

*Canadian Environmental  
Protection Act, 1999*



**PRIORITY SUBSTANCES LIST ASSESSMENT REPORT**



**2-Ethoxyethanol**

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*Canadian Environmental Protection Act, 1999*

## **PRIORITY SUBSTANCES LIST ASSESSMENT REPORT**

### **2-Ethoxyethanol**

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>
CTV	Critical Toxicity Value
EAA	ethoxyacetic acid
EALD	ethoxyacetaldehyde
EEV	Estimated Exposure Value
ENEV	Estimated No-Effects Value
GWP	Global Warming Potential
HC <sub>5</sub>	hazardous concentration for 5% of test species
IC <sub>50</sub>	inhibitory concentration for 50% of test species
K <sub>oc</sub>	soil sorption coefficient
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
LOAEL	Lowest-Observed-Adverse-Effect Level
LOEL	Lowest-Observed-Effect Level
NOAEL	No-Observed-Adverse-Effect Level
NOEL	No-Observed-Effect Level
NO <sub>x</sub>	nitrogen oxides
NPRI	National Pollutant Release Inventory
ODP	Ozone Depletion Potential
POCP	Photochemical Ozone Creation Potential
PSL	Priority Substances List



# SYNOPSIS

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2-Ethoxyethanol is not commercially produced in Canada. It is imported for use mainly as a component of formulated products. All environmental releases are reported to be to the atmosphere. Some 2-ethoxyethanol is also sent to landfills and other waste disposal sites.

2-Ethoxyethanol reacts with hydroxyl radicals in the air with a half-life of about 0.2–4 days. Much of the 2-ethoxyethanol released to the atmosphere is predicted to remain in air, but a substantial proportion would partition to water and to soil. 2-Ethoxyethanol 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-Ethoxyethanol 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-ethoxyethanol in the environment in Canada or elsewhere.

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

Exposure values for air were based on limited Canadian monitoring data. Because of the paucity of environmental monitoring data, exposure values for soil and water were estimated based on fugacity modelling. Estimated environmental concentrations of 2-ethoxyethanol are several orders of magnitude lower than the adverse effects thresholds calculated for sensitive organisms.

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

2-Ethoxyethanol has consistently induced hematological, reproductive (effects on testes and sperm parameters) and developmental effects in multiple species of experimental animals exposed by various routes. In addition, there is some limited evidence of effects on the blood and reduced sperm production in occupationally exposed human populations. Although monitoring data are very limited, the margins between upper-bounding estimates of exposure to 2-ethoxyethanol in the general environment and conservative effect levels for critical effects are large. Limited available data do not indicate that 2-ethoxyethanol is commonly present in consumer products in Canada. However, upper-bounding estimates of exposure to 2-ethoxyethanol based on uncertain data on composition of some consumer products which may contain the substance may approach or exceed these conservative effect levels, although the degree of confidence in these estimates of exposure is considered to be extremely low.

**Based on these considerations, it is concluded that 2-ethoxyethanol 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. Based on comparison of upper-bounding estimates of exposure in the general environment with conservative effect levels, it is concluded that 2-ethoxyethanol is not entering the general 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-ethoxyethanol is not considered to be “toxic” as defined in Section 64 of the *Canadian Environmental Protection Act* (CEPA, 1999).**



Although 2-ethoxyethanol was not detected in emissions from a range of consumer products in Canada, acquisition of additional more representative information on its use in consumer products in Canada is desirable.





# 1.0 INTRODUCTION

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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-ethoxyethanol (along with 2-methoxyethanol 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 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-ethoxyethanol is “toxic” under Paragraphs 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-ethoxyethanol is necessarily restricted because of the extremely limited data upon which to base estimates of population exposure. Therefore, a screening approach has been adopted for assessment of whether or not the substance would be considered “toxic” under Paragraph 64(c). Available information relevant to characterization of health hazards was critically evaluated to ascertain critical effects; lowest effect levels for

these effects from studies in experimental animals or exposed human populations 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, including environmental media and consumer products, estimated on the basis of the limited available Canadian data. On this basis, areas where additional information may be required to ensure that current measures are sufficiently protective have been identified.

Data relevant to assessment of population exposure and potential effects on human health were identified on the basis of a review prepared in 1996 by BIBRA Toxicology International as well as through literature searches, the strategies for which are described in Appendix A (prior to January 2000). All original studies that form the basis for determining whether 2-ethoxyethanol is “toxic” under Paragraph 64(c) of CEPA 1999 have been critically evaluated by staff of Health Canada.

Sections of the Assessment Report related to the environmental assessment of 2-ethoxyethanol 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 C. Staples of Assessment Technologies Inc.

Sections of the Assessment Report related to human health and the background supporting documentation were prepared by the following staff of Health Canada:

K. Hughes  
M.E. Meek  
L. Turner

Comments on the adequacy of data coverage in the sections of the supporting documentation related to health effects were provided in a written review by J.B. Knaak of Oxychem (retired).

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

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 comments received, the Assessment Report was revised as appropriate. A summary of the comments and responses is available on the Internet at:

[www.ec.gc.ca/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:

Existing Substances 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-Ethoxyethanol, one of the class of substances referred to as glycol ethers, has the empirical molecular formula  $C_4H_{10}O_2$ , the structural formula  $CH_3CH_2OCH_2CH_2OH$  and a molecular weight of 90.12. Its Chemical Abstracts Service (CAS) registry number is 110-80-5. 2-Ethoxyethanol is a colourless liquid with an estimated water solubility of 300 000 mg/L<sup>2</sup> (DMER and AEL, 1996), a log octanol/water partition coefficient ( $K_{ow}$ ) of -0.32 (Hansch *et al.*, 1995), a vapour pressure of 710 Pa (Riddick *et al.*, 1986) and a calculated Henry's law constant of 0.213 Pa·m<sup>3</sup>/mol (DMER and AEL, 1996).

Synonyms for 2-ethoxyethanol include 2-ethoxy-1-ethanol, ethylene glycol monoethyl ether and ethyl Cellosolve.

### 2.2 Entry characterization

#### 2.2.1 Production, importation and uses

2-Ethoxyethanol was not produced in Canada in 1995 or 1996, according to data reported to Environment Canada by 14 companies in a survey carried out under the authority of Section 16 of the *Canadian Environmental Protection Act, 1988* (CEPA) (Environment Canada, 1997b). According to these data, importation of 2-ethoxyethanol totalled 4.7 kilotonnes in 1995 and 3.0 kilotonnes in 1996. There was no export of 2-ethoxyethanol in 1995, and 2.3 tonnes were exported in 1996.

2-Ethoxyethanol has been used in paints, coatings, inks, cleaners, polishes, brake fluids and jet fuels and has been widely used as a solvent, chemical intermediate and solvent coupler of mixtures and water-based formulations (Stemmler *et al.*, 1997). Data reported to Environment Canada in the survey conducted under the authority of Section 16 of CEPA indicated that 68.2 and 42.8 tonnes of 2-ethoxyethanol were used in Canada in 1995 and 1996, respectively, mainly as a component of formulated products (Environment Canada, 1997b). 2-Ethoxyethanol is present as a minor ingredient (<1.25%) in 26 Canadian registered pest control products (wood preservatives) (Ballantine, 1997; Health Canada, 1998a).

#### 2.2.2 Sources and releases

##### 2.2.2.1 Natural sources

2-Ethoxyethanol has not been reported to occur as a natural product (U.S. EPA, 1986; WHO, 1990). There are no known reactions that would lead to the *in situ* production of glycol ethers in the atmosphere (Rogozen *et al.*, 1987).

##### 2.2.2.2 Anthropogenic sources

Total on-site environmental releases of 2-ethoxyethanol reported to the National Pollutant Release Inventory (NPRI) in 1994 amounted to 2.36 tonnes. Most of this (at least 81%) was released into the atmosphere from four facilities (producing plastics and synthetic resins, paint and varnish, petroleum products and printing ink) in Quebec (NPRI, 2000). (Facilities with more than

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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.

<sup>2</sup> This estimated value was based on reported values for structurally similar or homologous compounds (DMER and AEL, 1996).



10 full-time staff and that use or manufacture more than 10 tonnes of substances on the NPRI are required by law to report to Environment Canada.)

In 1995, total on-site environmental releases of 2-ethoxyethanol reported to the NPRI amounted to 8.1 tonnes (NPRI, 2000). Almost all of this was released into the atmosphere as emissions from storage from one facility (plastics manufacturing) in Ontario.

In 1996, total on-site environmental releases of 2-ethoxyethanol were 0.20 tonnes, released about equally from two facilities (producing motor vehicle stampings and industrial and household chemicals) in Ontario and Quebec (NPRI, 2000).

Releases reported to date for 1997 totalled 9.32 tonnes, from two printing ink industries in Ontario and Quebec (NPRI, 2000).

According to data reported under the CEPA Section 16 survey (with different reporting requirements from the NPRI), 5.8 tonnes of 2-ethoxyethanol were released to landfills in 1996, while 3.9 tonnes were released as waste and 0.9 tonnes were released to air from several facilities in Ontario and Quebec (Environment Canada, 1997b). (Industries surveyed by Environment Canada with commercial activities involving more than 1000 kg of 2-ethoxyethanol were required to supply data on uses and releases and other relevant information.)

The Canadian Chemical Producers' Association (1999a) reported total environmental emissions of 2-ethoxyethanol of 0.3, 0.015, 0.015 and 0.013 tonnes from member companies in 1992, 1993, 1994 and 1995, respectively, all of which were released to air by a single company. Reported emissions fell to 0 tonnes in 1996 (Canadian Chemical Producers' Association, 1999a), totalled 0.003 tonnes in 1997 and returned to 0 tonnes in 1998 (Canadian Chemical Producers' Association, 1999b).

## 2.3 Exposure characterization

### 2.3.1 Environmental fate

#### 2.3.1.1 Air

An atmospheric half-life of 9.8 hours was determined in a smog chamber with irradiation at a 2-ethoxyethanol:NO<sub>x</sub> ratio of 2:1 (Joshi *et al.*, 1982). A half-life of about 4 days was calculated for the reaction of 2-ethoxyethanol with atmospheric hydroxyl radicals, assuming an ambient concentration of hydroxyl radicals of 10<sup>6</sup> molecules/cm<sup>3</sup> (U.S. EPA, 1985). This calculation was based on the rate constant in water of 1 × 10<sup>9</sup> L/mol per second (Anbar and Neta, 1967), converted to a gas-phase reaction by the method of Guesten *et al.* (1981). Howard *et al.* (1991) estimated a half-life of 2-ethoxyethanol in air of 5.35–53.5 hours, based on reaction with hydroxyl radicals.

#### 2.3.1.2 Water

Howard *et al.* (1991) estimated half-lives of 2-ethoxyethanol of 168–672 hours and 336–1344 hours in surface water and groundwater, respectively, based on unacclimated aerobic biodegradation.

#### 2.3.1.3 Soils

A soil sorption coefficient (K<sub>oc</sub>) of 113 was calculated for 2-ethoxyethanol using the method of Sabljic (1984), indicating moderate mobility in soil (U.S. EPA, 1985). Retention values for 2-ethoxyethanol of 21 New Zealand and Fijian soils ranged from 8 to 178 mg/g; these values were well correlated with the cation exchange capacity and a number of measures of moisture content of these soils (Churchman and Burke, 1991).

There is little information available on the biodegradation of 2-ethoxyethanol in soil. Howard *et al.* (1991) estimated a half-life of 2-ethoxyethanol in soil of 168–672 hours, based on unacclimated aerobic biodegradation.



2-Ethoxyethanol underwent biooxidation to 2-ethoxyacetic acid (EAA) by the soil bacterium, *Alcaligenes* MC11, for which 2-ethoxyethanol was 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-ethoxyethanol as a source of carbon for aerobic growth (Kawai, 1995).

#### 2.3.1.4 Biota

A bioconcentration factor (BCF) of 0.5 was estimated for 2-ethoxyethanol, based on a log  $K_{ow}$  of  $-0.10$  and using the equation proposed by Lyman *et al.* (1982) (i.e.,  $\log BCF = 0.76 \log K_{ow} - 0.23$ ) (U.S. EPA, 1985). Bioaccumulation of 2-ethoxyethanol in aquatic organisms would therefore not be significant.

#### 2.3.1.5 Environmental distribution

Because of the high water solubility of 2-ethoxyethanol and its low log  $K_{ow}$ , physical adsorption to suspended solids and sediments should not be significant (U.S. EPA, 1985).

The environmental partitioning of 2-ethoxyethanol 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, 90.1 g/mol; vapour pressure, 710 Pa; water solubility, 300 000 mg/L; log  $K_{ow}$ ,  $-0.32$ ; Henry's law constant, 0.213 Pa·m<sup>3</sup>/mol; half-life<sup>3</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-ethoxyethanol is emitted into air, EQC (Equilibrium Criterion)

Level III fugacity 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-ethoxyethanol is emitted into water, more than 99% would be present in water. If 2-ethoxyethanol 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

Few data on levels of 2-ethoxyethanol in the environment have been identified for Canada or elsewhere. One study was conducted to determine concentrations of 2-ethoxyethanol in multiple media in Canada 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-ethoxyethanol in specific media are presented in the subsequent sections where identified.

##### 2.3.2.1 Multimedia exposure study

In a multimedia exposure study, exposure to a number of volatile organic chemicals was measured for 50 participants across Canada in 1997 (Conor Pacific Environmental Technologies, 1998). Thirty-five participants were randomly selected from the Greater Toronto area in Ontario, six from Queens Subdivision in Nova Scotia and nine from Edmonton, Alberta. For each participant, samples of drinking water, beverages and indoor, outdoor and personal air were collected over a 24-hour period; however, samples of food were not analysed for 2-ethoxyethanol. While confidence in the results of this survey was low (see Section 3.3.4), the concentration of 2-ethoxyethanol was below the method detection limit (0.05 µg/L) in all samples of drinking water.

<sup>3</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-ethoxyethanol 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.



Similarly, it was not detected (detection limit  $3.6 \mu\text{g}/\text{m}^3$ ) in any samples of indoor, outdoor or personal air. 2-Ethoxyethanol was not detected in composite beverage samples (method detection limit  $3.3 \mu\text{g}/\text{L}$ ).

#### 2.3.2.2 Ambient air

In the Windsor Air Quality Study, the concentrations of 2-ethoxyethanol in 24 samples of ambient air collected in the vicinity of an automotive plant and 7 samples in downtown Windsor (OMEE, 1994) were measured. Concentrations of 2-ethoxyethanol were less than the limit of detection ( $0.81 \mu\text{g}/\text{m}^3$ ) in all the samples collected in downtown Windsor. Of the 24 samples collected at the automotive plant, concentrations of 2-ethoxyethanol were above the limits of detection (which ranged from  $0.18$  to  $0.34 \mu\text{g}/\text{m}^3$ ) in 16 (over 66%); the mean value for these samples was  $0.43 \mu\text{g}/\text{m}^3$  when concentrations in samples where 2-ethoxyethanol was not detected were assumed to be equivalent to one-half the limit of detection (maximum  $0.86 \mu\text{g}/\text{m}^3$ ). The authors stated that the probable source of 2-ethoxyethanol in ambient air samples downwind of the plant was from paints and lacquers in which 2-ethoxyethanol is used as a solvent. In all of the samples from downtown Windsor or in the vicinity of the automotive plant, concentrations of 2-ethoxyethyl acetate, the acetate moiety of 2-ethoxyethanol, were below the limits of detection (range  $0.55$ – $2.9 \mu\text{g}/\text{m}^3$ ).

2-Ethoxyethanol was not detected in samples of ambient air collected at six locations in the United States in 1984–1985 (limit of detection  $0.25 \mu\text{g}/\text{m}^3$ ) (Sheldon *et al.*, 1988).

#### 2.3.2.3 Indoor air

In northern Italy, six indoor air samples collected from homes in 1983–1984 contained

2-ethoxyethanol concentrations of up to  $60 \mu\text{g}/\text{m}^3$  (De Bortoli *et al.*, 1986). 2-Ethoxyethanol was detected at concentrations of up to  $18.3 \mu\text{g}/\text{m}^3$  in indoor air samples collected in new buildings (hospital, office, nursing home) in the United States. In older buildings (office, nursing home, school), concentrations were lower (i.e., up to  $4.15 \mu\text{g}/\text{m}^3$ ) (Sheldon *et al.*, 1988).

#### 2.3.2.4 Surface water

Samples of water from a polluted river in Japan contained 250–1200  $\mu\text{g}$  2-ethoxyethanol/L (Yasuhara *et al.*, 1981).

#### 2.3.2.5 Consumer products

Limited available recent data do not indicate that 2-ethoxyethanol or its acetate<sup>4</sup> are commonly present in consumer products in Canada, although such applications are not regulated (Health Canada, 1998b). 2-Ethoxyethanol was not detected in the emissions of 13 consumer products, including window cleaners, all-purpose cleaners, paints, nail polish removers and hair dye, purchased in the Ottawa, Ontario, area (Cao, 1999). (These products were selected on the basis of other data presented here that suggested that 2-ethoxyethanol was present in similar products.) Glycol ethers, including 2-ethoxyethanol, are not registered for use as an active ingredient in therapeutic products used in Canada (Health Canada, 1998c). Of the cosmetic products registered for use in Canada, one nail polish contained 2-ethoxyethanol in the range of >0.3-1%, while 2-ethoxyethyl acetate was present in an eye makeup product and skin moisturizer at >30 to 100% and >1 to 3%, respectively (Health Canada Cosmetic Notification System, 2001). (The *Food and Drugs Act* stipulates that manufacturers and importers of new cosmetic products are required to notify Health Canada concerning the ingredients.) 2-Ethoxyethanol is a

<sup>4</sup> The acetate moiety of 2-ethoxyethanol, 2-ethoxyethyl acetate, is often used in consumer product formulations. Since the acetate is rapidly converted to the parent 2-ethoxyethanol in the body, data on the presence of the acetate in consumer products are considered relevant to estimation of population exposure to 2-ethoxyethanol.



component in 26 wood preservatives registered for use in Canada (<1.25%) (Ballantine, 1997; Health Canada, 1998a).

Earlier in the United States, concentrations of 2-ethoxyethanol of up to 5% were reported in various consumer products, including hard surface cleaners and windshield washing fluid (Flick, 1986). However, in a more recent listing of ingredients in “advanced” cleaning product formulations, none of the products contained 2-ethoxyethanol or 2-ethoxyethyl acetate (Flick, 1994). (These data were submitted voluntarily by numerous companies and other organizations and may not represent a comprehensive list of formulations of consumer products available in the United States.) Additional data on emissions of 2-ethoxyethanol and its acetate from several consumer products tested in the United States prior to 1990 are presented in Table 1 (although no information was provided in the secondary account regarding the number of products examined). A European patent application for hair dye lists a 2-ethoxyethanol concentration of 12% (Cotteret, 1995). According to the 1993 Products Register in Sweden (reporting of the composition of products manufactured or imported in Sweden is mandatory), 2-ethoxyethanol and its acetate were ingredients in 137 and 170 products, totalling 105–242 and 172–270 tonnes/year, respectively, of pure substance (Johanson and Rick, 1996).

#### 2.3.2.6 Fugacity modelling

Environmental concentrations of 2-ethoxyethanol were estimated by ChemCAN4 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 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-ethoxyethanol in Canada is 8 tonnes/year, released into the air by one facility in southern Ontario in 1995 (NPRI, 1998). “Ontario – Mixed Wood Plain” was therefore selected as the

geographic region for ChemCAN modelling of 2-ethoxyethanol. The input rate was 0.913 kg 2-ethoxyethanol/hour, all to the atmosphere. Chemical input values were as follows: molecular weight, 90.1 g/mol; vapour pressure, 710 Pa; water solubility, 300 000 mg/L; log  $K_{ow}$ , -0.32; Henry’s law constant, 0.213 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>; percentage 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-ethoxyethanol in southern Ontario predicted by ChemCAN4 modelling are as follows:  $6.9 \times 10^{-2}$  ng/m<sup>3</sup> in air;  $2.2 \times 10^{-5}$  µg/L in water;  $4.15 \times 10^{-4}$  ng/g dry weight in soil; and  $1.05 \times 10^{-5}$  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-ethoxyethanol on wildlife was identified. Data for experimental animals pertinent to the human health assessment are presented in Section 2.4.3. From the results of inhalation studies presented in this section, the species that were most sensitive to airborne 2-ethoxyethanol were rats and rabbits. Developmental effects (skeletal variations) were induced in rats exposed to 2-ethoxyethanol at a concentration of 50 ppm (184 mg/m<sup>3</sup>) for 10 days (Doe, 1984). Developmental toxicity (reduced mean number of implantations and number





**TABLE 1** Emissions of 2-ethoxyethanol and its acetate from consumer products in the United States

Product category	Number of products with detectable emissions <sup>1</sup>	Amount emitted (µg/g product)	Source
Cleaning compounds	4 (as 2-ethoxyethanol)	na <sup>2</sup>	Clinical Toxicology of Commercial Products database (CARB, 1991)
Spot/stain remover	1 (as 2-ethoxyethanol)	na	Clinical Toxicology of Commercial Products database (CARB, 1991)
Window/glass cleaner	2 (as 2-ethoxyethanol)	na	Clinical Toxicology of Commercial Products database (CARB, 1991)
Rug/upholstery cleaner	3 (as 2-ethoxyethanol)	na	Clinical Toxicology of Commercial Products database (CARB, 1991)
Coatings/inks	10 (as 2-ethoxyethanol) 4 (as 2-ethoxyethyl acetate)	na	Clinical Toxicology of Commercial Products database (CARB, 1991)
Coating thinners/strippers	6 (as 2-ethoxyethanol) 1 (as 2-ethoxyethyl acetate)	na	Clinical Toxicology of Commercial Products database (CARB, 1991)
Herbicide and fungicide	1 (as 2-ethoxyethanol)	na	Clinical Toxicology of Commercial Products database (CARB, 1991)
Medical/personal hygiene	1 (as 2-ethoxyethanol)	na	Clinical Toxicology of Commercial Products database (CARB, 1991)
Adhesives	3 (as 2-ethoxyethanol) 5 (as 2-ethoxyethyl acetate)	0.1–200 0.1–900	NASA/McDonnell Douglas Materials Testing Data Base (CARB, 1991)
Coatings	14 (as 2-ethoxyethanol) 66 (as 2-ethoxyethyl acetate)	0.09–450 0.05–1578	NASA/McDonnell Douglas Materials Testing Data Base (CARB, 1991)
Fabric	1 (as 2-ethoxyethanol) 3 (as 2-ethoxyethyl acetate)	0.23 0.07–0.7	NASA/McDonnell Douglas Materials Testing Data Base (CARB, 1991)
Pens/inks	6 (as 2-ethoxyethanol) 5 (as 2-ethoxyethyl acetate)	0.1–2800 0.49–4.3	NASA/McDonnell Douglas Materials Testing Data Base (CARB, 1991)
Foam/plastic products	2 (as 2-ethoxyethyl acetate)	0.095–0.7	NASA/McDonnell Douglas Materials Testing Data Base (CARB, 1991)

<sup>1</sup> No information on the number of products tested was provided in the secondary account of these studies (CARB, 1991).<sup>2</sup> na = not available.

of live fetuses) was also observed in Dutch rabbits exposed to 2-ethoxyethanol in air at a concentration of 50 ppm (184 mg/m<sup>3</sup>) (Tinston, 1983a).

#### 2.4.1.2 Aquatic organisms

Data on chronic toxicity have been identified only for protozoans, algae and hydra. The most sensitive organisms were microbial populations in waste stabilization ponds, with approximately a 40% inhibition of respirometric activity (i.e., changes in total organic carbon, chemical oxygen demand and 2-ethoxyethanol concentration) at 1 000 000 µg/L in a 5-day study (Davis *et al.*, 1989). Data on acute toxicity have been reported for invertebrates and fish, although in many studies the LC<sub>50</sub> for 2-ethoxyethanol 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). Hermens *et al.* (1984) reported a 48-hour IC<sub>50</sub> of 7 660 000 µg/L for *Daphnia magna*.

#### 2.4.2 Abiotic atmospheric effects

Worst-case calculations were made to determine if 2-ethoxyethanol 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-ethoxyethanol is not a halogenated compound.

The Photochemical Ozone Creation Potential (POCP) was estimated to be 73 (relative to the reference compound ethene, which has a POCP of 100), based on the following formula:

$$\text{POCP} = (k_{2\text{-ethoxyethanol}}/k_{\text{ethene}}) \times (M_{\text{ethene}}/M_{2\text{-ethoxyethanol}}) \times 100$$

where:

- $k_{2\text{-ethoxyethanol}}$  is the rate constant for the reaction of 2-ethoxyethanol with OH radicals ( $2.0 \times 10^{-11}$  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
- $M_{2\text{-ethoxyethanol}}$  is the molecular weight of 2-ethoxyethanol (90 g/mol).

The Global Warming Potential (GWP) was calculated to be  $5.1 \times 10^{-5}$  (relative to the reference compound CFC-11, which has a GWP of 1), based on the following formula:

$$\text{GWP} = (t_{2\text{-ethoxyethanol}}/t_{\text{CFC-11}}) \times (M_{\text{CFC-11}}/M_{2\text{-ethoxyethanol}}) \times (S_{2\text{-ethoxyethanol}}/S_{\text{CFC-11}})$$

where:

- $t_{2\text{-ethoxyethanol}}$  is the lifetime of 2-ethoxyethanol (0.002 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),
- $M_{2\text{-ethoxyethanol}}$  is the molecular weight of 2-ethoxyethanol (90 g/mol),
- $S_{2\text{-ethoxyethanol}}$  is the infrared absorption strength of 2-ethoxyethanol (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-ethoxyethanol does not contribute to stratospheric ozone depletion, its potential contribution to climate change is negligible and its potential contribution to ground-level ozone formation is moderate. The magnitude of these effects would depend on the concentration of 2-ethoxyethanol in the atmosphere, and concentrations of the substance in air in Canada are estimated to be very low. The contribution of 2-ethoxyethanol 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).



### 2.4.3 *Experimental animals and in vitro*

In view of the limited objective of this assessment relative to dose–response (i.e., characterization of lowest effect levels only for critical effects), presentation of data on health effects associated with 2-ethoxyethanol 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.

#### 2.4.3.1 Kinetics and metabolism

2-Ethoxyethanol is rapidly absorbed in humans and experimental animals exposed via ingestion, inhalation or dermal contact. In humans and laboratory animals, 2-ethoxyethanol is oxidized via alcohol dehydrogenases to the intermediate ethoxyacetaldehyde (EALD) and then rapidly converted via aldehyde dehydrogenases to EAA, the principal and putatively active metabolite, which is eliminated primarily in the urine. In rats, EAA may be conjugated with glycine or be *O*-deethylated and then further metabolized to carbon dioxide. A secondary pathway in rodents involves microsomal P450 mixed-function oxidases, with deethylation producing acetaldehyde and ethylene glycol.

Although little information is available regarding interspecies differences in the toxicokinetics and metabolism of 2-ethoxyethanol, there is some indication that humans may absorb the substance to a greater extent than do rats (the species most extensively investigated) (Groeseneken *et al.*, 1986, 1987). In addition, although relevant data are very limited, 2-ethoxyethanol may be converted to EAA at a greater rate in humans than in rats, with subsequent renal clearance of the metabolite being slower in humans (Groeseneken *et al.*, 1988); thus, the putatively active metabolite may be present in the blood of humans at higher levels and for longer durations than in rats.

The acetate moiety of 2-ethoxyethanol, 2-ethoxyethyl acetate, which is commonly used in occupational and residential environments, is rapidly hydrolysed to 2-ethoxyethanol via esterases in several tissues in the body (Stott and McKenna, 1985). (For this reason, data on the toxicity of 2-ethoxyethyl acetate have been included in this assessment.)

#### 2.4.3.2 Acute toxicity

2-Ethoxyethanol is of low to moderate acute toxicity in experimental animals following oral exposure, with reported LD<sub>50</sub>s in various species ranging from 1400 to 5490 mg/kg-bw (Laug *et al.*, 1939; Smyth *et al.*, 1941; Carpenter, 1947; Carpenter *et al.*, 1956; Stenger *et al.*, 1971; Truhaut *et al.*, 1979; Krasavage and Terhaar, 1981; Dow Chemical Company, unpublished data, cited in Clayton and Clayton, 1982; Cheever *et al.*, 1984). However, it is considered to be of low toxicity only following inhalation or dermal exposure, with LC<sub>50</sub>s (7 or 8 hours) in rats and mice of 1500–2000 ppm (5520–7360 mg/m<sup>3</sup>) (Werner *et al.*, 1943a; Pozzani *et al.*, 1959; Shell, unpublished data, cited in Tyl *et al.*, 1988) and dermal LD<sub>50</sub>s of 3314–3930 mg/kg-bw (covered application for 24 hours) in rabbits (Carpenter *et al.*, 1956; Krasavage and Terhaar, 1981; Daughtrey *et al.*, 1984). Target sites of 2-ethoxyethanol-induced acute toxicity include the hematopoietic system, liver, kidneys and stomach. 2-Ethoxyethanol and its acetate did not induce skin sensitization and have only low potential for irritation of skin and eyes (Werner *et al.*, 1943b; Carpenter and Smyth, 1946; Truhaut *et al.*, 1979; Krasavage and Terhaar, 1981; Barbee *et al.*, 1984; Daughtrey *et al.*, 1984; Kennah *et al.*, 1989; Zissu, 1995).

#### 2.4.3.3 Short-term toxicity

##### 2.4.3.3.1 Oral

Based on the few short-term oral studies available, the testes appear to be sensitive target organs in rats, mice and dogs, with histopathological effects (degeneration or atrophy)

and/or decreased weights being observed in rats, mice and dogs following repeated doses of 2-ethoxyethanol as low as 919 mg/kg-bw per day (in drinking water), 1000 mg/kg-bw per day (by gavage) and 186 mg/kg-bw per day (in capsules), respectively (Stenger *et al.*, 1971; Nagano *et al.*, 1979, 1984; NTP, 1993). 2-Ethoxyethyl acetate induced similar effects in the testes at gavage doses of 1000 mg/kg-bw per day or more in mice (Nagano *et al.*, 1979, 1984). Reductions in relative thymus weights were also observed in rats administered 357 mg/kg-bw per day or more in drinking water (i.e., doses lower than those that induced testicular effects); no effects on the thymus were observed in mice exposed to much higher doses (NTP, 1993). Hematological effects, consisting of reduced white blood cell counts and packed cell volume, were also observed in mice exposed to 2000 mg/kg-bw per day or more of 2-ethoxyethanol or the acetate by gavage (Nagano *et al.*, 1979, 1984). In the only other short-term oral study in which hematological parameters were investigated, there were slight dose-related decreases in hemoglobin and hematocrit levels in dogs administered 50–200 µL/kg-bw per day (46–186 mg/kg-bw per day) of 2-ethoxyethanol in gelatin capsules for 13 weeks (significance not reported) (Stenger *et al.*, 1971).

#### 2.4.3.3.2 Inhalation

Available data on the toxicity of 2-ethoxyethanol or 2-ethoxyethyl acetate following short-term exposure via inhalation are limited to studies designed primarily to investigate developmental toxicity and two early limited studies in small groups of dogs. Doe (1984) reported changes in red blood cell parameters in pregnant rats exposed to 250 ppm (920 mg/m<sup>3</sup>) 2-ethoxyethanol for 10 days, while no effects on the blood were observed at 50 ppm (184 mg/m<sup>3</sup>). Similarly, alterations in hematological parameters (red blood cells, white blood cells and platelets) were observed in pregnant rats exposed to 100 ppm or more of 2-ethoxyethyl acetate (equivalent to 368 mg 2-ethoxyethanol/m<sup>3</sup>) (Tyl *et al.*, 1988). In studies in rabbits, no effects on the blood were noted in pregnant females exposed to up to 175 ppm

(644 mg/m<sup>3</sup>) 2-ethoxyethanol, while a reduction in hemoglobin concentration was observed only following exposure to the highest concentration of 2-ethoxyethyl acetate tested (i.e., 400 ppm, equivalent to 1473 mg 2-ethoxyethanol/m<sup>3</sup>) (Doe, 1984).

Alterations in hematological parameters characteristic of anemia (i.e., effects on red blood cells) and an increase in calcium oxalate crystals in the urine were observed in dogs exposed to 840 ppm (3091 mg/m<sup>3</sup>) 2-ethoxyethanol vapour for 12 weeks (Werner, 1943b), although no such effects were noted in dogs exposed to 600 ppm 2-ethoxyethyl acetate vapour (equivalent to 2210 mg 2-ethoxyethanol/m<sup>3</sup>) for 6 months (Carpenter, 1947). No histopathological changes were observed in the limited range of organs examined in either study.

#### 2.4.3.4 Subchronic toxicity

##### 2.4.3.4.1 Oral

In the identified subchronic studies in which rats were administered 2-ethoxyethanol by the oral route, the critical targets were the male reproductive organs and the blood. Testicular degeneration was observed in the testes of male F344/N rats administered 2-ethoxyethanol in drinking water for 13 weeks at concentrations equivalent to doses of 400 mg/kg-bw per day or more, while atrophy of the prostate gland was observed at doses of 205 mg/kg-bw per day or more; the severity of these lesions increased with dose. Concentrations of spermatogonia and sperm were also significantly lower in rats administered 205 mg/kg-bw per day or more of 2-ethoxyethanol. In males, signs of mild anemia (reduced red blood cell count and hemoglobin concentration), which was characterized as macrocytic (increased mean cell volume), hypochromic (decreased mean cell hemoglobin concentration) and poorly regenerative, were observed at 792 mg/kg-bw per day and above as early as 1 week after initiation of exposure. The severity of the anemia increased with duration of exposure and was described as



marked to moderate after 3 and 13 weeks. Mild thrombocytopenia and leukopenia were also present in males exposed to 400 mg/kg-bw per day or more after 1 week of exposure; however, the thrombocytopenia appeared to be reversible, based on the lack of significant reduction in platelet count, while leukopenia was judged to be moderate after 13 weeks. Female rats also exhibited mild anemia (again characterized as macrocytic, hypochromic and poorly regenerative) after 1 week of exposure to 2-ethoxyethanol, with some parameters being affected at doses as low as 247 mg/kg-bw per day, as well as moderate to marked thrombocytopenia and moderate leukopenia. After 3 and 13 weeks of exposure, the severity of the anemia was considered to have progressed to moderate and was accompanied by moderate thrombocytopenia and marked leukopenia, which progressed to marked leukocytosis. Increased hematopoiesis and hemosiderin pigmentation of the spleen and liver were also noted, but were considered secondary to hematological effects. Alterations in clinical chemistry parameters indicative of general toxicity or liver dysfunction were noted in males and females at  $\geq 205$  and  $\geq 466$  mg/kg-bw per day, respectively. Based on effects on the thymus, testes, prostate gland and blood, the authors (NTP, 1993) considered the Lowest-Observed-Adverse-Effect Level (LOAEL) in male rats to be 205 mg/kg-bw per day (with a No-Observed-Adverse-Effect Level [NOAEL] of 109 mg/kg-bw per day). The authors considered the NOAEL in female rats to be 466 mg/kg-bw per day; however, in view of the observation of thrombocytopenia at all doses, 122 mg/kg-bw per day could be considered to be the Lowest-Observed-Effect Level (LOEL) in females (although the effect on platelet count appeared to have ameliorated somewhat at this exposure level), with numerous other parameters being significantly different from controls at the next dose.

A similar profile of effects was observed in other subchronic oral studies in different strains of rats. Hematological effects consistent with anemia as well as alterations in white blood cell parameters were observed in rats (strain

CR, COBS, CD, BR) administered 900 mg/kg-bw per day of 2-ethoxyethanol by gavage for 6 weeks (Krasavage and Vlaovic, 1982). Reduced hemoglobin and hematocrit were also reported in Wistar rats exposed for 13 weeks to 2-ethoxyethanol by gavage (100  $\mu$ L/kg-bw per day [93 mg/kg-bw per day] for 59 days followed by exposure to 400  $\mu$ L/kg-bw per day [372 mg/kg-bw per day] for 30 days) (Stenger *et al.*, 1971). Hemosiderin pigmentation was noted in the spleen of both strains of rats, with the lowest effect level being 186 mg/kg-bw per day in Wistar rats. Effects on male reproductive organs (including reduced testicular weights, atrophy and degeneration) and on sperm parameters (degenerated spermatozoa and hypospermia) were also observed in these strains of rats at doses of 450 mg/kg-bw per day (the lowest dose tested) and above for 6 weeks (Krasavage and Vlaovic, 1982) or 200  $\mu$ L/kg-bw per day (186 mg/kg-bw per day) and above for 13 weeks, but not at 100  $\mu$ L/kg-bw per day (93 mg/kg-bw per day) (considered to be the No-Observed-Effect Level [NOEL]) (Stenger *et al.*, 1971). Histopathological changes in the stomach and bone marrow were also noted at 450 mg/kg-bw per day or higher (Krasavage and Vlaovic, 1982).

Data on the effects in mice following subchronic oral exposure to 2-ethoxyethanol are limited to a single study in which B6C3F<sub>1</sub> mice were exposed via drinking water for 13 weeks (NTP, 1993). Based on the results of this study, mice appear to be less sensitive than rats to 2-ethoxyethanol-induced toxic effects. As in rats, the male reproductive system was a target organ in mice, with effects on weight and histopathology of testes observed at 5123 mg/kg-bw per day and above and 7284 mg/kg-bw per day, respectively, while effects on sperm parameters were noted at 5123 mg/kg-bw per day or more. In addition, effects on the estrous cycle were observed in females exposed to 1304 mg/kg-bw per day and above. Although hematological parameters were not examined in mice, hematopoiesis of the spleen was noted at the highest dose in males and



at 7255 mg/kg-bw per day and above in females. The incidence of a rather rare lesion, hypertrophy of the X-zone of the adrenal gland, resulting from marked lipid vacuolization, was significantly increased in female mice administered 2725 mg/kg-bw per day or more (and non-significantly increased at 1304 mg/kg-bw per day); this lesion was not observed in any of the subchronic oral studies in rats. Based on this study, the LOELs in male and female mice are considered to be 5123 and 1304 mg/kg-bw per day, with NOELs of 2003 and 722 mg/kg-bw per day, respectively.

#### 2.4.3.4.2 Inhalation

Identified information on the subchronic toxicity of inhaled 2-ethoxyethanol and its acetate is limited to earlier studies in rats and rabbits. Exposure to 25 ppm (92 mg/m<sup>3</sup>) 2-ethoxyethanol or more for 13 weeks was irritating to the eyes and nose of Sprague-Dawley rats. However, no exposure-related lesions were observed in the extensive range of tissues examined at the highest concentration of 400 ppm (1472 mg/m<sup>3</sup>) (other exposure groups were not examined), and the only systemic effects noted were reductions in relative weights of the pituitary gland in males and the spleen in females exposed to 400 ppm (1472 mg/m<sup>3</sup>) and alterations in leukocyte count and blood urea nitrogen in female rats at the highest concentration (Barbee *et al.*, 1984). In male and female Wistar rats exposed to 200 ppm 2-ethoxyethyl acetate (approximately equivalent to 737 mg 2-ethoxyethanol/m<sup>3</sup>) for 10 months, no hematological effects were noted, and the only histopathological change observed was renal tubular nephritis in males, although only a limited range of tissues was examined (Truhaut *et al.*, 1979).

Exposure to airborne 2-ethoxyethanol (≥25 ppm [92 mg/m<sup>3</sup>]) was also irritating to the eyes and nose of rabbits. Reduced weight and degeneration of the testes were observed at 400 ppm (1472 mg/m<sup>3</sup>) (histopathological examinations do not appear to have been conducted in animals exposed to lower

concentrations), while anemia was present in both sexes at this concentration (Barbee *et al.*, 1984). As in rats, exposure to 200 ppm 2-ethoxyethyl acetate (equivalent to 737 mg 2-ethoxyethanol/m<sup>3</sup>) via inhalation resulted in renal tubular nephritis in males; no effects on reproductive organs or blood parameters were reported (Truhaut *et al.*, 1979).

#### 2.4.3.5 Chronic toxicity and carcinogenicity

Although a final version of the only relevant chronic study identified was never published (data analyses were never completed due to problems encountered with the laboratory conducting the study; Eastin, 2000), according to an early account of preliminary results, the testes were the principal target in both rats and mice orally exposed to 2-ethoxyethanol for 2 years (Melnick, 1984).

#### 2.4.3.6 Genotoxicity

The available information on the genotoxicity of 2-ethoxyethanol suggests that 2-ethoxyethanol may have some weak potential, at most, to induce cytogenetic damage, but there is no evidence that it induces mutations. Neither 2-ethoxyethanol nor its acetate was mutagenic in several *in vitro* assays in *Salmonella* (Ong, 1980; Shimizu *et al.*, 1985; Zeiger *et al.*, 1985; Guzzie *et al.*, 1986; Slesinski *et al.*, 1988; Hüls AG, 1989; Hoflack *et al.*, 1995) or in a limited number of studies in cultured mammalian cells (Guzzie *et al.*, 1986; Myhr *et al.*, 1986; Slesinski *et al.*, 1988). Mixed or equivocal results have been reported for the induction of chromosomal aberrations, micronuclei or sister chromatid exchange by 2-ethoxyethanol or 2-ethoxyethyl acetate in various mammalian cell lines (Guzzie *et al.*, 1986; Galloway *et al.*, 1987; Slesinski *et al.*, 1988; Villalobos-Pietrini *et al.*, 1989; Elias *et al.*, 1996). 2-Ethoxyethanol did not induce morphological transformation or aneuploidy *in vitro*, although it did show weak potential to interfere with mitotic division (Elias *et al.*, 1996). While neither of the two principal metabolites of 2-ethoxyethanol, EALD and EAA, was mutagenic in *Salmonella*



(Hoflack *et al.*, 1995), the acetaldehyde consistently tested positive for numerous cytogenetic endpoints *in vitro*, although results for the acetic acid metabolite were negative or equivocal (Elias *et al.*, 1996).

In the limited *in vivo* database, there was no evidence of the induction of micronuclei in the bone marrow of mice exposed to 2-ethoxyethanol, 2-ethoxyethyl acetate or EAA (Guzzie *et al.*, 1986; Slesinski *et al.*, 1988; Elias *et al.*, 1996).

#### 2.4.3.7 Developmental toxicity

##### 2.4.3.7.1 Oral

Although only limited information is available on the developmental effects of 2-ethoxyethanol following oral exposure, adverse effects, including increased implantation loss, resorptions and embryo mortality, decreased fetal body weight and various skeletal and cardiovascular abnormalities, were observed in multiple strains of rats, often in the absence of maternal toxicity (Stenger *et al.*, 1971; Goad and Cranmer, 1984; Chester *et al.*, 1986). In only one of the three limited accounts could a NOEL be determined (NOEL = 47 mg/kg-bw per day; LOEL = 94 mg/kg-bw per day) (Stenger *et al.*, 1971). Similar developmental effects were observed at doses lower than those that were maternally toxic in the only identified relevant study in mice; severe malformations (e.g., exencephaly) were observed at higher doses (Wier *et al.*, 1987). Although the doses investigated in mice were higher than those in rats, mice appear to be less sensitive than rats to the developmental toxicity of ingested 2-ethoxyethanol, as only reduced fetal body weight was observed at the lowest dose tested (i.e., 1000 mg/kg-bw per day), whereas increased abnormalities were noted in rats at much lower doses.

##### 2.4.3.7.2 Inhalation

The developmental toxicity of inhaled 2-ethoxyethanol and its acetate has been investigated in rats and rabbits. In many of

these studies, fetotoxic effects were observed in multiple strains at concentrations lower than those causing maternal toxicity. In Wistar-derived Alpk/AP rats, the lowest concentration of 2-ethoxyethanol reported to induce developmental effects (skeletal variations) in the absence of maternal toxicity was 50 ppm (184 mg/m<sup>3</sup>), with a NOEL of 10 ppm (37 mg/m<sup>3</sup>) (Doe, 1984). In Sprague-Dawley and Fischer 344 rats, exposure to 2-ethoxyethyl acetate during gestation also resulted in increased incidences of skeletal variations at the lowest concentrations tested (130 and 50 ppm, respectively, equivalent to 479 and 184 mg 2-ethoxyethanol/m<sup>3</sup>) (Nelson *et al.*, 1984; Tyl *et al.*, 1988).

Exposure to 2-ethoxyethanol during pregnancy also induced neurological effects in the developing young, based on behavioural differences, consistent with decreased neuromotor function, and alterations in levels of several neurochemicals (particularly in the cerebrum) observed in Sprague-Dawley rats exposed to 100 ppm (368 mg/m<sup>3</sup>; the lowest concentration tested) and above (Nelson *et al.*, 1981, 1982a,b).

In Dutch rabbits, Tinston (1983a) observed reduced mean number of implantations and number of live fetuses at 50 ppm (184 mg/m<sup>3</sup>) 2-ethoxyethanol (the lowest concentration investigated) or more, in the absence of maternal effects. Conversely, Doe (1984) reported no clear effects on these endpoints at concentrations up to 175 ppm (644 mg/m<sup>3</sup>); however, there were increased incidences of skeletal defects and variations at this exposure level, but not at lower concentrations (10 or 50 ppm [37 or 184 mg/m<sup>3</sup>]). Developmental effects (increased malformations, anomalies and skeletal variations) were also observed in fetuses of New Zealand white rabbits exposed to 160 ppm (589 mg/m<sup>3</sup>) 2-ethoxyethanol (the lowest concentration tested) during gestation; slight maternal toxicity was also present at this exposure level. 2-Ethoxyethyl acetate was also developmentally toxic in both these strains of rabbits, with a LOEL of 100 ppm (equivalent to 368 mg 2-ethoxyethanol/m<sup>3</sup>), although no effects were noted at lower



concentrations (25 or 50 ppm as the acetate, equivalent to 92 or 184 mg 2-ethoxyethanol/m<sup>3</sup>) (Tinston, 1983b; Doe, 1984; Tyl *et al.*, 1988).

#### 2.4.3.7.3 Dermal

Dermally applied 2-ethoxyethanol or its acetate induced developmental effects, including increased resorptions, reduced number of live fetuses per litter, decreased fetal body weights and increased incidence of visceral malformations (predominantly of the cardiovascular system) and skeletal variants, in Sprague-Dawley rats at all doses tested (i.e.,  $\geq 4000$  mg/kg-bw per day, a dose that was not or only slightly maternally toxic) (Hardin *et al.*, 1982, 1984).

#### 2.4.3.8 Reproductive toxicity

##### 2.4.3.8.1 Oral

The majority of the relevant studies identified have been conducted by the oral route in male rats or mice. Ingested 2-ethoxyethanol, as well as the acetate moiety and the acetic acid metabolite, consistently induced effects on male reproductive organs or sperm parameters in multiple strains of both species. Testicular and epididymal weights were reduced in Long-Evans, Sprague-Dawley, F344/N and CR,COBS,CD,BR rats administered doses of 200 mg/kg-bw per day or more by gavage in water or olive oil or in the drinking water for 4 weeks or longer (Krasavage and Vlaovic, 1982; Oudiz and Zenick, 1986; NTP, 1993; Chung *et al.*, 1999), but not in Long-Evans rats exposed to 150 mg/kg-bw per day by gavage in water for 6 weeks (Hurtt and Zenick, 1986) or Sprague-Dawley rats administered 250 mg/kg-bw per day by gavage in water for 11 days (Foster *et al.*, 1983) (although these effects were noted at greater doses in rats exposed for these durations). Histopathological effects on the testes and spermatocytes were noted following oral exposure to 450 mg/kg-bw per day (the lowest dose tested) or more for 6 weeks (Krasavage and Vlaovic, 1982). Reductions in testicular or epididymal sperm counts or alterations in sperm motility or morphology were noted at doses as low as 150 mg/kg-bw per day (the lowest dose tested)

when administered for 6 weeks or longer, with regularly mated males being more sensitive to these effects than non-mated rats (Hurtt and Zenick, 1986). Sperm counts were not assessed in the only study in which lower doses were investigated (i.e., Chung *et al.*, 1999) or in a shorter-term study (11 days) in rats administered 250 mg/kg-bw per day (Foster *et al.*, 1983), although spermatocyte degeneration was observed in the latter study only at 500 mg/kg-bw per day or more. Repeated oral administration of EAA, the predominant metabolite of 2-ethoxyethanol, induced a similar profile of male reproductive effects in rats (Foster *et al.*, 1983, 1987), suggesting that this metabolite may be, at least in part, responsible for these effects.

Reduction in testicular or epididymal weights or alterations in sperm parameters were also observed in mice orally exposed to 2-ethoxyethanol or 2-ethoxyethyl acetate for 5 weeks or longer (Nagano *et al.*, 1979, 1984; Morrissey *et al.*, 1989; NTP, 1993; Chapin and Sloane, 1997), although this species appears to be less sensitive than rats, as the lowest dose associated with male reproductive effects in mice was 1000 mg/kg-bw per day (with a NOEL of 500 mg/kg-bw per day).

Although not as extensively investigated as in males, exposure to 2-ethoxyethanol in the drinking water for 13 weeks induced effects on the estrous cycle in female rats and mice at doses of 804 and 1304 mg/kg-bw per day or more, respectively, with uterine atrophy occurring in rats at higher doses (NTP, 1993).

Two oral studies were identified in which the effects of exposure to 2-ethoxyethanol, 2-ethoxyethyl acetate or EAA on reproductive ability were assessed in mice. In a continuous breeding study, in which both sexes were exposed in the drinking water, all three substances adversely affected reproductive success (in terms of decreased fertility and reductions in numbers and weights of pups), with the LOEL for 2-ethoxyethanol being approximately 1650 mg/kg-bw per day, while no adverse effects were noted at 850 mg/kg-bw per day. Effects were





observed at all doses of the EAA metabolite tested (i.e.,  $\geq 300$  mg/kg-bw per day). The results of cross-over mating trials indicated that exposure of either sex to 2-ethoxyethanol or its acetate adversely affected reproductive ability, while such effects were noted only when females were exposed to 2-ethoxyacetic acid. However, effects on reproductive organs and sperm or estrous cycle parameters were observed at similar doses for all compounds. Continuous exposure *in utero* and until mating to 1860 mg/kg-bw per day of 2-ethoxyethyl acetate also induced effects on reproductive success and organs and sperm parameters in males of the second generation; however, the authors indicated that it was unclear if the second generation was more sensitive than the first (Morrissey *et al.*, 1989; Chapin and Sloane, 1997). In a secondary account of a similar continuous-breeding study in mice (Gulati *et al.*, 1985), similar effects on reproductive success were observed at doses of 1800 mg/kg-bw per day or more of 2-ethoxyethyl acetate (which were attributed to exposure of females in a cross-over study) as well as effects on sperm and testes in males; in addition, histopathological changes in the testes were observed in the second generation.

#### 2.4.3.8.2 Inhalation

In subchronic studies in experimental animals, reduced testes weight and degeneration of the seminiferous tubules were noted in rabbits exposed to 400 ppm (1472 mg/m<sup>3</sup>); however, effects on the testes were not observed in similarly exposed rats (Barbee *et al.*, 1984) or in rats or rabbits exposed to higher concentrations of the acetate (Truhaut *et al.*, 1979).

In the only inhalation study on the effects of 2-ethoxyethanol on reproductive ability identified, no effects on mating behaviour or fertility were observed in female rats exposed to up to 649 ppm (2388 mg/m<sup>3</sup>) for 3 weeks prior to mating with unexposed males (Andrew and Hardin, 1984).

#### 2.4.3.9 Immunological effects

In the two relevant studies identified, there was no evidence that exposure to 2-ethoxyethanol or its acetate induced adverse effects on the immune system in rats or mice (the highest dose tested was 2400 mg/kg-bw per day for 10 days) (Houchens *et al.*, 1984; Smialowicz *et al.*, 1992).

#### 2.4.4 Humans

Several epidemiological studies, designed to investigate the potential effects on the lymphohematopoietic system or on reproduction and development, have been conducted in populations exposed to 2-ethoxyethanol or its acetate in the occupational environment. However, in most of these studies, many of which involved small populations, workers were also exposed to various other substances in the workplace. Although these studies are limited, effects on the blood and, possibly, reproductive effects in men were observed.

In a recent well-conducted cross-sectional study (Kim *et al.*, 1999), effects on white blood cells, suggestive of bone marrow depression, were observed in a group of 57 painters exposed to 2-ethoxyethyl acetate. White blood cell and granulocyte counts were reduced in an exposure-related manner in both the high- and low-exposure groups of workers (statistically significantly lower in those exposed to mean concentrations of 3.03 ppm 2-ethoxyethyl acetate [approximately equivalent to 11 mg 2-ethoxyethanol/m<sup>3</sup>], although not considered by the authors to be clinically significantly decreased), while a significantly higher proportion of all exposed painters had leukopenia. These effects remained after controlling for several potentially confounding factors. Bone marrow hypoplasia was noted in the three leukopenic men examined. The authors also noted that mean corpuscular volume was increased in the high-exposure group, which the authors hypothesized may be an early indicator of anemia. An increase in the prevalence of anemia was observed in a



group of 94 shipyard painters exposed to similar mean concentrations of 2-ethoxyethanol (2.7 ppm [10 mg/m<sup>3</sup>]), along with several other substances (Welch and Cullen, 1988). Hemoglobin levels had declined since first employment in these workers, but were not related to duration of exposure. Exposed workers also had a slightly higher prevalence of low polymorphonuclear leukocyte counts. Bone marrow hypoplasia was also observed in a survey of seven printers exposed to 2-ethoxyethanol and other substances (Cullen *et al.*, 1983).

Although only three relevant epidemiological investigations have been identified, reduced sperm production was consistently observed in populations occupationally exposed to mean concentrations of 2-ethoxyethanol of 9.9 or 24 mg/m<sup>3</sup> (with maximum levels up to 88 mg/m<sup>3</sup>), along with other substances (Welch *et al.*, 1988; Ratcliffe

*et al.*, 1989; Schrader *et al.*, 1996). In a case-control study of 1019 men with a clinical diagnosis of infertility or reduced fertility, there was a significant association between this diagnosis and the detection of EAA in the urine (odds ratio = 3.11) (Veulemans *et al.*, 1993). There was no consistent evidence of effects on male or female reproductive ability in other investigations of men or women exposed to 2-ethoxyethanol, although most of these studies are limited by the mixed exposures of the study populations and the lack of analyses for associations with 2-ethoxyethanol specifically (Beaumont *et al.*, 1995; Schenker *et al.*, 1995; Swan *et al.*, 1995; Correa *et al.*, 1996; Gray *et al.*, 1996; Ha *et al.*, 1996; Schenker, 1996; Swan and Forest, 1996; Chia *et al.*, 1997).



## 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-ethoxyethanol are to the atmosphere. Based on its predicted environmental partitioning, assessment endpoints for 2-ethoxyethanol 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 terrestrial biota, the EEV is 860 ng/m<sup>3</sup>, the highest concentration of 2-ethoxyethanol reported in Canada (near an automotive plant in Windsor) (OMEE, 1994).

The CTV is 50 ppm ( $1.8 \times 10^8$  ng/m<sup>3</sup>), the concentration that had minimal fetotoxic effects on rats and rabbits in inhalation studies. Dividing this CTV by a factor of 100 (to account for the extrapolation from laboratory to field conditions and interspecies and intraspecies variations in sensitivity) gives an ENEV of 0.5 ppm ( $1.8 \times 10^6$  ng/m<sup>3</sup>).

The conservative quotient is calculated as follows:

$$\begin{aligned}\text{Quotient} &= \frac{\text{EEV}}{\text{ENEV}} \\ &= \frac{860 \text{ ng/m}^3}{1.8 \times 10^6 \text{ ng/m}^3} \\ &= 4.78 \times 10^{-4}\end{aligned}$$

Therefore, concentrations of 2-ethoxyethanol in air in Canada are unlikely to cause adverse effects on populations of wildlife.

###### 3.1.2.1.2 Soil organisms

For a conservative risk characterization for soil organisms, the EEV is  $4.15 \times 10^{-4}$  ng/g, the estimated concentration of 2-ethoxyethanol in soil



using ChemCAN modelling based on reported releases in 1995. This value is believed to be conservative because releases of 2-ethoxyethanol in Canada appear to have significantly decreased since 1995.

No information was identified regarding the toxicity of 2-ethoxyethanol to soil organisms. Van Leeuwen *et al.* (1992) used quantitative structure–activity relationships to estimate that a sediment concentration of 2800 ng 2-ethoxyethanol/g would be hazardous to 5% of benthic species (HC<sub>5</sub>). 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 28 ng/g for soil organisms.

The conservative quotient is calculated as follows:

$$\begin{aligned} \text{Quotient} &= \frac{\text{EEV}}{\text{ENEV}} \\ &= \frac{4.15 \times 10^{-4} \text{ ng/g}}{28 \text{ ng/g}} \\ &= 1.48 \times 10^{-5} \end{aligned}$$

Therefore, concentrations of 2-ethoxyethanol in soil in Canada are 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  $2.2 \times 10^{-5}$  µg/L, the estimated concentration of 2-ethoxyethanol in water using ChemCAN modelling based on reported releases in 1995. This value is believed to be conservative because releases of 2-ethoxyethanol in Canada appear to have significantly decreased since 1995.

The CTV for aquatic organisms is  $7.7 \times 10^6$  µg/L, the 48-hour IC<sub>50</sub> for *Daphnia magna*. Dividing this CTV by a factor of 100 (to account for the conversion of a short-term IC<sub>50</sub>

to a long-term no-effects value, extrapolation from laboratory to field conditions, and interspecies and intraspecies variations in sensitivity) gives an ENEV of  $7.7 \times 10^4$  µg/L.

The conservative quotient is calculated as follows:

$$\begin{aligned} \text{Quotient} &= \frac{\text{EEV}}{\text{ENEV}} \\ &= \frac{2.2 \times 10^{-5} \text{ µg/L}}{7.7 \times 10^4 \text{ µg/L}} \\ &= 2.9 \times 10^{-10} \end{aligned}$$

Therefore, concentrations of 2-ethoxyethanol in water in Canada are 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. Few data on environmental concentrations of 2-ethoxyethanol in Canada or elsewhere were identified; limited monitoring data were identified for air only. The EEV for wildlife exposure is considered to be conservative, as it was based on the maximum concentration measured near an industrial facility in Windsor. In addition, 2-ethoxyethanol was not detected in ambient air in the multimedia exposure study in Canada (Conor Pacific Environmental Technologies, 1998) or in a survey of six locations in the United States (Sheldon *et al.*, 1988).

In view of the lack of adequate monitoring data, the ChemCAN4 model was used to estimate concentrations of 2-ethoxyethanol in the other environmental compartments (i.e., soil and water), based on the highest reported recent release of the substance in Canada, which occurred in 1995. 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. In the only relevant study identified from other countries, the concentration of 2-ethoxyethanol in a polluted river in Japan ranged up to 1200 µg/L (Yasuhara *et al.*, 1981), a value that is an order of magnitude lower than the ENEV for aquatic organisms.

No information was identified regarding the toxicity of 2-ethoxyethanol 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 rats were used for the assessment of risk to terrestrial biota. To account for these uncertainties, application factors were used in the environmental risk assessment to derive ENEVs.

Conservative risk quotients were very small for all environmental assessment endpoints. Therefore, despite the data gaps regarding the 2-ethoxyethanol 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-Ethoxyethanol does not deplete stratospheric ozone, and its potential for contributing to climate change is negligible. The potential of 2-ethoxyethanol for creation of photochemical ozone (smog) is moderate, but the low quantities of 2-ethoxyethanol 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-ethoxyethanol preclude the development of reliable estimates of typical exposure of the general population; instead, crude upper-bounding estimates of exposure to 2-ethoxyethanol from environmental media and consumer products have been developed in order to characterize potential exposure from these pathways.

The only environmental media for which available monitoring data allowed even crude estimation of exposure were air and water. Upper-bounding estimates of intake of 2-ethoxyethanol from these media by six age groups in the general population of Canada are presented in Table 2. These estimates are based on the limits of detection in air and tap water from the limited Canadian multimedia exposure study in which concentrations of 2-ethoxyethanol were below the limits of detection in all samples analysed (Conor Pacific Environmental Technologies, 1998). Although confidence in the results of this survey is low, comparison with estimates of intake in air and water on the basis of results of fugacity modelling and in ambient air based on the data from the Windsor study indicates that this approach is conservative in deriving upper-bounding estimates of intake in air. Based on these values, the average adult in Canada would be exposed to airborne levels of 2-ethoxyethanol no greater than 3.6 µg/m<sup>3</sup> and would not ingest more than 0.005 µg/kg-bw per day in drinking water, although it is recognized that these values likely overestimate exposure.

Since no monitoring data are available, it is not possible to determine the contribution of food to the overall intake of 2-ethoxyethanol. However, 2-ethoxyethanol is released primarily to air from industrial activities and through volatilization from consumer products and is unlikely to partition to food from air due to its



**TABLE 2** Upper-bounding estimates of intake of 2-ethoxyethanol by various age groups in the general population

Route of exposure	Upper-bounding estimates of intake of 2-ethoxyethanol by various age groups in the general population (µg/kg-bw per day)					
	0–6 months <sup>1</sup>	7 months–4 yrs <sup>2</sup>	5–11 yrs <sup>3</sup>	12–19 yrs <sup>4</sup>	20–59 yrs <sup>5</sup>	60+ yrs <sup>6</sup>
Ambient air <sup>7</sup>	0.13	0.27	0.21	0.12	0.10	0.09
Indoor air <sup>8</sup>	0.87	1.87	1.46	0.83	0.71	0.62
Drinking water <sup>9</sup>	0.005 <sup>10</sup>	0.002	0.002	0.001	0.001	0.001
<b>Total</b>	<b>1.0</b>	<b>2.1</b>	<b>1.7</b>	<b>0.9</b>	<b>0.8</b>	<b>0.7</b>

<sup>1</sup> Assumed to weigh 7.5 kg, to drink 0.8 L of water per day and to breathe 2.1 m<sup>3</sup> of air per day (EHD, 1998).

<sup>2</sup> Assumed to weigh 15.5 kg, to drink 0.7 L of water per day and to breathe 9.3 m<sup>3</sup> of air per day (EHD, 1998).

<sup>3</sup> Assumed to weigh 31.0 kg, to drink 1.1 L of water per day and to breathe 14.5 m<sup>3</sup> of air per day (EHD, 1998).

<sup>4</sup> Assumed to weigh 59.4 kg, to drink 1.2 L of water per day and to breathe 15.8 m<sup>3</sup> of air per day (EHD, 1998).

<sup>5</sup> Assumed to weigh 70.9 kg, to drink 1.5 L of water per day and to breathe 16.2 m<sup>3</sup> of air per day (EHD, 1998).

<sup>6</sup> Assumed to weigh 72.0 kg, to drink 1.6 L of water per day and to breathe 14.3 m<sup>3</sup> of air per day (EHD, 1998).

<sup>7</sup> Based on the limit of detection for 2-ethoxyethanol in 50 ambient air samples collected outside of Canadian residences, 3.6 µg/m<sup>3</sup> (Conor Pacific Environmental Technologies, 1998). The average Canadian is assumed to spend 3 hours of every day outdoors (EHD, 1998).

<sup>8</sup> Based on the detection limit (3.6 µg/m<sup>3</sup>) for 2-ethoxyethanol in 50 indoor air samples collected in Canadian residences (Conor Pacific Environmental Technologies, 1998). The average Canadian is assumed to spend 21 hours of every day indoors (EHD, 1998).

<sup>9</sup> Based on the detection limit (0.05 µg/L) for 2-ethoxyethanol in 50 drinking water samples collected in Canadian residences (Conor Pacific Environmental Technologies, 1998).

<sup>10</sup> Based on the assumption that infants were exclusively formula fed and consumed 800 mL of formula that was prepared with tap water.

Note: Insufficient data were available to estimate intake from soil or food.

volatility and very low octanol/water partition coefficient (log  $K_{ow}$  of -0.32). In addition, if intake in food is estimated on the basis of extrapolation from the results of fugacity modelling, this value would be several orders of magnitude less than the upper-bounding estimates calculated for air and drinking water on the basis of the limits of detection in the multimedia study. Likewise, exposure to 2-ethoxyethanol in soil is likely to be negligible in comparison with that in air, based on its release patterns and the relatively small quantities ingested.

Limited available recent data do not indicate that 2-ethoxyethanol or its acetate are commonly present in consumer products in Canada. Based primarily on earlier data, direct

exposure to 2-ethoxyethanol and 2-ethoxyethyl acetate might result from the use of a variety of consumer products containing these substances. Both inhalation and dermal absorption would be expected to be important routes of exposure for such consumer products, since many of those that might contain 2-ethoxyethanol or its acetate can contact the skin. Because most of the consumer products for which data are available are used primarily by adults, the estimated exposures have been derived for this age class only. (The differences among age classes in intake from a given medium as a result of age-specific differences would be small in relation to the variation in exposure from the various sources, in any case.) Upper-bounding estimates of intake of 2-ethoxyethanol (on a per event basis as well as



average daily intakes based on annual event frequencies) from exposure to household cleaning products and nail polish were developed from product use scenarios (Versar Inc., 1986), assuming 100% absorption for the product contacting the skin and for the inhaled product and 100% transfer of 2-ethoxyethanol from the product into air (in view of the lack of adequate data to support more refined estimates) (Table 3). These estimates should be interpreted with caution in view of the limited available information on the presence and concentrations of 2-ethoxyethanol and its acetate in consumer products currently used in Canada and should be considered as upper-bounding estimates only, as actual exposure is very likely much lower. Indeed, as discussed above, 2-ethoxyethanol was not detected in a recent investigation conducted by Health Canada of emissions of glycol ethers from several consumer products (Cao, 1999).

The worst-case estimate for exposure through use of a household cleaning product that is used on an almost daily basis (all-purpose spray cleaner, the only cleaning product for which composition data was available) was 1.6 or 0.5 mg/kg-bw per event or per day via inhalation and dermal absorption, respectively. Concentrations in indoor air resulting from use of such products could range up to 190 mg/m<sup>3</sup>, assuming complete volatilization.

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

### 3.3.2 Human health hazard characterization

Little information was identified on the effects of 2-ethoxyethanol in humans. However, although the epidemiological data are not conclusive, the results of available investigations in occupationally exposed populations are

suggestive of effects on the blood and on sperm production in men (Cullen *et al.*, 1983; Welch and Cullen, 1988; Welch *et al.*, 1988; Ratcliffe *et al.*, 1989; Veulemans *et al.*, 1993; Kim *et al.*, 1999). There is consistent evidence from short- and long-term toxicological studies in all species of experimental animals investigated that hematological, male reproductive and developmental effects are associated with exposure to 2-ethoxyethanol or its acetate by the oral, inhalation and dermal routes. The results of mechanistic studies suggest that metabolic activation to the acetic acid metabolite, EAA, is required for the induction of these effects. For example, co-exposure to substances that interfere with metabolism via alcohol or aldehyde dehydrogenases (e.g., toluene, xylene and ethanol) reduced the magnitude of testicular atrophy in male rats (Chung *et al.*, 1999) and the effects on neurological development in rats exposed to 2-ethoxyethanol *in utero* (Nelson *et al.*, 1982a,b, 1984). Metabolism via alcohol and aldehyde dehydrogenases to EAA is the principal metabolic pathway in both humans and laboratory animals; indeed, there is some evidence, although limited, that humans may have greater potential than rats for formation of EAA and slower clearance than in rats. Therefore, although there is only limited evidence of effects on the blood and sperm production in occupationally exposed human populations, based on the consistent evidence in experimental animals and the similarity in metabolism across species, hematopoietic, reproductive (in males) and developmental toxicity are considered critical effects for 2-ethoxyethanol.

### 3.3.3 Human health risk characterization

As discussed above in Section 1.0, due principally to the limitations of available monitoring data, upper-bounding estimates of exposure are compared with conservative effect levels for critical effects as a basis for characterization of rather crude margins of exposure.

Based on evaluation of available data, hematological, reproductive and developmental



**TABLE 3** Upper-bounding estimates of intake of 2-ethoxyethanol from consumer products by adult Canadians

Consumer product	Assumptions	Estimated intake per event (mg/kg-bw per event)	Estimated average daily intake (mg/kg-bw per day)
Nail polish	<p><b>Dermal</b><sup>1</sup></p> <ul style="list-style-type: none"> <li>based on the upper bound of the concentration range of 0.3–1% of 2-ethoxyethanol in nail polish (Health Canada, 1998d)</li> <li>assuming a typical quantity of product used per event for “nail polish &amp; enamel” of 0.28 g and a maximum event frequency of 0.71 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> $\frac{(0.01) (280 \text{ mg}) (0.71/\text{day})}{(70.9 \text{ kg-bw})}$	0.04	0.03
All-purpose spray cleaner	<p><b>Inhalation</b><sup>2</sup></p> <ul style="list-style-type: none"> <li>based on the upper end of the concentration range of 3-5% of 2-ethoxyethanol in hard surface cleaner (Flick, 1986)</li> <li>assuming 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/year (Versar Inc., 1986)</li> <li>a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998)</li> </ul> $\frac{(0.05) (360/365 \text{ days}) (76 \text{ 000 mg}) (0.47 \text{ hours}) (1.3 \text{ m}^3/\text{hour})}{(20 \text{ m}^3) (70.9 \text{ kg-bw})}$	1.6	1.6
	<p><b>Dermal</b><sup>1</sup></p> <ul style="list-style-type: none"> <li>based on the upper end of the concentration range of 3-5% of 2-ethoxyethanol in hard surface cleaner (Flick, 1986)</li> <li>assuming an event frequency of 360 days/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> $\frac{(0.05) (360/365 \text{ days}) (400 \text{ cm}^2) (0.88 \text{ g/cm}^3) (2.1 \times 10^{-3} \text{ cm}) (1000 \text{ mg/g})}{(70.9 \text{ kg-bw})}$	0.5	0.5

<sup>1</sup> Estimates of intake by dermal absorption of 2-ethoxyethanol in liquid consumer products are based on the assumptions that a portion of the skin contacts the liquid and the amount absorbed is directly proportional to the area of exposed skin. It is assumed that all of the ingredient present in the liquid is absorbed through the skin. Standard exposure scenarios for dermal absorption of ingredients of liquid consumer products (e.g., Versar Inc., 1986; U.S. EPA, 1997) often include recommended skin surface areas and surface film thickness depending on the type of product and the manner in which it is used. For example, in Versar Inc. (1986), surface areas assumed are 400 cm<sup>2</sup> for both palms of adult hands for scenarios involving some liquid cleaning products. Experimental data for surface film thickness are often not available for some types of consumer products and are estimated by analogy with other liquid substances.



<sup>2</sup> Estimates of intake by inhalation are based on the assumptions that the ingredient is completely and instantaneously released from the applied product, the concentration is homogenous throughout the assumed volume, and no air exchange occurs between this volume and adjacent areas. Standard exposure scenarios for inhalation intakes of volatile ingredients of consumer products used in indoor spaces (e.g., Versar Inc., 1986; U.S. EPA, 1997) often include recommended room volumes intended to be representative of the areas within a residence where the products are typically used. For example, in Versar Inc. (1986), a room volume of 20 m<sup>3</sup> is assumed for tasks involving all-purpose liquid spray cleaners.

effects are considered critical endpoints for assessment of potential risk to humans associated with exposure to 2-ethoxyethanol. Statistically significant alterations in blood parameters were observed in shipyard painters exposed to a mean 2-ethoxyethyl acetate concentration of 3.03 ppm (equivalent to 11 mg 2-ethoxyethanol/m<sup>3</sup>),<sup>5</sup> although the authors suggested that the magnitude of these changes was not of biological significance (Kim *et al.*, 1999). With respect to reproductive effects, in the only relevant studies in which exposure was quantified, reduced sperm production was observed in workers exposed to mean 2-ethoxyethanol concentrations of 9.9 mg/m<sup>3</sup> (Welch *et al.*, 1988) and 24 mg/m<sup>3</sup> (Ratcliffe *et al.*, 1989), although these men were also exposed to several other substances. In investigations in experimental animals, effect levels for hematological, reproductive and developmental effects were generally greater than concentrations associated with effects in the epidemiological studies (i.e., lowest LOELs of 184 mg/m<sup>3</sup> and 94 mg/kg-bw per day), which is consistent with the limited data that suggest that humans form the putatively active metabolite to a greater extent than do rats and clear the metabolite more slowly. Therefore, risk to human health is characterized through comparison of the upper-bounding estimates of population exposure with the levels associated with effects in exposed workers.

Based on comparison of the concentration associated with effects in humans in the study in which exposure was best characterized (i.e., alterations in hematological parameters in Kim *et al.*, 1999) of 11 mg/m<sup>3</sup> with the upper-bounding estimates of exposure levels in air in Canada of 3.6 µg/m<sup>3</sup> (based on the detection limit in the multimedia exposure study by Conor Pacific Environmental Technologies, 1998), the margin between effect level and exposure is about 3000. (Note: If this effect level is compared with the highest concentration of 2-ethoxyethanol detected outside of an automotive plant in Windsor [i.e., the maximum level detected in ambient air in Canada, 0.86 µg/m<sup>3</sup>], this margin would be even greater.) With respect to ingestion, although no epidemiological investigations of the effects of ingested 2-ethoxyethanol in humans were identified, the margin between the intake equivalent to inhalation of 2-ethoxyethanol at a concentration of 11 mg/m<sup>3</sup> (assuming 100% absorption) and the upper-bounding estimate of intake in drinking water is about 6 orders of magnitude. Margins between exposure and the effect levels from studies in animals would be even greater. Although intake of 2-ethoxyethanol in food could not be estimated, it is considered unlikely to be greater than these upper-bounding estimates for air or drinking water. These margins between upper-bounding estimates of exposure and the conservative effect levels are considered

<sup>5</sup> Since the acetate moiety of 2-ethoxyethanol is rapidly converted to 2-ethoxyethanol in the body, with similar resulting health effects, it was considered appropriate to develop effect levels on the basis of studies in which the toxicity of 2-ethoxyethyl acetate was investigated, converting the exposure levels of the acetate to equivalent concentrations or doses of 2-ethoxyethanol on a relative molecular weight basis.



adequate to account for the uncertainties in the database (including exposure estimates and interindividual variation in response).

However, upper-bounding estimates of exposure to 2-ethoxyethanol through use of some consumer products could approach or exceed the effect levels for health effects in humans. For example, upper-bounding estimates of indoor air concentrations resulting from use of all purpose spray cleaners containing the substance (the only household cleaning product for which information on composition was available) are more than an order of magnitude greater than these effect levels. However, the degree of confidence in these estimates of exposure from consumer products is considered to be extremely low (see Section 3.3.4), and they are very likely gross overestimates of actual exposure from products currently being used in Canada. Therefore, confirmation that 2-ethoxyethanol is not present in consumer products in Canada is a high priority.

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

Due to the paucity of data on levels of 2-ethoxyethanol in environmental media in Canada, there is a high degree of uncertainty in the estimates of exposure that have been developed in this assessment. While conservative upper-bounding estimates of exposure were determined on the basis of the detection limits reported in the multimedia exposure study, it is not known if these values grossly overestimate environmental levels or if the population is exposed to concentrations approaching these levels, although predicted concentrations in ambient air and drinking water based on fugacity modelling were several orders of magnitude below these detection limits, and levels were lower in the small survey of ambient air in Windsor (in which confidence is greater) than the detection limit reported for the multimedia study. In addition, although these data are considered adequate as a basis for developing crude bounding estimates of exposure, the

methodology employed in the multimedia study is considered experimental, for which confidence is low. Recoveries were often low (only 43% for 2-ethoxyethanol in air), concentrations in “blanks” were high, etc. There is a high degree of confidence, though, that this approach is conservative, based on comparison with other results. It should also be noted that uptake of 2-ethoxyethanol vapour via dermal absorption has not been considered in these estimates of exposure. As well, the contribution of food and soil to overall intake of 2-ethoxyethanol is unknown, as no relevant data were identified, although predictions based on fugacity modelling suggest that intake from these sources is likely much less than the upper-bounding estimates of intake from air and drinking water upon which the conclusions presented here are based.

There is an extremely low degree of confidence in the estimates of exposure to 2-ethoxyethanol from consumer products, due to the uncertainties regarding the presence and concentrations of the substance in products currently used in Canada. Therefore, it is likely that the values presented here greatly overestimate potential current exposures. These estimates were also determined based on the conservative assumptions of complete transfer of 2-ethoxyethanol from the product to air and 100% absorption of the inhaled substance and the amount contacting the skin. While 2-ethoxyethanol was not detected in emissions from a range of products recently tested by Health Canada (Cao, 1999), confirmation that it is not present in consumer products in Canada is desirable.

There is a moderate to high degree of confidence in the characterization of the health hazards associated with exposure to 2-ethoxyethanol for the purposes of identifying critical effects for risk characterization. Hematological, reproductive and developmental effects were consistently observed in investigations in experimental animals. Hematological and reproductive effects have also been observed in occupationally exposed human

populations, although the database in humans is somewhat limited. Additional investigations of exposed workers, in which exposure to 2-ethoxyethanol is quantified, would be helpful in further characterizing risks to humans, particularly since there is some indication that humans may be more sensitive than animal species to effects induced by this substance (additional research on the relative toxicokinetics would also be desirable). However, there is some uncertainty concerning the effects of 2-ethoxyethanol following long-term exposure, as no adequate chronic studies in animals are available. Likewise, no epidemiological investigations of the potential effects in humans in which both magnitude and duration of exposure to 2-ethoxyethanol were considered have been identified.

### 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-ethoxyethanol likely to be found in Canada therefore appear to be low. Therefore, available data indicate that it is unlikely that 2-ethoxyethanol is entering or may enter the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity, and it is not considered to be “toxic” as defined in CEPA 1999 Paragraph 64(a).

CEPA 1999 64(b): 2-Ethoxyethanol 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, it has been concluded that 2-ethoxyethanol 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): Based on comparison of upper-bounding estimates of exposure in the general environment with conservative effect levels, it is concluded that 2-ethoxyethanol is not entering the general 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-ethoxyethanol is not considered to be “toxic” as defined in Section 64(c) of the *Canadian Environmental Protection Act* (CEPA, 1999). Although 2-ethoxyethanol was not detected in emissions from a range of consumer products in Canada, acquisition of additional more representative information on its use in consumer products in Canada is desirable.



Overall  
conclusion: Based on critical assessment  
of relevant information,  
2-ethoxyethanol is not  
considered to be “toxic” as  
defined in Section 64 of  
CEPA 1999.

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

Although 2-ethoxyethanol was not detected in emissions from a range of products tested by Health Canada, information on its use in consumer products marketed in Canada is sparse. It is recommended, therefore, that additional information on patterns of use of consumer products containing 2-ethoxyethanol in Canada and levels of the compound in these products be sought. Depending upon the results of such investigations, it may be necessary to conduct a fuller assessment, including refined estimates of exposure and full dose–response analyses.



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# APPENDIX A SEARCH STRATEGIES EMPLOYED FOR IDENTIFICATION OF RELEVANT DATA

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## Environmental assessment

Data relevant to the assessment of whether 2-ethoxyethanol is “toxic” to the environment under CEPA 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, 1994, 1995, up to 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-ethoxyethanol. 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,c). Targeted companies with commercial activities involving more than 1000 kg of 2-ethoxyethanol were required to supply information on uses, releases, environmental concentrations, effects or other data that were available to them for 2-ethoxyethanol.

## Health assessment

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





CAB Abstracts, Food Science and Technology Abstracts, Pollution Abstracts and NTIS), 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 January 2000 were considered for inclusion in this draft.

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.

