Health Canada Santé Canada

Guidelines for Canadian Drinking Water Quality:

Guideline Technical Document

Methyl *Tertiary*-Butyl Ether (MTBE)

Prepared by the
Federal-Provincial-Territorial Committee on Drinking Water
of the
Federal-Provincial-Territorial Committee on Health and the Environment

Health Canada
Ottawa, Ontario

July 2006

Canada

This document may be cited as follows:

Health Canada (2006) Guidelines for Canadian Drinking Water Quality: Guideline Technical Document — Methyl *Tertiary*-Butyl Ether (MTBE). Water Quality and Health Bureau, Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa, Ontario.

The document was prepared by the Federal-Provincial-Territorial Committee on Drinking Water of the Federal-Provincial-Territorial Committee on Health and the Environment.

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Methyl *Tertiary*-Butyl Ether (MTBE)

1.0 Guideline

The aesthetic objective (AO) for methyl tertiary-butyl ether (MTBE) in drinking water is 0.015 mg/L (15 µg/L). This AO is the odour threshold of MTBE.

2.0 Executive summary

MTBE has been used as a common additive in gasoline, to help improve combustion and reduce exhaust emissions. However, this use has decreased significantly, and only a small percentage of Canadian gasoline supplies currently contain MTBE.

Health Canada recently completed its review of MTBE in drinking water. Based on this review, it was concluded that the odour of MTBE would make drinking water unacceptable to Canadians at concentrations much lower than those that may pose a health risk. An aesthetic objective of 0.015 mg/L is established for MTBE in drinking water. However, considering the limitations in the available data related to potential health effects, Health Canada and the Federal-Provincial-Territorial Committee on Drinking Water will continue to monitor the scientific literature and revise or update the guideline and its technical document as required.

2.1 Health effects and aesthetic considerations

There are few scientific data available on the health effects of MTBE in drinking water. The studies that have been conducted suggest that MTBE may be a carcinogen in animals, but there are flaws in each of these studies that prevent their use as a basis for developing a health-based drinking water guideline.

Available studies in human volunteers show that the most significant effect of MTBE contamination of drinking water is its pungent odour and taste. Of these, the most suitable and sensitive parameter on which to set a drinking water guideline for MTBE is odour. This is consistent with the approach used by the U.S. Environmental Protection Agency, which established a range of 0.02–0.04 mg/L as an approximate “threshold” for humans to detect the taste and odour of MTBE in drinking water.

2.2 Exposure

There is little information available on the concentrations of MTBE in Canadian drinking water supplies. The use of MTBE in gasoline has been more widespread in the United States than in Canada. Data from the United States show that even in areas where MTBE is regularly added to the gasoline, concentrations of MTBE in drinking water are unlikely to exceed 0.002 mg/L. The major route of human exposure to MTBE is likely from air inhalation, not oral ingestion.

2.3 Analysis and treatment

There are several recognized methods for the analysis of MTBE in drinking water, which can detect MTBE at levels well below the aesthetic objective of 0.015 mg/L. The technology is available to remove MTBE from drinking water supplies. In municipal treatment plants, MTBE can be reduced to a concentration of 0.015 mg/L or less using air stripping followed by activated carbon. It has also been shown in a pilot plant that it is possible to reduce MTBE levels to 0.001 mg/L using activated carbon after a combination of oxidation steps. Residential drinking water treatment devices can be purchased that are certified to reduce MTBE levels to 0.005 mg/L.

3.0 Identity, use and sources in the environment

MTBE is an aliphatic ether with structural formula $CH_3OC(CH_3)_3$. It is a volatile, clear, flammable, colourless liquid at room temperature, with a terpene-like odour. It is chemically stable and does not polymerize or decompose at normal ambient temperatures (Finnish Environment Institute, 2001). MTBE is highly soluble in water (48 g/L at 25°C) (Budavari et al., 1996), other ethers and alcohol. It also readily mixes with gasoline. This volatile organic compound (VOC) has a relatively high vapour pressure (33.5 kPa at 25°C) and a low log octanol/water partition coefficient (1.3) (Mackay et al., 1993). The conversion factor for MTBE in air at 25°C is: 1 ppm = 3.61 mg/m^3.

MTBE is produced by the reaction of isobutylene with methanol over an acid catalyst. MTBE has been manufactered in Canada since 1992. It was imported into Canada in the late 1980s as an octane enhancer for unleaded gasoline, mostly to Ontario and Quebec, with smaller amounts going to Alberta and British Columbia. The major use of MTBE is as a gasoline additive, with consumption and production for this purpose increasing markedly in the 1990s in most parts of the developed world. MTBE is added to gasoline at levels of up to 15% by volume as an oxygenate to improve combustion and lower exhaust emissions, particularly carbon monoxide emissions. Data collected by Environment Canada (2000) show that the use of MTBE in Canadian gasoline varies greatly by region. Atlantic Canada has by far the highest MTBE use (average level 0.85% by volume), followed by the West, mostly British Columbia (average level 0.21% by volume), and very little is used in Central Canada. Gasoline containing MTBE accounted for 10% of the Canadian gasoline pool in 1998 and 2% in 2000, and the percentage was projected to drop to below 1% by the end of 2001 (Environment Canada, 2003).

Fugitive emissions from gasoline refineries and gasoline filling stations are major environmental point sources of MTBE, whereas vehicles themselves emit sufficient MTBE to be a significant source in dense traffic areas. Surface water can be contaminated by gasoline spills and by the use of gasoline-powered boats, particularly those using two-stroke engines. Owing to the volatility of MTBE, most is lost to evaporation before it can become a drinking water problem. Spills and leaking storage tanks can cause more serious problems in groundwater. MTBE does not adsorb to soil particles to a great degree and is considered mobile (Environment Canada, 1993). It is also resistant to chemical and microbial decomposition in water (ATSDR, 1996).

This is seen as a serious potential long-term threat to drinking water supplies if MTBE comes to be widely used in gasoline.

4.0 Exposure

There are very few data available with which to establish the frequency of detection and level of MTBE in Canadian drinking water supplies. MTBE was detected in groundwater at 250 locations and in every Canadian province. Levels ranged from <0.005 to >3.4 mg/L, and 60% of samples contained MTBE at concentrations above 0.02 mg/L. Approximately 75% of samples were found in Western Canada. The majority (67%) of contaminated groundwater samples were measured at active or former service stations (Environment Canada, 2003).

Alberta collected data on levels of MTBE in drinking water from January 1998 to the end of 2000 but found only three positive samples, which were close to the limits of detection (Alberta Ministry of Environmental Protection, 2003). In Prince Edward Island, six groundwater sources used for drinking water had concentrations that ranged from 1 to 5 µg/L. After remediation, half of the sites had levels below 0.1 µg/L (Environment Canada, 2003).

The use of MTBE in gasoline has been more widespread and of longer duration in the United States than in Canada; hence, there are more data available from the United States. It has been estimated that 30% of the U.S. population lives in areas where MTBE is regularly added to the gasoline; even in these areas, it is unlikely that the MTBE level in drinking water will exceed 2 µg/L in 95% of cases, with possibly 5% showing higher levels in the vicinity of major spills and leaks (Stern and Tardiff, 1997). A study by the American Water Works Service Company was based on 2120 samples from 450 drinking water wells in 16 states. Forty-four samples (2%) from 17 wells (4%) were positive for MTBE, with a lower reporting limit of 0.2 µg/L and a maximum measured level of 8 µg/L (Siddiqui et al., 1998). In New Jersey, gasoline has contained between 10 and 15% MTBE for several years, and MTBE was detected in 82 out of 1300 samples of drinking water collected; the mean MTBE level was reported to be 0.2 µg/L, with the highest reported level being 16.4 µg/L (OSTP, 1998). Even in the United States, the database is not sufficient to give an accurate national picture, since MTBE has not been a mandated U.S. Environmental Protection Agency (EPA) reporting requirement.

The main source of human exposure to MTBE is likely from air inhalation, not oral ingestion (Health Canada, 1999). There are a large number of data available on ambient air levels. Indoor air data are all linked to ambient levels, with no consideration being given to a contribution from contaminated drinking water. Microenvironments such as gasoline filling stations or vehicles used for commuting on urban roads have also been studied. In a report commissioned by Health Canada, data from Alaska and Connecticut were used to model general human exposure to MTBE in various microenvironments for different age groups (Health Canada, 1999). For all except the 0- to 0.5-years age group, the largest exposure came from commuting in a vehicle, with indoor air being the second most important source. For the 0- to 0.5-years age group, indoor air was the most important source, presumably since there is very little commuting activity in vehicles at this age. In this age range, drinking water ingestion (for non-breast-fed infants) can

contribute up to 10% of total exposure (when considering water intake relative to body weight); in other age ranges, it is only about 2%. In the 20- to 59-year age group for an area where gasoline contains 15% MTBE, the mean and standard deviation for total exposure were modelled at 4.8 ± 1.8 µg/kg bw per day (Health Canada, 1999). Because of its volatility, there is potential for exposure in the home to airborne MTBE release from severely contaminated groundwater.

High ambient air concentrations of MTBE have occasionally been detected downwind of refineries that use MTBE (Environment Canada, 1996), and occupational exposure can obviously be much higher than the levels given above for the general population (IPCS, 1998).

5.0 Analytical methods

According to Rhodes and Verstuyft (2001), "on most chromatographic columns, MTBE comes off before the volatile range organics and may not be included in the volatile range result." Thus, owing to the volatility of MTBE, analytical methods for measuring MTBE in drinking water are based on purge and trap or head space gas chromatography (GC) using photoionization detectors (PIDs) or mass spectrometry (MS) detection (Rhodes and Verstuyft, 2001).

Two U.S. EPA methods (EPA Method 502.2 Rev. 2.1 and EPA Method 524.2 Rev. 4.1) are approved for measuring MTBE in drinking water. EPA Method 502.2 employs purge and trap capillary GC with PIDs and electrolytic conductivity detectors in series but does not list a method detection limit (MDL). EPA Method 524.2 uses purge and trap capillary GC with MS detectors in series and has an MDL of 0.09 µg/L (U.S. EPA, 2001).

The U.S. EPA (2001) recognizes four methods as being equivalent to the EPA standard methods for measuring MTBE in drinking water. The equivalent methods include American Society for Testing and Materials standard method D5790-95 (ASTM, 1996, 1998) and the American Public Health Association standard methods SM 6210D (APHA et al., 1992, 1995), SM 6200B (APHA et al., 2005) and SM 6200C (APHA et al., 2005). Methods SM 6200B and SM 6200C have an MDL of 0.45 and 0.41 µg/L , respectively (U.S. EPA, 2001). U.S. EPA methods specify that sample preparation for these methods must be conducted as specified in EPA Method 524.2 (Rhodes and Verstuyft, 2001).

Health Canada (1995) has used a technique based on EPA Methods 524 and 624 and utilizing purge and trap followed by GC. Using this method, the detection limit obtained for MTBE, based on a 5-mL sample, was 0.06 µg/L. Because MTBE is a solvent used to prepare some types of samples, achieving low levels of detection will depend on stringent control of analytical steps to prevent cross-contamination from MTBE that is normally present in some laboratories.

The U.S. EPA (2001) has established a minimum reporting level of 5 µg/L for MTBE in drinking water.

6.0 Treatment technology

6.1 Municipal-scale

Municipal water filtration plants that rely on conventional water treatment techniques (coagulation, sedimentation, precipitative softening, filtration and chlorination) have been found to be ineffective in reducing concentrations of VOCs in drinking water (Robeck and Love, 1983).

There are three existing technologies that public water systems can use to reliably remove MTBE from municipal drinking water: air stripping, activated carbon and advanced oxidation (Greene and Barnhill, 2001).

Air stripping is used for removing MTBE from drinking water sources in locations across the United States. However, MTBE is stripped from water at a relatively low rate (Greene and Barnhill, 2001).

Activated carbon adsorption is widely used to remove organic compounds such as MTBE from potable water. Granular activated carbon alone has a limited ability to take up MTBE, but a combination of air stripping and activated carbon in series has been successful in reducing MTBE to levels of 0.015 mg/L or less (Greene and Barnhill, 2001).

Advanced oxidation technologies are based on oxidation of contaminants using appropriate combinations of ultraviolet (UV) light, chemical oxidants and catalysts. Advanced oxidation has been shown to oxidize a wide range of organic chemicals, including MTBE. Advanced oxidation using UV and hydrogen peroxide has also been successful. In addition, when an activated carbon step is added after the oxidation step, this system can achieve relatively high removal rates, leaving very low residual levels of MTBE in the finished water. Using this combination, a pilot plant in Santa Monica, California, has reliably produced finished water with an MTBE level of 0.001 mg/L from raw water containing 1 mg MTBE/L (Greene and Barnhill, 2001).

6.1.1 Emerging municipal-scale treatment technologies

New drinking water treatment technologies for MTBE are being developed but are still mostly in the experimental stage. Some emerging treatment technologies include the following:

- *Synthetic resin adsorbents* — Resins are available that have a much higher adsorbent capacity for MTBE relative to activated carbon (Greene and Barnhill, 2001).
- *Electron beam* — This technology relies on the generation of electrons and hydroxyl radicals that rapidly oxidize chemicals in water (Kang et al., 1999).
- *Fluidized bioreactors* — Bioreactors use activated carbon to support microbial growth so that contaminants are either adsorbed onto the carbon or destroyed by resident microbes as the contaminants pass through the activated carbon unit (Greene and Barnhill, 2001).
- *Membranes* — Although membranes have been found to be effective in removing MTBE in residential-scale treatment devices, large-scale systems are in the developmental stage.

6.2 Residential-scale

Municipal treatment of drinking water is designed to reduce contaminants to levels at or below the guideline value. As a result, the use of residential-scale treatment devices on municipally treated water is generally not necessary but primarily based on individual choice.

In cases where an individual household obtains its drinking water from a private well, residential drinking water treatment devices may be an option for removing MTBE from the water. Residential treatment devices are available that are affordable and can remove MTBE from drinking water to make it compliant with the applicable guidelines or regulations. The most common types of treatment devices available for the removal of MTBE from drinking water in a residential setting are activated carbon filters and reverse osmosis systems. Treatment devices that are certified to remove MTBE incorporate some type of adsorption technology, usually activated carbon, or utilize reverse osmosis, usually in combination with one or more adsorption-type filters.

Water treatment systems are available that can remove or reduce MTBE. However, these systems can effectively remove MTBE only if they are properly installed and maintained. Home filtration systems may be installed at the faucet (point of use) or where water enters the home (point of entry). Certified point-of-use treatment devices are currently available for the reduction of MTBE. Periodic laboratory testing should be conducted on both the water entering a treatment device and the finished water it produces to verify that the treatment device is effective (NHDES, 2002). Treatment devices that remove MTBE from untreated water (such as from a private well) should be certified for the removal of MTBE. These treatment devices are certified to reduce MTBE levels from an average influent (challenge) concentration of 0.015 mg/L to a finished effluent concentration of 0.005 mg/L or less (NSF International, 2005).

Health Canada does not recommend specific brands of treatment devices, but it strongly recommends that consumers look for a mark or label indicating that the device has been certified by an accredited certification body as meeting the appropriate NSF International (NSF)/American National Standards Institute (ANSI) standard. These standards have been designed to safeguard drinking water by helping to ensure material safety and performance of products that come into contact with drinking water. Certification organizations provide assurance that a product or service conforms to applicable standards and must be accredited by the Standards Council of Canada (SCC). The following organizations have been accredited by the SCC to certify drinking water devices and materials as meeting NSF/ANSI standards:

- Canadian Standards Association International (www.csa-international.org);
- NSF International (www.nsf.org);
- Water Quality Association (www.wqa.org);
- Underwriters Laboratories Inc. (www.ul.com);
- Quality Auditing Institute (www.qai.org); and
- International Association of Plumbing & Mechanical Officials (www.iapmo.org).

An up-to-date list of accredited certification organizations can be obtained from the SCC (www.scc.ca).

7.0 Kinetics and metabolism

A 1997 study of radiolabelled MTBE in male and female Fischer-344 rats through four routes of administration (intravenous, oral, dermal and inhalation) confirmed that MTBE is rapidly absorbed by all routes except dermal and that the major routes of excretion are via expired air and urine (Miller et al., 1997). In the oral part of the study, doses of 40 and 400 mg/kg bw were used, and elimination half-lives from plasma were found to be 0.52 and 0.79 hour, respectively. Although *tertiary*-butyl alcohol (TBA) was the major metabolite found in blood, the major metabolites in urine were 2-methyl-1,2-propanediol and 2-hydroxyisobutyric acid for all routes of exposure. In another study in rats, ^{12}C- and ^{13}C-labelled MTBE and TBA were used to confirm that the major urinary metabolites are 2-methyl-1,2-propanediol and 2-hydroxyisobutyric acid (Bernauer et al., 1998).

There is evidence that the metabolism of MTBE is similar in rats and humans (Nihlén et al., 1998; Amberg et al., 1999), although there are some differences. For instance, urine metabolites 2-methyl-1,2-propanediol and 2-hydroxyisobutyric acid and blood metabolite TBA have all been identified in rats and humans, but the urine metabolite TBA has been identified only in humans (Nihlén et al., 1998; Amberg et al., 2001). Also, it has been shown *in vitro* that rat and mouse liver microsomes metabolize MTBE at an activity rate approximately twofold higher than in human microsomes (Hong et al., 1997). It appears that the metabolic pathway in both humans and rats leads first to oxidation by cytochrome P-450 (CYP) to TBA, which is then further oxidized to 2-methyl-1,2-propanediol and 2-hydroxyisobutyric acid. The microsomal enzymes responsible for metabolizing MTBE to TBA in rats have been demonstrated to be primarily CYP 2A6, with some activity from CYP 2E1 (Hong et al., 1999). Based on *in vitro* studies with rat liver microsomes, it appears that formaldehyde is also formed during the initial oxidation step (Brady et al., 1990).

Several inhalation studies with human volunteers exposed to MTBE show rapid uptake and moderately fast elimination from the blood. A study with 10 male volunteers exposed during light exercise in a chamber to three concentrations of MTBE (18, 90 and 180 mg/m^3) for 2 hours gave linear kinetics up to the highest concentration used. The kinetics profile was described as having four elimination half-lives from blood of 1 minute, 10 minutes, 1.5 hours and 19 hours (Nihlén et al., 1998). Urinary excretion was biphasic, with mean half-lives of 20 minutes and 3 hours. TBA was identified in both blood and urine following inhalation exposure (Nihlén et al., 1998).

Two recent human volunteer studies provide greater information on the kinetics and metabolism of orally administered MTBE in humans. Amberg et al. (2001) conducted a clinical study in which 5 and 15 mg of ^{13}C-labelled MTBE dissolved in 100 mL water were orally administered to six human volunteers and concentrations of metabolites in blood, urine and exhaled breath were observed. Maximum concentrations of MTBE and TBA in blood and exhaled breath were detected in the first 10–20 minutes after exposure. MTBE metabolism occurred with three elimination half-lives, and concentrations decreased to non-detectable levels after 12 hours; slower excretion of TBA in blood followed first-order kinetics, and concentrations were still

detectable 24 hours after dosing. Both MTBE and its metabolite TBA were present in blood. Metabolites present in urine were found to be identical to those found in human urine after inhalation exposure, with 2-hydroxyisobutyrate the major metabolite excreted and TBA, 2-methyl-1,2-propanediol and MTBE the minor products excreted. The minor urinary metabolites TBA and 2-methyl-1,2-propanediol were eliminated rapidly and were undetectable after 48–66 hours, whereas 2-hydroxyisobutyrate was still present in low concentrations up to 96 hours after administration. Differences in blood concentrations between equivalent oral and previously determined inhalation MTBE doses were attributed to differences in blood sampling design rather than evidence of hepatic first-pass effects; this was also supported by high percentages of recovered MTBE in exhaled breath. The authors concluded that excretion kinetics of oral MTBE exposure in humans were similar to the excretion kinetics following human inhalation exposure, as detailed in Amberg et al. (1999), and that differences in disposition and elimination did not differ by route of exposure.

Prah et al. (2004) published a study in which 14 volunteers were each exposed to MTBE via three routes, each administered 1 week apart. Volunteers drank 2.8 mg MTBE in 250 mL of sports drink (which masked the unpleasant taste of the chemical), were exposed for 1 hour dermally to MTBE dissolved in tap water at 51.3 µg/mL and inhaled 3.1 ppm MTBE in air for 1 hour. Concentrations of MTBE and metabolites in blood and exhaled breath were compared among the three exposure routes for up to 24 hours. Maximum concentrations of MTBE in blood were detected at 15 minutes via oral exposure, at 60 minutes via inhalation exposure and at 65 minutes via dermal exposure. MTBE in blood and exhaled breath followed a three-compartment model for all three exposure routes, with shortest half-lives for inhalation exposures and longest for dermal exposures. At 24 hours, MTBE declined to below the detection limit. The metabolite TBA was found in higher blood concentrations via the oral route than via the inhalation or dermal route and was still elevated above pre-exposure baseline levels at 24 hours. It was suggested that this was due to the occurrence of first-pass metabolism, based on TBA's water solubility and its blood/air partition ratio, which would reduce its ability to be eliminated by exhalation. A dermal permeation coefficient was estimated to be 0.028 cm/h, similar to that of ethyl ether. This study demonstrated that MTBE can be absorbed dermally from an aqueous medium in measurable quantities. The authors concluded that if MTBE is the critical toxicant, then exposure via the oral route might actually reduce the risk of adverse effects; however, if TBA is the critical toxicant, then MTBE exposure by dermal or inhalation exposure (which would produce proportionally less TBA) might reduce toxic effects.

8.0 Health effects

8.1 Effects in humans

There have been no epidemiological or occupational studies of human health effects following oral ingestion of MTBE. There have been numerous studies of the human response to MTBE in air, particularly in areas where MTBE has been added to gasoline. Following the

introduction of gasoline containing 15% v/v MTBE to Alaska in 1992, there were numerous consumer complaints of headaches, eye irritation and coughs (Beller and Middaugh, 1992). A similar response was observed coinciding with the introduction of 11% by volume of MTBE into gasoline in Milwaukee, Wisconsin, in 1995. Controlled studies of human physiological responses to MTBE have given uncertain results and have been discussed in depth in several reviews (U.S. EPA, 1997; IPCS, 1998). In general, no measurable changes were observed in subjects exposed to levels of MTBE in air that caused many complaints of such non-specific effects as headache and irritation.

8.2 Effects on experimental animals and *in vitro*

Most toxicological studies in animals have focused on inhalation exposure, but this review will focus on the few oral studies, except where their paucity necessitates using inhalation data to provide vital information. Most of the oral studies use dosing by gavage with MTBE in corn oil rather than in the drinking water; this limits the relevance of these studies in a human risk assessment for drinking water, as corn oil can affect the rate and extent of absorption of volatile organic solvents compared with their administration in drinking water.

8.2.1 Acute toxicity

The LD_{50} of MTBE by gavage in rats was reported in an unpublished study as 3866 mg/kg bw (ARCO Chemical Company, 1980). Death is associated with central nervous system depression, laboured respiration and ataxia. These data indicate a low acute toxicity.

8.2.2 Short-term exposure

In a 2-week study of MTBE in a corn oil vehicle administered by gavage at 0, 357, 714, 1071 or 1428 mg/kg bw per day to male and female Sprague-Dawley rats (10 per dose group), the highest dose produced immediate anaesthesia, with complete recovery within 2 hours. The only other clinical sign was loose stools throughout the study in the treated animals, which could be due to the irritative effect on the gastrointestinal tract from a single large bolus dose. There was a dose-related decrease in body weight gain, but it was statistically significant only in the females at the highest dose. A statistically significant increase in relative kidney weights was observed in both sexes at the highest dose and in the males at the 1071 mg/kg bw per day dose. All exposed female rats had statistically significantly lower relative lung weights. Cholesterol levels were significantly increased in the high-dose males and in the two mid-dose female groups. Blood urea nitrogen and creatinine were significantly decreased in the high-dose females. None of these effects on clinical chemical parameters showed a clear dose–response relationship. Of most significance was increased renal tubular disease (hyaline droplet nephropathy) in the dosed male rats (Robinson et al., 1990). The no-observed-adverse-effect level (NOAEL) was set at 714 mg/kg bw per day based on increases in relative kidney weight.

The same authors conducted a similar study over a 90-day period. The doses of MTBE were 0, 100, 300, 900 or 1200 mg/kg bw per day in corn oil administered to groups of 10 male

and female Sprague-Dawley rats. A brief episode of anaesthesia was again observed at the highest dose. All treated groups displayed diarrhoea throughout the study. Again, the only statistically significant effect on body weight was in the high-dose females. Relative kidney weights were increased in the top three dose groups of female rats and in the top two groups of male rats. Relative liver weights were increased in the male rats at the two highest dose levels. In the female rats, the relative liver, thymic and cardiac weights were increased at the 900 mg/kg bw per day dose level. Blood urea nitrogen was decreased and cholesterol elevated at all dose levels in the female rats, but there was no dose–response relationship; hence, these changes could not be used in setting a NOAEL. Based on an increase in relative kidney weight, the NOAEL was set at 100 mg/kg bw per day (Robinson et al., 1990).

The only neurotoxicity studies found for MTBE were those where exposure was by the inhalation route. A single 6-hour exposure of male and female F344 rats to 800 ppm MTBE had no apparent effect, but there were laboured respiration, ataxia, decreased muscle tone, abnormal gait, impaired treadmill performance and decreased hind limb grip strength at 4000 and 8000 ppm. These effects were not observable 6 and 24 hours after exposure had ceased (Daughtrey et al., 1997).

An extension of the study reported above to 13 weeks of daily exposure under the same conditions gave very similar results. There was an absolute, but not relative, decrease in brain weight in the high dose group. No significant changes were observed in brain or peripheral nervous system histopathology that were attributable to MTBE (Miller et al., 1997). The NOAEL from these studies was set at 800 ppm, equivalent to a dose of 210 mg/kg bw per day.

8.2.3 Long-term exposure and carcinogenicity

There are three long-term rodent studies with MTBE that examined potential carcinogenicity. Two were by the inhalation route, and one was by gavage. The oral study used groups of 60 male and female Sprague-Dawley rats dosed by gavage with MTBE dissolved in olive oil at 0, 250 or 1000 mg/kg bw per day, 4 days/week, for 104 weeks (Belpoggi et al., 1995). Dosing commenced at 8 weeks of age, and the animals were maintained until natural death. There were no significant effects of the MTBE treatment on body weight gain or on food or water consumption, despite the fact that the authors stated that the reason that the animals were dosed for only 4 days/week was that the highest dose would not have been tolerated by the rats if it had been given every day. There was a dose-related increase in the incidence of leukaemia and lymphomas (control, 2/60; 250 mg/kg bw per day, 6/60; 1000 mg/kg bw per day, 12/60) in the female rats, but none in the male rats. There was also a significant increase in testicular interstitial Leydig cell adenomas in the high-dose males (control, 2/60; 250 mg/kg bw per day, 2/60; 1000 mg/kg bw per day, 11/60). The results of this study have been subject to detailed critiques by at least two groups of reviewers, which have focused on a lack of detail in the reporting and on the conduct of the histopathology (U.S. NSTC, 1997; IPCS, 1998), and a request for a pathology review by the U.S. Interagency Oxygenated Fuels Assessment Steering Committee has not been successful. In addition, other studies of MTBE by inhalation and oral exposure have resulted in various

changes to kidney structure and function in male rats, as well as some central nervous system depression in both sexes (Robinson et al., 1990; Bird et al., 1997). However, these effects were not reported by Belpoggi et al. (1995), which is an unexplained inconsistency; consequently, this study is not deemed to be useful in a human health risk assessment.

The two inhalation studies, one in CD-1 mice (Burleigh-Flayer et al., 1992) and the other in F-344 rats (Chun et al., 1992), have been summarized in a single publication in the peer-reviewed literature (Bird et al., 1997). In both studies, 50 animals per sex were exposed to 0, 400, 3000 or 8000 ppm MTBE vapour in air for 6 hours/day, 5 days/week. Mice were exposed for 18 months and rats for 24 months. Both species showed central nervous system depression at the 8000 ppm dose, although the rats adapted after 1 week. In the mice, there was reduced body weight gain (males, 16%; females, 24%) and early mortality at the highest dose. At both 3000 and 8000 ppm , there were increases in absolute and relative liver weights in both sexes and in kidney weights in the males. The only carcinogenic effect seen was an increased incidence of hepatocellular adenomas in female mice at the 8000 ppm dose; however, as these results were detected only at the highest dose, which exceeded the maximum tolerated dose, the authors of the study did not consider these tumour findings to result from a direct DNA-acting phenomenon (U.S. EPA, 1997).

In the rat study, the males dosed at 3000 and 8000 ppm had to be euthanized early due to severe progressive nephrosis. Absolute and relative liver and kidney weights for the females were increased in the 3000 and 8000 ppm groups (liver, 20% and 42%; kidney, 18% and 29%), but there were no histopathological changes in the livers. Chronic nephropathy was increased in all treated males and in the females at 3000 and 8000 ppm. The combined incidence of renal tubular adenomas and carcinomas was significantly increased in the male rats at the 3000 ppm dose level. The significance of this effect to human risk assessment has been brought into question because of evidence that MTBE causes a mild induction of α-2u-globulin nephropathy and enhanced renal cell proliferation in male F344 rats (Prescott-Mathews et al., 1997). This effect is species- and sex-specific and is not seen in humans. As was seen in the oral study in rats discussed previously, there was a significant increase in the incidence of interstitial testicular Leydig cell adenomas in this study. However, in the inhalation study, the effect was not significant in comparison with historical data from F344 control rats from the facility.

8.2.4 Mutagenicity/genotoxicity

A large number of studies using *in vitro* and *in vivo* mammalian and non-mammalian systems have been conducted to assess the mutagenicity of MTBE. A detailed review has been conducted by IPCS (1998). The majority of these studies have produced negative results. One positive result was in a study that found that MTBE induced forward mutations in the mouse lymphoma cell line with microsomal activation. It is believed that the positive result was due to the formaldehyde formed by microsomal metabolism (Mackerer et al., 1996). Williams-Hill et al. (1999) reported increased mutagenicity in *Salmonella typhimurium* TA102 by MTBE and TBA. However, two independent laboratories did not replicate this result (McGregor et al., 2005). A

comprehensive study with five strains of *Salmonella typhimurium* with and without metabolic activation using doses of MTBE up to 10 mg per plate was completely negative (Cinelli and Seeberg, 1989). This conclusion is supported in other work (Cinelli et al., 1992). Despite one positive report of unscheduled DNA synthesis (UDS) (Zhou et al., 2000), the literature generally reports negative UDS results: MTBE did not induce UDS in primary rat hepatocytes (Seeberg, 1989), nor was UDS seen in other *in vitro* (Cinelli et al., 1992) and *in vivo* UDS assays (Vergnes and Chun, 1994; McKee et al., 1997). MTBE also did not significantly increase the frequency of recessive lethal mutations in *Drosophila melanogaster* (Sernau, 1989), did not significantly increase the incidence of chromosome aberrations in rat bone marrow cells (Vergnes and Morabit, 1989), did not induce micronuclei *in vivo* in mouse bone marrow cells (Vergnes and Kintigh, 1993) and did not significantly increase the frequency of somatic cell mutations or chromosome aberrations in spleen lymphocytes in mice (Ward et al., 1994). The weight of evidence suggests that MTBE is not genotoxic.

8.2.5 Reproductive and developmental toxicity

There are no published reproduction studies with MTBE administered by the oral route. A two-generation inhalation reproduction study in male and female Sprague-Dawley CD rats used concentrations of 0, 400, 3000 or 8000 ppm MTBE for 6 hours/day, 5 days/week, for 10 weeks prior to mating and during mating, gestation and lactation days 5–21. At the two highest doses, significant reductions in body weight and body weight gain were seen in the male and female F_1 and F_2 pups during the later periods of lactation. Pup survival was significantly reduced in the F_1 litters on lactation days 0–4 and in F_2 litters on postnatal day 4 in the 8000 ppm dose group. Clinical signs of toxicity (hypoactivity and lack of startle reflex) were noted in adults of both generations at the two highest doses. Increased liver weights were reported in the F_1 generation at 3000 and 8000 ppm in both sexes, but no histopathological effects were noted (Bevan et al., 1997a). No evidence of reduced fertility was observed. The NOAEL for parental and pup toxicity was 400 ppm (105 mg/kg bw per day).

Two major developmental studies by the inhalation route are available. A study in rats and mice was performed at 0, 250, 1000 or 2500 ppm MTBE for 6 hours/day on days 6–15 of gestation. The dams were sacrificed on day 20 for rats and day 18 for mice. No effects were seen even at the highest dose in the rats. In the mouse study, dose-related increases in skeletal malformations were observed, but they were not statistically significant (Conaway et al., 1985). In another study, mice and rabbits were exposed to 0, 1000, 4000 or 8000 ppm MTBE on days 6–15 of gestation (mice) and on days 6–18 of gestation (rabbits). Mouse dams were sacrificed on gestation day 18 and rabbit dams on day 28. In the rabbit study, no developmental effects were seen at any dose, but maternal toxicity was seen at the two highest doses. In the mice, maternal toxicity was again seen at the two highest doses. Fetal skeletal variations and a reduction in fetal weight were seen at the higher doses (Bevan et al., 1997b). Skeletal developmental effects were seen in both mouse studies; based on these studies, the U.S. EPA (1997) derived a lowest

developmental NOAEL of 250 ppm (65.6 mg/kg bw per day). However, none of these developmental effects met statistical significance, although there was a dose-related trend.

Moser et al. (1996, 1998) studied the potential antiestrogenic effects of MTBE in mice. A number of adverse effects of MTBE on the reproductive system of mice were demonstrated, including lower relative uterine and ovarian weights, increase in overall length of the estrous cycle and changes in histology of the uterus, cervix and vagina indicative of decreased estrogen action. However, the authors were unable to identify the mechanism of MTBE-induced reduction in estrogen action, suggesting that MTBE may exert an antiestrogenic action by a mechanism that does not involve a change in circulating estrogen or estrogen receptor binding.

8.2.6 Mode of action

The metabolite TBA administered in drinking water to Fischer-344 rats was associated with increased incidences of renal tubular adenoma and carcinoma in the males and also increased the severity of chronic progressive nephropathy (Cirvello et al., 1995). In $B6C3F_1$ mice, TBA produced thyroid follicular cell adenoma and hyperplasia in the females and inflammation and hyperplasia of the urinary bladder in both sexes (Cirvello et al., 1995). It is apparent that some, but not all, of the cancers seen following MTBE administration could be attributable to metabolites.

An *in vitro* study published by Iavicoli et al. (2002) examined the effects of MTBE on cell proliferation and cell cycle distribution and its ability to transform cultured rodent fibroblasts. The results showed that extracellular MTBE significantly inhibited the growth of normal rat fibroblasts by decreasing cell growth in a time- and dose-dependent manner, likely through inhibition of cell proliferation rather than direct cytotoxic effects (i.e. necrosis). In addition, it was also demonstrated that MTBE reduced the percentage of cells in the G2/M-phase and caused a compensatory accumulation of cells in the S-phase of the cell cycle. Furthermore, evidence demonstrating apoptosis was observed, although the exact mechanism was not determined. Finally, it was demonstrated that MTBE caused a 2.5-fold increase in the number of transformed cells in mouse fibroblasts even after short-term 24-hour exposure. The authors concluded that the effects of MTBE on rodent fibroblasts are consistent with other *in vivo* models of tumorigenesis and that MTBE should be considered a potential carcinogen.

In a study by de Peyster et al. (2003), mechanisms of action of Leydig cell carcinogenesis were investigated in male Sprague-Dawley rats, both *in vivo* and *in vitro*. This study was undertaken with the assumption that high concentrations of MTBE were indeed responsible for increased Leydig cell tumour incidence from previous cancer bioassays (Chun et al., 1992; Belpoggi et al., 1995). Results demonstrated that *in vitro*, Leydig cell testosterone production declined following exposure to high levels of MTBE or TBA. High-dose gavage also showed decreases in circulating testosterone levels immediately following treatment; however, the longer the sampling or the lower the dose, the less dramatic or even non-detectable the testosterone reduction after 28 days of treatment. Reduced testosterone occurred at times when there was no clear evidence that changes in other hormones (such as decreases in luteinizing hormone and

prolactin or increases in corticosterone) were responsible for the increase. The exact mechanism of rat Leydig cell carcinogenesis was not determined, although a number of known mechanisms, including peroxisome proliferation (a characteristic of some Leydig cell carcinogens), were rejected. Overall, the authors suggested that the mechanism underlying MTBE Leydig cell carcinogenesis could involve inhibition of testosterone synthesis in the Leydig cell. The exact mechanism is likely to be complex or multifaceted, and changes in liver, thyroid and adrenals could be possible contributors.

9.0 Aesthetic considerations

From a drinking water perspective, one of the most important aspects of MTBE is its objectionable taste and odour. The U.S. EPA (1997) set a non-statutory drinking water advisory for MTBE in drinking water of 20–40 µg/L based on its unpleasant taste and odour. This range of values was derived from four literature citations, one of which showed that odour tended to have a lower threshold of detection than taste, whereas two others showed the opposite relationship. The taste and odour responses reported were in the range of 15–180 µg/L for odour and 24–135 µg/L for taste. The cited studies all used comparatively small numbers of human subjects and gave a wide range of results, indicative of the variability in individual responses. The four studies included those by Young et al. (1996), in which the geometric means for taste and odour were 48 and 34 µg/litre, respectively; the American Petroleum Institute (API, 1993), in which calculated threshold values were 39 µg/L for taste, 45 µg/L for odour detection and 55 µg/L for odour recognition and subjects described the taste of MTBE in water as "nasty," bitter, nauseating and similar to that of rubbing alcohol; Prah et al. (1994), in which the concentration of MTBE in distilled water that was identified as having an odour by 50% of the study participants was 180 µg/L; and Dale et al. (1997), in which the range for 60% probability of detecting the odour of MTBE in odour-free water was 43–71 µg/L, whereas the corresponding range for taste was 24–37 µg/L.

A recent study specifically designed to set an odour threshold for MTBE in drinking water used a panel of 57 people and a protocol based on the American Society for Testing and Materials method E679-91 (Stocking et al., 2001). Eight concentrations of MTBE in water ranging between 2 and 100 µg/L were used with a 1.75 step factor. The geometric mean detection threshold for the 57 subjects and the recommended odour threshold was 15 µg/L.

10.0 Classification and assessment

The available scientific data on the health effects of MTBE are considered inconclusive, which limits their use for human carcinogenic risk assessment. MTBE has been classified in Group VIA, unclassifiable with respect to carcinogenicity in humans, because data from epidemiological and/or animal studies are inadequate due to major qualitative or quantitative limitations (Health Canada, 1994). This categorization is supported by the International Agency for Research on Cancer (IARC, 1999), which has classified MTBE in Group 3, not classifiable as to

its carcinogenicity to humans, based on limited evidence in experimental animals and inadequate evidence in humans

The weight of evidence suggests that MTBE is not genotoxic. A large number of studies using *in vitro* and *in vivo* mammalian and non-mammalian systems have been conducted to assess the mutagenicity of MTBE. With one exception, these studies have all produced negative results. The one positive result may have been due to the formaldehyde formed by microsomal metabolism. These results suggest that the mechanism of action of MTBE is more likely to be non-genotoxic than genotoxic, although no one mechanism appears to explain all of the observed effects.

No human cancer studies in relation to MTBE exposure have been published for either the general population or occupationally exposed cohorts. There have been three lifetime rodent studies conducted with MTBE in order to determine its potential carcinogenicity. All produced some evidence of carcinogenicity, but the results cannot be extrapolated to humans. Although the only oral study had serious reporting and quality control problems, the dose-related increase in lymphomas and leukaemia in female rats cannot be dismissed. The occurrence of an increased incidence of hepatocellular adenomas in the mouse inhalation study was associated with hepatocellular hypertrophy and altered estrogen metabolism, which raises doubts about the relevance of this observation to human risk estimation. There were increased incidences of renal tubular adenomas and carcinomas in the male rat inhalation study at the two highest doses, but there is evidence that it is related to male rat α-2u-globulin nephropathy, which is not relevant to humans.

The increase in testicular interstitial Leydig cell adenomas in both the oral study and the rat inhalation study is significant, but it should be noted that this effect was seen only at the highest dose in the oral study, and it was within the historical range for control rats in the inhalation study. The incidence of this type of tumour can be influenced by hormonal changes that may not be relevant to human risk assessment owing to differences between rats and humans in the regulation of gonadotrophins. While de Peyster et al. (2003) have proposed a mechanism for Leydig cell carcinogenesis (assumed to result from high-dose exposure to MTBE) in rats, the authors note that rat Leydig cell physiology is not identical to human physiology and that rat responsiveness to xenobiotics is often an unreliable predictor of effects in humans.

The U.S. EPA has concluded that MTBE is an animal carcinogen and that the chemical poses a potential carcinogenic risk to humans, but that animal data do not support confident, quantitative estimation of human risk at low exposure due to the limitations of the various cancer studies (U.S. EPA, 1997). Therefore, the U.S. EPA has established a drinking water advisory based on consumer acceptability of taste and odour effects at 20–40 µg/L. The U.S. EPA has estimated that the margin of safety between the advisory range and levels associated with observed effects in animals is in the range of 4–5 orders of magnitude. Therefore, there is little likelihood that MTBE in drinking water at concentrations between 20 and 40 µg/L would cause adverse effects in humans (U.S. EPA, 1997). MTBE remains on the U.S. EPA's Contaminant Candidate List for drinking water standards.

The California EPA has established a Public Health Goal of 13 µg/L (OEHHA, 1999) based on the rat gavage and inhalation carcinogenicity studies (Chun et al., 1992; Belpoggi et al., 1995). This was done despite the acknowledgement of major limitations regarding MTBE's mode of action as well as lack of evidence for relevance to human cancer causation; however, it was stated that there was potential for widespread use of and exposure to MTBE in California and that experimental flaws in the available studies were not severe enough to exclude their use in a risk assessment (OEHHA, 1999).

Since the most significant effect of MTBE contamination of drinking water is its pungent odour and taste, a theoretical health-based quantitative risk assessment (Walker and Williams, 2002) was attempted to ensure that a drinking water guideline based on organoleptic properties would be protective of any potential health effects identified in the current animal toxicological database. However, owing to the limitations in the database, this assessment could not establish a health-based target for the ingestion of MTBE through drinking water.

11.0 Rationale

Health Canada has determined that there exist too many uncertainties and limitations in the MTBE database to have confidence in a quantitative risk assessment for human health. The most suitable and sensitive parameter on which to base a drinking water guideline for MTBE is odour. A study of human volunteers found that most would consider the water acceptable for consumption at a level of 15 µg/L for MTBE based on its odour threshold. This value is also below the range of 20–40 µg/L established by the U.S. EPA as an approximate "threshold" for organoleptic responses to MTBE in drinking water. It should be noted that because of differences in individual sensitivity, not all individuals respond equally to taste and odour, and participants in taste and odour panels are often chosen for their above-average sensitivity to basic tastes and odours, in order to be conservative.

The limited available exposure data indicate that MTBE is unlikely to be found in Canadian drinking water supplies at levels that may pose risks to human health. In addition, there are treatment technologies available at both the municipal and residential scales to reduce concentrations of MTBE in drinking water to below the proposed aesthetic objective (AO).

The AO for MTBE is therefore 0.015 mg/L, based on odour detection thresholds. Because the AO is lower than levels associated with potential toxicological effects, consumption of drinking water containing MTBE at this level would also be protective of human health.

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Appendix A: List of acronyms

ANSI	American National Standards Institute
AO	aesthetic objective
bw	body weight
CYP	cytochrome P-450
EPA	Environmental Protection Agency
GC	gas chromatography
LD_{50}	median lethal dose
MDL	method detection limit
MS	mass spectrometry
MTBE	methyl *tertiary*-butyl ether
NOAEL	no-observed-adverse-effect level
NSF	NSF International
PID	photoionization detector
SCC	Standards Council of Canada
TBA	*tertiary*-butyl alcohol
UDS	unscheduled DNA synthesis
UV	ultraviolet
VOC	volatile organic compound
v/v	volume to volume