Canadian Environmental Protection Act

PRIORITY SUBSTANCES LIST ASSESSMENT REPORT No. 5

METHYL *tertiary*-BUTYL ETHER

Government of Canada
Environment Canada
Health and Welfare Canada

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TABLE OF CONTENTS

Overview of Findings

Methyl *tertiary*-butyl ether (MTBE) is used in Canada as an octane enhancer in gasoline. Methyl *tertiary*-butyl ether can enter the environment at any stage in the production, storage, and transport of undiluted MTBE or MTBE-blended gasoline. Although data on concentrations of MTBE in the environment are not available, modelling of the fate of MTBE has provided predictions for concentrations of MTBE in the various media to which humans and other organisms may be exposed.

The highest concentrations of MTBE predicted in surface water in Canada are at least eight orders of magnitude lower than the concentration that induces adverse effects in fathead minnow, the most sensitive aquatic species identified. The effect levels reported in inhalation studies conducted on laboratory mammals are considered relevant to wild mammals. The highest predicted atmospheric concentration is at least seven orders of magnitude lower than the lowest reported effect level in a subchronic inhalation study in mammals.

Because of its low rate of release, its short persistence in the atmosphere, and the resulting low concentrations of MTBE in the atmosphere, MTBE is not associated with depletion of stratospheric ozone or with global warming, and is not expected to contribute significantly to the formation of ground-level ozone.

Based on predicted concentrations of MTBE in ambient air and water and limited information on concentrations in shellfish, the total average daily intakes of MTBE have been estimated for various age groups in the general population. These estimates are much less (by approximately 45 000 times) than the intake to which it is believed that a person can be exposed over a lifetime without deleterious effect, *i.e.*, the Tolerable Daily Intake derived on the basis of data from bioassays in animal species.

Based on these considerations, the federal Minister of the Environment and the federal Minister of Health and Welfare have concluded that the predicted concentrations of MTBE in the environment in Canada do not constitute a danger to the environment or to the environment on which human life depends, or to human life or health. Therefore, MTBE is not considered to be "toxic" as defined under Section 11 of the *Canadian Environmental Protection Act*.

1.0 Introduction

The *Canadian Environmental Protection Act* (CEPA) requires the federal Minister of the Environment and the federal Minister of Health and Welfare to prepare and publish a Priority Substances List 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" as defined in Section 11 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
>
> (a) having or that may have an immediate or long-term harmful effect on the environment;
>
> (b) constituting or that may constitute a danger to the environment on which human life depends; or
>
> (c) constituting or that may constitute a danger in Canada to human life or health."

Substances that are assessed as "toxic" according to Section 11 may be placed on Schedule I of the Act. Consideration can then be given to developing regulations, guidelines, or codes of practice to control any aspect of these substances' life cycle, from the research and development stage through manufacture, use, storage, transport, and ultimate disposal.

The assessment of whether methyl *tertiary*-butyl ether (MTBE) is "toxic", as defined in CEPA, was based on the determination of whether it **enters** or is likely to enter the Canadian environment in a concentration or quantities or under conditions that could lead to **exposure** of humans or other biota at levels that could cause adverse **effects**.

Data relevant to the assessment of the entry, environmental exposure, and environmental effects of MTBE were obtained from searches of electronic databases between 1989 and 1991. These databases included: BIOSIS Previews, Chemical Evaluation Search and Retrieval System (CESARS), Chemical Abstracts, Environment Canada Departmental Library Catalogue (ELIAS), FATERATE, Federal Register, International Register of Potentially Toxic Chemicals (IRPTC), National Technical Information Service (NTIS), Pollution Abstracts, Registry of Toxic Effects of Chemical Substances (RTECS), SOLUB, TOXLINE, and the Toxic Releases Inventory Data Base. Additional information was obtained from members of the Canadian Petroleum Products Institute (CPPI) and other representatives of the petroleum industry and from C.S. Liu of Alberta Environment. Trade information, including production, import, storage, and use data, was obtained from industry through a mandatory request for information under CEPA, Section 16. Although much of the research on MTBE has been conducted

outside Canada, available Canadian data on sources, use patterns, fate, and effects of MTBE on the Canadian environment were emphasized.

To identify data relevant to the estimation of exposure of the general human population to MTBE, several commercial databases were searched from the early 1970s to July 1991. These included: Environmental Bibliography, ENVIROLINE, Pollution Abstracts, ELIAS, AQUAREF, BIOSIS Previews, MICROLOG, Cooperative Documents Project (CODOC), Integrated Risk Information System (IRIS) , and Chemical Hazard Response Information System (CHRIS).

To identify toxicological data relevant to the assessment of effects on human health, on-line literature searches were conducted in June 1991 on the following databases: Hazardous Substances Data Bank, RTECS, TOXLINE, TOXLIT, Federal Register, and NTIS. Additional relevant information was obtained from the Canadian Petroleum Products Institute, the MTBE Health Effects Testing Task Force (a committee of American producers and users of MTBE overseeing toxicological testing of MTBE), and the United States Environmental Protection Agency (U.S. EPA). Non-validated studies of Industrial Bio-Test Laboratories Inc. have been cited in this report but are not used in assessing whether MTBE is "toxic" under CEPA.

Data relevant to the assessment of whether MTBE is "toxic" to human health obtained after the completion of the human health-related sections of this report (*i.e.*, October 1991) were not considered for inclusion. Similarly, data relevant to the assessment of whether MTBE is "toxic" to the environment obtained after April 1992 have not been considered.

Review articles were consulted where appropriate. However, all original studies that form the basis for determining whether MTBE is "toxic" under CEPA have been critically evaluated by the following Environment Canada staff (entry, and environmental exposure and effects) and Health and Welfare Canada staff (human exposure and effects on human health):

Environment Canada	Health and Welfare Canada
A. Bobra	G. Long
D. Caldbick	M.E. Meek
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K. Lloyd	
C. B. Prakash	

In this report, an overview of findings concerning MTBE that will appear in the *Canada Gazette* is presented. Section 2.0 is an extended summary of the technical information that is critical to the assessment. This information is presented in greater detail in a Supporting Document that is available upon request. The assessment of whether MTBE is "toxic" under CEPA is presented in Section 3.0.

The human health-related sections of the Supporting Document and/or Assessment Report were reviewed externally by S. Ridlon, Chairman of the MTBE Health Effects Testing Task Force, and British Industrial Biological Research Association (BIBRA) Toxicology International. These sections were then approved by the Standards and Guidelines Rulings Committee of the Bureau of Chemical Hazards of Health and Welfare Canada. Environmental components of the Supporting Document were reviewed externally by G. Grappolini, Petro-Canada Products, on behalf of the Canadian Petroleum Products Institute, and by C. S. Liu from Alberta Environment. The final Assessment Report was reviewed and approved by the Environment Canada/ Health and Welfare Canada CEPA Management Committee.

Copies of this assessment report and of the unpublished supporting document are available upon request from:

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2.0 Summary of Critical Supporting Data

2.1 Identity and Physical/Chemical Properties of Substance

Methyl *tertiary*-butyl ether (CAS Registry Number 1634-04-4) is an aliphatic ether with structural formula $CH_3OC(CH_3)_3$. It is a volatile, clear, flammable, colourless liquid at room temperature, and has a terpene-like odour. Methyl *tertiary*-butyl ether is miscible in gasoline and soluble in water, alcohol, and ether. It has a relatively high vapour pressure (3.35×10^4 Pa at 25°C) (Ambrose *et al.*, 1976), a high water solubility (4.8×10^4 mg/L at 20°C) (Merck & Co., Inc., 1989) and a low log octanol/water partition coefficient (1.3) (Veith *et al.*, 1983).

Methyl *tertiary*-butyl ether is produced by reacting isobutylene with methanol over an acid catalyst. Common analytical methods used to quantify MTBE include gas chromatography with mass spectrometry, flame ionization, or an oxygen specific response flame ionization detector.

2.2 Production and Uses

The first plant ever to produce MTBE in Canada began operating in 1992 in an industrialized area of Edmonton, Alberta. The plant is to produce an estimated 500 000 tonnes of MTBE per year, most of which is intended for export to the United States. The MTBE will be shipped by rail from Edmonton to Kitimat, British Columbia and from there it will be shipped by ocean tanker (Solsberg, 1991).

From 1986 to 1990, Canada imported between 7000 and 25 000 tonnes/year of MTBE for the purpose of blending as an octane enhancer in unleaded gasoline. Most of the imports entered Ontario and Quebec, and smaller amounts went to Alberta and British Columbia. Over the next five years, it is estimated that importation will increase to approximately 38 000 tonnes/year. Assuming that Canada's overall consumption of gasoline will not change appreciably over the next four years, it is estimated that MTBE-blended gasolines will continue to account for approximately 2% of the total unleaded gasoline in Canada, as it has during the past five years. The average concentrations of MTBE in these blended gasolines range from 6.5 to 9.6% by volume (Environment Canada, 1991).

Worldwide production of MTBE has increased dramatically since 1979, when it was approved in the United States and other countries for use in gasoline. In western Europe, unleaded gasoline can contain 10 to 15% MTBE by volume. In the United States, concentrations of up to 15% MTBE by volume in unleaded gasoline have been approved by the U.S. EPA. Methyl *tertiary*-butyl ether is currently among the 50 highest production volume chemicals in the United States. Total production of MTBE in the United States was estimated to be 3 200 000 tonnes/year (Chemical Market Reporter, 1990). World production capacity in 1989 was 7 425 000 tonnes and is projected to rise to 19 413 000 tonnes/year by 1994. The growing demand for MTBE as a gasoline-blending component results from the expanded market for high octane unleaded

gasolines, and the increased pressure to reduce evaporative emissions, carbon monoxide (CO) emissions, and the aromatic contents of gasoline (Prakash, 1989).

2.3 Sources and Releases

Methyl *tertiary*-butyl ether can enter the environment at any stage in the production, storage, and transport of undiluted MTBE or MTBE-blended gasoline. The largest environmental releases are through fugitive emissions from chemical manufacturing plants, gasoline terminals, service stations, and from spills (U.S. EPA, 1986). No data are available on releases of MTBE from engine combustion of MTBE-blended gasoline. Canadian data on environmental releases are not available. Releases of MTBE from ten plants in the United States have been estimated to range from 0.003 to 0.07% of the total MTBE used or produced, with an average of 97% of released MTBE being emitted into air, 1.7% into water, and 1.3% into soil (TOXNET-TRI, 1991). Assuming that 0.07% of all the projected production of MTBE at the Edmonton plant would be released into the environment in similar proportions, this would result in annual releases of 340 tonnes of MTBE into the air, 6 tonnes into water, and 5 tonnes into soil.

2.4 Environmental Fate and Concentrations

2.4.1 *Fate*

Mechanisms affecting the environmental fate of MTBE include photo-oxidation (Japar *et al.*, 1990; 1991), volatilization (Thomas, 1982), and biodegradation (Fujiwara *et al.*, 1984). In the environment, MTBE should be found primarily in the atmosphere and in water because of its relatively high vapour pressure, high water solubility, and low octanol/water partition coefficient.

Based on measured rate constants for reactions with hydroxyl radicals in air, the photo-oxidation half-life for MTBE has been estimated to be between 20.7 and 265 hours (Atkinson, 1985; Wallington *et al.*, 1988). The atmospheric oxidation of MTBE produces *tertiary*-butyl formate (major product), 2-methoxy-2-methyl propanal, and other minor products (Japar *et al.*, 1991). In water, biodegradation appears to be the only degradation process of any significance. The half-life of MTBE was estimated to be between 28 and 180 days for aerobic biodegradation in surface waters and between 112 and 720 days for anaerobic biodegradation in deep water or groundwater (Fujiwara *et al.*, 1984). Based on physical/chemical properties, the half-life for volatilization of MTBE from surface waters to the atmosphere was estimated to be 9 hours (U.S. EPA, 1986).

2.4.2 *Concentrations*

No information was found in the literature on MTBE concentrations in air, surface waters, groundwater, soil, or sediment in Canada. In a study carried out in Nova Scotia for the detection of organic and inorganic contaminants in shellfish, MTBE was not detected (detection limit of 0.01 μg/g) in 21 samples that were assayed (Environment Canada, 1989).

Concentrations of MTBE in ground-level air at three refineries in the United States were less than 30 $\mu g/m^3$ (API, 1989). Trace quantities of MTBE (5 ng/L) were detected in estuarine water and sediment samples adjacent to motorways and centres of heavy urban road traffic in the United Kingdom (Bianchi and Varney, 1989).

There have been several incidents of MTBE being detected in groundwater in areas where underground storage tanks containing MTBE-blended gasoline have leaked. In some of these incidents in the United States, MTBE concentrations ranged from 1.96 µg/L to 236 mg/L (Garrett, 1987). When present in groundwater at high concentrations, MTBE can act as a cosolvent and enhance the mobility of other gasoline components (Rao *et al.*, 1990; Garrett *et al.*, 1986).

Bioconcentration of MTBE in aquatic biota is not significant. Whole body, steady-state bioconcentration factors (BCF) of 1.1 and 1.08 have been reported for carp, *Cyprinus carpio* (Fujiwara *et al.*, 1984). Fish exposed for 28 days and then transferred to clean water eliminated almost all of the MTBE residues within 3 days (Fujiwara *et al.*, 1984). Concentrations in fish would therefore be expected to be close to the concentrations in water.

Because of the lack of data on the behaviour of MTBE in the Canadian environment, estimates of fate and concentrations of MTBE in the environment were generated using the Level III Fugacity Computer Model of Mackay and Paterson (1991) developed for southern Ontario. Based on estimates for import into southern Ontario (Environment Canada, 1991) and data on releases in the United States (TOXNET-TRI, 1991), it was assumed that MTBE would be released into the environment at rates of 119 mol/hour into air, 3.6 mol/hour into water, and 0.6 mol/hour into soil. Modelling indicated that at steady-state, 56.2% MTBE would be found in the air, 43.3% in surface water, <0.01% in sediment, and 0.5% in soil. This would result in steady-state concentrations of 1.5 ng/m^3 in air, 0.12 ng/L in water, 0.28 ng/kg (dry weight) in soil, and 0.068 ng/kg (dry weight) in sediment.

A release of 1% of the total estimated 1992 Canadian production of 500 000 tonnes/year would result in emissions and concentrations approximately 50 times greater than those estimated in the previous paragraph. The 1% release was chosen to represent a worst-case scenario, corresponding to approximately ten times the estimated maximum United States emission rate from chemical plants.

2.5 Toxicokinetics and Metabolism

Methyl *tertiary*-butyl ether appears to be rapidly and completely absorbed from the gastrointestinal tract of rats, whereas absorption following dermal exposure is limited (Bio-Research Laboratories Ltd., 1990a). Following oral, inhalation, dermal, or intravenous exposure in experimental animals, MTBE is rapidly eliminated unchanged, or as metabolites, principally *tertiary*-butanol in expired air and *tertiary*-butanol, 2-methyl-1,2-propanediol and *alpha*-hydroxyisobutyric acid in urine (Savolainen *et al.*, 1985; Exxon Biomedical Sciences, Inc., 1988; Bio-Research Laboratories, Ltd. 1990a; 1990b; 1990c; 1990d).

Available data indicate that accumulation of MTBE and/or metabolites following repeated exposure by inhalation is unlikely (Bio-Research Laboratories Ltd., 1990c) and that the metabolism of MTBE to *tertiary*-butanol may be saturated at high doses (Bio-Research Laboratories Ltd., 1990a; 1990b; 1990d). Methyl *tertiary*-butyl ether and its metabolite *tertiary*-butanol have been detected in the blood, urine, fatty tissue, and mothers' milk of patients undergoing gallstone treatment by transhepatic gallbladder litholysis using MTBE (Leuschner *et al.*, 1991).

2.6 Mammalian Toxicology

The acute toxicity of MTBE is low following inhalation, oral, or dermal administration. The oral (gavage) LD_{50} in male and female albino rats is approximately 3.8 g/kg b.w. (Industrial Bio-Test Laboratories, Inc., 1969; ARCO Chemical Co., 1980). Reported LC_{50}s in rats for 4-hour inhalation exposures to MTBE are 85 g/m^3 (Industrial Bio-Test Laboratories, Inc., 1969) and 120 g/m^3 (ARCO Chemical Co., 1980). Methyl *tertiary*-butyl ether did not induce dermal sensitization in guinea pigs (ARCO Chemical Co., 1980).

Short-term repeated dose toxicity studies for MTBE are limited to a two-week inhalation study in small groups of rats and monkeys (Industrial Bio-Test Laboratories, Inc., 1970a; 1970b), a nine-day inhalation study in rats (Bio/dynamics Inc., 1984) and a 14-day study in which the compound was administered orally by gavage to rats (Robinson *et al.*, 1990). At high concentrations (> 1020 ppm; > 3731 mg/m^3), inhalation of MTBE induced clinical signs of eye irritation and chronic inflammatory changes in the nasal mucosa and trachea (Bio/dynamics Inc., 1984) and profound anaesthesia following ingestion of 1428 mg/kg b.w. (Robinson *et al.*, 1990). Decreases in body weight gain have also been observed following ingestion of lower doses (714 mg/kg b.w.) (Robinson *et al.*, 1990).

Subchronic toxicity studies are limited to one oral and three inhalation studies in rats. In an inhalation study conducted by Greenough *et al.* (1980), anaesthesia was the only adverse effect observed in rats at concentrations as low as 250 ppm (915 mg/m^3). However, this effect was not observed at higher concentrations in a more recent investigation in another strain of rats.

In the most extensive bioassay, Dodd and Kintigh (1989) reported a "no-observed-adverse-effect-level (NOAEL)" of 797 ppm (2915 mg/m^3), based on neurobehavioural effects observed at concentrations of 3920 ppm (14 339 mg/m^3) and above. Increases in the relative weights of the liver and kidney in male rats were observed at this concentration (797 ppm), which might more appropriately have been considered a lowest-observed-effect-level (LOEL).

Data on the chronic toxicity and potential carcinogenicity of MTBE have not been identified. However, an oncogenicity study in CD-1 mice and F344 rats is under way and is expected to be completed in late 1992 (Kneiss, 1991).

In four inhalation studies conducted to date, MTBE has not induced developmental effects in rats, rabbits, or mice at doses below those that were toxic to the mother (Conaway *et al.*, 1985; Tyl, 1989; Biles *et al.*, 1987). Adverse effects on reproduction in the absence of parental toxicity have not been observed in one- and two-generation studies in rats (Biles *et al.*, 1987; Neeper-Bradley, 1991).

Methyl *tertiary*-butyl ether has been assayed in several *in vitro* and *in vivo* genotoxicity tests covering a range of genetic endpoints. Although there is no convincing evidence that MTBE is genotoxic in studies conducted to date, definitive conclusions cannot be reached because of the limitations of several of the available investigations.

2.7 Effects on Humans

Available data on the toxicity of MTBE to humans are restricted to case reports of adverse effects following its use as a treatment for gallstones. In general, only mild effects have been reported, including a faint odour on the breath, nausea, vomiting, drowsiness, and mild inflammatory changes in the gallbladder following repeated treatment with several millilitres of MTBE (Allen *et al.*, 1985; Sauerbruch *et al.*, 1985; Murray *et al.*, 1988; Thistle *et al.*, 1989; Van Sonnenberg *et al.*, 1991). Ponchon *et al.* (1988), however, noted the potential for adverse effects from treatment with MTBE, describing a case in which leakage of 15 mL of MTBE resulted in coma and acute renal failure.

2.8 Effects on the Environment

Few data are available on the toxicity of MTBE to aquatic biota. Data on acute toxicity are available for one species of invertebrate, four species of fish, and one species of amphibian. The experimental data ranged from a 96-hour LC_{50} of 672 mg/L for the fathead minnow, *Pimephales promelas* (Geiger *et al.*, 1988), to a 96-hour LC_{50} of > 10 000 mg/L for a copepod, *Nitocra spinipes* (Tarkpea and Svanberg, 1982).

No data are available for toxicity to wild mammals, birds, terrestrial plants, or soil biota. The toxicity of MTBE to wild mammals can be assessed by extrapolation from the results of toxicity studies conducted using laboratory mammals (see Section 2.6).

Methyl *tertiary*-butyl ether is not considered to be a greenhouse gas or to contribute to stratospheric ozone depletion, since its low rate of release to the atmosphere and its short atmospheric half-life (less than 12 days) result in very low atmospheric concentrations. Because MTBE is a volatile organic compound, it could contribute to the formation of ground-level ozone. The extent of its contribution is not known, but it is believed to be relatively small given the low concentrations of MTBE in air compared to those of other volatile organic compounds (CCME, 1990).

3.0 Assessment of "Toxic" Under CEPA

As described in the Introduction, the following assessment will consider the entry of MTBE to the environment, the exposure to humans and other biota, and potential harmful effects to humans and other biota.

3.1 Entry

From 1986 to 1990, Canada imported between 7000 and 25 000 tonnes/year of MTBE for the purpose of gasoline blending. Approximately 2% of the unleaded gasoline in Canada is blended with MTBE, which accounts for about 6.5 to 9.6% by volume of the resulting blend. It is expected that 500 000 tonnes/year will be produced in Canada starting in 1992, with most of this production being exported. Methyl *tertiary*-butyl ether can enter the environment at any stage in the production, storage, use, and transport of MTBE or MTBE-blended gasoline.

The largest environmental releases are likely to occur as fugitive emissions from chemical manufacturing plants, gasoline terminals, service stations, and spills. Therefore, although data are not available on the absolute amounts of MTBE entering the Canadian environment and on the resulting environmental concentrations, it is concluded that MTBE enters the Canadian environment.

3.2 Exposure

No data are available on environmental concentrations in Canada. Based on steady-state fugacity modelling, environmental concentrations in southern Ontario are estimated to be 1.5 ng/m^3 in air and 0.12 ng/L in water. Under a worst-case scenario, it was assumed that approximately 1% of the predicted Canadian MTBE production could be emitted to the environment, resulting in environmental concentrations of 75 ng/m^3 in air and 6 ng/L in water.

Human exposure to MTBE is difficult to estimate because of the lack of data on concentrations of MTBE in ambient and indoor air, drinking water, or in food in Canada, the United States, and other countries. Based on fugacity modelling, it is estimated that inhalation in air would be the principal route of exposure {e.g., 35 ng/day based on a predicted concentration of 1.5 ng/m^3 and an assumed inhalation volume of air for adults of 23 m^3 daily (EHD, 1988)}. Intake in drinking water would be considerably less {0.18 ng/day based on a predicted concentration of 0.12 ng/L and an assumed volume ingested of 1.5 L daily for adults (EHD, 1988)}. Based on data available concerning the physical/chemical properties of MTBE and the limited information on concentrations in shellfish, intake in food is expected to be negligible compared to that inhaled.

It is recognized that there may be additional exposure (including dermal) of the general population to MTBE at self-serve gasoline stations. Available data, however, are insufficient to estimate exposure from this source and absorption following dermal exposure appears to be limited.

It is estimated, therefore, that the average daily intake of MTBE for Canadian adults would not exceed 35 ng/day (< 0.5 ng/(kg b.w.·day) for a 70 kg man) (EHD, 1988). For 5- to 11-year-olds, the age group with greatest predicted exposure on a body weight basis, estimated intake is 0.67 ng/(kg b.w.·day) {assuming average body weight of 27 kg, inhalation volume of 12 m^3/day, drinking water intake of 0.3 L/day (EHD, 1988), and predicted concentrations of MTBE of 1.5 ng/m^3 in air and 0.12 ng/L in water}.

These estimated intakes are based on mean predicted concentrations in the general environment. Elevated levels, for example, present in groundwater in areas where underground storage tanks containing MTBE-blended gasoline have leaked, were not considered relevant to estimation of exposure for the general population.

3.3 Effects

3.3.1 *Human health*

Limited data are available on the toxicity of MTBE to human health. Epidemiological studies of exposed populations are not available and information on chronic toxicity or carcinogenicity in experimental animals has not been identified. An oncogenicity study is in progress, however, and should be completed within the next few years. Although there is no convincing evidence that MTBE is genotoxic from *in vitro* and *in vivo* studies covering a range of genetic endpoints, it is not possible to draw definitive conclusions due to the limitations of several of the available investigations. Methyl *tertiary*-butyl ether has been classified, therefore, in Group V (inadequate data to assess) of the classification scheme developed for use in the derivation of the "Guidelines for Canadian Drinking Water Quality" (EHD, 1989). In studies conducted to date, MTBE has also not induced adverse reproductive effects in rats or developmental effects in rabbits, rats, or mice at doses below those that were maternally toxic.

For compounds classified in Group V, a Tolerable Daily Intake (TDI) is derived on the basis of a no- or lowest-observed (adverse) effect level (NO(A)EL or LO(A)EL) in humans or animals divided by an uncertainty factor. With the exception of the one- and two-generation studies designed to specifically investigate reproductive and developmental effects (Biles *et al.*, 1987; Neeper-Bradley, 1991), the longest term studies of the effects of MTBE are sub-chronic investigations. Those in which an adequate range of endpoints has been examined are restricted to one oral (Robinson *et al.*, 1990) and two inhalation studies (Greenough *et al.*, 1980; Dodd and Kintigh, 1989) in rats. The inhalation studies are the most relevant to this assessment since, based upon concentrations in air and water predicted by fugacity modelling and a limited amount of information on MTBE levels in shellfish in Canada, air is expected to be the principal medium of exposure to MTBE for the general population. In an inhalation study conducted by Greenough *et al.* (1980), anaesthesia was the only adverse effect observed in rats at concentrations as low as 250 ppm (915 mg/m^3). However, this effect was not observed at higher concentrations in a more recent, extensive investigation on another strain of rats (Dodd and Kintigh, 1989). This was the most extensive subchronic study in which there was assessment of neurobehavioural effects and histopathological examination of the nervous system, in addition to traditional endpoints in groups exposed

to three concentrations and controls. The "NOAEL" in this study was considered to be 797 ppm (2915 mg/m^3) based on neurobehavioural effects, including increased body temperature in female rats, decreased hind limb grip in males, and increased motor activity in females observed at the next highest concentration. However, increases in the relative weights of the liver and kidney in males were recorded at 797 ppm (2915 mg/m^3). It might be more appropriate, therefore, to consider this concentration as a LOEL. On the basis of this "NOAEL", a Tolerable Daily Intake (TDI) is conservatively (owing to the paucity of available data), derived as follows:

$$\text{TDI} = \frac{2915 \text{ mg/m}^3 \times (6/24) \times (5/7) \times 0.144 \text{ m}^3/\text{d}}{10\,000 \times 0.25 \text{ kg}}$$

$$= \frac{75.5 \text{ mg / (kg b.w. • day)}}{2500}$$

$$= 0.030 \text{ mg / (kg b.w. • day)} \quad \text{which is: } 30 \text{ µg / (kg b.w. • day)}$$

$$\text{or } 30\,000 \text{ ng / (kg b.w. • day)}$$

where:

2915 mg/m^3= the "NOAEL" in the most extensive sub-chronic study by the most appropriate route of exposure (*i.e.*, inhalation) conducted to date (Dodd and Kintigh, 1989)

$6/24$ and $5/7$ = conversion of dosing for 6 hours/day, 5 days/week to continuous exposure

0.144 m^3/day = assumed inhaled air volume of adult rats (Altman and Dittmer, 1972)

0.25 kg = assumed body weight of adult rats (NIOSH, 1985)

10 000 = uncertainty factor (×10 for intraspecies variation; ×10 for interspecies variation; ×10 for less than chronic study; ×10 for lack of data on carcinogenicity and chronic toxicity and minimal effects - increases in liver and kidney weights in males - observed at the "NOAEL" in the critical study)

In the two-generation reproductive toxicity study conducted by Neeper-Bradley (1991), clinical signs and transient reductions in body weight were observed in F_0 and F_1 animals exposed to 3000 ppm (10 974 mg/m^3). Based on these results, the NOEL was considered to be 400 ppm (1463 mg/m^3), which is slightly less than the "NOAEL" from the subchronic study (Dodd and Kintigh, 1989) used here in the derivation of the TDI. However, the assessment of neurobehavioural effects and histopathological examination was more extensive and the difference between administered doses less in the subchronic study by Dodd and Kintigh (1989).

3.3.2 *Environment*

Very few data are available on the toxicity of MTBE to aquatic biota. The most sensitive species identified was the fathead minnow, with a 96-hour LC_{50} of 672 mg/L.

No data are available for toxicity of MTBE to wild mammals, birds, terrestrial plants, or soil biota. The effect levels reported in inhalation studies conducted on laboratory animals are considered relevant to wild mammals. The lowest reported effect level was 797 ppm (2915 mg/m^3) for rats under conditions of subchronic (13-week) exposure by inhalation.

3.4 Conclusions

Methyl *tertiary*-butyl ether is used in Canada for gasoline blending and is produced for export. Both sources can lead to entry of MTBE into the Canadian environment. This entry results in concentrations of MTBE that may be estimated for the various media to which humans and other organisms are exposed.

3.4.1 *Effects on the environment (Paragraph 11 (a))*

The concentration of MTBE in surface water predicted under a worst-case scenario (6 ng/L) is 1.12×10^8 times lower than the 96-hour LC_{50} for the fathead minnow (672 mg/L).

The highest predicted airborne concentration of MTBE (75 ng/m^3) is 3.9×10^7 times lower than the lowest reported effect level in a subchronic inhalation study in rats (2915 mg/m^3).

Given the low predicted concentrations of MTBE in the environment and the lack of bioaccumulation, concentrations in food for wildlife are expected to be at least several orders of magnitude lower than those causing acute toxicity. In addition, given the low toxicity of MTBE to aquatic organisms, wildlife food sources are not expected to be at risk due to environmental concentrations of MTBE.

Therefore, on the basis of available data, MTBE is not considered to be "toxic" as defined under Paragraph 11 (*a*) of CEPA.

3.4.2 *Effects on the environment on which human life depends (Paragraph 11 (b))*

Due to its low rate of release and its short persistence in the atmosphere, MTBE is not expected to be involved in global warming or in the depletion of stratospheric ozone. The contribution of MTBE to the formation of ozone in the lower atmosphere is believed to be relatively small because of its low predicted atmospheric concentrations.

Therefore, on the basis of available data, MTBE is not considered to be "toxic" as defined under Paragraph 11 (*b*) of CEPA.

3.4.3 *Effects on human health (Paragraph 11 (c))*

It is difficult to estimate exposure of the Canadian population owing to the lack of data on concentrations of MTBE in ambient and indoor air, drinking water, or food. Based on fugacity modelling and limited information on concentrations in shellfish, it is estimated that the average daily intake of MTBE for the age group of the Canadian population most exposed on a body weight basis (*i.e.*, 5- to 11-year-olds) is 0.67 ng/(kg b.w.·day). Although not based on actual data on concentrations in air, water or food, this estimated average daily intake is considerably less (by approximately 45 000 times) than the Tolerable Daily Intake previously derived.

Therefore, on the basis of available data, MTBE is not considered to be "toxic" as defined under Paragraph 11 (*c*) of CEPA.

3.4.4 *General conclusions*

Therefore, on the basis of available data, MTBE is not considered to be "toxic" as defined under Paragraphs 11 (*a*), (*b*) and (*c*) of CEPA.

4.0 Recommendations for Research and Evaluation

1. Given the almost total absence of data on environmental concentrations in Canada, concentrations of MTBE in air, water, groundwater, soil, and biota should be monitored in areas adjacent to major sources, including MTBE production and storage facilities, service stations, and areas of high vehicle traffic. This research is considered to be of medium priority.

2. Long-term toxicity tests should be undertaken using aquatic and terrestrial organisms. This research is considered to be of low priority.

3. When available, the results of the ongoing carcinogenicity bioassay and data on concentrations of MTBE in ambient air in Canada should be assessed with respect to their implications for a possible designation of "toxic" under the Act. This assessment is considered to be of high priority.

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