

Methyl *tertiary*-Butyl Ether (MTBE) in Drinking-water

Background document for development of
WHO *Guidelines for Drinking-water Quality*

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Preface

One of the primary goals of WHO and its member states is that “all people, whatever their stage of development and their social and economic conditions, have the right to have access to an adequate supply of safe drinking water.” A major WHO function to achieve such goals is the responsibility “to propose ... regulations, and to make recommendations with respect to international health matters”

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as *International Standards for Drinking-water*. It was subsequently revised in 1963 and in 1971 under the same title. In 1984–1985, the first edition of the WHO *Guidelines for Drinking-water Quality* (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published on selected chemicals in 1998 and on microbial aspects in 2002. The third edition of the GDWQ was published in 2004, and the first addendum to the third edition was published in 2005.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation related to aspects of protection and control of public drinking-water quality is accordingly prepared and updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other supporting information to the GDWQ, describing the approaches used in deriving guideline values and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants of potential health concern in drinking-water. In the first and second editions, these constituted Volume 2 of the GDWQ. Since publication of the third edition, they comprise a series of free-standing monographs, including this one.

For each chemical contaminant or substance considered, a lead institution prepared a background document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Denmark, Finland, France, Germany, Italy, Japan, Netherlands, Norway, Poland, Sweden, United Kingdom and United States of America prepared the documents for the third edition and addenda.

Under the oversight of a group of coordinators, each of whom was responsible for a group of chemicals considered in the GDWQ, the draft health criteria documents were submitted to a number of scientific institutions and selected experts for peer review. Comments were taken into consideration by the coordinators and authors. The draft documents were also released to the public domain for comment and submitted for final evaluation by expert meetings.

During the preparation of background documents and at expert meetings, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health Criteria monographs and Concise International Chemical Assessment Documents, the

International Agency for Research on Cancer, the Joint FAO/WHO Meetings on Pesticide Residues and the Joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite, in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO Internet site and in the current edition of the GDWQ.

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The work of the following working group coordinators was crucial in the development of this document and others contributing to the first addendum to the third edition:

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The draft text was discussed at the Working Group Meeting for the first addendum to the third edition of the GDWQ, held on 17–21 May 2004. The final version of the document takes into consideration comments from both peer reviewers and the public. The input of those who provided comments and of participants in the meeting is gratefully acknowledged.

The WHO coordinator was Dr J. Bartram, Coordinator, Water, Sanitation and Health Programme, WHO Headquarters. Ms C. Vickers provided a liaison with the International Programme on Chemical Safety, WHO Headquarters. Mr Robert Bos, Water, Sanitation and Health Programme, WHO Headquarters, provided input on pesticides added to drinking-water for public health purposes.

Ms Penny Ward provided invaluable administrative support at the Working Group Meeting and throughout the review and publication process. Ms Marla Sheffer of Ottawa, Canada, was responsible for the scientific editing of the document.

Many individuals from various countries contributed to the development of the GDWQ. The efforts of all who contributed to the preparation of this document and in particular those who provided peer or public domain review comment are greatly appreciated.

Acronyms and abbreviations used in the text

ASTM	American Society for Testing and Materials
CAS	Chemical Abstracts Service
CYP	cytochrome P-450
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency (USA)
FAO	Food and Agriculture Organization of the United Nations
GAC	granular activated carbon
GC	gas chromatography
GDWQ	<i>Guidelines for Drinking-water Quality</i>
ISO	International Organization for Standardization
LD ₅₀	median lethal dose
MS	mass spectrometry
MTBE	methyl <i>tertiary</i> -butyl ether
NOAEL	no-observed-adverse-effect level
PID	photoionization detector
ppm	part per million
TBA	<i>tertiary</i> -butyl alcohol
USA	United States of America
WHO	World Health Organization

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1. GENERAL DESCRIPTION

1.1 Identity

CAS No.:	1634-04-4
Molecular formula:	C ₅ H ₁₂ O

Methyl *tertiary*-butyl ether is commonly referred to as MTBE.

1.2 Physicochemical properties¹

<i>Property</i>	<i>Value</i>	<i>Reference</i>
Boiling point	55.2 °C	ATSDR, 1996
Vapour pressure	33.5 kPa at 25 °C	Mackay et al., 1993
Water solubility	48 g/litre at 25 °C	Budavari et al., 1996
Log octanol–water partition coefficient	1.24	ATSDR, 1996
Henry's law constant	5.95×10^{-2} kPa·m ³ /mol	ATSDR, 1996

1.3 Organoleptic properties

From a drinking-water perspective, one of the most important aspects of MTBE is its objectionable taste and odour. Some studies suggest that odour tends to have a lower threshold of detection than taste, whereas others show the opposite relationship. The taste and odour responses reported in four recent studies were in the range of 24–135 µg/litre and 15–180 µg/litre, respectively. The four studies all used comparatively small numbers of human subjects and gave a wide range of results, indicative of the variability in individual responses (US EPA, 1997). They included studies 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/litre for taste, 45 µg/litre for odour detection and 55 µg/litre for odour recognition, and subjects described the taste of MTBE in water as “nasty,” bitter, nauseating and similar to 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/litre; 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/litre, whereas the corresponding range for taste was 24–37 µg/litre.

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 (ASTM) method E679-91 (Stocking et al., 2001). Eight concentrations of MTBE in water ranging between 2 and 100 µg/litre 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/litre.

¹ Conversion factor in air at 25 °C: 1 ppm = 3.61 mg/m³.

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1.4 Major uses and sources in drinking-water

The major use of MTBE is as a petrol additive, with production and consumption for this purpose increasing markedly in the 1990s in most parts of the developed world. MTBE is added to petrol at levels of up to 15% by volume as an oxygenate to improve combustion and lower exhaust emissions, particularly carbon monoxide emissions.

Fugitive emissions from petrol refineries and petrol 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 petrol spills and by the use of petrol-powered boats, particularly those using two-stroke engines. Spills and leaking storage tanks can cause more serious problems in groundwater. MTBE is seen as a potentially serious long-term threat to drinking-water supplies if it comes to be widely used at high concentrations in petrol, particularly where there is inadequate control on leakage from underground storage tanks.

1.5 Environmental fate

MTBE is resistant to chemical and microbial decomposition in water. In surface water, MTBE will usually be removed very rapidly due to its high volatility. In groundwater, it will be more persistent than in surface water because its volatilization to air will be reduced or eliminated (ATSDR, 1996). MTBE does not adsorb to soil particles to a great degree and is considered mobile (Environment Canada, 1993).

2. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

2.1 Air

There are a large number of data available on levels of MTBE in ambient air. Indoor air data are all linked to ambient levels, with no consideration being given to a contribution from contaminated drinking-water. Microenvironments such as petrol 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, USA, 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-year 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-year age group, indoor air was the most important source, presumably since there is very little commuting in vehicles at this age. In the 20- to 59-year age group for an area where petrol contains 15% MTBE, the mean and standard deviation for total exposure were modelled at 4.8 ± 1.8 $\mu\text{g}/\text{kg}$ of body weight per day (Health Canada, 1999).

High ambient air concentrations of MTBE have occasionally been detected downwind of refineries that use MTBE (Environment Canada, unpublished data, 1996), and

occupational exposure can obviously be much higher than the levels given above for the general population (IPCS, 1998).

2.2 Water

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/litre, and 60% of samples contained MTBE at concentrations above 0.02 mg/litre. 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).

The Canadian province of 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 (K. Chinniah, Alberta Ministry of Environmental Protection, personal communication, 2003). In the province of Prince Edward Island, six groundwater sources used for drinking-water had concentrations that ranged from 1 to 5 µg/litre. After remediation, half of the sites had levels below 0.1 µg/litre (Environment Canada, 2003).

The use of MTBE in petrol has been more widespread and of longer duration in the USA than in Canada; hence, there are more data available from the USA. It has been estimated that 30% of the US population lives in areas where MTBE is regularly added to the petrol; even in these areas, it is unlikely that the MTBE level in drinking-water will exceed 2 µg/litre in 95% of cases, with possibly 5% showing higher levels in the vicinity of major spills and leaks (Stern & 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/litre and a maximum measured level of 8 µg/litre (Siddiqui et al., 1998). In New Jersey, USA, petrol has contained between 10% and 15% MTBE for several years, and MTBE was detected in 82 of 1300 samples of drinking-water collected; the mean MTBE level was reported to be 0.2 µg/litre, with the highest reported level being 16.4 µg/litre (OSTP, 1998). Even in the USA, the database is not sufficient to give an accurate national picture, since MTBE has not been a mandated US Environmental Protection Agency (EPA) reporting requirement.

In a two-season survey ($n = 156$) of MTBE residues in Dutch drinking-water sources and drinking-water, a median concentration of 10 ng/litre (range 10–420 ng/litre) was observed. During the second season, a median of 20 ng/litre was detected during resampling of the positive locations; a level of 2900 ng/litre was detected at one point source of contamination (Morgenstern et al., 2003).

MTBE was detected in the groundwater at 13% of monitoring locations in England and Wales. Concentrations were typically very low (<1 µg/litre), although three water supply boreholes had concentrations above the odour/taste threshold. In one case, MTBE in mains water was detected by the public (Environment Agency, 2001).

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Average MTBE concentrations of 200–250 µg/litre have been reported in the lower Rhine and lower Main rivers. In a 2-year survey of bank infiltrated water of the lower Rhine, levels ranging from 43 to 110 ng/litre were reported, whereas at the lower Main site, a range of 52–250 ng/litre was detected. A mean MTBE concentration of 35 ng/litre was detected (maximum 71 ng/litre) in tap water from Frankfurt am Main (Achten et al., 2002).

2.3 Food

There is no indication that MTBE is a concern in any raw or processed food items (ATSDR, 1996).

2.4 Estimated total exposure and relative contribution of drinking-water

The main source of human exposure to MTBE is likely to be from inhalation of air, not oral ingestion (Health Canada, 1999). For the 0- to 0.5-year age group, 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, the contribution is only about 2%.

3. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

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/m³) for 2 h gave linear kinetics up to the highest concentration used. The kinetics profile was described as having four elimination half-lives from blood of 1 min, 10 min, 1.5 h and 19 h (Nihlén et al., 1998). Urinary excretion was biphasic, with mean half-lives of 20 min and 3 h.

Several studies in humans have identified *tertiary*-butyl alcohol (TBA) as a metabolite that is present in both blood and urine following inhalation exposure to MTBE (Nihlén et al., 1998).

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 of body weight were used, and elimination half-lives from plasma were found to be 0.52 and 0.79 h, respectively. Although 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, ¹²C- and ¹³C-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, the urinary metabolites 2-methyl-1,2-propanediol and 2-hydroxyisobutyric acid have both been identified in rats and humans, but TBA is a human urinary metabolite that has not been identified in rats (Nihlén et al., 1998). Also, it has been shown *in vitro* that rat and mouse liver microsomes metabolize MTBE at an activity rate approximately 2-fold higher than 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 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 CYP2A6, with some activity from CYP2E1 (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).

Two recent human volunteer studies provide additional information on the kinetics and metabolism of orally administered MTBE in humans. Amberg et al. (2001) conducted a clinical study in which 5 mg and 15 mg of ¹³C-labelled MTBE dissolved in 100 ml of water were orally administered to six human volunteers and concentrations of metabolites in blood, urine and exhaled breath were measured. Maximum concentrations of MTBE and TBA in blood and exhaled breath were detected in the first 10–20 min after exposure. MTBE metabolism occurred with three elimination half-lives, and concentrations decreased to non-detectable levels after 12 h. Slower excretion of TBA in blood followed first-order kinetics, and concentrations were still detectable 24 h after dosing. Both MTBE and metabolites, including 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 h, whereas 2-hydroxyisobutyrate was still present in low concentrations up to 96 h 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, which was also supported by high percentages of recovered MTBE in exhaled breath. The authors concluded that the 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, 1 week apart. Volunteers drank 2.8 mg of MTBE in 250 ml of sports drink (which masked the unpleasant taste of the chemical), were dermally exposed to MTBE dissolved in tap water at 51.3 µg/ml for 1 h and inhaled MTBE at 11.2 mg/m³ in air for 1 h. Concentrations of MTBE and metabolites in blood and exhaled breath were compared among the three exposure routes up to 24 h. Maximum concentrations of MTBE in blood were detected at 15 min via oral exposure, at 60 min via inhalation exposure and at 65 min via dermal exposure. MTBE in blood and exhaled breath followed a three-compartment model via all three exposure routes,

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with shortest half-lives via inhalation exposures and longest half-lives for dermal exposures. At 24 h, MTBE declined to below the detection limit. The metabolite TBA was found in greater blood concentrations via the oral route than via the inhalation or dermal route and was still elevated above pre-exposure baseline levels at 24 h. 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 coefficient, 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 the dermal or inhalation route (which would produce proportionally less TBA) might reduce toxic effects.

4. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

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 give vital information. Most of the oral studies use dosing by gavage with MTBE in corn oil rather than in the drinking-water, which also limits the value of animal data for making a human risk assessment relevant 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.

4.1 Acute exposure

The LD₅₀ of MTBE by gavage in rats was reported in an unpublished study as 3866 mg/kg of body weight (ARCO Chemical Company, 1980). Death is associated with central nervous system depression, laboured respiration and ataxia. These data indicate a low acute toxicity.

A single 6-h inhalation exposure of male and female F344 rats to MTBE at 2900 mg/m³ had no apparent effect, but there was laboured respiration, ataxia, decreased muscle tone, abnormal gait, impaired treadmill performance and decreased hind limb grip strength at 14 000 and 29 000 mg/m³. These effects were not observable 6 and 24 h after exposure had ceased (Daughtrey et al., 1997).

4.2 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 of body weight per day to male and female Sprague-Dawley rats (10 per dose group), the highest dose produced immediate anaesthesia, with complete recovery within 2 h. 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 of body weight 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 of body weight 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 of body weight 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 of body weight 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 of body weight per day (Robinson et al., 1990).

In a neurotoxicity study in which exposure was by the inhalation route, daily exposure of male and female F344 rats to MTBE at 2900 mg/m³ for 13 weeks resulted in 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 this study was set at 2900 mg/m³, which was stated as being equivalent to a dose of 210 mg/kg of body weight per day.

4.3 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 MTBE concentrations of 0, 1400, 11 000 or 29 000 mg/m³ for 6 h per day, 5 days per 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 F₁ and F₂ pups during the later periods of lactation. Pup survival was significantly reduced in the F₁ litters on lactation days 0–4 and in F₂ litters on postnatal day 4 in the 29 000 mg/m³ 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 F₁ generation at 11 000 and 29 000 mg/m³ in both sexes, but no

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histopathological effects were noted (Bevan et al., 1997a). No evidence of reduced fertility was observed. The NOAEL for parental and pup toxicity was 1400 mg/m³ (105 mg/kg of body weight per day).

Two major developmental studies by the inhalation route are available. A study in rats and mice was performed at MTBE concentrations of 0, 900, 3600 or 9000 mg/m³ for 6 h per 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 MTBE at 0, 3600, 14 000 or 29 000 mg/m³ 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 US EPA (1997) derived a lowest developmental NOAEL of 900 mg/m³ (65.6 mg/kg of body weight 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.

4.4 Mutagenicity and related end-points

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). With one exception, these studies have all produced negative results. The 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). 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 totally negative (Cinelli & Seeberg, 1989). MTBE also did not induce unscheduled DNA synthesis in primary rat hepatocytes (Seeberg, 1989), 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 & Morabit, 1989), did not induce micronuclei *in vivo* in mouse bone marrow cells (Vergnes & 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.

4.5 Carcinogenicity

Three long-term rodent studies with MTBE have looked for potential carcinogenicity. Two were by the inhalation route, and one was by gavage. The oral study of MTBE used groups of 60 male and female Sprague-Dawley rats dosed daily by gavage with MTBE dissolved in olive oil for 4 days per week for 104 weeks at doses of 0, 250 or 1000 mg/kg of body weight per day (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 per 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 of body weight per day, 6/60; 1000 mg/kg of body weight 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 of body weight per day, 2/60; 1000 mg/kg of body weight per day, 11/60). The results of this study have been subject to detailed critiques by at least two groups of reviewers that have focused on a lack of detail in the reporting and on the conduct of the histopathology (US NSTC, 1997; IPCS, 1998), and a request for a pathology review by the US Interagency Oxygenated Fuels Assessment Steering Committee has not been successful. Hence, the conclusions of this study are the subject of some doubt.

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 MTBE vapour at concentrations of 0, 1400, 11 000 or 29 000 mg/m³ in air for 6 h per day, 5 days per week. Mice were exposed for 18 months and rats for 24 months. Both species showed central nervous system depression at the 29 000 mg/m³ 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 11 000 and 29 000 mg/m³, 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 29 000 mg/m³ 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 (US EPA, 1997).

In the rat study, the males dosed at 11 000 and 29 000 mg/m³ had to be euthanized early due to severe progressive nephrosis. Absolute and relative liver and kidney weights for the females were increased in the 11 000 and 29 000 mg/m³ 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

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at 11 000 and 29 000 mg/m³. The combined incidence of renal tubular adenomas and carcinomas was significantly increased in the male rats at the 11 000 and 29 000 mg/m³ dose levels. 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 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.

The metabolite TBA administered in drinking-water to Fischer-344 rats caused 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 B6C3F1 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 possible that some, but not all, of the cancers seen following MTBE administration could be attributable to metabolites.

5. EFFECTS ON HUMANS

There have been no studies of human health effects following oral exposure to MTBE. There have been numerous studies of the human response to MTBE in air, particularly in areas where MTBE has been added to petrol. Following the introduction of petrol containing 15% by volume MTBE to Alaska, USA, in 1992, there were numerous consumer complaints of headaches, eye irritation and coughs (Beller & Middaugh, 1992). A similar response was observed coinciding with the introduction of 11% by volume MTBE into petrol in Milwaukee, Wisconsin, USA, in 1995. Controlled studies of human physiological responses to MTBE have given uncertain results and have been discussed in depth in several reviews (US 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.

6. PRACTICAL ASPECTS

6.1 Analytical methods and analytical achievability

According to Rhodes & 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, due 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 & Verstuyft, 2001).

Two US EPA methods (EPA Method 502.2 and EPA Method 524.2) are approved for measuring MTBE in drinking-water. The first (EPA Method 502.2) employs purge

and trap capillary GC with PIDs and electrolytic conductivity detectors in series. The second (EPA Method 524.2) uses purge and trap capillary GC with MS detectors in series. These methods have a lower detection limit of 0.5 µg/litre (US EPA, 2001), well below the odour threshold.

The US EPA (2001) recognizes four methods as being equivalent to the EPA standard methods for measuring MTBE in drinking-water. The equivalent methods include ASTM 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., 1998) and SM 6200C (APHA et al., 1998).

US EPA methods now all specify that sample preparation for these methods must be conducted as specified in EPA Method 524.2 (Rhodes & 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/litre. 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.

No International Organization for Standardization (ISO) methods are available for the analysis of MTBE in water.

6.2 Treatment and control methods and technical achievability

MTBE concentrations in groundwater supplies may be reduced by air stripping (possibly followed by granular activated carbon, or GAC) to below 0.03 mg/litre.

MTBE can be stripped by aeration, but high air to water flow rates (or long contact times) are needed. Pilot tests on groundwater containing MTBE at 13–14 µg/litre gave removals of 44%, 51% and 63% at air to water ratios of 44:1, 75:1 and 125:1, respectively, in a countercurrent packed column. A full-scale aerator with an air to water ratio of 200:1 gave 95% removal. The installation of the aeration system reduced by one-third to one-half the cost of operating the GAC adsorption system (McKinnon & Dyksen, 1984).

Other pilot plant trials found that air stripping was ineffective at removing MTBE (Dyksen et al., 1992). However, another report states air stripping to be effective at removing MTBE but confirms that very high air to water ratios are necessary (Karpel Vel Leitner et al., 1994).

Groundwater contaminated with MTBE and petrol was treated by air stripping with catalytic oxidation of the air stream and carbon polish of the treated water (Bass & Riley, 1995).

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It is reported that MTBE is difficult to remove by adsorption onto GAC (Dyksen et al., 1992). Isotherm data have been found for MTBE adsorption onto activated carbon (F400). Capacities of 4.8 mg/g and 2 mg/g have been calculated for solutions containing 628 µg/litre and 102 µg/litre, respectively, at equilibrium (Speth & Miltner, 1990).

Filtration of contaminated groundwater through F300 GAC (empty bed contact time 12 min) reduced concentrations from 25–35 µg/litre to non-detectable levels for approximately 2 months. The GAC had to be replaced after 4 months of operation because of taste and odour complaints (McKinnon & Dyksen, 1984).

Small-scale column tests using two coconut-based GACs showed that the treatment capacity up to breakthrough (5 µg/litre) was 2.5 and 4.5 litres/g GAC for an influent concentration of 20 µg/litre (Shih et al., 2003).

A removal of 26% was achieved from raw water when MTBE was treated with ozone at 3 mg/litre with a contact time of 4.3 min. A greater removal of 77% was achieved when the water was treated with hydrogen peroxide and ozone. The ozone dose was 3 mg/litre, the contact time was 4.3 min and the hydrogen peroxide to ozone molar ratio was 0.5 (Dyksen et al., 1992).

Laboratory experiments using a semi-batch system were used to determine the effects of ozone and ozone plus hydrogen peroxide on pH 8 buffered solutions containing MTBE (176 mg/litre). Ozone and hydrogen peroxide were dosed continuously using 0.35 mg of peroxide per mg of ozone. The ozone doses required for 80% destruction were 530 mg/litre for ozone alone and 300 mg/litre in the presence of peroxide (Karpel Vel Leitner et al., 1994).

Ozone and ozone/peroxide were evaluated for removal of MTBE spiked into two impounded surface waters using a 0.23 m³/h pilot plant. Ozone at 4 mg/litre gave 33% removal, and addition of hydrogen peroxide at 1.3 mg/litre improved this to 79%. An ozone concentration of at least 6 mg/litre was necessary to achieve the same MTBE removal as an ozone plus peroxide concentration of 4 mg/litre. Removals from the two waters were similar. About 20–30% MTBE removal was due to air stripping rather than oxidation. The percentage MTBE removal was independent of raw water MTBE concentration over the range 18–76 µg/litre. Decreasing the pH from 8.3 to 6.5 had little effect on MTBE removal (Liang et al., 1999).

Studies have shown that photocatalytic degradation using titanium dioxide is capable of complete degradation of MTBE to innocuous products or partial degradation to potentially biodegradable products (Barreto et al., 1995).

7. CONCLUSIONS

No human cancer studies in relation to MTBE exposure have been published for either the general population or occupationally exposed cohorts. There have been a number of human studies of neurological and clinical effects of exposure to MTBE by

inhalation, with mixed results. In general, no objective changes could be seen at levels of MTBE normally found, even in such microenvironments as petrol filling stations.

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.

There have been three lifetime rodent studies conducted with MTBE in order to determine its potential carcinogenicity. All produced some evidence of carcinogenicity, but caution should be exercised in extrapolating the results to humans. The only oral study had serious reporting and quality control problems. Nevertheless, the dose-related increase in lymphomas and leukaemia in female rats cannot be dismissed, even though significant questions remain because of the quality of the study. 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 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 of questionable relevance to humans.

IPCS (1998) concluded that MTBE should be considered a rodent carcinogen but that it is not genotoxic and the carcinogenic response is evident only at high levels of exposure that also induce other adverse effects. The weight of evidence supports a conclusion that MTBE is a rodent carcinogen, but the data are insufficient to reach any conclusions about its potential to cause human cancer.

The available data are therefore considered inconclusive and limited in their use for human carcinogenic risk assessment (IPCS, 1998). The International Agency for Research on Cancer (IARC, 1999) 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. A health-based guideline value has not been derived for MTBE, due to the fact that any guideline value that would be derived

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would be significantly higher than the concentration at which it would be detected by odour — 15 µg/litre is the lowest level eliciting a response in the study by Young et al. (1996), which used taste- and odour-sensitive participants.

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