there was no consistent evidence of immunosuppression at repeated doses of up to 1000 mg 2-methoxyethanol/kg-bw per day or 1920 mg MAA/kg-bw per day, although decreased thymus weights were observed and there was evidence of enhancement or modulation of immune system response in some studies (House *et al.*, 1985; Kayama *et al.*, 1991; Riddle *et al.*, 1992, 1996; Smialowicz *et al.*, 1992b, 1994). The results of studies in rats in which enzyme inhibitors were administered indicated that the parent compound was not in itself immunotoxic, but that both the aldehyde and acid metabolites (MALD and MAA) suppressed immune system function (Smialowicz *et al.*, 1991a,b, 1993).

#### 2.4.2.10 Neurotoxicity

Although the database is limited to two studies in rats and a single study in mice, 2-methoxyethanol appears to induce neurological effects following acute or short-term inhalation exposure, including inhibition of conditioned avoidance response, increased barbiturate-induced sleeping time or partial hind limb paralysis at concentrations of 125 ppm (389 mg/m<sup>3</sup>) or greater and altered enzyme activities in the brain at 50 ppm (156 mg/m<sup>3</sup>) or more (Goldberg *et al.*, 1962; Savolainen, 1980). In addition, as noted above in Section 2.4.2.7.2, repeated exposure of pregnant rats to 25 ppm (78 mg/m<sup>3</sup>) induced effects on avoidance conditioning and neurochemical changes in the offspring (Nelson *et al.*, 1984b).



### 2.4.3 Humans

#### 2.4.3.1 Case reports

Several cases of adverse health effects following incidental or occupational exposure to 2-methoxyethanol have been identified in the literature. In general, effects on the nervous, respiratory and hematological systems (which appeared to be reversible after several months) have been associated with exposure in the work environment via inhalation and dermal contact. Although data on exposure levels were sparse, workplace concentrations in these case reports ranged from 8 to 3960 ppm (25 to 12 316 mg/m<sup>3</sup>) (Zavon, 1963; Ohi and Wegman, 1978); however, these workers were also exposed to other substances in addition to 2-methoxyethanol. Abnormal development of male reproductive organs was reported in two boys whose mother had been intensively exposed to 2-methoxyethyl acetate via inhalation and dermal contact during pregnancies (no quantitative estimates of exposure were presented) (Bolt and Golka, 1990).

#### 2.4.3.2 Clinical studies

In the only relevant clinical study identified (which was primarily intended to investigate the toxicokinetics of 2-methoxyethanol in humans), there were no changes in pulmonary ventilation or heart rates in seven male volunteers exposed to 5 ppm (16 mg/m<sup>3</sup>) 2-methoxyethanol for 4 hours (Groeseneken *et al.*, 1989).

#### 2.4.3.3 Epidemiological studies

Several epidemiological studies have been conducted in which a potential association between either glycol ethers as a class or an industrial process in which glycol ethers are used and various health endpoints (including hematological, immunological, neurological or reproductive and developmental effects as well as acute myeloid leukemia) has been investigated. In these studies, there was no conclusive evidence that occupational exposure to 2-methoxyethanol specifically induces adverse health effects in

humans, as all of the populations studied were also exposed to other solvents. However, available limited data from several cross-sectional surveys are suggestive of an association between hematological abnormalities, as well as effects on the immune and nervous systems, and exposure to 2-methoxyethanol along with other substances via inhalation and dermal contact. Alterations in various blood parameters (including red blood cell, white blood cell [or specifically granulocyte or polymorphonuclear leukocyte] or platelet counts and hemoglobin levels) were observed in workers exposed to 2-methoxyethanol while treating collars in a shirt factory (25–76 ppm or 78–236 mg/m<sup>3</sup>; Greenburg *et al.*, 1938), painting in a shipyard (up to 5.7 ppm or 17.7 mg/m<sup>3</sup>; Welch and Cullen, 1988) or laying parquet floors (up to 48 ppm or 149 mg/m<sup>3</sup>; Denkhaus *et al.*, 1986) or in the manufacture and packaging of the compound (up to 20 ppm or 62 mg/m<sup>3</sup>; Cook *et al.*, 1982). Significant differences in the distribution of lymphocyte subpopulations were also noted in the parquet floor workers compared with controls (Denkhaus *et al.*, 1986).

Decreased sperm production was also noted in a cross-sectional study of 73 shipyard painters exposed to 2-methoxyethanol along with 2-ethoxyethanol (Welch *et al.*, 1988), while difficulty in having children was reported in 40 men employed in the manufacture or packaging of 2-methoxyethanol compared with 25 unexposed workers, although there were no significant differences in sperm count or hormone levels in small subgroups of these employees (Cook *et al.*, 1982). With respect to potential effects on female reproduction, although the results of a historical cohort study in 891 women indicated that there was an increase in spontaneous abortions in those engaged in the fabrication departments at 14 semiconductor plants compared with non-fabrication workers (relative risk [RR] = 1.45, 95% confidence interval [CI] = 1.02–2.06), particularly in those exposed to glycol ethers (RR = 1.56, 95% CI = 1.02–2.31; RR = 3.38, 95% CI = 1.61–5.73 for those with the highest qualitative exposure





scores), it is not possible to discern the role of 2-methoxyethanol specifically, in view of the lack of data on exposure. In the prospective portion of this study, involving 481 women, there was again a significant association between occurrence of spontaneous abortions and exposure to glycol ethers (RR = 2.0, 95% CI = 1.46–2.75) and a non-significant reduction in fecundability (p = 0.08) (Beaumont *et al.*, 1995; Schenker *et al.*, 1995; Swan *et al.*, 1995; Schenker, 1996; Swan and Forest, 1996).

#### 2.4.4 Abiotic atmospheric effects

Worst-case calculations were made to determine if 2-methoxyethanol has the potential to contribute to depletion of stratospheric ozone, ground-level ozone formation or climate change (Bunce, 1996).

The Ozone Depletion Potential (ODP) is 0, as 2-methoxyethanol is not a halogenated compound.

The Photochemical Ozone Creation Potential (POCP) was estimated to be 61 (relative to the reference compound ethene, which has a POCP of 100), based on the following formula:

$$\text{POCP} = \left( \frac{k_{2\text{-methoxyethanol}}}{k_{\text{ethene}}} \right) \times \left( \frac{M_{\text{ethene}}}{M_{2\text{-methoxyethanol}}} \right) \times 100$$

where:

- $k_{2\text{-methoxyethanol}}$  is the rate constant for the reaction of 2-methoxyethanol with OH radicals ( $1.4 \times 10^{-11}$  cm<sup>3</sup>/mol per second),
- $k_{\text{ethene}}$  is the rate constant for the reaction of ethene with OH radicals ( $8.5 \times 10^{-12}$  cm<sup>3</sup>/mol per second),
- $M_{\text{ethene}}$  is the molecular weight of ethene (28.1 g/mol), and
- $M_{2\text{-methoxyethanol}}$  is the molecular weight of 2-methoxyethanol (76 g/mol).

The Global Warming Potential (GWP) was calculated to be  $8.4 \times 10^{-5}$  (relative to the reference compound CFC-11, which has a GWP of 1), based on the following formula:

$$\text{GWP} = \left( \frac{t_{2\text{-methoxyethanol}}}{t_{\text{CFC-11}}} \right) \times \left( \frac{M_{\text{CFC-11}}}{M_{2\text{-methoxyethanol}}} \right) \times \left( \frac{S_{2\text{-methoxyethanol}}}{S_{\text{CFC-11}}} \right)$$

where:

- $t_{2\text{-methoxyethanol}}$  is the lifetime of 2-methoxyethanol (0.0028 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),
- $M_{2\text{-methoxyethanol}}$  is the molecular weight of 2-methoxyethanol (76 g/mol),
- $S_{2\text{-methoxyethanol}}$  is the infrared absorption strength of 2-methoxyethanol (2389/cm<sup>2</sup> per atmosphere, default), and
- $S_{\text{CFC-11}}$  is the infrared absorption strength of CFC-11 (2389/cm<sup>2</sup> per atmosphere).

These figures suggest that 2-methoxyethanol does not contribute to stratospheric ozone depletion, that its potential contribution to climate change is negligible and that its potential contribution to ground-level ozone formation is moderate. The magnitude of these effects would depend on the concentration of 2-methoxyethanol in the atmosphere, and concentrations of the substance in air in Canada are estimated to be very low. The contribution of 2-methoxyethanol to ozone formation is therefore considered negligible compared with those of other more abundant smog-forming substances, such as the reference compound, ethene (Bunce, 1996).



## 3.0 ASSESSMENT OF “TOXIC” UNDER CEPA 1999

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### 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

In Canada, most environmental releases of 2-methoxyethanol are to the atmosphere. Based on its predicted environmental partitioning, assessment endpoints for 2-methoxyethanol relate to terrestrial organisms, including terrestrial wildlife and soil organisms, and aquatic organisms.

#### 3.1.2 Environmental risk assessment

##### 3.1.2.1 Terrestrial organisms

###### 3.1.2.1.1 Wildlife

For a conservative risk characterization for wildlife, the EEV is 0.146 ng/m<sup>3</sup>, the estimated concentration of 2-methoxyethanol in air using ChemCan modelling based on reported releases in 1994. This value is believed to be conservative because releases of 2-methoxyethanol in Canada appear to have significantly decreased since 1994.

The CTV is 10 ppm ( $3.1 \times 10^7$  ng/m<sup>3</sup>), the LOEL in an inhalation study with rabbits (Hanley *et al.*, 1984a,b), based on fetal toxicity. Dividing this CTV by a factor of 10 (to account for the extrapolation from laboratory to field conditions and interspecies and intraspecies variations in sensitivity) gives an ENEV of 1 ppm ( $3.1 \times 10^6$  ng/m<sup>3</sup>).

The conservative quotient is calculated as follows:

$$\begin{aligned}\text{Quotient} &= \frac{\text{EEV}}{\text{ENEV}} \\ &= \frac{0.146 \text{ ng/m}^3}{3.1 \times 10^6 \text{ ng/m}^3} \\ &= 4.7 \times 10^{-8}\end{aligned}$$

Therefore, concentrations of 2-methoxyethanol in air in Canada are unlikely to cause adverse effects on populations of wildlife. Concentrations of 2-methoxyethanol in Canadian indoor and outdoor air samples were all below the detection limit of 5 µg/m<sup>3</sup> ( $5 \times 10^3$  ng/m<sup>3</sup>) (Conor Pacific Environmental Technologies, 1998), a value that



is well below the ENEV. Maximum reported concentrations of 2-methoxyethanol in indoor air samples from Italy ( $70 \mu\text{g}/\text{m}^3$  or  $7 \times 10^4 \text{ ng}/\text{m}^3$ ; De Bortoli *et al.*, 1986) and Germany ( $220 \mu\text{g}/\text{m}^3$  or  $2.2 \times 10^5 \text{ ng}/\text{m}^3$ ; Schriever and Marutzky, 1990) were also below the ENEV.

### 3.1.2.1.2 Soil organisms

For a conservative risk characterization for soil organisms, the EEV is  $9.4 \times 10^{-4} \text{ ng}/\text{g}$  dry weight, the estimated concentration of 2-methoxyethanol in soil using ChemCan modelling based on reported releases in 1994. This value is believed to be conservative because releases of 2-methoxyethanol in Canada appear to have significantly decreased since 1994.

No information was identified regarding the toxicity of 2-methoxyethanol to soil organisms. Van Leeuwen *et al.* (1992) used quantitative structure–activity relationships to estimate that a sediment concentration of 1800 ng 2-methoxyethanol/g would be hazardous to 5% of benthic species. Using this sediment HC<sub>5</sub> value as a CTV and an application factor of 100 (to account for the extrapolation from benthic to soil organisms) gives an ENEV of 18 ng/g for soil organisms.

The conservative quotient is calculated as follows:

$$\begin{aligned} \text{Quotient} &= \frac{\text{EEV}}{\text{ENEV}} \\ &= \frac{9.4 \times 10^{-4} \text{ ng}/\text{g}}{18 \text{ ng}/\text{g}} \\ &= 5.2 \times 10^{-5} \end{aligned}$$

Therefore, concentrations of 2-methoxyethanol in soil in Canada appear to be unlikely to cause adverse effects on populations of soil organisms.

### 3.1.2.2 Aquatic organisms

For a conservative risk characterization for aquatic organisms, the EEV is  $4.8 \times 10^{-5} \mu\text{g}/\text{L}$ , the estimated concentration of 2-methoxyethanol in water using ChemCan modelling based on reported releases in 1994. This value is believed to be conservative because releases of 2-methoxyethanol in Canada appear to have significantly decreased since 1994.

The CTV for aquatic organisms is 2200  $\mu\text{g}/\text{L}$ , the 2-day toxicity threshold for the flagellate protozoan, *Chilomonas paramecium*, based on inhibition of cell multiplication. Dividing this CTV by a factor of 10 (to account for the extrapolation from laboratory to field conditions and interspecies and intraspecies variations in sensitivity) gives an ENEV of 220  $\mu\text{g}/\text{L}$ .

The conservative quotient is calculated as follows:

$$\begin{aligned} \text{Quotient} &= \frac{\text{EEV}}{\text{ENEV}} \\ &= \frac{4.8 \times 10^{-5} \mu\text{g}/\text{L}}{220 \mu\text{g}/\text{L}} \\ &= 2.2 \times 10^{-7} \end{aligned}$$

Therefore, concentrations of 2-methoxyethanol in water in Canada appear to be unlikely to cause adverse effects on populations of aquatic organisms.

### 3.1.2.3 Discussion of uncertainty

There are several sources of uncertainty in this environmental risk assessment. Very few data were identified on environmental concentrations of 2-methoxyethanol in Canada or elsewhere. The ChemCan v. 4.0 model was therefore used to estimate environmental concentrations of 2-methoxyethanol in the various environmental compartments, based on the highest reported

recent release of the substance in Canada, which occurred in 1994. These values are believed to be conservative because releases of 2-methoxyethanol in Canada appear to have significantly decreased since then and because conservative estimates of persistence were used as inputs to the model. Kane (1993) compared measured environmental concentrations of five industrial chemicals and six pesticides with environmental concentrations estimated for the substances by the ChemCan model. Sixty percent of the measured environmental concentrations were within 1 order of magnitude of predicted values, and 75% were within 2 orders of magnitude. The few data that are available on the concentration of 2-methoxyethanol in the Canadian environment, including indoor air and tap water, support the conclusion that levels are very low.

No information was identified regarding the toxicity of 2-methoxyethanol to soil organisms or to terrestrial wildlife through atmospheric exposure. An estimation of a hazardous concentration to benthic species was the basis for the assessment of risk to soil organisms. The results of an inhalation toxicity study using a laboratory strain of rabbits were used for the assessment of risk to wildlife. To account for these uncertainties, application factors were used in the environmental risk assessment to derive ENEVs.

Usage and environmental releases of 2-methoxyethanol in Canada appear to be declining. Conservative risk quotients are very small for all environmental assessment endpoints. Therefore, despite the data gaps regarding the environmental concentrations and effects of 2-methoxyethanol on soil organisms and terrestrial wildlife, the data available at this time are considered adequate for drawing a conclusion about the environmental risk of the substance in Canada.

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

2-Methoxyethanol does not deplete stratospheric ozone, and its potential for contributing to climate change is negligible. The potential of 2-methoxyethanol for creation of photochemical ozone (smog) is moderate, but the low quantities of 2-methoxyethanol in the atmosphere are unlikely to make its contribution significant relative to that of other smog-forming substances.

### **3.3 CEPA 1999 64(c): Human health**

#### *3.3.1 Estimates of potential exposure in humans*

The limitations of the available monitoring data for 2-methoxyethanol preclude the development of reliable estimates of typical exposure of the general population; instead, worst-case or bounding estimates of exposure to 2-methoxyethanol from environmental media and consumer products have been developed in order to characterize potential exposure from these pathways.

Because most of the consumer products for which suitable data are available are used primarily by adults, the estimated exposures have been derived for this age class only, although the limitations of the available data preclude confident estimation of intake for even one age group. (The differences among age classes in intake from a given medium, as a result of age-specific differences in intakes of environmental media and in body weight, would be small in relation to the variation in exposure from the various sources, in any case.) Worst-case or bounding estimates of intake of 2-methoxyethanol by Canadian adults from various sources and the assumptions upon which they are based are summarized in Table 1.



**TABLE 1** Worst-case/bounding estimates of intake of 2-methoxyethanol by adult Canadians

| Exposure medium                                | Assumptions <sup>1</sup>  | Estimated intake (mg/kg-bw per day) |
|--|---|-------------------------------------|
| <b>Environmental media (indirect exposure)</b> |   |                                     |
| <b>Air</b>                                     | <ul style="list-style-type: none"> <li>based on the limit of detection for 2-methoxyethanol in air in the Canadian multimedia study (5 µg/m<sup>3</sup>) (Conor Pacific Environmental Technologies, 1998)</li> <li>an average Canadian adult is assumed to weigh 70.9 kg and breathe 16.2 m<sup>3</sup> of air per day (EHD, 1998)</li> </ul>   | 0.0011                              |
| <b>Water</b>                                   | <ul style="list-style-type: none"> <li>based on the limit of detection for 2-methoxyethanol in water in the Canadian multimedia study (0.6 µg/L) (Conor Pacific Environmental Technologies, 1998)</li> <li>an average Canadian adult is assumed to weigh 70.9 kg and consume 1.5 L of tap water per day (EHD, 1998)</li> </ul>  | 0.000 013                           |
| <b>Consumer products (direct exposure)</b>     |   |                                     |
| <b>Nail polish remover</b>                     | <ul style="list-style-type: none"> <li>based on the upper bound of the concentration range of &gt;30–100% of 2-methoxyethanol in nail polish remover</li> <li>assumes a typical quantity of product used per event for “nail polish &amp; enamel remover” of 3.06 g and a maximum event frequency of 0.29 times per day for users only (U.S. EPA, 1997)</li> <li>a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998)</li> </ul> $\frac{(1.0) (0.29/\text{day}) (3060 \text{ mg})}{(70.9 \text{ kg})}$   | 12.5                                |
| <b>All-purpose liquid cleaner</b>              | <p><b>Inhalation</b></p> <ul style="list-style-type: none"> <li>based on a maximum concentration of 2% 2-methoxyethanol in all-purpose liquid cleaner (Flick, 1986, 1989)</li> <li>assumes a mass of 35 g is used per event, a 0.47-hour duration of exposure, a room volume of 20 m<sup>3</sup>, a breathing rate of 1.3 m<sup>3</sup>/hour for an average adult during light-level activity and a frequency of use of 360 days per year (Versar Inc., 1986)</li> <li>a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998)</li> </ul> $\frac{(0.02) (35 \text{ 000 mg}) (0.47 \text{ hours}) (1.3 \text{ m}^3/\text{hour}) (360/365 \text{ days})}{(20 \text{ m}^3) (70.9 \text{ kg})}$ | 0.30                                |

TABLE 1 (continued)

| Exposure medium           | Assumptions <sup>1</sup>  | Estimated intake (mg/kg-bw per day)   |
|---------------------------|---|---|
|                           | <p><b>Dermal</b></p> <ul style="list-style-type: none"> <li>based on a maximum concentration of 2% 2-methoxyethanol in all-purpose liquid cleaner (Flick, 1986, 1989)</li> <li>assumes an event frequency of 360 days per year, an exposed surface area of 400 cm<sup>2</sup> (both palms), a product density of 1.19 g/cm<sup>3</sup> and a film thickness on the hands of 2.1 × 10<sup>-3</sup> cm (Versar Inc., 1986)</li> <li>a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998)</li> </ul> <p><u>(0.02) (360/365 days) (400 cm<sup>2</sup>) (1.19 g/cm<sup>3</sup>) (2.1 × 10<sup>-3</sup> cm) (1000 mg/g)</u><br/>(70.9 kg)</p>  | 0.28  |
| All-purpose spray cleaner | <p><b>Inhalation</b></p> <ul style="list-style-type: none"> <li>based on a maximum concentration of 2% 2-methoxyethanol in all-purpose spray cleaner (Flick, 1986, 1989)</li> <li>assumes a mass of 76 g is used per event, a 0.47-hour duration of exposure, a room volume of 20 m<sup>3</sup>, a breathing rate of 1.3 m<sup>3</sup>/hour for an average adult during light-level activity and a frequency of use of 360 days per year (Versar Inc., 1986)</li> <li>a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998)</li> </ul> <p><u>(0.02) (76 000 mg) (0.47 hours) (1.3 m<sup>3</sup>/hour) (360/365 days)</u><br/>(20 m<sup>3</sup>) (70.9 kg)</p> <p><b>Dermal</b></p> <ul style="list-style-type: none"> <li>based on a maximum concentration of 2% 2-methoxyethanol in all-purpose spray cleaner (Flick, 1986, 1989)</li> <li>assumes an event frequency of 360 days per year, an exposed surface area of 400 cm<sup>2</sup> (both palms), a product density of 0.88 g/cm<sup>3</sup> and a film thickness on the hands of 2.1 × 10<sup>-3</sup> cm (Versar Inc., 1986)</li> <li>a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998)</li> </ul> <p><u>(0.02) (360/365 days) (400 cm<sup>2</sup>) (0.88 g/cm<sup>3</sup>) (2.1 × 10<sup>-3</sup> cm) (1000 mg/g)</u><br/>(70.9 kg)</p> | 0.65<br>[estimated indoor air concentration of 76 mg/m <sup>3</sup> ]<br><br>0.21 |
| Varnish                   | <p><b>Inhalation</b></p> <ul style="list-style-type: none"> <li>based on a maximum concentration of 1.1% 2-methoxyethanol in varnish (Versar Inc., 1986)</li> <li>assumes a mass of 150 g is used per event, a 0.47-hour duration of exposure, a room volume of 125 m<sup>3</sup>, a breathing rate of 1.3 m<sup>3</sup>/hour for an average adult during light-level activity and a frequency of use of 24 days per year (Versar Inc., 1986)</li> <li>a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998)</li> </ul> <p><u>(0.011) (150 000 mg) (0.47 hours) (1.3 m<sup>3</sup>/hour) (24/365 days)</u><br/>(125 m<sup>3</sup>) (70.9 kg)</p>  | 0.0075<br>[estimated indoor air concentration of 13 mg/m <sup>3</sup> ]           |



TABLE 1 (continued)

| Exposure medium | Assumptions <sup>1</sup>  | Estimated intake (mg/kg-bw per day) |
|-----------------|---|-------------------------------------|
|                 | <p><b>Dermal</b></p> <ul style="list-style-type: none"> <li>• based on a maximum concentration of 1.1% 2-methoxyethanol in varnish (Versar Inc., 1986)</li> <li>• assumes an event frequency of 24 days per year, an exposed surface area of 190 cm<sup>2</sup> (10% of the hands and forearms), a product density of 0.88 g/cm<sup>3</sup> and a film thickness on the hands of 15.88 × 10<sup>-3</sup> cm (Versar Inc., 1986)</li> <li>• a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998)</li> </ul> <p><u>(0.011) (24/365 days) (190 cm<sup>2</sup>) (0.88 g/cm<sup>3</sup>) (15.88 × 10<sup>-3</sup> cm) (1000 mg/g)</u><br/>(70.9 kg)</p> | 0.027                               |

<sup>1</sup> For all of the consumer products, it is assumed that 100% of the 2-methoxyethanol is absorbed.

The only environmental media for which available monitoring data allowed even crude estimation of exposure were air and water. These estimates are based on the limits of detection in air and tap water from the Canadian multimedia study in which concentrations of 2-methoxyethanol were below the limit of detection in all of the samples of air and tap water that were analysed for 50 participants (Conor Pacific Environmental Technologies, 1998). However, although the limits of detection for this substance were relatively high, the lack of detection in these media is not surprising in view of the decline in use and production of 2-methoxyethanol in Canada over the last several years. Based on these values, the average adult in Canada would be exposed to airborne levels of 2-methoxyethanol no greater than 5 µg/m<sup>3</sup> and would not ingest more than 0.013 µg/kg-bw per day, although it is recognized that these values likely overestimate exposure. In addition, concentrations of 2-methoxyethanol in ambient air and surface water predicted by fugacity modelling (presented in Section 2.3.2.9), based on the highest reported release in recent years,

were several orders of magnitude below these detection limits. Therefore, the estimated worst-case or bounding estimates of intake from air (0.0011 mg/kg-bw per day) and water (0.000 013 mg/kg-bw per day) are substantially less than those for consumer products.

Although no monitoring data are available, food is unlikely to be a principal source of exposure to 2-methoxyethanol in humans, since 2-methoxyethanol is released primarily to air from industrial activities and consumer products (no releases to other media have been reported). 2-Methoxyethanol is unlikely to partition to food from air due to its high volatility and very low octanol/water partition coefficient (log K<sub>ow</sub> of -0.77). [In fact, even if intake in food is estimated on the basis of extrapolation from the results of the fugacity modelling, this value would still be several orders of magnitude less than the worst-case scenarios calculated for air and drinking water on the basis of the limit of detection in the multimedia study.] Likewise, exposure to 2-methoxyethanol in soil is likely to be negligible in comparison with that in air, based on its release

patterns and physical/chemical properties and the results of fugacity modelling.

Direct exposure to 2-methoxyethanol can result from the use of a variety of consumer products containing these substances. Both inhalation and dermal absorption are expected to be important routes of exposure for most consumer products, since many of those products expected to contain 2-methoxyethanol can contact the skin. Estimated intakes from the few products for which quantitative data were identified are presented in Table 1. However, since information on current compositions and use patterns of these products in Canada is extremely limited, these values likely overestimate current exposures considerably in view of the decline in use of this compound in many countries. The highest estimated worst-case intake of 2-methoxyethanol for consumer products was for nail polish remover (12.5 mg/kg-bw per day). This estimate was developed from product use scenarios (U.S. EPA, 1997), assuming 100% of the applied compound was absorbed, and refers to dermal absorption only. Upper-bounding estimates of intake of 2-methoxyethanol from exposure to household cleaning products and varnish were developed from product use scenarios (Versar Inc., 1986), assuming 100% absorption for the product contacting the skin and for the inhaled product (in view of lack of adequate data to support a more refined estimate). Worst-case estimates of indoor air concentrations resulting from the use of products such as an all-purpose spray cleaner were calculated to be up to 76 mg/m<sup>3</sup>.

It should be noted that these estimates have been made for only a limited range of media and products for which at least some data were available. In addition, they do not represent typical exposures, since the limitations of the available data preclude development of such estimates; most are instead maximal or near-maximal estimates of potential exposure.

### 3.3.2 Human health risk characterization

As discussed in Section 1.0, a screening approach was adopted for assessment of 2-methoxyethanol as a Priority Substance under CEPA 1999, in view of the paucity of data upon which to base estimates of population exposure as well as the considerable decline in the production and use of this substance in recent years. In this approach, estimates of worst-case exposure are compared with conservative effect levels for critical effects in order to determine the margin between these estimates. On this basis, areas where additional information may be required to ensure that current measures for reduction of population exposure are sufficiently protective may be identified.

Exposure to 2-methoxyethanol has been associated with a range of adverse health effects in experimental animals, including effects on weights and histopathology of various organs, hematological, immunological and neurological effects, and reproductive and developmental toxicity, including teratogenicity. In many studies, effects were observed at the lowest dose or concentration tested. For example, the lowest reported LOELs (oral exposure) for developmental toxicity were 12 and 16 mg/kg-bw per day in monkeys and rats (lower doses were not investigated), respectively, with increased malformations occurring in rats at 31 mg/kg-bw per day (in the absence of maternal toxicity) (Nelson *et al.*, 1989; Scott *et al.*, 1989). In inhalation studies, developmental effects were observed at concentrations of 10 ppm (31 mg/m<sup>3</sup>) or more in rabbits, but not at 3 ppm (9 mg/m<sup>3</sup>) (Hanley *et al.*, 1984a,b). The lowest reported LOEL for developmental toxicity (including malformations) following dermal exposure was approximately 48 mg/kg-bw per day in rats, the lowest dose tested in the study (Hellwig, 1993). There is some indication that 2-methoxyethanol may be weakly genotoxic in somatic cells, likely through activation to the intermediate acetaldehyde metabolite, and that it causes genetic damage to male germ cells in rats at high doses or concentrations (i.e., >500 mg/kg-bw per day) (Anderson *et al.*, 1987, 1996), which is in





concordance with the observed effects on male reproduction.

Data from case reports or other epidemiological studies are not conclusive with respect to evaluation of adverse effects associated with exposure to 2-methoxyethanol in humans, although they are suggestive of effects on the hematological system and, perhaps, on reproduction in men and women employed in occupations involving exposure to 2-methoxyethanol as well as other substances. Such potential associations would be consistent with the observations in experimental animals.

In available studies, therefore, 2-methoxyethanol has induced a wide range of adverse effects, including those considered to be severe and irreversible (e.g., teratogenicity), with some occurring at relatively low doses. Although information on the mode(s) of induction of these effects has not been critically examined for the purposes of this assessment, it cannot be precluded at this time that there may be some probability of adverse effects occurring at any level of exposure, as there is some evidence of interaction with genetic material, at least at high doses, particularly for the metabolite MALD.

Based on comparison of the lowest LOEL reported in oral studies in animals (i.e., 12 mg/kg-bw per day or 12 000 µg/kg-bw per day), since a NOEL was not identified in these studies, with the worst-case exposure scenario for ingestion of 2-methoxyethanol in drinking water of 0.013 µg/kg-bw per day, the margin between exposure and effect level is about 6 orders of magnitude. With respect to inhalation, comparison of a NOEL for toxic effects of 3 ppm or 9 mg/m<sup>3</sup> (9000 µg/m<sup>3</sup>) with a worst-case exposure level in air (5 µg/m<sup>3</sup>) indicates that the margin would be about 3 orders of magnitude. However, estimates of exposure to 2-methoxyethanol through use of some consumer products (based on the very limited information available) approach or are within a few orders of magnitude of effect levels for adverse health effects in animals. For example, estimated intake through use of a nail polish remover containing up to 100% 2-methoxyethanol

could range up to 12.5 mg/kg-bw per day (i.e., exposure through use of this product would be similar to the lowest effect level for oral exposure and within an order of magnitude of a dermal LOEL of 48 mg/kg-bw per day). Use of other products, such as an all-purpose spray cleaner, could result in exposure to concentrations in indoor air of up to 76 mg/m<sup>3</sup>, which would exceed the NOEL for developmental toxicity. Margins between exposure and lowest reported effect level for severe, irreversible effects (i.e., teratogenicity) would also be less than an order of magnitude.

Therefore, on the basis of these values, while the margin between levels of exposure that induce effects in experimental animals and estimates of exposure from air and drinking water may be large, the margin between effect levels and worst-case estimates of exposure from some consumer products may be insufficient to address the requisite elements of uncertainty (e.g., interspecies and intraspecies [interindividual] variation) against which adequacy would be judged.

### 3.3.3 *Uncertainties and degree of confidence in the human health risk characterization*

Due to the paucity of data on levels of 2-methoxyethanol in environmental media in Canada, there is a high degree of uncertainty in the estimates of exposure to this substance that are presented in this assessment. While a worst-case exposure scenario was determined on the basis of the detection limits in a small number of samples in a multimedia study, it is not known if these values grossly overestimate environmental levels or if the general population is exposed to levels approaching these values, although predicted concentrations in ambient air and drinking water (using fugacity modelling) were several orders of magnitude less than these detection limits. Although environmental levels are expected to decline in the wake of reduced use of 2-methoxyethanol by many countries, there is some uncertainty as to whether or not such a decline has occurred in environmental media

in Canada due to lack of adequate monitoring data. In addition, the only media in which 2-methoxyethanol was measured in the multimedia study were drinking water and air, although there is a moderate degree of certainty that food and soil do not represent important sources of exposure, based on the physical and chemical properties of this substance, the sources of release to the environment, as well as the results of fugacity modelling.

There is a low degree of confidence in the estimates of exposure to 2-methoxyethanol through the use of various consumer products, due to the large uncertainties concerning the presence and levels of the substance in products currently available in Canada. For example, it should be noted that 2-methoxyethanol was not detected in emissions from similar products recently investigated by Health Canada (Cao, 1999), and thus these estimates are likely very conservative. These estimates were also calculated assuming 100% absorption through the skin, in view of the lack of adequate data to support a lower percent absorption. Therefore, it is considered important to determine whether or not 2-methoxyethanol is present in consumer products currently available in Canada and, if so, to investigate levels of 2-methoxyethanol in and the use patterns of such products, in order to better characterize the risk to human health.

There is a moderate to high degree of confidence in the available data to serve as a basis for hazard characterization for the non-neoplastic effects associated with exposure to 2-methoxyethanol, as hematological, immunological, reproductive and developmental effects (including teratogenicity at relatively low exposure levels) have been repeatedly demonstrated in acute, short-term and subchronic studies in experimental animals, although no chronic studies have been identified and epidemiological data are inadequate (although it is notable that, even though confounded by concurrent exposures to other substances, the results of the available epidemiological studies are consistent with those from studies in animals).

However, in the absence of any long-term investigations in animals, and in view of the limited evidence of weak genotoxicity (and stronger evidence of the genotoxicity of the initial metabolite), there is some uncertainty with regard to the potential of 2-methoxyethanol to induce neoplastic effects.

### 3.4 Conclusions

CEPA 1999 64(a): Based on conservative estimates of exposure and effects in Canada, risk quotients for terrestrial wildlife, soil organisms and aquatic organisms are less than one. The environmental risks associated with estimated concentrations of 2-methoxyethanol likely to be found in Canada therefore appear to be low. Therefore, available data indicate that it is unlikely that 2-methoxyethanol 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 2-methoxyethanol is not considered to be “toxic” as defined in CEPA 1999 Paragraph 64(a).

CEPA 1999 64(b): 2-Methoxyethanol is not involved in the depletion of stratospheric ozone and likely does not contribute significantly to climate change. Because of its very low estimated concentration in air in Canada, it is unlikely to play a significant role in tropospheric ozone



production. Therefore, based on available data, 2-methoxyethanol is not 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 not considered to be “toxic” as defined in CEPA 1999 Paragraph 64(b).

CEPA 1999 64(c): There is considerable evidence that 2-methoxyethanol causes a range of adverse effects in experimental animals (including those considered to be severe and irreversible, such as teratogenicity), some for which it cannot be precluded that there is some probability of occurrence at any level of exposure. In addition, the margins between worst-case estimates of exposure to 2-methoxyethanol via some consumer products (although data are extremely limited) and effect levels for adverse health effects in experimental animals are considered inadequate to address requisite elements of uncertainty. Thus, on the basis principally of its high health hazard potential, 2-methoxyethanol is considered to constitute a danger in Canada to human life or health and is, therefore, deemed “toxic” under Paragraph 64(c) of CEPA 1999.

Overall conclusion: Based on critical assessment of relevant information, 2-methoxyethanol is considered to be “toxic” as defined in Section 64 of CEPA 1999.

### 3.5 Considerations for follow-up (further action)

While 2-methoxyethanol appears not to be produced in Canada currently, information on its use, in particular on its potential presence in consumer products, is sparse. It is recommended, therefore, that additional information be acquired on patterns of use of the compound in Canada and its potential presence in consumer products, as a basis for risk management.

Depending upon patterns of use, it may be necessary to conduct a fuller assessment of the potential adverse effects of 2-methoxyethanol, since the conclusions included herein are based not only on limited data on potential for exposure but also on screening of available data on toxicity. However, in view of the profile of inherent toxicity of 2-methoxyethanol, it would be prudent to eliminate or reduce, to the extent possible, the potential for exposure of the general population to this compound.



## 4.0 REFERENCES

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- Abbondandolo, A., S. Bonatti, C. Corsi, G. Corti, R. Fiorio, C. Leporini, A. Mazzaccaro and R. Nieri. 1980. The use of organic solvents in mutagenicity testing. *Mutat. Res.* 79: 141–150.
- Aich, S. and C.K. Manna. 1996. Action of ethylene glycol monomethyl ether on male reproductive organs of Indian wild rat. *Endocr. Regul.* 30: 153–162.
- Anderson, D., M.H. Brinkworth, P.C. Jenkinson, S.A. Clode, D.M. Creasy and S.D. Gangolli. 1987. Effect of ethylene glycol monomethyl ether on spermatogenesis, dominant lethality, and F<sub>1</sub> abnormalities in the rat and the mouse after treatment of F<sub>0</sub> males. *Teratogen. Carcinogen. Mutagen.* 7: 141–158.
- Anderson, D., A. Dhawan, T.-W. Yu and M.J. Plewa. 1996. An investigation of bone marrow and testicular cells *in vivo* using the comet assay. *Mutat. Res.* 370: 159–174.
- Au, W.W., D.L. Morris and M.S. Legator. 1993. Evaluation of the clastogenic effects of 2-methoxyethanol in mice. *Mutat. Res.* 300: 273–279.
- Basler, A. 1986. Aneuploidy-inducing chemicals in yeast evaluated by the micronucleus test. *Mutat. Res.* 174: 11–13.
- Beaumont, J.J., S.H. Swan, S.K. Hammond, S.J. Samuels, R.S. Green, M.F. Hallock, C. Dominguez, P. Boyd and M.B. Schenker. 1995. Historical cohort investigation of spontaneous abortion in the semiconductor health study: epidemiologic methods and analyses of risk in fabrication overall and in fabrication work groups. *Am. J. Ind. Med.* 28: 735–750.
- Benville, P. 1974. Acute toxicity of nine solvents to rainbow trout fingerlings. Unpublished; transmitted from Tiburon Laboratory, National Oceanic and Atmospheric Administration (NOAA), July 10, 1974 (cited in Dawson *et al.*, 1977).
- Berndtson, W.E. and R.H. Foote. 1997. Disruption of spermatogenesis in rabbits consuming ethylene glycol monomethyl ether. *Reprod. Toxicol.* 11(1): 29–36.
- BIBRA International. 1996/Health Canada. 1998. 2-Methoxyethanol and its acetate. Prepared by BIBRA International under contract to Health Canada, March 29, 1996. Updated and modified by Priority Substances Section, Health Canada, 1998.
- Bolt, H.M. and K. Golka. 1990. Maternal exposure to ethylene glycol monomethyl ether acetate and hypospadias in offspring: a case report. *Br. J. Ind. Med.* 47: 352–353.
- Bridie, A.L., C.J.M. Wolff and M. Winter. 1979. The acute toxicity of some petrochemicals to goldfish. *Water Res.* 13: 623–626.
- Bringmann, G. and R. Kuehn. 1978. *Grenzwerte der schwadwirkung wassergefahrender stoffe gegen Blaualgen (Microcystis aeruginosa) und grunalgen (Scenedesmus quadricauda) Im. Vom Wasser* 50: 45–60.
- Bringmann, G. and R. Kuehn. 1981. Comparison of the effect of harmful substances on flagellates and ciliates as well as on bacteriovirus saprozoic protozoans. *Gas-Wasserfach: Wasser Abwasser* 122: 308–313.
- Bunce, N. 1996. Atmospheric properties of substances on the Priority Substances List #2 (PSL2). Report to Environment Canada. University of Guelph, Guelph, Ontario. 13 pp.



- Butterworth, M., D. Creasy and J.A. Timbrell. 1995. The detection of subchronic testicular damage using urinary creatine: studies with 2-methoxyethanol. *Arch. Toxicol.* 69: 209–211.
- Canadian Chemical Producers' Association. 1997. Reducing emissions 4. A Responsible Care initiative. 1995 emissions inventory and five year projections. Ottawa, Ontario.
- Canadian Chemical Producers' Association. 1999a. Reducing emissions 6. A Responsible Care initiative. 1997 emissions inventory and five year projections. Ottawa, Ontario.
- Canadian Chemical Producers' Association. 1999b. Reducing emissions 7. A Responsible Care initiative. 1998 emissions inventory and five year projections. Ottawa, Ontario.
- Cao, X.L. 1999. Emissions of glycol ethers from consumer products — A final report for 1998/1999 CEPA project. Health Canada, Ottawa, Ontario. June 1999.
- CARB (State of California Air Resources Board). 1991. Assessment of indoor concentrations, indoor sources and source emissions of selected volatile organic compounds. National Technical Information Service, U.S. Department of Commerce, Springfield, Virginia.
- Carpenter, C.P. and H.F. Smyth, Jr. 1946. Chemical burns of the rabbit cornea. *Am. J. Ophthalmol.* 29: 1363–1372.
- Carpenter, C.P., U.C. Pozzani, C.S. Weil, J.H. Nair, G.A. Keck and H.F. Smyth, Jr. 1956. The toxicity of butyl Cellosolve solvent. *Arch. Ind. Health* 14: 114–131.
- Chapin, R.E. and J.C. Lamb. 1984. Effects of ethylene glycol monomethyl ether on various parameters of testicular function in the F344 rat. *Environ. Health Perspect.* 57: 219–224.
- Chapin, R.E., S.L. Dutton, M.D. Ross and J.C. Lamb. 1985a. Effects of ethylene glycol monomethyl ether (EGME) on mating performance and epididymal sperm parameters in F344 rats. *Fundam. Appl. Toxicol.* 5: 182–189.
- Chapin, R.E., S.L. Dutton, M.D. Ross, R.R. Swaisgood and J.C. Lamb IV. 1985b. The recovery of the testis over 8 weeks after short-term dosing with ethylene glycol monomethyl ether: histology, cell-specific enzymes, and rete testis fluid protein. *Fundam. Appl. Toxicol.* 5: 515–525.
- Chapin, R.E., R.E. Marissa, D.K. Galatea, E. Hope, L.H. Barnes, S.A. Russell and S.R. Kennedy. 1993. Are mouse strains differentially susceptible to the reproductive toxicity of ethylene glycol monomethyl ether? A study of three strains. *Fundam. Appl. Toxicol.* 21: 8–14.
- Chiewchanwit, T. and W.W. Au. 1994. Cytogenetic effects of 2-methoxyethanol and its metabolite, methoxyacetaldehyde, in mammalian cells *in vitro*. *Mutat. Res.* 320: 125–132.
- Chiewchanwit, T., H. Ma, R. El Zein, L. Hallberg and W.W. Au. 1995. Induction of deletion mutations by methoxyacetaldehyde in Chinese hamster ovary (CHO)-AS52 cells. *Mutat. Res.* 335: 121–128.
- Conor Pacific Environmental Technologies. 1998. A report on multimedia exposures to selected PSL2 substances. Prepared on contract for Health Canada (Project No. 741-6705).
- Cook, R.R., K.M. Bodner, R.C. Kolesar, C.S. Uhlmann, P.F.D. VanPeenen, G.S. Dickson and K. Flanagan. 1982. A cross-sectional study of ethylene glycol monomethyl ether process employees. *Arch. Environ. Health* 37: 346–351.

- Creasy, D.M., J.C. Flynn, T.J.B. Gray and W.H. Butler. 1985. A quantitative study of stage-specific spermatocyte damage following administration of ethylene glycol monomethyl ether in the rat. *Exp. Mol. Pathol.* 43: 321–336.
- Davis, J.B., J.L. Almekinder, N. Flagler, G. Travlos, R. Wilson and R.R. Maronpot. 1997. Ovarian luteal cell toxicity of ethylene glycol monomethyl ether and methoxy acetic acid *in vivo* and *in vitro*. *Toxicol. Appl. Pharmacol.* 142: 328–337.
- Dawson, G.W., A.L. Jennings, D. Drozdowski and E. Rider. 1977. The acute toxicity of 47 industrial chemicals to fresh and saltwater fishes. *J. Hazard. Mater.* 1: 303–318.
- De Bortoli, M., H. Knöppel, E. Pecchio, A. Peil, L. Rogora, H. Schauenburg, H. Schlitt and H. Vissers. 1986. Concentrations of selected organic pollutants in indoor and outdoor air in Northern Italy. *Environ. Int.* 12: 343–350.
- Denkhaus, W., D.V. Steldern, U. Botzenhardt and H. Konietzko. 1986. Lymphocyte subpopulations in solvent-exposed workers. *Int. Arch. Occup. Environ. Health* 57: 109–115.
- Devillers, J. and D. Chessel. 1995. Can the enucleated rabbit eye test be a suitable alternative for the *in vivo* eye test? A chemometrical response. *Toxicol. Model.* 1: 21–34.
- DMER (Don Mackay Environmental Research) and AEL (Angus Environmental Limited). 1996. Pathways analysis using fugacity modelling of 2-methoxyethanol for the second Priority Substances List. Report prepared for Chemicals Evaluation Division, Commercial Chemicals Evaluation Branch, Environment Canada, by DMER, Peterborough, Ontario, and AEL, Don Mills, Ontario. March 1996.
- Doe, J.E., D.M. Samuels, D.J. Tinston and G.A. de S. Wickramaratne. 1983. Comparative aspects of the reproductive toxicology by inhalation in rats of ethylene glycol monomethyl ether and propylene glycol monomethyl ether. *Toxicol. Appl. Pharmacol.* 69: 43–47.
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals). 1995. The toxicology of glycol ethers and its relevance to man. Brussels, Belgium. 350 pp. (ECETOC Technical Report No. 64).
- EHD (Environmental Health Directorate). 1998. Exposure factors for assessing total daily intake of Priority Substances by the general population of Canada. Ottawa, Ontario. Draft, March 1998.
- Elias, Z., M.C. Daniere, A.M. Marande, O. Poirot, F. Terzetti and O. Schneider. 1996. Genotoxic and/or epigenetic effects of some glycol ethers: results of different short-term tests. *Occup. Hyg.* 2: 187–212.
- Environment Canada. 1997a. Environmental assessments of Priority Substances under the *Canadian Environmental Protection Act*. Guidance manual version 1.0 — March 1997. Chemicals Evaluation Division, Commercial Chemicals Evaluation Branch, Hull, Quebec (EPS 2/CC/3E).
- Environment Canada. 1997b. Results of the CEPA Section 16 Notice respecting the second Priority Substances List and di(2-ethylhexyl) phthalate. Use Patterns Section, Commercial Chemicals Evaluation Branch, Hull, Quebec.
- Environment Canada. 1997c. Notice respecting the second Priority Substances List and di(2-ethylhexyl) phthalate. *Canada Gazette*, Part I, February 15, 1997. pp. 366–368.
- Environment Canada. 1999. *Canadian Environmental Protection Act* — Priority Substances List supporting document for the environmental assessment of 2-methoxyethanol, 2-ethoxyethanol, 2-butoxyethanol. Commercial Chemicals Evaluation Branch, Hull, Quebec.



- Environment Canada and Health Canada. 2000. Publication after assessment of a substance — 2-methoxyethanol, 2-ethoxyethanol, 2-butoxyethanol — specified on the Priority Substances List (Subsection 77(1) of the *Canadian Environmental Protection Act, 1999*). *Canada Gazette*, Part I, August 19, 2000. pp. 2622–2626.
- Exon, J.H., G.G. Mather, J.L. Bussiere, D.P. Olson and P.A. Talcott. 1991. Effects of subchronic exposure of rats to 2-methoxyethanol or 2-butoxyethanol: thymic atrophy and immunotoxicity. *Fundam. Appl. Toxicol.* 16: 830–840.
- Fairhurst, S., R. Knight, T.C. Marrs, J.W. Scawin, M.S. Spurlock and D.W. Swanston. 1989. Percutaneous toxicity of ethylene glycol monomethyl ether and of dipropylene glycol monomethyl ether in the rat. *Toxicology* 57: 209–215.
- Feuston, M.H., K.R. Bodnar, S.L. Kerstetter, C.P. Grink, M.J. Belcak and J. Singer. 1989. Reproductive toxicity of 2-methoxyethanol applied dermally to occluded and nonoccluded sites in male rats. *Toxicol. Appl. Pharmacol.* 100: 145–161.
- Feuston, M.H., S.L. Kerstetter and P.D. Wilson. 1990. Teratogenicity of 2-methoxyethanol applied as a single dermal dose to rats. *Fundam. Appl. Toxicol.* 15: 448–456.
- Flick, E.W. 1986. Household and automotive cleaners and polishes. 3rd edition. Noyes Publications, Park Ridge, New Jersey.
- Flick, E.W. 1989. Advanced cleaning product formulations: household, industrial, automotive. Vol. 1. Noyes Publications, Park Ridge, New Jersey.
- Foote, R.H., P.B. Farrel, D.H. Schlafer, M.M. McArdle, V. Trouern-Trend, M.E. Simkin, C.C. Brockett, J.R. Giles and J. Li. 1995. Ethylene glycol monomethyl ether effects on health and reproduction in male rabbits. *Reprod. Toxicol.* 9(6): 527–539.
- Foster, P.M.D., D.M. Creasy, J.R. Foster, L.V. Thomas, M.W. Cook and S.D. Gangolli. 1983. Testicular toxicity of ethylene glycol monomethyl and monoethyl ethers in the rat. *Toxicol. Appl. Pharmacol.* 69: 385–399.
- Foster, P.M.D., D.M. Creasy, J.R. Foster and T.J.B. Gray. 1984. Testicular toxicity produced by ethylene glycol monomethyl and monoethyl ethers in the rat. *Environ. Health Perspect.* 57: 207–217.
- Ghanayem, B.I. and R.E. Chapin. 1990. Calcium channel blockers protect against ethylene glycol monomethyl ether (2-methoxyethanol)-induced testicular toxicity. *Exp. Mol. Pathol.* 52: 279–290.
- Goldberg, M.E., C. Haun and H.F. Smyth, Jr. 1962. Toxicologic implication of altered behavior induced by an industrial vapor. *Toxicol. Appl. Pharmacol.* 4: 148–164.
- Grant, D., S. Sulsh, H.B. Jones, S.D. Gangolli and W.H. Butler. 1985. Acute toxicity and recovery in the hemopoietic system of rats after treatment with ethylene glycol monomethyl and monobutyl ethers. *Toxicol. Appl. Pharmacol.* 77: 187–200.
- Greenburg, L., M.R. Mayers, L.J. Goldwater, W.J. Burke and S. Moskowitz. 1938. Health hazards in the manufacture of “fused collars.” I. Exposure to ethylene glycol monomethyl ether. *J. Ind. Hyg. Toxicol.* 20: 134–147.
- Groeseneken, D., H. Veulemans, R. Masschelein and E. Van Vlem. 1989. Experimental human exposure to ethylene glycol monomethyl ether. *Int. Arch. Occup. Environ. Health* 61: 243–247.



- Gulati, D.K., E. Hope, L.H. Barnes, L. Hommell, S. Russell and K.B. Poonacha. 1990a. Reproductive toxicity of ethylene glycol monomethyl ether (CAS No. 109-86-4) in Sprague-Dawley rats, litter two, 1-76. Environmental Health Research and Testing Inc. Unpublished report (NTIS-PB 90-252313) [cited in ECETOC, 1995].
- Gulati, D.K., E. Hope, K.L. Christman, L.H. Barnes and S. Russell. 1990b. Reproductive toxicity of ethylene glycol monomethyl ether (CAS No. 109-86-4) in Sprague-Dawley rats, litter two, 1-72. Environmental Health Research and Testing Inc. Unpublished report (NTIS-PB 90-252321) [cited in ECETOC, 1995].
- Hanley, T.R., Jr., J.T. Young, J.A. John and K.S. Rao. 1984a. Ethylene glycol monomethyl ether (EGME) and propylene glycol monomethyl ether (PGME): Inhalation fertility and teratogenicity studies in rats, mice and rabbits. *Environ. Health Perspect.* 77: 7-12.
- Hanley, T.R., Jr., B.L. Yano, K.D. Nitschke and J.A. John. 1984b. Comparison of the teratogenic potential of inhaled ethylene glycol monomethyl ether in rats, mice, and rabbits. *Toxicol. Appl. Pharmacol.* 75: 409-422.
- Hansch, C. and A.J. Leo. 1985. Medchem project. Issue No. 26. Pomona College, Claremont, California.
- Harada, T. and Y. Nagashima. 1975. Utilization of alkyl ether compounds by soil bacteria. *J. Ferment. Technol.* 53: 218-222.
- Health Canada. 1994. *Canadian Environmental Protection Act* — Human health risk assessment for Priority Substances. Canada Communication Group, Ottawa, Ontario.
- Health Canada. 1998a. Glycol ethers in consumer products. Personal communication from P. Chowhan, Product Safety Bureau, Ottawa, Ontario.
- Health Canada. 1998b. Glycol ethers in therapeutic products. Personal communication from S. Kealey, Drugs Directorate, Ottawa, Ontario.
- Health Canada. 1998c. Glycol ethers in cosmetic products. Personal communication from C. Denman, Health Protection Branch, Ottawa, Ontario.
- Health Canada. 1998d. Glycol ethers in pesticides. Personal communication from V. Bergeron, Pest Management Regulatory Agency, Ottawa, Ontario.
- Health Canada. 1999. Datasheets for recent studies on 2-methoxyethanol. Priority Substances Section, Ottawa, Ontario.
- Hellwig, J. 1993. Study of the prenatal toxicity of 2-methoxyethanol in rats after dermal application. Unpublished report. Abstract Toxicologie. BASF AG, Ludwigshafen, Germany (No. OR53/89002) [cited in ECETOC, 1995].
- Hobson, D.W., A.P. D'Addario, R.H. Bruner and D.E. Uddin. 1986. A subchronic dermal exposure study of diethylene glycol monomethyl ether and ethylene glycol monomethyl ether in the male guinea pig. *Fundam. Appl. Toxicol.* 6: 339-348.
- Hoflack, J.C., L. Lambolez, Z. Elias and P. Vasseur. 1995. Mutagenicity of ethylene glycol ethers and of their metabolites in *Salmonella typhimurium* his<sup>-</sup>. *Mutat. Res.* 341: 281-287.





- Holladay, S.D., C.E. Comment, J. Kwon and M.I. Luster. 1994. Fetal hematopoietic alterations after maternal exposure to ethylene glycol monomethyl ether: prolymphoid cell targeting. *Toxicol. Appl. Pharmacol.* 129: 53–60.
- Holloway, A.J., H.D.M. Moore and P.M.D. Foster. 1990. The use of rat *in vitro* fertilization to detect reductions in the fertility of spermatozoa from males exposed to ethylene glycol monomethyl ether. *Reprod. Toxicol.* 4: 21–27.
- Hong, H.L., J. Canipe, C.W. Jameson and G.A. Boorman. 1988. Comparative effects of ethylene glycol and ethylene glycol monomethyl ether exposure on hematopoiesis and histopathology in B6C3F1 mice. *J. Environ. Pathol. Toxicol. Oncol.* 8(7): 27–38.
- House, R.V., L.D. Lauer, M.J. Murray, E.C. Ward and J.H. Dean. 1985. Immunological studies in B6C3F1 mice following exposure to ethylene glycol monomethyl ether and its principal metabolite methoxyacetic acid. *Toxicol. Appl. Pharmacol.* 77: 358–362.
- Howard, P.H. 1990. Handbook of environmental fate and exposure data for organic chemicals. Vol. II. Solvents. Lewis Publishers Inc., Chelsea, Michigan.
- Howard, P.H., R.S. Boethling, W.F. Jarvis, W.M. Meylan and E.M. Michalenko. 1991. Handbook of environmental degradation rates. Lewis Publishers Inc., Chelsea, Michigan.
- Jacobs, G.A. 1992. Eye irritation tests on two ethylene glycol ethers. *J. Am. Coll. Toxicol.* 11: 738.
- Jacobs, G., M. Martens and G. Mosselmans. 1987. Proposal of limit concentrations for skin irritation within the context of a new EEC directive on the classification and labelling of preparations. *Regul. Toxicol. Pharmacol.* 7: 370–378.
- Jacobs, G.A., A. Castellazzi and P.J. Dierickx. 1989. Evaluation of a non-invasive human and an *in vitro* cytotoxicity method as alternatives to the skin irritation test on rabbits. *Contact Dermatitis* 21: 239–244.
- Johanson, G. and U. Rick. 1996. Use and use patterns of glycol ethers in Sweden. *Occup. Hyg.* 2: 105–110.
- Kane, D.M. 1993. Evaluation of CHEMCAN2 — a fugacity-based multimedia exposure model used to predict the environmental fate of organic chemicals in Canada. Draft report, January 14, 1993. 28 pp.
- Kawai, F. 1995. Bacterial degradation of glycol ethers. *Appl. Microbiol. Biotechnol.* 44: 532–538.
- Kawamoto, T., K. Matsuno, F. Kayama, M. Hirai, K. Arashidani, M. Yoshikawa and Y. Kodama. 1990. Acute oral toxicity of ethylene glycol monomethyl ether and diethylene glycol monomethyl ether. *Bull. Environ. Contam. Toxicol.* 44: 602–608.
- Kayama, F., U. Yamashita, T. Kawamoto and Y. Kodama. 1991. Selective depletion of immature thymocytes by oral administration of ethylene glycol monomethyl ether. *Int. J. Immunopharmacol.* 13(5): 531–540.
- Knöppel, H. and H. Schauenburg. 1989. Screening of household products for the emission of volatile organic compounds. *Environ. Int.* 15: 413–418.
- Ku, W.W., B.I. Ghanayem, R.E. Chapin and R.N. Wine. 1994. Comparison of the testicular effects of 2-methoxyethanol (ME) in rats and guinea pigs. *Exp. Mol. Pathol.* 61: 119–133.
- Ku, W.W., R.N. Wine, B.Y. Chae, B.I. Ghanayem and R.E. Chapin. 1995. Spermatoocyte toxicity of 2-methoxyethanol (ME) in rats and guinea pigs: evidence for the induction of apoptosis. *Toxicol. Appl. Pharmacol.* 134: 100–110.

- Lee, K.P. and L.A. Kinney. 1989. The ultrastructure and reversibility of testicular atrophy induced by ethylene glycol monomethyl ether (EGME) in the rat. *Toxicol. Pathol.* 17(4) (Part 2): 759–773.
- Lee, K.P., L.A. Kinney and R. Valentine. 1989. Comparative testicular toxicity of bis(2-methoxyethyl) ether and 2-methoxyethanol in rats. *Toxicology* 59: 239–258.
- Loveday, K.S., B.E. Anderson, M.A. Resnick and E. Zeiger. 1990. Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells *in vitro*. V: Results with 46 chemicals. *Environ. Mol. Mutagen.* 16: 272–303.
- Lucas, S.V. 1984. GC/MS analysis of organics in drinking water concentrates and advanced waste treatment concentrates. Vol. 2. Computer-printed tabulations of compound identification results for large-volume concentrates. Health Effects Research Laboratory, Research Triangle Park, North Carolina (EPA-600/1-84-020b).
- Lyman, W.J., W.F. Reehl and D.H. Rosenblatt. 1982. Handbook on chemical property estimation methods. Environmental behavior of organic compounds. McGraw-Hill, New York, N.Y.
- Ma, H., J. An, A.W. Hsie and W.W. Au. 1993. Mutagenicity and cytotoxicity of 2-methoxyethanol and its metabolites in Chinese hamster cells (the CHO/HPRT and AS52/GPT assays). *Mutat. Res.* 298: 219–225.
- McGregor, D.B. 1984. Genotoxicity of glycol ethers. *Environ. Health Perspect.* 57: 97–103.
- McGregor, D.B., M.J. Willins, P. McDonald, M. Holmström, D. McDonald and R.W. Niemeier. 1983. Genetic effects of 2-methoxyethanol and bis(2-methoxyethyl)ether. *Toxicol. Appl. Pharmacol.* 70: 303–316.
- Medinsky, M.A., G. Singh, W.E. Bechtold, J.A. Bond, P.J. Sabourin, L.S. Birnbaum and R.F. Henderson. 1990. Disposition of three glycol ethers administered in drinking water to male F344/N rats. *Toxicol. Appl. Pharmacol.* 102: 443–455.
- Meek, M.E., R. Newhook, R.G. Liteplo and V.C. Armstrong. 1994. Approach to assessment of risk to human health for Priority Substances under the *Canadian Environmental Protection Act*. *Environ. Carcinogen. Ecotoxicol. Rev.* C12(2): 105–134.
- Miller, R.R., J.A. Ayres, L.L. Calhoun, J.T. Young and M.J. McKenna. 1981. Comparative short-term inhalation toxicity of ethylene glycol monomethyl ether and propylene glycol monomethyl ether in rats and mice. *Toxicol. Appl. Pharmacol.* 61: 368–377.
- Miller, R.R., J.A. Ayres, J.T. Young and M.J. McKenna. 1983. Ethylene glycol monomethyl ether. I. Subchronic vapor inhalation study with rats and rabbits. *Fundam. Appl. Toxicol.* 3: 49–54.
- Ministers' Expert Advisory Panel. 1995. Report of the Ministers' Expert Advisory Panel on the second Priority Substances List under the *Canadian Environmental Protection Act* (CEPA). Government of Canada, Ottawa, Ontario. 26 pp.
- Nagano, K., E. Nakayama, M. Koyano, H. Oobayashi, H. Adachi and T. Yamada. 1979. Testicular atrophy of mice induced by ethylene glycol mono alkyl ethers. *Jpn. J. Ind. Health* 21: 29–35 (in Japanese, with English abstract and tables).
- Nagano, K., E. Nakayama, H. Oobayashi, T. Yamada, H. Adachi, T. Nishizawa, H. Ozawa, M. Nakaichi, H. Okuda, K. Minami and K. Yamazaki. 1981. Embryotoxic effects of ethylene glycol monomethyl ether in mice. *Toxicology* 20: 335–343.



- Nagano, K., E. Nakayama, M. Koyano, H. Oobayashi, T. Nishizawa, H. Okuda and K. Yamazaki. 1984. Experimental studies on toxicity of ethylene glycol alkyl ethers in Japan. *Environ. Health Perspect.* 57: 75–84.
- Nelson, B.K., J.V. Setzer, W.S. Brightwell, P.R. Mathinos, M.H. Kuczuk, T.E. Weaver and P.T. Goad. 1984a. Comparative inhalation teratogenicity of four glycol ether solvents and an amino derivative in rats. *Environ. Health Perspect.* 57: 261–271.
- Nelson, B.K., W.S. Brightwell, J.R. Burg and V.J. Massari. 1984b. Behavioral and neurochemical alterations in the offspring of rats after maternal or paternal inhalation exposure to the industrial solvent 2-methoxyethanol. *Pharmacol. Biochem. Behav.* 20: 269–279.
- Nelson, B.K., C.V. Vorhees, W.J. Scott and L. Hastings. 1989. Effects of 2-methoxyethanol on fetal development, postnatal behavior, and embryonic intracellular pH of rats. *Neurotoxicol. Teratol.* 11: 273–284.
- Nelson, B.K., D.L. Conover, W.S. Brightwell, P.B. Shaw, D. Werren, R.M. Edwards and J.M. Lary. 1991. Marked increase in the teratogenicity of the combined administration of the industrial solvent 2-methoxyethanol and radiation in rats. *Teratology* 43: 621–634.
- NPRI (National Pollutant Release Inventory). 1996. Summary report 1994. *Canadian Environmental Protection Act*. Environment Canada, Ottawa, Ontario. 240 pp.
- NPRI (National Pollutant Release Inventory). 1998. *Canadian Environmental Protection Act*. Environment Canada, Ottawa, Ontario ([www2.ec.gc.ca/pdb/npri/](http://www2.ec.gc.ca/pdb/npri/)).
- NTP (National Toxicology Program). 1993. NTP technical report on toxicity studies of ethylene glycol ethers 2-methoxyethanol, 2-ethoxyethanol, 2-butoxyethanol (CAS Nos. 109-86-4, 110-80-5, 111-76-2) administered in drinking water to F344/N rats and B6C3F<sub>1</sub> mice. U.S. Department of Health and Human Services. 122 pp. + appendices. (NTP Toxicity Report Series No. 26; NIH Publication No. 93-3349).
- Ohi, G. and D.H. Wegman. 1978. Transcutaneous ethylene glycol monomethyl ether poisoning in the work setting. *J. Occup. Med.* 20: 675–676.
- Rachamin, G., R. Kusiak, L. Wong and S. Guirguis. 1996. Exposure to glycol ethers in Ontario workplaces. Health and Safety Studies Unit, Occupational Health and Safety Branch, Ontario Ministry of Labour, January 1996.
- Rao, K.S., S.R. Cobel-Geard, J.T. Young, T.R. Hanley, Jr., W.C. Hayes, J.A. John and R.R. Miller. 1983. Ethylene glycol monomethyl ether II. Reproductive and dominant lethal studies in rats. *Fundam. Appl. Toxicol.* 3: 80–85.
- Reader, S.C.J., C. Shingles and M.D. Stonard. 1991. Acute testicular toxicity of 1,3-dinitrobenzene and ethylene glycol monomethyl ether in the rat: Evaluation of biochemical effect markers and hormonal responses. *Fundam. Appl. Toxicol.* 16: 61–70.
- Riddick, J., W.B. Bunger and T.K. Sakano. 1986. *Organic solvents: physical properties and methods of purification*. 4th edition. John Wiley and Sons, New York, N.Y. 1325 pp.
- Riddle, M., W. Williams, D. Andrews, C. Copeland, R. Luebke and R. Smialowicz. 1992. Species and strain comparisons of immunosuppression by 2-methoxyethanol (ME) and 2-methoxyacetic acid (MAA). *Toxicologist* 12: 177 (abstract 632).

- Riddle, M.M., W.C. Williams and R.J. Smialowicz. 1996. Repeated high dose oral exposure or continuous subcutaneous infusion of 2-methoxyacetic acid does not suppress humoral immunity in the mouse. *Toxicology* 109: 67–74.
- Ritter, E.J., W.J. Scott, Jr., J.L. Randall and J.M. Ritter. 1985. Teratogenicity of dimethoxyethyl phthalate and its metabolites methoxyethanol and methoxyacetic acid in the rat. *Teratology* 32: 25–31.
- Rogozen, M.B., H.E. Rich, M.A. Gutman and D. Grosjean. 1987. Evaluation of potential toxic air contaminants, Phase I. State of California Air Resources Board, Sacramento, California, December 23, 1987 (Final Report Contract A4-131-32).
- Samuels, D.M., J.E. Doe and D.J. Tinston. 1984. The effects on the rat testis of single inhalation exposures to ethylene glycol monoalkyl ethers, in particular ethylene glycol monomethyl ether. *Arch. Toxicol., Suppl.* 7: 167–170.
- Savolainen, H. 1980. Glial cell toxicity of ethyleneglycol monomethylether vapor. *Environ. Res.* 22: 423–430.
- Schenker, M.B. 1996. Reproductive health effects of glycol ether exposure in the semiconductor industry. *Occup. Hyg.* 2: 367–372.
- Schenker, M.B., E.B. Gold, J.J. Beaumont, B. Eskenazi, S.K. Hammond, B.L. Lasley, S.A. McCurdy, S.J. Samuels, C.L. Saiki and S.H. Swann. 1995. Association of spontaneous abortion and other reproductive effects with work in the semiconductor industry. *Am. J. Ind. Med.* 28: 639–659.
- Schriever, E. and R. Marutzky. 1990. VOC emissions of coated parqued floors. *In: Indoor Air '90. Proceedings of the 5th International Conference on Indoor Air Quality and Climate, July 29 – August 3,* 1990, Toronto, Ontario, Vol. 3. Canada Mortgage and Housing Corporation, Ottawa, Ontario. pp. 551–555.
- Scott, W.J., R. Fradkin, W. Wittfoht and H. Nau. 1989. Teratologic potential of 2-methoxyethanol and transplacental distribution of its metabolite, 2-methoxyacetic acid, in non-human primates. *Teratology* 39: 363–373.
- Sleet, R.B., J.A. Greene and F. Welsch. 1988. The relationship of embryotoxicity to disposition of 2-methoxyethanol in mice. *Toxicol. Appl. Pharmacol.* 93: 195–207.
- Sleet, R.B., F. Welsch, C.B. Myers and M.C. Marr. 1996. Developmental phase specificity and dose–response effects of 2-methoxyethanol in rats. *Fundam. Appl. Toxicol.* 29: 131–139.
- Smialowicz, R.J., M.M. Riddle, R.W. Luebke, C.B. Copeland, D. Andrews, R.R. Rogers, L.E. Gray and J.W. Laskey. 1991a. Immunotoxicity of 2-methoxyethanol following oral administration in Fischer 344 rats. *Toxicol. Appl. Pharmacol.* 109: 494–506.
- Smialowicz, R.J., M.M. Riddle, R.R. Rogers, C.B. Copeland, R.W. Luebke and D.L. Andrews. 1991b. Evaluation of the immunotoxicity of orally administered 2-methoxyacetic acid in Fischer 344 rats. *Fundam. Appl. Toxicol.* 17: 771–781.
- Smialowicz, R.J., W.C. Williams, M.M. Riddle, D.L. Andrews, R.W. Luebke and C.B. Copeland. 1992a. Comparative immunosuppression of various glycol ethers orally administered to Fischer 344 rats. *Fundam. Appl. Toxicol.* 18: 621–627.



- Smialowicz, R.J., M.M. Riddle, W.C. Williams, C.B. Copeland, R.W. Luebke and D.L. Andrews. 1992b. Differences between rats and mice in the immunosuppressive activity of 2-methoxyethanol and 2-methoxyacetic acid. *Toxicology* 74: 57–67.
- Smialowicz, R.J., M.M. Riddle and W.C. Williams. 1993. Methoxyacetaldehyde, an intermediate metabolite of 2-methoxyethanol, is immunosuppressive in the rat. *Fundam. Appl. Toxicol.* 21: 1–7.
- Smialowicz, R.J., M.M. Riddle and W.C. Williams. 1994. Species and strain comparisons of immunosuppression by 2-methoxyethanol and 2-methoxyacetic acid. *Int. J. Immunopharmacol.* 16(8): 695–702.
- Smyth, H.F., Jr., J. Seaton and L. Fischer. 1941. The single dose toxicity of some glycols and derivatives. *J. Ind. Hyg. Toxicol.* 23: 259–268.
- Stemmler, K., W. Mengon, D.J. Kinnison and J.A. Kerr. 1997. OH radical-initiated oxidation of 2-butoxyethanol under laboratory conditions related to the troposphere: product studies and proposed mechanism. *Environ. Sci. Technol.* 31: 1496–1504.
- Swan, S.H. and W. Forest. 1996. Reproductive risks of glycol ethers and other agents used in semiconductor manufacturing. *Occup. Hyg.* 2: 373–385.
- Swan, S.H., J.J. Beaumont, S.K. Hammond, J. VonBehren, R.S. Green, M.F. Hallock, S.R. Woskie, C.J. Hines and M.B. Schenker. 1995. Historical cohort study of spontaneous abortion among fabrication workers in the semiconductor health study: agent-level analysis. *Am. J. Ind. Med.* 28: 751–769.
- Timbrell, J.A., R.P. Draper, M. Butterworth and D.M. Creasy. 1996. Detection of testicular toxicity of 2-methoxyethanol using urinary creatine. *Occup. Hyg.* 2: 153–160.
- Toraason, M. and M. Breitenstein. 1988. Prenatal ethylene glycol monomethyl ether (EGME) exposure produces electrocardiographic changes in the rat. *Toxicol. Appl. Pharmacol.* 95: 321–327.
- Toraason, M., B. Stringer, P. Stober and B.D. Hardin. 1985. Electrocardiographic study of rat fetuses exposed to ethylene glycol monomethyl ether (EGME). *Teratology* 32: 33–39.
- Toraason, M., M.J. Breitenstein and R.J. Smith. 1986a. Ethylene glycol monomethyl ether (EGME) inhibits rat embryo ornithine decarboxylase (ODC) activity. *Drug Chem. Toxicol.* 9: 191–203.
- Toraason, M., R.W. Niemeier and B.D. Hardin. 1986b. Calcium homeostasis in pregnant rats treated with ethylene glycol monomethyl ether (EGME). *Toxicol. Appl. Pharmacol.* 86: 197–203.
- Toraason, M., B. Stringer and R. Smith. 1986c. Ornithine decarboxylase activity in the neonatal rat heart following prenatal exposure to ethylene glycol monomethyl ether. *Drug Chem. Toxicol.* 9(1): 1–14.
- U.S. EPA (United States Environmental Protection Agency). 1986. Health and environmental effects profile for 2-methoxyethanol. Environmental Criteria and Assessment Office, Cincinnati, Ohio (EPA/600/x-87/025; NTIS PB89-119531).
- U.S. EPA (United States Environmental Protection Agency). 1992. Initial submission: Letter from Eastman Kodak Co. to Office of Toxic Substances regarding toxicity studies of nine glycol ethers with attachments and cover letter dated 092892 (Doc #88-920008915; NTIS/OTS0570960).



- U.S. EPA (United States Environmental Protection Agency). 1997. Exposure factors handbook. Vol. III: Activity factors. Office of Research and Development, National Center for Environmental Assessment, Washington, D.C., August 1997 (EPA/600/P-95/002Fc).
- Vachhrajani, K.D. and K.K. Dutta. 1992. Stage specific effect during one seminiferous epithelial cycle following ethylene glycol monomethyl ether exposure in rats. *Ind. J. Exp. Biol.* 30: 892–896.
- Van Leeuwen, C.J., P.T.J. Van Der Zandt, T. Aldenberg, H.J.M. Verhaar and J.L.M. Hermens. 1992. Application of QSARs, extrapolation and equilibrium partitioning in 2-methoxyethanol effects assessment. I. Narcotic industrial pollutants. *Environ. Toxicol. Chem.* 11: 267–282.
- Versar Inc. 1986. Standard scenarios for estimating exposure to chemical substances during use of consumer products. Vol. 1. Prepared for Exposure Evaluation Division, Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, D.C. (EPA Contract No. 68-02-3968, dated September 1986).
- Villalobos-Pietrini, R., S. Gómez-Arroyo, M. Altamirano-Lozano, P. Orozco and P. Ríos. 1989. Cytogenetic effects of some cellosolves. *Rev. Int. Contam. Ambient.* 5: 41–48.
- Welch, L.S. and M.R. Cullen. 1988. Effect of exposure to ethylene glycol ethers on shipyard painters: III. Hematologic effects. *Am. J. Ind. Med.* 14: 527–536.
- Welch, L.S., S.M. Schrader, T.W. Turner and M.R. Cullen. 1988. Effects of exposure to ethylene glycol ethers on shipyard painters: II. Male reproduction. *Am. J. Ind. Med.* 14: 509–526.
- Welsch, F. and R.B. Sleet. 1987. Metabolism and disposition of a teratogenic dose of 2-methoxyethanol (ME) in pregnant CD-1 mice. *Teratology* 36: 16A.
- Whittaker, S.G., F.K. Zimmermann, B. Dicus, W.W. Piegorsch, S. Fogel and M.A. Resnick. 1989. Detection of induced mitotic chromosome loss in *Saccharomyces cerevisiae* — an interlaboratory study. *Mutat. Res.* 224: 31–78.
- WHO (World Health Organization). 1990. 2-Methoxyethanol, 2-ethoxyethanol, and their acetates. International Programme on Chemical Safety, Geneva, Switzerland. 126 pp. (IPCS Environmental Health Criteria 115).
- Wickramaratne, G.A. de S. 1986. The teratogenic potential and dose–response of dermally administered ethylene glycol monomethyl ether (EGME) estimated in rats with the Chernoff-Kavlock assay. *J. Appl. Toxicol.* 6: 165–166.
- Williams, W.C., M.M. Riddle, C.B. Copeland, D.L. Andrews and R.J. Smialowicz. 1995. Immunological effects of 2-methoxyethanol administered dermally or orally to Fischer 344 rats. *Toxicology* 98: 215–223.
- Zavon, M.R. 1963. Methyl cellosolve intoxication. *Am. Ind. Hyg. Assoc. J.* 24: 36–41.
- Zeiger, E., B. Anderson, S. Haworth, T. Lawlor and K. Mortelmans. 1992. *Salmonella* mutagenicity tests: V. Results from the testing of 311 chemicals. *Environ. Mol. Mutagen.* 19 (Suppl. 21): 2–141.



Zimmermann, F.K., V.W. Mayer, I. Scheel and M.A. Resnick. 1985. Acetone, methyl ethyl ketone, ethyl acetate, acetonitrile and other polar aprotic solvents are strong inducers of aneuploidy in *Saccharomyces cerevisiae*. *Mutat. Res.* 149: 339–351.

Zissu, D. 1995. Experimental study of cutaneous tolerance to glycol ethers. *Contact Dermatitis* 32: 74–77.



# APPENDIX A SEARCH STRATEGIES EMPLOYED FOR IDENTIFICATION OF RELEVANT DATA

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## Environmental assessment

Data relevant to the assessment of whether 2-methoxyethanol is “toxic” to the environment under CEPA 1999 were identified from existing review documents, published reference texts and on-line searches, conducted between January and May 1996, of the following databases: ASFA (Aquatic Sciences and Fisheries Abstracts, Cambridge Scientific Abstracts; 1990–1996), BIOSIS (Biosciences Information Services; 1990–1996), CAB (Commonwealth Agriculture Bureaux; 1990–1996), CESARS (Chemical Evaluation Search and Retrieval System, Ontario Ministry of the Environment and Michigan Department of Natural Resources; 1996), CHRIS (Chemical Hazard Release Information System; 1964–1985), Current Contents (Institute for Scientific Information; 1993 – January 15, 1996), ELIAS (Environmental Library Integrated Automated System, Environment Canada library; January 1996), Enviroline (R.R. Bowker Publishing Co.; November 1995 – June 1996), Environmental Abstracts (1975 – February 1996), Environmental Bibliography (Environmental Studies Institute, International Academy at Santa Barbara; 1990–1996), GEOREF (Geo Reference Information System, American Geological Institute; 1990–1996), HSDB (Hazardous Substances Data Bank, U.S. National Library of Medicine; 1996), Life Sciences (Cambridge Scientific Abstracts; 1990–1996), NTIS (National Technical Information Service, U.S. Department of Commerce; 1990–1996), Pollution Abstracts (Cambridge Scientific Abstracts, U.S. National Library of Medicine; 1990–1996), POLTOX (Cambridge Scientific Abstracts, U.S. National Library of Medicine; 1990–1995), RTECS (Registry of Toxic Effects of Chemical Substances, U.S. National Institute for Occupational Safety and Health; 1996), Toxline

(U.S. National Library of Medicine; 1990–1996), TRI93 (Toxic Chemical Release Inventory, U.S. Environmental Protection Agency, Office of Toxic Substances; 1993), USEPA-ASTER (Assessment Tools for the Evaluation of Risk, U.S. Environmental Protection Agency; up to December 21, 1994), WASTEINFO (Waste Management Information Bureau of the American Energy Agency; 1973 – September 1995) and Water Resources Abstracts (U.S. Geological Survey, U.S. Department of the Interior; 1990–1996). Reveal Alert was used to maintain an ongoing record of the current scientific literature pertaining to the potential environmental effects of 2-methoxyethanol. Data obtained after September 30, 1999, were not considered in this assessment unless they were critical data received during the 60-day public review of the report (August 19 to October 18, 2000).

In addition, a survey of Canadian industry was carried out under the authority of Section 16 of CEPA (Environment Canada, 1997b, 1997c). Targeted companies with commercial activities involving more than 1000 kg of 2-methoxyethanol were required to supply information on uses, releases, environmental concentrations, effects or other data that were available to them for 2-methoxyethanol.

## Health assessment

In addition to studies included in the review prepared by BIBRA International, recent data have been identified through searching the following databases beginning in August 1996 using the chemical name or the CAS number for both 2-methoxyethanol and 2-methoxyethyl acetate: CAB Abstracts, Canadian Research Index, DIALOG (Cancerlit, Environmental Bibliography, Waternet, Water Resources





Abstracts, Enviroline, Pollution Abstracts and NTIS), Food Science and Technology Abstracts, Medline, Toxline Plus and TOXNET (CCRIS [Chemical Carcinogenesis Research Information System, U.S. National Cancer Institute], GENE-TOX [Genetic Toxicology, U.S. Environmental Protection Agency] and EMIC [Environmental Mutagen Information Center database, Oak Ridge National Laboratory]). Data acquired as of October 1999 were considered for inclusion in this assessment.

As well as these databases, officials at the Product Safety Bureau and Drugs Directorate of Health Canada, along with the Pest Management Regulatory Agency, were contacted to obtain information relevant to this assessment.

