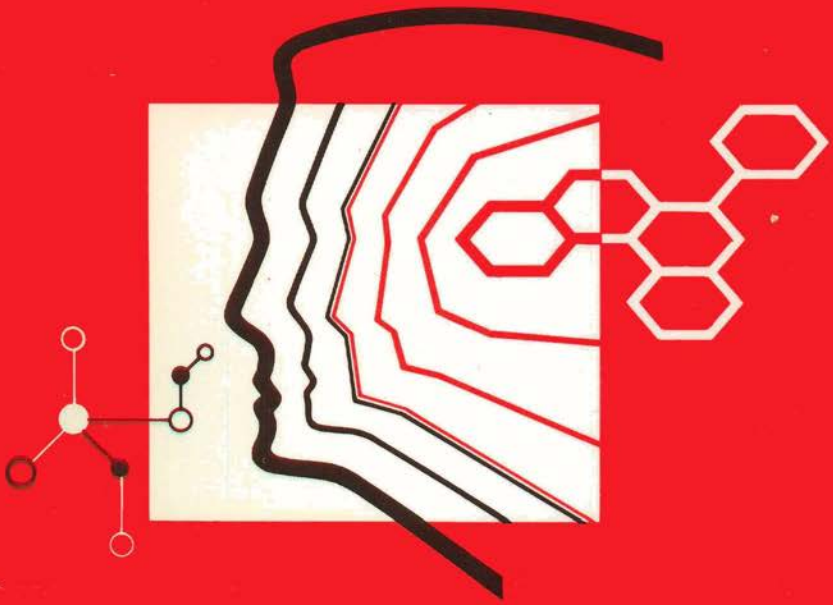
IPCS

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

UNEP

Environmental Health Criteria 206

Methyl *tertiary*-Butyl Ether



IOMC

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS
A cooperative agreement among UNEP, ILO, FAO, WHO, UNIDO, UNITAR and OECD

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Environmental Health Criteria 206

METHYL *TERTIARY*-BUTYL ETHER

First draft prepared by Dr M. Gillner, National Chemicals Inspectorate, Solna, Sweden, with contributions from Ms A.-S. Nihlén, Institute for Working Life, Solna, Sweden

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World Health Organization
Geneva, 1998

The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organisation (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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CONTENTS

ENVIRONMENTAL HEALTH CRITERIA FOR METHYL *TERTIARY*-BUTYL ETHER

NOTE TO READERS OF THE CRITERIA MONOGRAPHS

Every effort has been made to present information in the criteria monographs as accurately as possible without unduly delaying their publication. In the interest of all users of the Environmental Health Criteria monographs, readers are requested to communicate any errors that may have occurred to the Director of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda.

* * *

A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Case postale 356, 1219 Châtelaine, Geneva, Switzerland (telephone no. + 41 22 – 9799111, fax no. + 41 22 – 7973460, E-mail irptc@unep.ch).

* * *

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Environmental Health Criteria

P R E A M B L E

Objectives

In 1973 the WHO Environmental Health Criteria Programme was initiated with the following objectives:

(i) to assess information on the relationship between exposure to environmental pollutants and human health, and to provide guidelines for setting exposure limits;

(ii) to identify new or potential pollutants;

(iii) to identify gaps in knowledge concerning the health effects of pollutants;

(iv) to promote the harmonization of toxicological and epidemiological methods in order to have internationally comparable results.

The first Environmental Health Criteria (EHC) monograph, on mercury, was published in 1976 and since that time an ever-increasing number of assessments of chemicals and of physical effects have been produced. In addition, many EHC monographs have been devoted to evaluating toxicological methodology, e.g., for genetic, neurotoxic, teratogenic and nephrotoxic effects. Other publications have been concerned with epidemiological guidelines, evaluation of short-term tests for carcinogens, biomarkers, effects on the elderly and so forth.

Since its inauguration the EHC Programme has widened its scope, and the importance of environmental effects, in addition to health effects, has been increasingly emphasized in the total evaluation of chemicals.

The original impetus for the Programme came from World Health Assembly resolutions and the recommendations of the 1972 UN Conference on the Human Environment. Subsequently the work became an integral part of the International Programme on Chemical Safety (IPCS), a cooperative programme of UNEP, ILO and WHO. In this manner, with the strong support of the new partners, the importance of occupational health and environmental effects was fully

recognized. The EHC monographs have become widely established, used and recognized throughout the world.

The recommendations of the 1992 UN Conference on Environment and Development and the subsequent establishment of the Intergovernmental Forum on Chemical Safety with the priorities for action in the six programme areas of Chapter 19, Agenda 21, all lend further weight to the need for EHC assessments of the risks of chemicals.

Scope

The criteria monographs are intended to provide critical reviews on the effect on human health and the environment of chemicals and of combinations of chemicals and physical and biological agents. As such, they include and review studies that are of direct relevance for the evaluation. However, they do not describe *every* study carried out. Worldwide data are used and are quoted from original studies, not from abstracts or reviews. Both published and unpublished reports are considered and it is incumbent on the authors to assess all the articles cited in the references. Preference is always given to published data. Unpublished data are only used when relevant published data are absent or when they are pivotal to the risk assessment. A detailed policy statement is available that describes the procedures used for unpublished proprietary data so that this information can be used in the evaluation without compromising its confidential nature (WHO (1990) Revised Guidelines for the Preparation of Environmental Health Criteria Monographs. PCS/90.69, Geneva, World Health Organization).

In the evaluation of human health risks, sound human data, whenever available, are preferred to animal data. Animal and *in vitro* studies provide support and are used mainly to supply evidence missing from human studies. It is mandatory that research on human subjects is conducted in full accord with ethical principles, including the provisions of the Helsinki Declaration.

The EHC monographs are intended to assist national and international authorities in making risk assessments and subsequent risk management decisions. They represent a thorough evaluation of risks and are not, in any sense, recommendations for regulation or

standard setting. These latter are the exclusive purview of national and regional governments.

Content

The layout of EHC monographs for chemicals is outlined below.

- Summary — a review of the salient facts and the risk evaluation of the chemical
- Identity — physical and chemical properties, analytical methods
- Sources of exposure
- Environmental transport, distribution and transformation
- Environmental levels and human exposure
- Kinetics and metabolism in laboratory animals and humans
- Effects on laboratory mammals and *in vitro* test systems
- Effects on humans
- Effects on other organisms in the laboratory and field
- Evaluation of human health risks and effects on the environment
- Conclusions and recommendations for protection of human health and the environment
- Further research
- Previous evaluations by international bodies, e.g., IARC, JECFA, JMPR

Selection of chemicals

Since the inception of the EHC Programme, the IPCS has organized meetings of scientists to establish lists of priority chemicals for subsequent evaluation. Such meetings have been held in: Ispra, Italy, 1980; Oxford, United Kingdom, 1984; Berlin, Germany, 1987; and North Carolina, USA, 1995. The selection of chemicals has been based on the following criteria: the existence of scientific evidence that the substance presents a hazard to human health and/or the environment; the possible use, persistence, accumulation or degradation of the substance shows that there may be significant human or environmental exposure; the size and nature of populations at risk (both human and other species) and risks for environment; international concern, i.e. the substance is of major interest to several countries; adequate data on the hazards are available.

If an EHC monograph is proposed for a chemical not on the priority list, the IPCS Secretariat consults with the Cooperating Organizations and all the Participating Institutions before embarking on the preparation of the monograph.

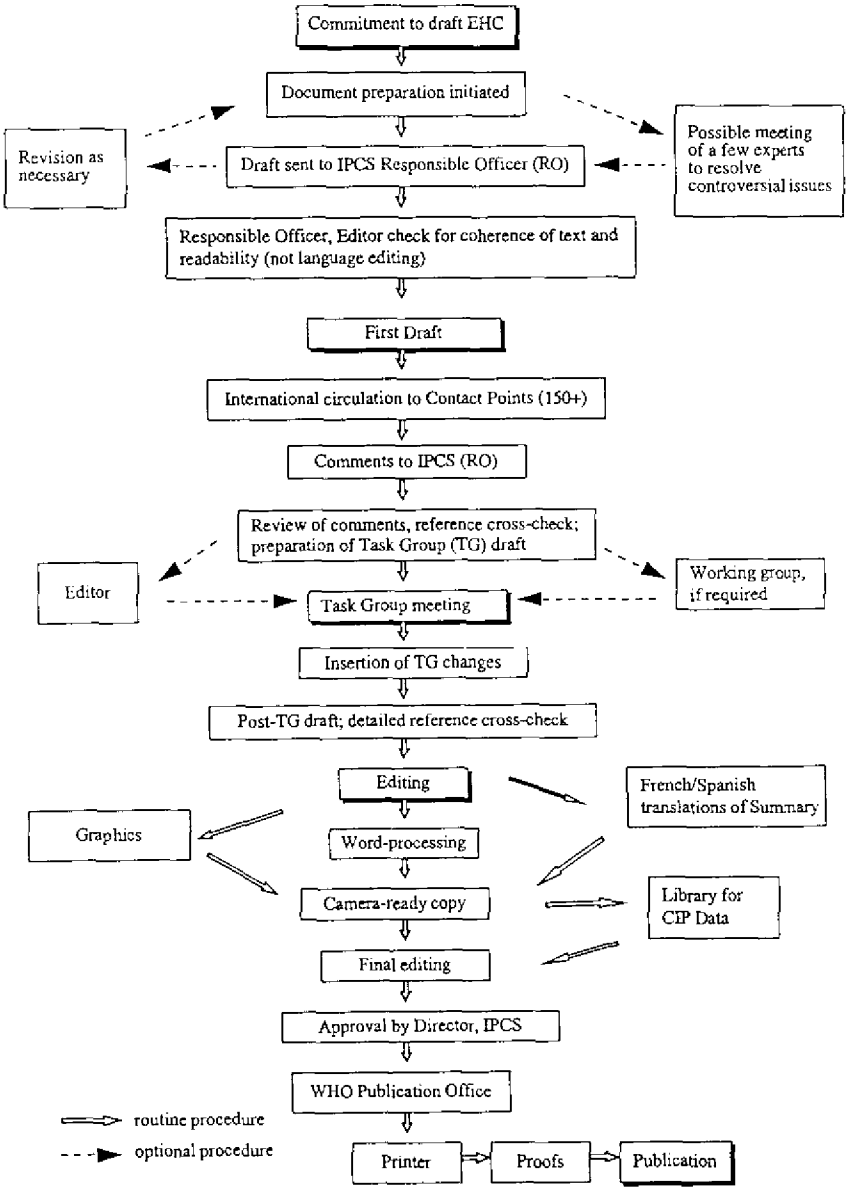
Procedures

The order of procedures that result in the publication of an EHC monograph is shown in the flow chart. A designated staff member of IPCS, responsible for the scientific quality of the document, serves as Responsible Officer (RO). The IPCS Editor is responsible for layout and language. The first draft, prepared by consultants or, more usually, staff from an IPCS Participating Institution, is based initially on data provided from the International Register of Potentially Toxic Chemicals, and reference data bases such as Medline and Toxline.

The draft document, when received by the RO, may require an initial review by a small panel of experts to determine its scientific quality and objectivity. Once the RO finds the document acceptable as a first draft, it is distributed, in its unedited form, to well over 150 EHC contact points throughout the world who are asked to comment on its completeness and accuracy and, where necessary, provide additional material. The contact points, usually designated by governments, may be Participating Institutions, IPCS Focal Points, or individual scientists known for their particular expertise. Generally some four months are allowed before the comments are considered by the RO and author(s). A second draft incorporating comments received and approved by the Director, IPCS, is then distributed to Task Group members, who carry out the peer review, at least six weeks before their meeting.

The Task Group members serve as individual scientists, not as representatives of any organization, government or industry. Their function is to evaluate the accuracy, significance and relevance of the information in the document and to assess the health and environmental risks from exposure to the chemical. A summary and recommendations for further research and improved safety aspects are also required. The composition of the Task Group is dictated by the range of expertise required for the subject of the meeting and by the need for a balanced geographical distribution.

EHC PREPARATION FLOW CHART



The three cooperating organizations of the IPCS recognize the important role played by nongovernmental organizations. Representatives from relevant national and international associations may be invited to join the Task Group as observers. While observers may provide a valuable contribution to the process, they can only speak at the invitation of the Chairperson. Observers do not participate in the final evaluation of the chemical; this is the sole responsibility of the Task Group members. When the Task Group considers it to be appropriate, it may meet *in camera*.

All individuals who as authors, consultants or advisers participate in the preparation of the EHC monograph must, in addition to serving in their personal capacity as scientists, inform the RO if at any time a conflict of interest, whether actual or potential, could be perceived in their work. They are required to sign a conflict of interest statement. Such a procedure ensures the transparency and probity of the process.

When the Task Group has completed its review and the RO is satisfied as to the scientific correctness and completeness of the document, it then goes for language editing, reference checking, and preparation of camera-ready copy. After approval by the Director, IPCS, the monograph is submitted to the WHO Office of Publications for printing. At this time a copy of the final draft is sent to the Chairperson and Rapporteur of the Task Group to check for any errors.

It is accepted that the following criteria should initiate the updating of an EHC monograph: new data are available that would substantially change the evaluation; there is public concern for health or environmental effects of the agent because of greater exposure; an appreciable time period has elapsed since the last evaluation.

All Participating Institutions are informed, through the EHC progress report, of the authors and institutions proposed for the drafting of the documents. A comprehensive file of all comments received on drafts of each EHC monograph is maintained and is available on request. The Chairpersons of Task Groups are briefed before each meeting on their role and responsibility in ensuring that these rules are followed.

WHO TASK GROUP ON ENVIRONMENTAL HEALTH CRITERIA FOR METHYL *TERTIARY*-BUTYL ETHER

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WHO TASK GROUP ON ENVIRONMENTAL HEALTH CRITERIA FOR METHYL *TERTIARY*-BUTYL ETHER (MTBE)

A WHO Task Group on Environmental Health Criteria for methyl *tertiary*-butyl ether met at the Conference Facility, Lord Elgin Hotel, Ottawa, Canada from 17 to 21 April 1997. Dr E.M. Smith, IPCS, welcomed the participants on behalf of Dr M. Mercier, Director of the IPCS, and the three IPCS cooperating organizations (UNEP/ILO/ WHO). The Group reviewed and revised the draft and made an evaluation of the risks for human health and the environment from exposure to methyl *tertiary*-butyl ether.

The first draft of the EHC was prepared by Dr M. Gillner, National Chemicals Inspectorate, Solna, Sweden, with contributions from Ms A.-S. Nihlén, Institute for Working Life, Solna, Sweden. Dr M. Gillner and Ms Nihlén also prepared the second draft, incorporating comments received following circulation of the first drafts to the IPCS contact points for Environmental Health Criteria monographs.

Dr E.M. Smith and Dr P.G. Jenkins, both of the IPCS Central Unit, were responsible for the scientific aspects of the monograph and for the technical editing, respectively.

The efforts of all who helped in the preparation and finalization of the monograph are gratefully acknowledged.

The financial support of the Swedish National Chemicals Inspectorate in preparing the monograph and the Canadian Health Protection Branch, Environmental Health Directorate, in funding the Task Group meeting in Ottawa are gratefully acknowledged.

ABBREVIATIONS

AED	atomic emission detector
ALAT	alanine aminotransferase
AP	alkaline phosphatase
AUC	area under the curve
BCF	bioconcentration factor
BTEX	benzene, toluene, ethyl benzene and xylenes
BUN	blood urea nitrogen
bw	body weight
CHOL	cholesterol
CL	total plasma clearance
CNS	central nervous system
CO	carbon monoxide
DEN	diethylnitrosamine
DIPE	diisopropyl ether
DMN	*N*-nitrosodimethylamine
EC	electron capture
EROD	7-ethoxyresorufin-*O*-deethylase
ETBE	ethyl *tertiary*-butyl ether
FID	flame ionization detector
FOB	functional observational battery
FTIR	Fourier-transform infrared
GC	gas-chromatography
GC-MS	gas-chromatography/mass spectrometry
GC-O	gas-chromatography using an oxygen-selective detector
Hb	haemoglobin
HC	hydrocarbon
HPLC	high-performance liquid chromatography
HPRT	hypoxanthine-guanine phosphoribosyl transferase
IL-1	interleukin-1
IL-4	interleukin-4
ip	intraperitoneal
IR	infrared
iv	intravenous
K_{oc}	adsorbtion coefficient to soil organic carbon
K_{ow}	octanol/water partition coefficient
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LGL	large granular lymphocyte
LOAEL	lowest-observed-adverse-effect level
LOEL	lowest-observed-effect level

LT_{50}	median lethal time
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCS	multiple chemical sensitivities
MCV	mean corpuscular volume
MTBE	methyl *tertiary*-butyl ether
NADPH	reduced nicotinamide adenine dinucleotide phosphate
NIR	near infrared
NMOC	non-methane organic carbon
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NO_x	oxides of nitrogen (NO, NO_2, N_2O_4 and N_2O_3)
PID	photoionization detector
ppb	parts per billion
ppbv	parts per billion (by volume)
ppm	parts per million
PROD	7-pentoxyresorufin-*O*-dealkylase
RBC	red blood cell
RFG	reformulated gasoline
RID	refractive index detector
RPLC	reversed-phase liquid chromatography
sc	subcutaneous
SCE	sister chromatid exchange
SD	standard deviation
TBA	*tertiary*-butyl alcohol
TBF	*tertiary*-butyl formate
TWA	time-weighted average
UDS	unscheduled DNA synthesis
V/F	distribution volume
VOC	volatile organic compound

1. SUMMARY

Methyl *tertiary*-butyl ether (MTBE) is one of several ethers that may be used as fuel additives and is currently by far the dominant one. Ethyl *tertiary*-butyl ether (ETBE), *tertiary*-amyl methyl ether (TAME), *tertiary*-amyl ethyl ether (TAEE) and diisopropyl ether (DIPE), among others, may supplement, or serve as alternatives to MTBE for oxygenation or octane enhancement purposes and may be found, therefore, in association with MTBE.

1.1 Identity, physical and chemical properties, analytical methods

MTBE is a volatile, colourless liquid at room temperature with a terpene-like odour. It has low viscosity and a boiling point of 55.2 °C. The freezing point is -109 °C. The density is 0.7404 at 20 °C. The vapour pressure is relatively high, 33 500 Pa at 25 °C. MTBE is flammable and can form explosive mixtures with air. It is very soluble in other ethers and alcohol. It mixes with gasoline (petrol), and is soluble in water (42 000 g/m^3 at 19.8 °C). The log *n*-octanol/water partition coefficient is 0.94–1.3. It is unstable in acid solution.

MTBE is analysed in all matrices generally by gas chromatography (GC) using a range of capillary columns and detector systems that are suited to the specific matrix. Reverse-phase liquid chromatography (RPLC) has also been used for analysis of petrol samples. Sorption/desorption, including purge and trap systems, and headspace procedures have been used to prepare air, water, sediment and biological samples for analysis.

1.2 Sources of human and environmental exposure

MTBE is not known to occur naturally in the environment. Industrially, it is derived from the catalytic reaction of methanol and isobutylene, and has been produced in several countries in increasing volumes since the late 1970s. MTBE is currently among the 50 highest production volume chemicals. In 1996, the USA capacity for production was approximately 10.6 million tonnes, and it is anticipated that the use of MTBE will continue to increase. Approximately 25% of

gasoline in the USA is blended with MTBE. MTBE is almost exclusively used to provide both octane enhancement and an increase in the oxygen content of gasoline. MTBE has been added to gasoline in concentrations up to 17% by volume.

1.3 Environmental transport, distribution and transformation

After discharge into air, MTBE will largely remain in the air, with smaller amounts entering soil and water. In the atmosphere, MTBE can partition into rain. However, only a small amount is removed from the atmosphere in this manner. Atmospheric transformation by hydroxyl radicals produces a number of products including the photochemically stable *tertiary*-butyl formate (TBF) and 2-methoxy-2-methylpropanol, which is expected to be highly reactive with hydroxyl radicals, yielding CO_2, formaldehyde, acetone and water. When MTBE is discharged into water, a significant amount is dissolved, with some partitioning into air. Partitioning into biota and into sediment is low. Biodegradability in conventional assays is limited. Generally, biodegradability is believed to be slow in the environment. When MTBE is released to the soil, it is transported to the air through volatilization, to surface water through run-off and to groundwater as a result of leaching. MTBE can persist in groundwater.

1.4 Environmental levels and human exposure

There are few data on environmental levels and human exposure.

In studies of MTBE in urban air of some cities using oxygenated gasoline with 15% MTBE, ambient concentrations ranged from non-detectable to 100.9 $\mu g/m^3$ (0.028 ppm), with several median concentrations ranging from 0.47 to 14.4 $\mu g/m^3$ (0.00013 to 0.004 ppm). Concentrations of MTBE in urban air of some cities where MTBE was used as an octane enhancer at lower concentrations ranged from non-detectable to 26.4 $\mu g/m^3$ (0.0073 ppm).

Concentrations at ground level or near refineries ranged from 15 to 281 $\mu g/m^3$. Median levels in urban air near blending facilities were

1508 μg/m³ (0.419 ppm), with ranges of 216–35 615 μg/m³ (0.06 to 9.8 ppm).

At service stations in areas where oxygenated gasoline containing 10–15% MTBE is used, concentrations were highest in the breathing zone during consumer refuelling (range of 300 to 136 000 μg/m³ (0.09 to 38 ppm), with levels rarely exceeding 3600 μg/m³ (10 ppm), slightly lower at the pump island (non-detectable to 5700 μg/m³ (1.6 ppm) and lowest at the station perimeter (non-detectable to 500 μg/m³ (0.14 ppm). Levels were generally higher at service stations without vapour recovery systems.

Levels in the automobile cabin were 7 to 60 μg/m³ (0.002 to 0.017 ppm) during commutes and 20 to 610 μg/m³ (0.006 to 0.172 ppm) during refuelling.

Based on limited monitoring confined almost exclusively to the USA, MTBE has been detected in snow, stormwater, surface water (streams, rivers, and reservoirs), groundwater and drinking-water. Concentrations of MTBE detected in stormwater ranged from 0.2 to 8.7 μg/litre with a median of less than 1.0 μg/litre. For streams, rivers and reservoirs, the range of detection was from 0.2 to 30 μg/litre, and the range of medians for several studies was 0.24 to 7.75 μg/litre.

MTBE has generally not been detected in deeper groundwater or in shallow groundwater in agricultural areas. When detected, the concentration is less than 2.0 μg/litre. MTBE is more frequently found in shallow groundwater (top 5–10 feet of these aquifers) in urban areas. In this setting, the concentrations range from less than 0.2 μg/litre to 23 mg/litre, with a median value below 0.2 μg/litre.

MTBE is infrequently detected in public drinking-water systems from groundwater. In all but 3 out of 51 systems in which it was reported, the concentration was ≤20 μg/litre. There are inadequate data to characterize the concentration of MTBE in public drinking-water systems from surface water. MTBE has been found at high levels (i.e. ≥1000 μg/litre) in a few private wells used for drinking-water. However, it is doubtful that humans would consume water with

concentrations of MTBE greater than about 50–100 μg/litre because of its low taste and odour threshold.

Workers with potential exposure to MTBE include those involved in the production and distribution and use of MTBE and MTBE-containing gasoline, including service station attendants and mechanics.

Short-term exposure (<30 min) in routine manufacturing operations and maintenance of neat MTBE ranged from 715 to 43 000 μg/m^3 (0.2 to 12 ppm), with average median values being about 3400 μg/m^3 (0.95 ppm). Longer-term (30 min to 8 h) exposure ranged from 360 to 890 000 μg/m^3 (0.01 ppm to 250 ppm), with median levels being about 540 μg/m^3 (0.15 ppm). For workers in blending operations, short-term values ranged from non-detectable to 360 000 μg/m^3 (100 ppm), the average median being about 5700 μg/m^3 (1.6 ppm). Long-term values ranged from non-detectable to 257 000 μg/m^3 (72 ppm), the average median being about 2000 μg/m^3 (0.6 ppm).

Exposures were highest during transportation of neat MTBE and fuel mixtures through pipelines, barges, railroad cars and trucks (neat MTBE only), short-term values ranging from 4 to 3750 mg/m^3 (0.001 to 1050 ppm) with an average median value of 140 mg/m^3 (39 ppm). Long-term values ranged from 0.036 to 2540 mg/m^3 (0.01 to 712 ppm), the average median value being 2.85 mg/m^3 (0.8 ppm). In distribution (i.e. loading of MTBE fuel mixtures on trucks and delivering and unloading at service stations), short-term values ranged from non-detectable to 225 mg/m^3 (63 ppm), the average median values being around 21 mg/m^3 (6 ppm). Long-term values ranged from 0.036 to 22 mg/m^3 (0.01 to 6.2 ppm), the average median value being 1.79 mg/m^3 (0.5 ppm).

Median short-term exposure levels of service station attendants ranged generally from 1.071 to 21.42 mg/m^3 (0.3 to 6 ppm) and rarely exceeded 35.7 mg/m^3 (10 ppm). Median long-term exposure levels of service station attendants averaged 1.79 mg/m^3 (0.5 ppm). Median exposures of mechanics were below detection levels for one short-term study; the average median value for long-term exposure was approximately 360 μg/m^3 (0.1 ppm).

1.5 Kinetics and metabolism

Toxicokinetic data on MTBE in humans are mainly derived from controlled studies in healthy adult volunteers and in a population exposed to oxygenated gasoline. MTBE is rapidly absorbed into the circulation following inhalation exposure. In healthy human volunteers exposed by inhalation, kinetics of MTBE are linear up to concentrations of 268 mg/m^3 (75 ppm). *Tertiary*-butyl alcohol (TBA), a metabolite of MTBE, was measured in blood and urine of exposed humans. The peak blood levels of MTBE and TBA ranged from 17.2 to 1144 µg/litre, and 7.8 to 925 µg/litre, respectively, in humans exposed to 5.0 to 178.5 mg/m^3 (1.4 to 50 ppm) MTBE. Based on a monocompartmental model, rapid (36–90 min) and slower (19 h) components of MTBE half-life have been identified.

In rodents, MTBE is well absorbed and distributed following oral administration and inhalation exposure, with lower dermal absorption. At 400 mg/kg oral and 28 800 mg/m^3 (8000 ppm) inhalation exposure, the percentage of total absorbed dose eliminated in expired air increased with a corresponding decrease in the percentage eliminated in urine, indicating a saturation of metabolism. TBA was not identified in the urine of exposed rats. There is evidence of further metabolism of TBA, based on the identification of 2-methyl-1,2-propanediol and α-hydroxyisobutyric acid excreted in the urine. *In vitro* studies provide evidence that MTBE is metabolized to TBA, formaldehyde and acetone.

1.6 Effects on laboratory animals and *in vitro* systems

In rats, the acute median oral lethal dose (LD_{50}) is approximately 3800 mg/kg bw. The acute median lethal concentration (LC_{50}) value for a 15-min inhalation exposure is about 141 000 mg/m^3 air in mice. Signs of intoxication include CNS depression, ataxia and laboured respiration. When the dose was non-lethal, recovery was complete. The LD_{50} for dermal toxicity in rabbits is >10 200 mg/kg bw.

In a single identified study, MTBE was "moderately" irritating to skin, causing moderate erythema and oedema following dermal application to rabbits. It was also irritating to the eyes of rabbits,

causing mild, reversible changes. In the only identified study, MTBE induced slight to severe respiratory irritation following exposure of mice to 300 to 30 000 mg/m^3, respectively. It did not induce skin sensitization in studies in guinea-pigs.

Repeated exposure results primarily in increases in organ weights and histopathological effects in the kidney of rats and the liver of mice. Lowest reported effect levels for nephrotoxicity following ingestion in 90-day studies are 440 mg/kg bw per day (increases in relative kidney weight and hyaline droplet formation in Sprague-Dawley rats). With inhalation exposure to 2880 mg/m^3 (800 ppm), there were increases in kidney weight associated at higher concentrations with a mild increase in hyaline droplets in the proximal tubules in Fischer-344 rats. In inhalation oncogenicity studies, at 1440 mg/m^3 (400 ppm) the incidence and severity of chronic progressive nephropathy was increased in male rats; in male mice, at this level, there were increases in absolute liver weight (which correlated with increases in hepatocellular hypertrophy at higher concentrations) and an increase in relative kidney weight.

Exposure to MTBE also results in reversible central nervous system (CNS) effects including sedation, hypoactivity, ataxia and anaesthesia at higher concentrations and biphasic effects on motor activity at lower concentrations. In a single 6-h inhalation exposure study in rats, dose levels from 2880 mg/m^3 (800 ppm) produced reversible dose-related changes in motor activity in single sexes. These effects were transient and not evident in longer-term studies.

One- and two-generation inhalation reproductive studies in rats and four developmental studies in rats, mice and rabbits have been identified. In these studies, specific reproductive effects were not observed in rats at concentrations up to 28 800 mg/m^3. MTBE has not induced developmental effects at concentrations below those that were toxic to the mothers. Decreases in uterine weight and increases in estrogen metabolism in mice have been observed at 28 800 mg/m^3.

MTBE has been adequately tested in a broad range of mutagenicity and other genotoxicity tests. The results from these studies indicate that MTBE is not genotoxic, although a mouse lymphoma cell

tk locus mutation assay was positive, due to the metabolism of MTBE to formaldehyde.

Carcinogenicity studies have been conducted involving inhalation exposure of Fischer-344 rats and CD-1 mice and gavage dosing of Sprague-Dawley rats. In neither of the inhalation studies were methods of statistical analysis used that adjusted for survival differences. There were significant increases in tumour incidence in all three studies, namely renal tubular cell tumours and Leydig cell tumours in the male Fischer-344 rats, Leydig cell tumours in male and leukaemias/ lymphomas (combined) in female Sprague-Dawley rats, and liver cell tumours in female CD-1 mice. The renal tubular cell tumours and the leukaemia/lymphomas were not observed consistently, therefore, in the different studies in rats. In addition, the sex-specific kidney tumours were associated with sex-specific α2u-globulin nephropathy, which was observed in several studies of short duration. Increases in Leydig cell tumours occurred at the highest dose level (1000 mg/kg bw) in the Sprague-Dawley rats, but interpretation of the increases recorded for Fischer-344 rats was complicated by the very high concurrent and historical control incidences. The mouse liver tumours occurred at incidences in the control and 28 800 mg/m^3 (8000 ppm exposed groups, respectively, of 2/50 and 10/50 in females and 12/49 and 16/49 in males. The increases were modest and were accompanied by hepatocellular hypertrophy.

1.7 Effects on humans

Following the introduction of two separate fuel programmes in the USA requiring the use of gasoline oxygenates (not necessarily MTBE), consumers in some areas have complained about acute health symptoms such as headache, eye and nose irritation, cough, nausea, dizziness and disorientation. Epidemiological studies of human populations exposed under occupational as well as non-occupational conditions, and experimental studies of human volunteers exposed under controlled conditions, have not been able to identify a basis for these complaints. Although results are mixed, community studies conducted in Alaska, New Jersey, Connecticut, and Wisconsin, USA, have provided limited or no evidence of an association between MTBE exposure and the prevalence of health complaints.

In controlled experimental studies on adult volunteers exposed in inhalation chambers to MTBE at concentrations ranging from 5.0 mg/m^3 (1.4 ppm) up to 270 mg/m^3 (75 ppm), there were no evident effects in terms of either subjective reports of symptoms or objective indicators of irritation or other effects up to 180 mg/m^3 (50 ppm) for as long as 2 h. From this evidence it appears unlikely that MTBE alone induces adverse acute health effects in the general population under common conditions of inhalation exposure. However, the potential effects of mixtures of gasoline and MTBE, and the manner in which most persons are exposed to MTBE in conjunction with the use of oxygenated fuels, have not been examined experimentally or through prospective epidemiological methods. Moreover, the role of factors such as awareness of MTBE, due in part to its distinctive odour, for example, have not been investigated.

1.8 Effects on other organisms in the laboratory and field

The experimental acute toxicity (LC_{50}) of MTBE to fish, amphibians and crustaceans is > 100 mg/litre. There are no data on chronic or sub-lethal toxicity to aquatic species, or on toxicity to terrestrial organisms.

1.9 Evaluation of human health risks and effects on the environment

Based on collective evidence, it appears unlikely that MTBE alone induces adverse acute health effects in the general population under common exposure conditions.

In studies on animals, MTBE is "moderately" acutely toxic and induces mild skin and eye irritation but not sensitization. Repeated exposure affects primarily the kidney of rats and the liver of mice, with lowest reported adverse effect levels of 440 mg/kg bw per day in rats following ingestion and 1440 mg/m^3 (400 ppm) following inhalation. MTBE has not induced adverse reproductive or developmental effects at concentrations less than those that were toxic to the parents.

MTBE is not genotoxic but has induced tumours in rodents primarily at high concentrations that also induce other adverse effects. These data are considered currently inadequate for use in human carcinogenic risk assessment. The Task Group concluded that, in order to provide quantitative guidance on relevant limits of exposure and to estimate risk, acquisition of additional data in several areas is necessary.

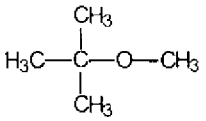
It does not appear that the concentrations of MTBE in ambient water are toxic to aquatic organisms except during spills. Although there are no data on the terrestrial toxicity of MTBE, this appears not to be of concern since concentrations in ambient air are low and its half-life is relatively short.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 Identity

Chemical formula: $C_5H_{12}O$

Chemical structure:



Relative molecular mass: 88.15

Common name: methyl *tertiary*-butyl ether

IUPAC Chemical name: 2-methoxy-2-methyl propane

CAS registry number: 1634-04-4

Synonyms: 1,1-dimethylethyl methyl ether; ether *tert*-butyl methyl; éther methyl *tert*-butylique (French); MBE; methyl 1,1-dimethylethyl ether; methyl-*t*-butyl ether; methyl *tert*-butyl ether; (2-methyl-2-propyl) methyl ether; metil-terc-butileter (Spanish); 2-methoxy-2-methylpropane; MTBE; propane, 2-methoxy-2-methyl- (CA); *t*-butyl methyl ether; *tert*-butoxymethane; *tert*-butyl methyl ether

Major trade names: 3 D Concord
Driveron
HSDB 5487
UN 2398

Constituent components of typical commercial grade:
(ARCO, 1989)

Component	Weight %
MTBE	97.5
di-, tri-isobutylene, and *t*-butyl alcohol	0.6
Methanol	0.2
C4 hydrocarbons	1
C5 hydrocarbons	0.4
other	0.3
water content	<0.05

2.2 Physical and chemical properties

Table 1 lists the physical and chemical properties of MTBE.

2.3 Conversion factors

1 ppm = 3.57 mg/m^3 at 25 °C (1 atmosphere pressure)
1 mg/m^3 = 0.28 ppm at 25 °C (1 atmosphere pressure)

2.4 Analytical methods

Analytical methods that have been used for MTBE and for *tertiary*-butanol (TBA), which is an intermediate in the aerobic bacterial degradation of MTBE and in its mammalian metabolism, are given for various media.

Some commonly used methods are summarized in Table 2.

2.4.1 Procedures

2.4.1.1 Air

Air samples are collected in stainless steel canisters, and the volatile compounds concentrated in a two-stage trap to sorb the

Table 1. Physical and chemical properties of MTBE

Physical state	Liquid	
Colour	Colourless	
Odour	Strong, characteristic terpene-like	
Freezing point (°C)	-109	Windholz, 1983
Boiling point (°C) Selected value[a]	53.6-55.2 55.2	Mackay et al., 1993
Flash point (°C)	-28	Budavari et al., 1996
Ignition temperature (°C)	224	Budavari et al., 1996
Spontaneous ignition temperature (°C)	460	Wibowo, 1994
Flammability	Flammable/combustible	
Flammability limits	1.5–8.5% in air	ECETOC, 1997
Vapour pressure (Pa at 25 °C) Selected value[a]	32 659 to 33 545 33 500	Mackay et al., 1993 Mackay et al., 1993
Density (g/cm^3 at 20 °C) Selected value[a]	0.7404 to 0.7478 0.7404	Mackay et al., 1993
Relative vapour density (air=1)	3.1	Wibowo, 1994
Log k_{ow} octanol/water partition coefficient Selected value[a]	0.94 to 1.30 0.94	Mackay et al., 1993
Henry's law constant at 25 °C (Pa m^3/mol) Selected value[a]	59.46 to 304.96 70.31	Mackay et al., 1993
Dimensionless Henry's law constant (H/RT) at 25 °C Selected value[a]	0.0239 to 0.1221 0.018 at 20 °C	Zogorski et al., 1996

Table 1 (contd).

Water solubility g/m^3 at 25 °C Selected value[a]	32 200 to 54 353 42 000 (at 19.8 °C)	Mackay et al., 1993
Solubility of MTBE in water (g/litre) at 25 °C	48	Budavari et al., 1996
Solubility of water in MTBE (g/litre) at 25 °C	15	Budavari et al., 1996
Solubility in organic solvents:	- very soluble in other ethers and alcohols - mixes with gasoline	
Viscosity, g/sec. -cm	0.003 to 0.004 (calculated)	Lyman et al., 1990
Other properties	Unstable in acid solution pK_a = -3.70 at 23 °C (measured)	
Organoleptic properties		
Taste	134 µg/litre (0.134 ppm)	TRC, 1993
Odour		
- detection threshold	0.19 mg/m^3	TRC, 1993
- recognition threshold	0.29 mg/m^3 (0.08 ppm)	TRC, 1993

[a] Criteria of selection were based on:
i) the age of the data and acknowledgement of previous conflicting or supporting values;
ii) the method of determination;
iii) the perception of the objectives of the investigators, and their need for quantitative values; and
iv) information derived from Quantitative-Structure-Property-Relationships.

Table 2. Summary of analytical procedures for MTBE

Matrix	Procedure	Detector	Detection limit	Reference
Air	Sorption/desorption	GC-MS	0.72–3.6 µg/m^3	Kelly et al., 1993
Vehicle emission	Sorption/desorption	GC-FID	18–36 µg/m^3	Hoekman, 1993
Water	Static headspace	GC-PID	10.8 µg/m^3 (water) 1.08 µg/m^3 (air)	Chang et al., 1992
Water	Purge and trap	GC-MS	5 µg/litre	Bianchi & Varney, 1989
Water	Purge and trap	GC-MS	0.52–0.090 µg/litre	Munch & Eichelberger, 1992
Water	Purge and trap	GC-MS	0.06 µg/litre	Raese et al., 1995
Sediment	Purge and trap	GC-MS	10–100 ng/kg	Bianchi et al., 1991
Blood	Purge and trap	GC-MS	0.01 µg/litre	Bonin et al., 1994
Gasoline	Direct	GC-FID	18-36 µg/m^3 (5–10 ppbv)	Johansen, 1984

organic compounds and to collect water. Drying is done by purging with dry N_2 at 25 °C, and the organic compounds thermally desorbed at 220 °C by back-flushing with helium. The samples can be analysed by gas chromatography/mass spectrometry (GC-MS) using a capillary column (Kelly et al., 1993). Harper & Fiore (1995) used a passive diffusion technique to collect samples.

Automobile exhaust samples are collected in 3-litre bags. Diluted emissions are concentrated in variable temperature control traps, operating between -60 °C and 180 °C (DB 1 column) or between -99 °C and 180 °C (GS-Q megabore column). Using these twin columns, separation of all the major components is possible (Hoekman, 1993).

2.4.1.2 *Soil, water and sediment*

Static headspace analysis can be used for samples of soil and groundwater. Samples are collected in filled bottles, air is introduced, and the bottles are shaken and equilibrated before analysis of the gas phase.

One method is by GC-FID/PID using a megabore DB-1 capillary column (Roe et al., 1989). Samples of groundwater can be collected with a cone penetrometer coupled with a porous probe, and analysed by GC using a photoionization detector (PID) (Chiang et al., 1992).

For samples of water and sediment, purge and trap procedures are widely used to concentrate volatile components before analysis. For water samples, the analytes are desorbed by open-loop stripping for 60 min at 60 °C and collected on a mixture of Tenax TA and Chromosorb-106. Desorption is then done using helium at 150 °C before analysis.

Analysis can be by GC-MS (Bianchi & Varney 1989). An expanded procedure for volatile organic compounds developed by the US Environmental Protection Agency (US EPA) uses a three-trap collection system (Tenax, silica gel and charcoal) followed by GC-MS quantification: for MTBE, a detection limit of 0.09 µg/litre was attained using a DB-624 capillary column and a purging efficiency of

74% (Munch & Eichelberger 1992). An essentially similar procedure has been used for estuarine sediment samples with an OV-1701 capillary column (Bianchi et al., 1991).

MTBE in ambient groundwater has been analysed by the US Geological Survey since 1991 using a purge and trap GC-MS method (Raese et al., 1995). The estimated detection limit for reagent water spiked with MTBE at 0.2 µg/litre is 0.06 µg/litre. A method for the concurrent analysis of MTBE, TBA and *tert*-butyl formate (TBF) has been developed (Church et al., 1997). The method employs direct aqueous injection and GC-MS, and has a detection level of 0.1 µg/litre for MTBE.

2.4.1.3 *Gasoline*

Samples of gasoline can be analysed directly by GC using the following procedures. They have all shown good selectivity for oxygenates:

- An infrared (IR) detector, using a column of Poropak Q plus Poropak N, gave a limit of detection of 0.1% (w/v) with the detector set at 8.3 µm (Cochrane & Hillman 1984).
- A detector system (GC-O-FID), in which oxygenates are catalytically cracked to CO followed by reduction to methane, has a selectivity better than $1:10^7$ (Verga et al., 1988).
- FID with a dual column system using Durawax 1 and Durabond-S gives acceptable accuracy and repeatability at a concentration of 1% (w/w) (Levy & Yancey 1986). An alternative procedure uses switching (Johansen 1984).
- Atomic emission detection (AED) using 777 nm near infrared (NIR) emission and a DB-1 capillary column is a sensitive method (Diehl et al., 1995).
- Reversed-phase liquid chromatography (RPLC) with a Hi-Chrom "reversible column" packed with Spherisorb ODS-11 and a refractive index detector (RID) can be used with a mobile phase of acetonitrile:water (6:4) and back-flushing suited to the relevant analytes (Pauls 1985). It is important that the analyte is completely dissolved in the mobile phase.

2.4.1.4 Biological samples

Headspace or purge-and-trap concentrations of MTBE are directly applicable to blood and urine samples. The purge and trap procedure is coupled to quantification by GC-MS using ^{2}H-labelled standards. Direct GC analysis of samples is less commonly used but Schuberth (1996), using the full headspace technique combined with capillary GC and ion-trap detection, determined MTBE with a detection limit of 0.4–1 nmol in blood and brain tissue.

a) Blood, urine and tissues

The purge-and-trap system can be used for the analysis of blood samples. Sorption is done with a Tenax trap and a cryogenic trap decreasing in temperature to -150 °C with desorption at 180 °C. GC-MS analysis uses a DB 624 column. This has been applied to MTBE and to TBA using [$^{2}H_{12}$] MTBE and [$^{2}H_{9}$] TBA as the respective standards (Bonin et al., 1994).

Headspace analysis has been used for the analysis of both MTBE and metabolically produced TBA in a range of matrices including blood and urine. For blood samples, GC with an SE 50 column and FID can be used (Savolainen et al., 1985). Analysis of TBA produced from MTBE by hepatic microsomes from rats can be made with a Carbowax B/5% Carbowax 20M packed column and FID (Brady et al., 1990). A procedure applicable to blood and urine samples uses an SPB-1 column and FID (Streete et al., 1992). However, this procedure appears not to have been validated using samples contaminated with MTBE or TBA. The procedure can be applied to tissue samples after treatment with a proteolytic enzyme before analysis.

Analysis of MTBE (and TBA) in brain (cerebral hemispheres) and in perirenal fat from rats dosed with MTBE was made by homogenizing the samples in dimethyl formamide, centrifuging, and direct GC analysis of the supernatant using a packed column with Carbowax 20M and FID (Savolainen et al., 1985).

b) Bacterial cultures

Samples of bacterial cultures that metabolize MTBE have been analysed for both MTBE and its metabolite TBA by direct GC analysis using FID and a Quadrex methyl silicone capillary column (Salanitro et al., 1994). Analysis of MTBE (and TBA) in bacterial cultures that degraded TBA, though not MTBE, used a GC capillary column coated with a cross-bound phase (CP-Sil 13, Chrompack) and an FID detector (Allard et al., 1996).

^{14}C-labelled MTBE has been used in a few investigations. In one study dealing with aerobic biodegradation, $^{14}CO_2$ was collected after incubation as $Ba^{14}CO_3$, and the fraction incorporated into cells was separated by filtration though 0.45 μm Millipore filters (Salanitro et al., 1994). In another study on the accumulation of MTBE into plants, samples were extracted with dimethylformamide for counting (Schroll et al., 1994).

3. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

3.1 Natural occurrence

Natural sources of MTBE have not been reported in the scientific literature.

3.2 Anthropogenic sources

3.2.1 Production levels and processes

MTBE is an oxygenate (oxygen-containing hydrocarbon) that is industrially produced in several countries, including Austria, Belgium, Canada, Finland, France, Germany, Italy, Japan, Mexico, the Netherlands, Norway, Portugal, Sweden, Taiwan, the United Kingdom, the USA and Venezuela.

The worldwide annual production of MTBE in 1995 was about 15 million tonnes. In the USA, in 1994 MTBE ranked 18th in terms of production volume (6 175 000 tonnes (13.61 billion pounds)) and in 1995 there was an increase to 12th position (8 000 000 tonnes (17.62 billion pounds)) (CEN, 1996). During the years 1985–1995, production of MTBE in the USA showed an annual increase of 25% (Storck et al., 1996). The potential demand for MTBE is expected to increase to 284 000 barrels/day (12.2 million tonnes per year) in the year 2000.

North America is the largest consumer of MTBE, accounting for about two-thirds of the world's annual use. In 1996 the USA was the world's largest consumer of MTBE with a usage of 246 000 barrels/day (10.6 million tonnes per year). Western Europe, the eastern Mediterranean area and Asia, and Latin America used progressively smaller amounts of MTBE in 1995. Most growth in the production capacity of MTBE is expected to occur in the eastern Mediterranean area, South America and the USA.

MTBE is prepared principally by reacting isobutylene (contained in a mixed C4 stream) with methanol over an acidic ion-exchange

resin catalyst such as sulfonated styrene cross-linked with divinyl benzene in the liquid phase and at 38–93 °C and 100–200 psi. It can also be prepared from methanol, TBA and diazomethane (Budavari et al., 1996).

3.2.2 Uses

The main use of MTBE is as an additive to gasoline. MTBE was first added to gasoline in the late 1970s on a voluntary basis as an octane enhancer when the phase-out of tetraethyl lead commenced, and this use continues. MTBE is also added to gasoline in higher amounts (up to 15% by volume) as part of national mandated air pollution abatement programmes to reduce ambient air levels of carbon monoxide (CO) or ozone, or both, and in reformulated gasoline (RFG) (10-11% by volume) to reduce the emissions of benzene and other volatile hydrocarbons. MTBE is also used in the manufacture of isobutene (Lewis, 1993) and a minor proportion is used as a therapeutic agent for *in vivo* dissolution of cholesterol gallstones in humans (Allen et al., 1985a,b; Di Padova et al., 1986; Murray et al., 1988; Sternal & Davis, 1992).

In the USA, oxygenated gasolines are required in two national programmes to improve air quality (the oxygenated fuels programme and the reformulated gasoline programme) outlined in the 1990 Clean Air Act Amendments. MTBE is not specifically required in these programmes, but it is the most widely used oxygenate. The winter oxygenates programme requires gasoline sold in areas that do not meet federal air quality standards for CO to contain no less than 2.7% oxygen by weight, which is equal to 15% MTBE by volume. According to the reformulated gasoline programme, large metropolitan areas with serious ozone problems are required to use reformulated gasoline (RFG): this is a special blend of gasoline that must contain 2% oxygen by weight and a maximum of 1% benzene and 25% aromatic hydrocarbon by volume. To meet this requirement, reformulated gasoline would contain 11% MTBE by volume. About 90% of the MTBE consumed in the USA in 1996 was used in reformulated gasoline. At the end of 1996, MTBE was used in approximately 25% of the total gasoline pool.

During the winter driving season, 15% MTBE by volume is added to gasoline as an oxygenate to reduce CO emissions from motor vehicles. The extent of CO reductions depends on the fuel metering system and emissions control technology used on the vehicle (Prakash, 1989). The addition of oxygenates to gasoline blends generally reduces the hydrocarbon (HC) emissions to the atmosphere. However, the levels of exhaust nitrogen oxides (NO_x) increase when the oxygenate concentration exceeds about 2% oxygen by weight (SNV, 1993). It also increases the aldehyde emissions from automobile exhausts, but has not been found to have any major influence on the chemical composition of particulate emissions from vehicles (Watson et al., 1990). The aldehyde (not specified) emissions are significantly reduced by three-way catalytic converters (Prakash, 1989).

In a model analysis of changes in the concentrations of eight volatile organic compounds (VOCs), i.e. acetaldehyde, benzene, 1,3-butadiene, ethylbenzene, formaldehyde, toluene, xylenes, and particulate organic matter (POM), resulting from the use of reformulated gasoline and oxyfuel containing MTBE, Spitzer (1997) concluded that, with the exception of formaldehyde, exhaust emissions of these VOCs would be decreased. The increased formaldehyde emissions would, however, be offset by the reduction in the formation in the atmosphere of formaldehyde from the other VOCs. Erdal et al. (1997) modelled atmospheric ozone pollution reduction by the use of MTBE in gasoline. Ozone is formed by the reaction of sunlight with NO_x and VOCs. The use of MTBE reduces VOC and NO_x exhaust emissions and also reduces fuel evaporation. The model estimates a reduction in peak ambient ozone levels of 3.6–18 $\mu g/m^3$ (1–5 ppb).

It is estimated that MTBE-blended gasolines account for approximately 2% of the total unleaded gasoline in Canada (Environment Canada, 1992). Levels of MTBE in blended gasolines range from 0.04% to 9.09% by volume, depending on the grade of gasoline, season and geographical area. Since the use of oxygenates is not required in Canada as part of an air abatement programme, each refiner blends in the amounts of MTBE that it requires in order to obtain a good gasoline end-product, depending on the batch of crude oil and the technology used in the refinery. In 1997, the maximum

concentration of MTBE allowed in Canadian gasoline was 2.7% mass oxygen (approximately 15% by volume).

3.2.3 Sources and releases to the environment

Similar to hydrocarbon components of gasoline, fuel oxygenates such as MTBE enter the environment during all phases of the petroleum fuel cycle. Sources include, for example, auto emissions, evaporative losses from gasoline stations and vehicles, storage tank releases, pipeline leaks, other accidental spills, and refinery stack releases. Annual estimates of MTBE mass releases to the environment from all potential sources have not been reported in the scientific literature. However, releases from storage tanks, vehicular emissions and evaporative losses from gasoline stations and vehicles are perceived to be important sources (Zogorski et al., 1996; US Interagency Assessment, 1997).

3.2.3.1 *Industrial releases*

No information on industrial releases of MTBE to the environment have been found in the scientific literature, except in the case of the USA and Canada.

Industrial releases of MTBE in the USA have been characterized for 1993. A total of 136 facilities released MTBE to the environment, with an estimated total release of 1700 tonnes. Approximately 84% of the release was by petroleum refineries, and almost all of the MTBE was released to air (Zogorski et al., 1996).

In 1994, the total Canadian industrial release of MTBE from refiners and manufacturers was approximately 28.2 tonnes, the bulk of which was released into the air (98.1%) and a small amount into water (1.9%) (Environment Canada, 1996a). The highest amounts of MTBE released were 9.5, 9.1, 8.4 and 1.0 tonnes by industries located in Sarnia, Burnaby, Edmonton and Saint John, respectively.

3.2.3.2 *Storage tank release*

Releases of gasoline containing MTBE from storage tanks may contaminate soil and groundwater. In some cases, MTBE may enter

drinking-water supplies. In 1989 it was estimated that in the USA there were approximately 14 000 above-ground storage tank facilities with an estimated 70 000 tanks, of which 30–40% were used for gasoline storage (API, 1989a). A subsequent survey of 299 storage facilities showed that 40% had identified subsurface contamination (API, 1994). Many sites have been identified with soil or groundwater hydrocarbon contamination that required corrective action. The extent of MTBE contamination at these sites is largely undocumented because monitoring of MTBE has not been required. More stringent release-prevention and -detection standards are now required in the USA and, when fully implemented by December 1998, these requirements should considerably decrease the annual volume of gasoline released to soil and groundwater.

It is important to note that when gasoline containing MTBE enters groundwater, high concentrations of MTBE (i.e. in excess of 1000 µg/litre) can occur. While comprehensive data on the occurrence of MTBE in drinking-water provided from groundwater do not exist, there have been some instances reported in the USA where drinking-water supplies have been disrupted because of high MTBE levels. For example, two well fields serving the city of Santa Monica, California, have been contaminated with MTBE necessitating the purchase of alternative water for drinking-water.

3.2.3.3 *Engine emissions from on-road and off-road vehicles and recreational boats*

The use of gasoline containing MTBE in on-road and off-road vehicles, boats and small engines will result in MTBE releases to the environment unless recovery systems are employed. The extent of these emissions has not been thoroughly studied, and there are few scientific citations.

Drivas et al. (1991) estimated ambient air concentrations of evaporative and exhaust emissions of MTBE gasoline blends during two different situations representing worst-case concentrations: a car idling in an open garage and a car just stopped and turned off (hot-soak evaporative emission) in a closed garage. The predicted

maximum exhaust air concentration of MTBE was calculated to be 0.24 mg/m^3 (0.07 ppm).

MTBE was not detected in samples from light-duty vehicle emissions measured in the Caldecott Tunnel, San Francisco Bay Area, in August 1994, when the average oxygen content of gasoline sold in the area was 0.3% by weight (Kirchstetter et al., 1996). In October, when the average oxygen content in MTBE gasoline was 2.0% by weight, the concentration of MTBE in emissions was 3.3% by weight of total VOCs.

Comparison of emissions from vehicles using a standard fuel and a reformulated fuel that contained MTBE (11% by volume) showed a reduction in mass emission rates in the latter (Hoekman, 1992). Although there was a decrease in the emissions of aromatics and alkanes, the levels of alkenes and carbonyl compounds increased, and there was considerable variation among the vehicles that were tested. A study in California showed that increasing the concentration of MTBE from 0.3% by weight in August to 1.6 % MTBE plus 0.4% ethanol in October resulted in lowered emission of aromatics but increased emissions of isobutene (86%), cisbut-2-ene (150%), formaldehyde (39%), propionaldehyde (200%), methacrolein (50%) and butyraldehyde (40%) (Kirchstetter et al., 1996).

Boat motors and small engines used in chain saws, other power tools, snowmobiles, lawn mowers and garden tillers, for example, may also release MTBE to the environment via exhaust, evaporative losses and release of uncombusted fuel. The magnitude and significance of these releases are not documented. In 1997 MTBE was detected in several public water supply reservoirs that, in part, provide drinking-water for Southern California. The predominant source of MTBE is thought to be associated with small engines used on recreational boats. Such engines are known to be inefficient, and release uncombusted gasoline and emissions to water and air.

3.3 Other pertinent information

All aspects of the effectiveness of fuel oxygenates on ambient air quality, including carbon monoxide, hydrocarbons, oxides of nitrogen,

aromatics, aldehydes and alcohols, and associated atmospheric degradation products, have been reviewed in a number of reports (e.g., Prakash, 1989; Environment Canada, 1993; Schuetzle et al., 1994; HEI, 1996; Kirchstetter et al., 1996; US Interagency Assessment, 1997).

Overall, these studies indicate that, when compared to other gasolines, MTBE gasoline blends generally reduce CO and hydrocarbon exhaust emissions and increase aldehyde and NO_x emissions.

4. ENVIRONMENTAL BEHAVIOUR AND FATE

4.1 Transport and distribution between media

A diagram depicting the movement of MTBE in the environment is shown in Fig. 1.

4.1.1 Air

It can be predictable from its physicochemical properties that, when MTBE is released into air, the greater part will exist in the atmosphere, with small amounts entering soil and water (Mackay et al., 1993). Based on its Henry's law constant, MTBE should partition into atmospheric water, including rain. The concentration of MTBE in precipitation would be in direct proportion to its concentration in air. However, falling precipitation removes only a negligible amount of the gas-phase compound (Zogorski et al., 1996). Therefore, chemical degradation of MTBE should be the major removal process from the air (Mackay et al., 1993).

4.1.2 Water

Transport and distribution of a substance between and within media in the aquatic environment is dependent upon its solubility, movement of the water itself, exchanges at the air-water interfaces, adsorption to sediment and particulate matter, and bioconcentration in aquatic organisms. The residence time in water is also dependent upon the type of environmental conditions encountered, such as temperatures, wind speeds, currents and ice cover (Environment Canada, 1993).

MTBE can volatilize from surface water and be removed by aeration (Zogorski et al., 1996). According to calculations by Pankow et al. (1996), no single volatilization half-life ($t_{½}$) will characterize the loss process from water. In surface water, the most important factors for the volatilization rates are the depth and velocity of the flow. In deep and slow-moving flows, the $t_{½}$ values at both 5 °C and 25 °C are 85 and 78 days for calm and windy conditions, respectively. These rates were shown to be similar to those for benzene, toluene, ethyl

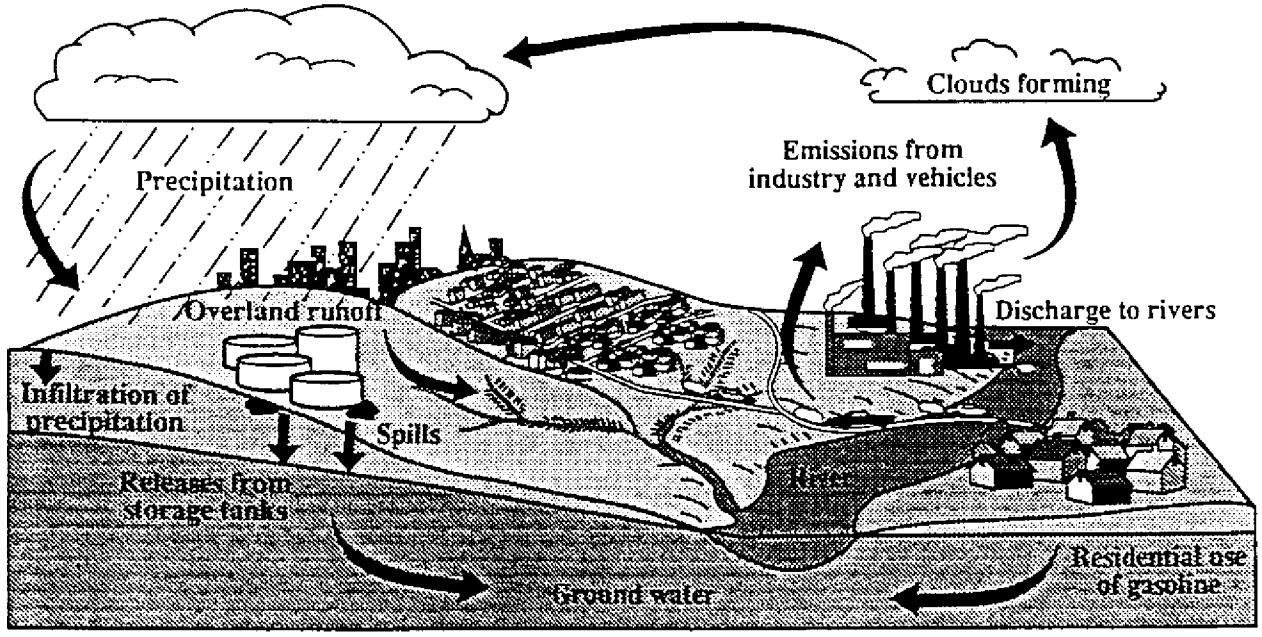


Fig. 1.The movement of fuel oxygenates in the environment (Zogorski et al., 1996).

benzene and xylene (BTEX) compounds. In shallow and fast-moving flows, changing from calm to windy conditions causes a significantly accelerated volatilization rate. Under these circumstances, MTBE volatilizes more slowly than benzene, although it was suggested that this is of no practical significance, as both substances volatilize quickly in such flows. It was concluded that the $t_{½}$ values for MTBE are highly dependent on depth and mean flow velocity. Thus, quite large as well as very small $t_{½}$ values are possible.

Based on physicochemical properties, it can be predicted that a release of MTBE into water would result in significant amounts being dissolved. Most of the MTBE remains in the surface water, with some partitioning into air and much smaller amounts into sediment and soil (Mackay et al., 1993). The low K_{ow} of 0.94 suggests that partitioning from the water to particulates and sediment is not significant. On the basis of bioconcentration data, MTBE is not subject to bioaccumulation or biomagnification in aquatic organisms (Environment Canada, 1993). In the water compartment, the key removal process should be volatilization. The amount transferred to sediment is negligible (Mackay et al., 1993; Environment Canada, 1993).

For a gasoline containing 10% MTBE by weight, and assuming that it does not undergo depletion of the MTBE concentration in the gasoline due to dissolution into the water, the water solubility of the MTBE from gasoline will be approximately 5 gm/litre at 25 °C. By comparison, the total hydrocarbon solubility for non-oxygenated fuel is about 120 mg/litre (Poulsen et al., 1992; Zogorski et al., 1996).

The ability of MTBE to enhance the solubility in water of monocyclic aromatic gasoline components including BTEX compounds has been examined in models, and an increase was predicted only at co-solvent concentrations of greater than 1% (Mihelcic, 1990). In confirmation of this, the co-solvent effect of MTBE on the aqueous solubility of hydrocarbons in gasoline was found to be minimal (Cline et al., 1991). Measurements made in the laboratory in shake-flasks showed that up to 15% MTBE was unlikely to result in enhanced concentrations of BTEX in contaminated groundwater (Poulsen et al., 1992). Such high concentrations of MTBE seem unlikely to be achieved in groundwater after spillage of gasoline containing MTBE,

and although MTBE is widely distributed in shallow urban groundwater at low concentrations in the USA, its occurrence in these samples was not associated with correspondingly increased concentrations of BTEX (Squillace et al., 1996).

4.1.3 Soil

Based on its physicochemical properties, it can be predicted that when MTBE is released to the soil, it can be transported to the air through volatilization, to surface water through run-off, and to groundwater as a result of leaching. In the first two instances, the release would have to be at, or near the soil surface. If the release of MTBE occurs below the soil surface, for example from an underground storage tank, then the most likely transport mechanism will be leaching to groundwater. Based on its vapour pressure, volatilization of MTBE from soil and other surfaces is expected to be significant. Soil adsorption and mobility are based on the reported and estimated K_{oc} (organic carbon sorption coefficient) values. Compounds with a K_{oc} of <100 are considered to be moderately mobile. Thus MTBE, with a Koc of 91, does not adsorb to soil particles to a great degree and would be considered mobile. Parameters other than K_{oc} affecting the leaching of MTBE to groundwater include the soil type (e.g., sandy versus clay), the amount and frequency of rainfall, the depth of groundwater, and the extent of degradation of the MTBE (Environment Canada, 1993).

4.1.4 Multimedia

Several multimedia models using various emission rates and environmental parameters have been used to predict the distribution and concentration of MTBE in the environment (Environment Canada, 1993; Mackay et al., 1993; Hsieh & Ouimette, 1994).

4.2 Bioconcentration

Fujiwara et al. (1984) conducted studies on the bioconcentration of MTBE in Japanese carp (*Cyprinus carpio*) in a flow-through system at 25 °C. The mean whole-body steady-state bioconcentration factor (BCF) was 1.5. Further observations indicated that fish exposed for 28

days and then transferred to clean water eliminated almost all MTBE residues within 3 days. These experimental data support the hypothesis that MTBE has little tendency to bioaccumulate. Veith & Kosian (1983) calculated a BCF of 2.74 ($r^2 = 0.927$) for a 28-day exposure of fathead minnows, based on a Quantitative Structure-Activity Relationship (QSAR).

Compounds with log K_{ow} values of approximately 5.0 or less do not have significant food chain build-up. MTBE belongs to this group (Environment Canada, 1993). Uptake from water is more important than from food for this group of compounds.

When ^{14}C-labelled MTBE was applied to the soil in a closed aerated system, the concentrations of MTBE in the roots and the aerial parts of lettuce and radish showed that transport was dominated by foliar uptake; subsequently, translocation into the roots took place (Schroll et al., 1994). Although neither MTBE nor its potential metabolite TBA was detected in the plants, a considerable fraction of the ^{14}C label was unaccounted for and was presumed to be associated with plant constituents.

4.3 Biodegradation and transformation

Only a limited amount of work has been accomplished on the biodegradability of MTBE. Moreover, the studies are difficult to compare because they have been performed under a wide variety of conditions. Aerobic and anaerobic experiments have been conducted. For most studies, it has been demonstrated that MTBE is difficult to biodegrade. In contrast, BTEX is more readily biodegraded (Zogorski et al., 1996). Half-lives for MTBE in various environmental compartments are shown in Table 3

4.3.1 Aerobic conditions

Results from tests involving biodegradation of MTBE have been variable.

Pence (1987a) used an acclimated culture containing active sludge, soil inoculum and raw sewage. The uptake of oxygen was

Table 3. Half-life ranges of MTBE in various compartments

Environmental compartment	Half-life ranges (h)	Comments	Reference
Air	20.7–265	Based upon measured photo-oxidation half-life	Howard et al., 1991
	10–30		Mackay et al., 1993
Soil	672–4320	Estimation based upon aerobic biodegradation half-life	US EPA, 1989
	300–1000		Mackay et al., 1993
Surface water	672–4320	Estimation based upon aerobic biodegradation half-life	Howard et al., 1991
	300–1000		Mackay et al., 1993
Sediment	1000–3000		Mackay et al., 1993
Groundwater	1344–8640	Estimation based upon aerobic biodegradation half-life	Howard et al., 1991
	2688–17 289	Estimation based on anaerobic degradation half-life	Howard et al., 1991

measured in a mineral medium supplemented with MTBE added to the acclimated culture at a concentration of 5 mg/litre on days 0, 7 and 11. The results showed that MTBE was poorly biodegradable under these conditions; only 5.4% biodegradation occurred within 28 days.

No biodegradation of MTBE after 60 days was found in experiments using aquifer soil material as inoculum; with two types of activated sludge as inoculum, no degradation of MTBE occurred after 40 days (Möller Jensen & Arvin, 1990).

With a standard activated sludge, and based on the oxygen uptake rate, MTBE was biodegraded very slowly (Fujiwara et al., 1984). The hydrocarbon components of gasoline blended with MTBE were, however, readily degraded even though the MTBE remained.

A mixed bacterial culture was obtained by enrichment of a hydrocarbon-contaminated soil in a basal mineral medium containing:

(i) TBA (1 g/litre) as sole carbon source or (ii) methylamine (2 g/litre) as principal carbon source supplemented with TBA. During incubation of the first culture, the concentration of TBA fell to zero in 20 days, but incubation of methylamine-grown cells with MTBE showed no reduction in the concentration of MTBE after 42 days (Allard et al., 1996). Whereas MTBE was apparently recalcitrant under the conditions used, TBA, which is one of its putative degradation products, was biodegradable.

In contrast to these results, a mixed bacterial culture obtained by continuous aerobic enrichment of a sludge sample from an industrial bioreactor was able to degrade MTBE at concentrations up to 200 mg/litre (Salanitro et al., 1994). Cell suspensions incubated with MTBE produced TBA as a transient metabolite. MTBE labelled with ^{14}C in the methyl group was degraded to $^{14}CO_2$ and cellular material when low substrate concentrations (2 mg/litre) were used, although not at a concentration of 20 mg/litre. This experiment clearly demonstrated oxidation of the methoxy group but left unresolved the fate of the carbon atoms of the *tertiary*-butyl group.

Fifteen pure bacterial strains, with the capacity to degrade MTBE using it as the sole carbon source, have been isolated from bioreactor sludges and other sources. Several strains have been identified as belonging to the genera *Rhodococcus, Flavobacterium, Pseudomonas* and *Oerskovia*. These strains degrade up to 40% of MTBE (200 mg/litre) in 1–2 weeks of incubation at 22–25 °C. These strains also grow on *tert*-butanol, butyl formate, isopropanol, acetone and pyruvate as sole carbon sources. Cultures of *Methylobacterium*, *Rhodococcus* and *Arthrobacter* degraded MTBE within 1–2 weeks of incubation at 23–25 °C. Growth on MTBE as the sole carbon source was slow compared with growth on a nutrient-rich medium. When these compounds are mixed with MTBE, there is a reduction in the degradation of MTBE. However, when the microbes were initially grown on *tert*-butanol and then transferred to medium containing MTBE, there was a greater degradation of MTBE (Mo et al., 1997).

A mixed culture isolated from biological sludges has been used in bioreactors utilizing MTBE as a sole carbon source for over a year.

The microbes were able to degrade MTBE at a concentration of 160 mg/litre after 3 days of incubation in batch experiments. Mixed cultures have greater capacity for degradation of MTBE than pure cultures. The addition of other ethers causes a reduction in MTBE degradation. In soil microcosm studies, significant MTBE degradation by mixed cultures was observed at 24 °C and 10 °C (Mo et al., 1997).

Howard et al. (1991) estimated, on the basis of screening tests for aerobic biodegradation with unacclimatized aqueous systems (Fujiwara et al., 1984), that the half-lives of MTBE in water and soil under aerobic conditions ranged from 672 to 4320 h.

MTBE was found to be degraded by a number of propane-oxidizing bacteria. The initial oxidation of MTBE produced nearly stoichiometric amounts of TBA. The methoxy group of MTBE was further oxidized to formaldehyde and finally to CO_2. At 28 °C, rates of MTBE degradation by these bacteria ranged from 3.9 to 9.2 nmol/min per mg cell protein weight (Steffan et al., 1997).

4.3.2 Anaerobic conditions

Biodegradability of MTBE to methane under anaerobic conditions has been determined by measuring the production of CH_4 and CO_2 during exposure of MTBE to a large population of anaerobic bacteria. MTBE was biodegraded anaerobically only to a very limited extent (Pence, 1987b), and an average cumulative theoretical gas production of only 7.1% was achieve within 56 days. Anaerobic biodegradation to methane must exceed 50% to meet the validation requirements for demonstration of anaerobic biodegradability.

The anaerobic degradation of MTBE has been examined in different soils (unsaturated clay, sandy loam and silty loam) collected from various depths at three different sites (Novak et al., 1992; Yeh & Novak, 1994). The experiments were conducted in static small-volume anaerobic microcosms, and three different oxygen-free conditions were simulated; with nitrate as electron acceptor (denitrification), sulfate-reducing conditions, and anaerobic fermentation. Factors influencing the degradation of MTBE, ETBE and TBA were determined, and included anaerobic microbial populations, soil anions, soil

moisture content, organic content, nitrogen availability, rate of ammonium "fixation", and soil pH. The soils were moderately acidic (pH 5.0–6.0) with the exception of surface soils. The concentration of the added MTBE was monitored for more than 250 days. Three parameters were evaluated: degradation rate, lag time and time for 80% of the compound to be degraded. No anaerobic degradation of MTBE was found in organic-rich soils over the 250-day study period. The only situation in which MTBE degradation occurred was in an oligotrophic soil containing a low level of organic matter and with a pH of 5.0–6.0. About 10% of the MTBE was lost during the first two months, although this decrease cannot unambiguously be attributed to biodegradation. Several conclusions may be drawn from the experiments with TBA and ETBE:

- Whereas degradation of TBA in soil from the oligotrophic site could be enhanced by addition of nitrate, the degradation of TBA was inhibited by adding readily degraded ethanol.

- Biodegradation of ETBE under denitrifying conditions was extremely sensitive to the presence of readily degraded substrates.

These results illustrate that care should be exercised in assessing biodegradability when several readily degraded substrates are available, a condition that may be encountered in groundwater contaminated with oxygenate additives.

Suflita & Mormile (1993) used sediment suspensions prepared from samples collected from an aquifer polluted with leachate from a municipal landfill. They assessed the formation of methane from a range of substrates, and after at least 249 days no evidence for anaerobic degradation of MTBE could be found. Whereas unbranched alkanols and ketones were readily degraded, ethers in general were resistant; in addition, oxygenates containing a tertiary or quaternary carbon atom proved more recalcitrant than their unbranched or moderately branched chemical analogues to anaerobic degradation. Comparable experiments using a wider range of sediment samples (Mormile et al., 1994) showed similar results under sulfate-reducing or denitrifying conditions, although under methanogenic conditions a

single sample transformed MTBE into TBA. Likewise, the ethers were unaffected by incubation with cultures of the acetogenic bacteria *Acetobacterium woodii* and *Eubacaterium limosum* that convert aromatic methoxy groups to acetate.

Based on the above-mentioned studies, MTBE is classed as recalcitrant under anaerobic conditions.

Howard et al. (1991) estimated that the half-life of MTBE in water under anaerobic conditions ranges from 2688 to 17 280 h.

4.4 Abiotic degradation

4.4.1 Air

4.4.1.1 Photolysis

Direct photolysis of MTBE is assumed to be environmentally insignificant since it does not absorb radiation above 230 nm (Calvert & Pitts, 1966). However, under laboratory conditions MTBE in an oxygenated slurry system containing TiO_2 as catalyst was readily degraded by UV light from a mercury lamp. MTBE was rapidly photocatalytically degraded, 76% of the initial concentration being converted to degradation products, including TBA. After 4 h MTBE was no longer detectable (Barreto et al., 1995).

4.4.1.2 Hydrolysis

MTBE does not contain hydrolysable functional groups, and, therefore, it is inert to environmental hydrolysis. Hydrolysis of MTBE is assumed to be insignificant (Howard et al., 1991).

4.4.1.3 Photooxidation

MTBE is subject to photooxidation in the atmosphere. This will occur under the influence of various mechanisms, such as the reaction with hydroxyl radicals, water, alkoxy and peroxy radicals, oxygen atoms, and ozone. On the basis of the rate constant of each of the reactions and the concentrations of the reactants, the reaction with the hydroxyl radical is considered to be the most important removal

process for MTBE in the atmosphere. Several products are generated as a result. These include *tertiary*-butyl formate (TBF), the major product, 2-methoxy-2-methyl propanol, formaldehyde, acetone, NO_2, and the methyl radical. Molar yields of products identified from the reaction of hydroxyl radicals with MTBE are given in Table 4). TBF is unreactive to further photo-oxidation, while 2-methoxy-2-methyl propanol is expected to be highly reactive with hydroxyl radicals, yielding equimolar amounts of CO_2, formaldehyde, acetone and water.

Table 4. Molar yields of products identified from the reaction of hydroxyl radicals with MTBE

Product	Molar yield[a]	Molar yield[b]
TBF	0.68	0.76
Formaldehyde	0.48	0.37
Methyl acetate	0.14	0.17
TBA	0.062	–
Acetone	0.026	0.02

[a] Smith et al., 1991.
[b] Tuazon et al., 1991.

Of these products, formaldehyde is highly reactive with the hydroxyl radical (Wallington et al., 1988; Japar et al., 1991). Rates of reaction of oxygenates and their decomposition products with hydroxyl radicals are given in Table 5.

Factors influencing atmospheric lifetime, such as time of day, sunlight intensity and temperature, also include those affecting the availability of hydroxyl radicals. Based upon measured rate constants for reactions with hydroxyl radicals in air (Cox & Goldstone, 1982; Atkinson, 1985; Wallington et al., 1988, 1989; Atkinson, 1990; Japar et al., 1990), the half-life for MTBE has been estimated to be between 20.7 and 265 h (Howard et al., 1991). Hence, MTBE is not considered to be a greenhouse gas, nor would it contribute to the depletion of the ozone layer (Environment Canada, 1993).

Table 5. Rates of reaction of oxygenates and their decomposition products with hydroxyl radicals at 25 °C

Compound	Rate (10^{-12} cm^3 sec^{-1} molecule^{-1})	Reference
MTBE	3.2	Japar et al., 1991
ETBE	8.5	Japar et al., 1991
TBF	0.74	Smith et al., 1991
TBA	1.1	Japar et al., 1991
Formaldehyde	9.0	Atkinson & Pitts, 1978
2-methoxy-2-methyl propanal[a]	30	Japar et al., 1991

[a] Estimated from rates for other aldehydes

4.4.2 Natural waters

MTBE is not expected to adsorb significantly to bed sediments of suspended sediments, hydrolyse, directly photolyse, or photo-oxidize via reaction with photochemically produced radicals in water. While MTBE is reported to be chemical unstable in acidic solutions (Budavari et al., 1996), it is not expected to be hydrolysed in natural waters under normal pH conditions (Lyman et al., 1990).

4.4.3 MTBE half-life ranges in environmental compartments

The half-life of a chemical in the environment depends not only on the intrinsic properties of the chemical, but also on the nature of the surrounding environment, such as sunlight intensity, hydroxyl radical concentration, the nature of the microbial community and temperature. Table 6 lists the half-life ranges in various environmental compartments estimated by Mackay et al. (1993) and Howard et al. (1991); these estimates are somewhat uncertain, as implied by the order of magnitude range for some compartments.

4.5 Ozone-forming potential

Photochemical ozone-creation potentials (POCP) ranging from 20.4 to 34.6 have been determined for MTBE using a model that

Table 6. Half-life ranges of MTBE in various compartments

Environmental compartment	Half-life ranges (h)	Comments	Reference
Soil	672–4320 300–1000	Estimation based upon aerobic biodegradation half-life	Howard et al., 1991 Mackay et al., 1993
Air	20.7–265 10–30	Based upon measured photo-oxidation half-life	Howard et al., 1991 Mackay et al., 1993
Surface water	672–4320 300–1000	Estimation based upon aerobic biodegradation half-life	Howard et al., 1991 Mackay et al., 1993
Sediment	1000–3000		Mackay et al., 1993
Groundwater	1344–8640	Estimation based upon aerobic biodegradation half-life	Howard et al., 1991

simulates the formation of photochemical ozone episodes (Derwent et al., 1996). The POCP values reflect the ability of a substance to form tropospheric ozone as a result of its atmospheric degradation reactions. The POCP values are calculated relative to ethylene (a chemical that is thought to be important in such ozone formation and is given a POCP of 100). Based on the emissions and the POCP value, MTBE (itself) is likely to play a minor role in photochemical smog and low-level (tropospheric) ozone formation near to sources of release.

4.6 Remediation

Examples of remedial methods that can be considered for MTBE are air stripping, carbon absorption and soil vapour extraction. Intrinsic bioremediation may be limited due to the variability of rates of biodegradation of MTBE which have been previously mentioned (Zogorski et al., 1996).

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

The major sources of MTBE to the general population are probably associated with the distribution, storage and use of oxygenated gasoline. The main source of non-occupational exposure to MTBE is evaporative emissions from gasoline. A large portion of the population is exposed during time spent at service stations, while driving cars, in public parking garages, and in homes with attached garages. These exposures generally occur through inhalation. In addition, discharges into the soil or groundwater are a potential for contaminated water supply and can lead to exposure when such water is drunk. Dermal contact with MTBE may occur through accidental spills of MTBE-blended gasoline or through the use of gasoline as a solvent. In Canada, it has been estimated that gasolines blended with MTBE account for only 2% of the total annual gasoline consumption. MTBE is used in small quantities by a few Canadian refiners to boost octane levels in gasoline. A limited survey of the MTBE content of unleaded regular, mid-range and premium gasoline across Canada in 1995 showed a range of 0 to 5.2% by volume for winter grade gasoline and 0 to 9% by volume in summer grade gasoline. In the USA, oxygenated gasoline containing 10–15% MTBE is used in different areas and about 30% of the US population is exposed to MTBE.

5.1 Environmental levels

5.1.1 Exposure

Ambient air and microenvironment concentrations of MTBE and other fuel oxygenates have been measured in Canada, the USA and Finland. When available, air data are presented below in conjunction with data on MTBE levels in gasoline and with information on the proximity of the samples to various point sources of MTBE.

Brown (1997) estimated average daily and average lifetime doses of MTBE from exposure in air and drinking-water for a US population. Concentration data and several of the population characteristics were estimated as distributions rather than as point values.

Arithmetic mean occupational doses via air were in the range of 0.1 to 1.0 mg/kg-day, while doses from residential exposures, commuting and refuelling were in the range of 0.0004 to 0.006 mg/kg-day. Lifetime doses for workers were in the range of 0.01 to 0.1 mg/kg-day. The cumulative dose distribution for the entire population of the MTBE-using regions of the USA was estimated by combining the distributions of doses and the numbers of people in each exposure category. In the MTBE-using areas, arithmetic mean doses via air were estimated to be 0.0053 and 0.00185 mg/kg-day for the chronic and lifetime cases, respectively. It was found that 1.5% of the population used water contaminated with MTBE leakage with an estimated geometric mean concentration of 0.36 µg/litre and a 95th percentile concentration of 64 µg/litre. Including ingestion, inhalation, and dermal absorption of contaminated water, the estimated arithmetic mean does of the population exposed via water was 1.4×10^{-3} mg/kg-day.

5.1.1.1 *Levels in ambient air and various microenvironments*

a) Canada

The concentrations of MTBE in ambient air at various selected locations in Canada have been measured as part of the National Air Pollution Surveillance Programme in 1995 and 1996. This programme is a joint project of the federal, provincial and municipal levels of government. Its purpose is to monitor and assess, on a continuing basis, the quality of the ambient air in the various regions of Canada. The sites selected for monitoring of MTBE were based on usage of gasoline with MTBE and/or because of nearby manufacturers of MTBE.

Pollutants from air were collected intermittently using the canister methodology. Concentrations of MTBE was measured using the detection principle of gas chromatography furnished with an ion trap detector. Air samples were first passed through a cryogenic concentration trap to gather enough analyte before injection into a GC capillary column to allow compound speciation and quantification. Approximately 200 ml of the canister sample was concentrated. A cryogenic trap held at -150 °C was used to concentrate the air sample.

Once the sample was concentrated, the trap was heated to 150 °C and the sample was back-flushed onto the column. MTBE and other hydrocarbons were separated using a fused silica capillary column. The GC oven was programmed to remain at 60 °C for 3 min, then increased to 280 °C at a rate of 8 °C/min. Calibration standards were prepared using the static dilution technique. The detection limits were 0.05 to 0.1 $\mu g/m^3$.

Table 7 lists the ambient concentration of MTBE in air at various locations in Canada from 1995 to 1996.

Table 7. Concentrations of MTBE in ambient air in Canada (1995–1996) (Environment Canada, 1996b)

City[a]	Industrial site(s) and distance(s) to monitoring site (where applicable)	Sample date	MTBE concentration ($\mu g/m^3$)[b]
Edmonton(1)[c]	Two petroleum refineries - 1 km. Acetic acid plant - 2.5 km	20/7/95	7.21
		26/7/95	11.39
		1/8/95	0.81
		7/8/95	2.93
		8/8/95	5.50
		12/9/95	2.49
		27/5/96	3.35
Edmonton(2)[d]	N/A	26/7/95	≤ DL
		1/8/95	≤ DL
		1/9/95	≤ DL
		6/9/95	≤ DL
		24/9/95	≤ DL
		30/9/95	≤ DL
		27/5/96	≤ DL
Halifax[d]	N/A	3/4/96	≤ DL
		15/4/96	0.13
		21/4/96	0.15

Table 7 (contd).

City[a]	Industrial site(s) and distance(s) to monitoring site (where applicable)	Sample date	MTBE concentration ($\mu g/m^3$)[b]
Montreal(1)[c]	Two refineries (BTX, petroleum) - 1.6, 2.5 km	21/8/95	1.54
		21/8/95	0.59
		12/9/95	1.06
		16/3/96	< DL
		15/5/96	0.42
		21/5/96	0.28
		27/5/96	0.23
Montreal(2)[d]	N/A	16/3/95	0.15
		16/5/96	0.18
		21/5/96	0.22
		27/5/96	0.37
Montreal(3)[e]	N/A	10/3/96	0.16
		16/3/96	0.28
		9/5/96	0.95
Montreal(4)[f]	N/A	9/5/96	0.22
		15/5/96	< DL
		21/5/96	0.70
St. John[c]	Petroleum refinery - 3 km	9/5/96	1.02
		15/5/96	3.73
Stouffville[f]	N/A	6/10/95	0.19
		18/10/95	0.35
Toronto(1)[g]	N/A	29/8/95	< DL
		2/9/95	< DL
		2/9/95	0.07
Toronto(2)[d]	N/A	17/8/95	0.03
		29/8/95	< DL
		2/9/95	< DL
Vancouver(1)[f]	N/A	23/8/95	0.27
		29/8/95	0.89
		29/8/95	0.16
		30/8/95	0.33
Vancouver(2)[f]	N/A	22/3/95	0.14

Table 7 (contd).

City[a]	Industrial site(s) and distance(s) to monitoring site (where applicable)	Sample date	MTBE concentration ($\mu g/m^3$)[b]
Vancouver(3)[c]	Two gasoline processing and storage plants - 0.5, 3 km	1/8/95	2.13
		13/8/95	1.82
		25/8/95	3.35
		2/9/95	1.78
		2/9/95	26.43
		21/2/96	0.31
		10/3/96	1.10
		16/3/96	0.48
		16/3/96	0.39
		22/3/96	1.55
		28/3/96	≤ DL
Vancouver(4)[e]	N/A	10/3/96	1.07
Vancouver(5)[f]	N/A	28/3/96	0.40
Vancouver(6)[c]	Pipeline transfer point	1/9/95	1.79
		2/9/95	1.90
		22/3/96	0.89
Windsor[d]	N/A	2/8/95	0.08
		17/8/95	0.05
		17/8/95	0.11
		21/8/95	0.40
		29/8/95	0.27
		29/8/95	0.14
		16/3/96	≤ DL
		21/4/96	0.15
		27/4/96	≤ DL
Winnipeg[d]	N/A	4/3/96	0.02
		27/3/96	≤ DL

[a] ( ) = different monitoring sites in same city.
[b] DL = detection limit = 0.1 $\mu g/m^3$.
[c] Monitoring site in vicinity of petroleum refinery and/or industrial chemical plant, or pipeline transfer area.
[d] Monitoring site in urban area.
[e] Monitoring site in urban area on busy street.
[f] Monitoring site in suburban area.

Table 8 shows some MTBE atmospheric concentrations at the fence line of a petroleum refinery at St John, New Brunswick, Canada, during a period when there were complaints of odour. The same collection and analytical methodology was used. The maximum concentration is not considered representative of the area.

Table 8. MTBE concentrations at petroleum refinery boundary (St. John, New Brunswick, Canada) during period of odour complaints

Sampling date	MTBE concentration ($\mu g/m^3$)
19/7/95	281
2/8/95	15
14/8/95	71
28/8/95	36

b) USA

In many urban areas in the USA having elevated levels of ozone or CO, oxygenates such as MTBE are regulated for use in gasoline at concentrations of 2.0% and 2.7% oxygen by weight (called reformulated and oxygenated gasoline, respectively). These concentrations are achieved by adding MTBE at 11% and 15% by volume, respectively. In other areas, MTBE is used as an octane enhancer in premium gasoline at concentrations up to 9% by volume, but usually at much lower concentrations. It is important to note that MTBE is the predominant oxygenate currently in use in these gasoline mixtures, followed by ethanol (approximately 65% and 35% of the oxyfuels sold contain MTBE and ethanol, respectively). Oxygenates used to a minor extent include ETBE, TAME and DIPE (HEI, 1996). In 1994, oxygenates were added to more than one-third of the gasoline market in the USA.

MTBE air quality data were collected in the USA as a result of special studies in six urban centres: Fairbanks (Alaska), Stamford (Connecticut), Albany (New York), Milwaukee (Wisconsin), Boston (Massachusetts) and Houston (Texas) (Zogorski et al., 1996). In addition, collection of MTBE air quality data for selected monitoring sites in California started in 1996. Although these data cannot be used

to define quantitatively the air quality in these cities and are not sufficient to provide a national perspective, they can be used to estimate approximate ranges of MTBE in ambient air in the locations sampled (Zogorski et al., 1996; US Interagency Assessment, 1997). Non-occupational and consumer exposure to MTBE is shown in Table 9, and service station attendants and garage workers in Table 10.

Owing to health complaints (Gordian et al., 1995) following the introduction of oxygenated fuels (15% MTBE) during the 1992 winter season in Fairbanks, Alaska, the sale of these fuels was suspended in mid-December 1992, one month after their introduction. Zweidinger (1993) analysed air samples for MTBE in ambient air and in various microenvironments in Fairbanks taken immediately prior to the suspension (phase I), during the phase-out period (Phase II), and two months after the suspension, at which time the MTBE fuels were expected to be at nominal levels (Phase III). Fuel samples collected from Fairbanks gasoline stations during Phases II and III indicated that the average percentage by weight of MTBE in unleaded regular gasoline decreased from 8.5% to 1% while the average for premium gasoline decreased from 14.7 to 5.6%. For comparison, ambient air samples were also collected in the spring of 1993 from Stamford, Connecticut, where 15% MTBE oxygenated gasoline was sold but there were no consumer health complaints, and Albany, New York, where MTBE was only present in gasoline at nominal levels to enhance octane and there were also no health complaints (Zweidinger, 1993).

Ambient air samples in these cities were generally collected over an 8-h period and were taken from the following areas: (1) outside city limits, for background levels; (2) in residential areas away from heavy traffic, and (3) in areas adjacent to major roadways or intersections. The median and range of MTBE concentrations for the selected locations and phases are shown in Table 11 (Zweidinger, 1993).

In Fairbanks, MTBE levels in all ambient environments were lower when the use of MTBE as an oxygenate in gasoline was discontinued. Overall MTBE ambient air concentrations ranged from non-detectable levels to a maximum of 100.9 $\mu g/m^3$ (28.0 ppbv) in the phases prior to and during the phase-out of MTBE in Alaskan gasoline

Table 9. Non-occupational and consumer exposure to MTBE in the USA[a] (adapted from HEI, 1996)

Sampling site	Oxygenate content (vol %)	Vapour recovery system	Detection frequency[b]	Detection limit (ppm)	MTBE (ppm)		Sampling, collection and analysis[c]	Comments[a]	Reference
					Range	Median (Mean)			
Community air									
Milwaukee WI	RFG in use*	Yes (in some cases)	6/11	0.000025	<0.00413	0.00013	Jan-March 1995; 24-h samples; collected in evacuated canisters; GC(FID)	Approximately 50% contained MTBE, remainder ETBE or ethanol	Allen & Grande (1995)
			3/5	0.000025	≤0.00106	0.00052	Feb-March 1995; 2-h samples; collected in evacuated canisters; GC(FID)		
Parking garage ramp									
Milwaukee WI	RFG in use*	NA	8/8		up to 0.0037	(0.002)	Feb-March 1995; 2- to 3-h samples; collected in evacuated canisters; GC(FID)	Approximately 50% contained MTBE, remainder ETBE or ethanol	Allen & Grande (1995)
Automobile cabin for commuters									
New Jersey	15 MTBE	NA	20/20		0.002–0.017*	0.004	April 1993; approximately 1-h samples; absorbed onto carboxen 569: collected in evacuated canisters; GC/MS	Estimated from graphed data in the original report	Lioy et al. (1994)
Connecticut			20/20		0.003–0.009*	0.0056			

Table 9 (contd).

Service station refuelling									
Phoenix, AZ	12*	No	40/40		0.09–38	5.8	Oct-Nov 1990; each sample was collected during the refuelling of 8 to 10 vehicles; each refuelling was sampled for 1 to 2 min, absorbed onto charcoal; GC (FID)	Samples taken from one station in which only premium gasoline was oxygenated	API (1993)
Los Angeles, CA	13	Yes	6/6		1.1–6.5	3.6			
New Jersey, New York	10–15*	Yes	4/4		NS	0.370	April 1993; 5-min breathing-zone samples before, during and after refuelling; absorbed onto carboxen 569; GC/MS	Estimated from graphed date in the original report	Lioy et al. (1994)
Connecticut		No	4/4		NS–4.1	0.572			
Milwaukee WI							Jan-March 1995; 15-min breathing-zone samples; adsorbed onto charcoal; GC(FID)	RFG with MTBE used only in higher grades; *ethanol used in regular gasoline; **2% MTBE used in regular gasoline	Allen & Grande (1995)
Station A	9–10*	Yes	6/6		NS	(0.39)			
Station D	9**	No	2/2		NS	(2.93)			
Northeast and southwest areas (short-term sample)	10–17*	Yes	8/17	<0.32	<2.1	0.57	Feb-April 1994; 15- to 20-min personal breathing zone samples; adsorbed onto charcoal; GC(FID)	Northeast = Connecticut and New Jersey locations; Southwest = Arizona locations	API (1995c)

Table 9 (contd).

Sampling site	Oxygenate content (vol %)	Vapour recovery system	Detection frequency[b]	Detection limit (ppm)	MTBE (ppm)		Sampling, collection and analysis[c]	Comments[a]	Reference
					Range	Median (Mean)			
In automobile while refuelling									
Connecticut, New Jersey and New York Service Stations									
Self-serve	10–15*	Yes	4/4		0.006–0.072	0.03	April 1993; 5-min breathing-zone samples before, during and after refuelling; adsorbed onto carboxen 589; GC/MS	Estimated from graphed data in the original report	Lioy et al. (1994)
Full-serve		Yes	8/8		0.008–0.172	0.034			
Self-serve		No	4/4		NS	0.015			
Full-serve		No	4/4		0.005–0.103	0.041			
Service station pump island									
New Jersey: Full-serve		Yes	4/4		0.120–1.600	0.440	April 1995; 4-h breathing-zone samples during both refuelling and not refuelling; collected in 6-litre evacuated canisters; GC/MS		API (1995a)
New York: Self-serve		Yes	6/6		0.014–0.080	0.048			
Connecticut: Self-serve		No	9/10	0.09	≤1.500	0.170			
New Jersey	15	Yes	3/3		0.08–0.24	0.24	Nov-Dec 1994; 7- to 8-h samples; adsorbed onto charcoal; GC (FID)		Cook & Kovein (1995)

Table 9 (contd).

Service station perimeter									
Phoenix AZ	12	No	24/24		0.009–0.09	0.02	Oct-Nov 1990; 12-h samples; 4 perimeter samples plus samples upwind and downwind from the pump island for each sample set; adsorbed onto charcoal; GC(FID)		API (1993)
New Jersey: Full-serve		Yes	15/16	0.001	<0.036	0.003	April 1995; 4-h samples; collected in 6-litre evacuated canisters; GC/MS		API (1995a)
New York: Full-serve		Yes	24/24		0.002–0.083	0.007			
Connecticut: Self-serve		No	38/40	0.001	>0.140	0.014			
Milwaukee WI									
Station A	9–10*	Yes	2/2		NS	(0.0024)	Jan-March 1995; 2-h area samples; collected in evacuated canisters; GC(FID)	*RFG, MTBE used only in higher grades; ethanol in lower grades **2% MTBE in regular gasoline	Allen & Grande (1995)
Station B	2–9**	No	1/1		NS	(0.0045)			

[a] Asterisks in any column indicate that further explanation is provided in the comments column.
[b] Number of samples in which MTBE was detected divided by total number of samples.
[c] GC/MS = gas chromatography with verification by mass spectrometry; GC(FID) = gas chromatography with flame ionization detection.
NA = not applicable; NS = not stated.

Table 10. Non-industrial occupational exposures to MTBE[a] (adapted from HEI, 1996)

Sampling site	Oxygenate content (vol %)	Vapour recovery system	Detection frequency[b]	Detection limit (ppm)	MTBE (ppm) Range	MTBE (ppm) Median (Mean)	Sampling, collection and analysis[c]	Comments[a]	Reference
Service station attendants during refuelling									
Phoenix AZ 1–2 min	12	No	40/40		0.09–38	5.8	Oct-Nov 1990; each breathing-zone sample was collected during the refuelling of 8–10 vehicles; each refuelling was sampled for 1–2 min; adsorbed onto charcoal; GC (FID)		API (1993)
Los Angeles CA 1–2 min	13	Yes	6/6		1.1–6.5	3.6			
New Jersey, New York, Connecticut: 5 min	10–15	Yes	4/4		NS	0.37*	April 1993; 5-min breathing-zone samples before, during, and after refuelling; adsorbed onto carboxen 589; GC/MS	Estimated from graphed data in original report	Lioy et al. (1994)
		No	4/4		≤4.1	0.572			
Milwaukee WI Station A 15 min	RFG 9–10	Yes	NS/6		NS	0.31	Jan-March 1995; 15-min breathing-zone samples during refuelling; collected in evacuated canisters	This station used MTBE in middle and premium grade gasoline, and ethanol in regular gasoline	Allen & Grande (1995)

Table 10 (contd).

Northeast and southwest in winter 15–20 min	10–17	Yes	8/17	0.32	<2.1	0.57	Feb-April 1994; personal breathing-zone samples; mostly 15- to 20-min personal breathing-zone samples during refuelling; adsorbed onto charcoal; GC (FID)	Northeast = Connecticut and New Jersey locations; Southwest = Arizona locations	API (1995c)
Various USA locations							1982–1993: data reported by American Petroleum Institute member companies; higher frequency of measurements in 1989–1993; GC(FID) and other procedures	Service station and retail outlet personnel	API (1995b)
<30 min	NS	NS	9/11	0.16	0.16–136.1	2.6			
30 min–6 h			5/5		0.01–2.7	0.34			
6–9 h TWA			13/13		0.09–34.0	0.59			
>9 h			11/11		0.01–17.20	1.1			
New Jersey 4 h (full-serve)	13–10	Yes	4/4		0.084–0.52	0.245	April 1995; 4-h breathing-zone samples, during refuelling and not refuelling; collected in 8-litre evacuated canisters; GC/MS		API (1995a)
New York 4 h (self-serve)		Yes	5/6		0.077–0.78	0.205			
Connecticut 4 h (self-serve)		No	10/10		0.170–2.60	1.5			

Table 10 (contd).

Sampling site	Oxygenate content (vol %)	Vapour recovery system	Detection frequency[b]	Detection limit (ppm)	MTBE (ppm) Range	MTBE (ppm) Median (Mean)	Sampling, conditions, collection and analysis[c]	Comments[a]	Reference
Phoenix AZ 4 h	14	No	42/42		0.04–3.88	0.55	Oct-Nov 1990; 4-h (half-shift) breathing-zone samples (average time 224 min); adsorbed onto charcoal; GC(FID)		Hartle (1993)
Northeast and southwest in winter >8 h	10–17	Yes	18/21	0.03–0.11	≤0.5	0.27	Feb-April 1994; personal breathing-zone samples, most sampling times were > 6 h; adsorbed onto charcoal; GC(FID)	Northeast = Connecticut and New Jersey locations; Southwest = Arizona locations	API (1995c)
New Jersey (full shift)	15	Yes	21/21	NS	0.12–1.42	0.48	Nov-Dec 1994; breathing-zone samples for 3–8 h; adsorbed onto charcoal; GC (FID)		Cook & Kovein (1994)

Table 10 (contd).

Service station attendants at pump island									
New Jersey 4 h (full-serve)	13–16	Yes	4/4		0.12–1.60	0.44	April 1995; 4-h breathing-zone samples during refuelling and not refuelling; collected in 6-litre evacuated canisters; GC/MS		API (1995a)
New York 4 h (self-serve)		Yes	6/6	0.0005	0.014–0.08	0.048			Cook & Kovein (1994)
Connecticut 4 h (self-serve)	15	No	9/10	NS	<1.5	0.17	Nov-Dec 1994; 7- to 8-h samples; adsorbed onto charcoal; GC (FID)		
New Jersey 8 h		Yes	3/3		0.08–0.24	0.24			
Parking garage ramp									
Milwaukee WI 2–3 h	RFG in use	NA	8/8		0.0023–0.0037	(0.002)	Feb-March 1995; 2- to 3-h samples; collected in evacuated canisters; GC(FID)	Approximately 50% contained MTBE, remainder contained ETBE or ethanol	Allen & Grande (1995)

Table 10 (contd).

Sampling site	Oxygenate content (vol %)	Vapour recovery system	Detection frequency[b]	Detection limit (ppm)	MTBE (ppm)		Sampling, conditions, collection and analysis[c]	Comments[a]	Reference
					Range	Median (Mean)			
Mechanics									
Northeast and southwest in winter							Feb-April 1994; personal breathing-zone samples, most short-term sampling times were 15–20 min; most long-term sampling times were >6 h; adsorbed onto charcoal; GC(FID)	Northeast = Connecticut and New Jersey locations; Southwest = Arizona locations	API (1995c)
15 min	10–17	Yes	4/13 (<0.26)	<0.25–<0.35	<32	ND			
>6 h			17/20 (<1.5)	<0.02–<0.05	<2.6	0.09			
Northern New Jersey 1 h	15	NS	NS/13		0.3–6.1		April 1993; 1-h breathing-zone samples (active); adsorbed onto carboxen; GC/MS	Workers at service stations and garages for State vehicles	Mohr et al. (1994)
Stamford Connecticut 8-h TWA	13–17	NA	20/28	0.03	≤12.04	0.11	April 1993; full-shift samples (approximately 8 h); adsorbed onto charcoal; GC(FID)	Mechanics with the Department of Public Works and in auto dealers' garages	Buchta (1993b)

Table 10 (contd).

Fairbanks AK 8-h TWA	15	NS	NS/10		0.01–0.81	0.10	Dec 1992; full-shift samples (approximately 8 h); collected in evacuated canisters in environment where workers spent most of their day; GC		Moolenaar et al. (1994)
Other vehicle-related workers									
Stamford	13–17	NS	0/7	0.03	<DL	<DL	April 1993; 8-h personal breathing–zone samples; adsorbed onto charcoal; GC(FID)	Workers who spent time in traffic	Buchta (1993b)
Connecticut 8-h TWA			1/4		≤0.15	<DL		Workers in various jobs (mostly workers in garages who performed tasks difference from the mechanics)	

[a] Number of samples in which MTBE was detected divided by total number of samples.
[b] GC/MS = gas chromatography with verification by mass spectrometry; GC(FID) = gas chromatography with flame ionization detection.
[c] Asterisks in any column indicate that further explanation is provided in the comments column.
TWA = time-weighted average; NA = not applicable; NS = not stated.

Table 11. Concentrations of MTBE in µg/m³ (ppbv) in ambient 8-h air samples taken in Fairbanks, Stamford and Albany, USA, as a result of the oxyfuels programme (Zweidinger, 1993; Zweidinger, personal communication)[a]

Sampling site	Fairbanks Phase I early December 1992	Fairbanks Phase II late December 1992	Fairbanks Phase III Feb/Mar 1993	Stamford April 1993	Albany May 1993
Background:					
number of samples	0	1	5	2	0
median	–	ND	ND	0.72 (0.2)	–
range	–	1	ND–4.3(1.2)	ND–1.1(0.3)	–
Residential:					
number of samples	2	11	11	2	3
median	14.4(4)	16.6(4.6)	2.5(0.7)	1.1(0.3)	ND
range	7.2–21.6 (2.9–6.0)	16.1–100.9 (1.7–28.0)	ND–9(2.5)	ND–1.8(0.5)	ND–0.4(0.1)
Roadside:					
number of samples	7	7	10	2	7
median	18(5)	35(9.7)	4.3(1.2)	7.2(2.0)	0.72(0.2)
range	10.8–43.2 (3.0–12.0)	15.1–64.5 (4.2–17.9)	ND–12.3(3.4)	4.3–10.1 (1.2–2.8)	ND–2.5(0.7)

[a] For the calculation of a median when n = 2, the two sample values are averaged together; in the case of an ND value, half the detection limit value is substituted in the calculation, i.e. 0.36 µg/m³ (0.1 ppbv).

ND = non-detectable; detection limit = 0.72 µg/m³ (0.2 ppbv).

(Phases I and II) and ranged from not detectable to 12.3 $\mu g/m^3$ (3.4 ppbv) when MTBE use was reduced to nominal levels in fuels (Phase III). Background levels were low during Phase III, ranging from not detectable to 4.3 $\mu g/m^3$ (1.2 ppbv) MTBE. Since sampling was limited during Phases I and II, the levels of MTBE in ambient air outside city limits cannot be compared for the three sampling periods over which MTBE concentrations in gasoline were being reduced.

Phase II ambient residential and roadside area air samples presented the highest levels of MTBE, with concentrations ranging from 6.1 to 100.9 $\mu g/m^3$ (1.7 to 28.0 ppbv) and 15.1 to 28.5 $\mu g/m^3$ (4.2 to 17.9 ppbv) respectively, and with medians of 6.1 $\mu g/m^3$ (4.6 ppbv) and 34.9 $\mu g/m^3$ (9.7 ppbv), respectively. Owing to lack of samples or small sample size in Phase I data, comparisons between the phases were limited to the roadside category. However, in this category, it was unexpectedly found that, although Phase 1 sampling occurred prior to suspension of MTBE, the data showed roadside levels of MTBE in ambient air to be slightly lower than those during the suspension period.

In Stamford, Connecticut, limited measurements of MTBE taken in the spring of 1993 showed that residential, roadside and gas station ambient air results were consistently lower than those taken in Fairbanks during the oxygenates programme, with ranges of not detectable to 1.1 $\mu g/m^3$ (0.3 ppbv), not detectable to 1.8 $\mu g/m^3$ (0.5 ppbv) and 4.3 to 10.1 $\mu g/m^3$ (1.2 to 2.8 ppbv), respectively. Limited residential and roadside ambient MTBE air samples taken in Albany, New York, in May 1993 were lower than levels during a comparable phase of MTBE use in Fairbanks (Phase III). Ambient temperature and other meteorological conditions differed significantly among the cities where samples were collected.

In Fairbanks, Stamford and Albany, roadside ambient air levels were found to be generally higher than residential area ambient air levels (Table 11). Consequently, this roadside category may also be considered to be a microenvironment, especially for those samples taken in downtown city street canyons. For this particular study, it was not possible to discern whether this was the case. Table 12 presents information on air samples taken in more clearly defined micro-environments such as service stations and vehicle interiors (Zweidinger, 1993).

Table 12. Concentrations of MTBE in µg/m³ (ppbv) in various microenvironmental 8-h ambient air samples taken in Fairbanks, Stamford and Albany, USA, as a result of the oxyfuels programme (Zweidinger, 1993; Zweidinger, personal communication)

Sampling site	Fairbanks Phase I, early Dec 1992	Fairbanks Phase II, late Dec 1992	Fairbanks Phase III, Feb/Mar 1993	Stamford April 1993	Albany May 1993
Service station pump island:					
number of samples	1	1	6	4	4
median	194.6 (54)	134.8 (37.4)	11.5 (3.2)	13.7 (3.8)[a]	64.2 (17.8)
range	–	–	6.1–49.7 (1.7–13.8)	ND–26.7 (7.4)	23.3–194.6 (6.6–54)
Commercial vehicle interiors:					
number of samples	8	–	6	–	–
median	126.1 (35)	–	31.7 (8.8)	–	–
range	25.2–1207.3 (7–335)	–	1.4–129 (0.4–35.8)	–	–
Indoors - commercial garage service areas:					
number of samples	5	–	10	8	–
median	1088.4 (302)	–	148.5 (41.2)	484 (134.8)	–
range	367.6–2922.8 (102–811)	–	21.3–496 (5.9–137.6)	4.7–1546.5 (1.3–429.1)	–

Table 12 (contd).

Indoors - residential area:					
number of samples	–	3	5	–	–
median	–	6.5 (1.8)	2.9 (0.8)	–	–
range	–	6.1–15.1 (1.7–4.2)	1–4 (0.3–1.1)	–	–
Indoors - public buildings near roadway:					
number of samples	–	4	5	4	–
median	–	32.4 (9)	6.5 (1.8)	1.8 (0.5)	–
range	–	ND–37.1 (10.3)	ND–10.5 (2.9)	1.4–1.8 (0.4–0.5)	–
Indoors - home with attached garage:					
number of samples	–	5	4	–	–
median	–	27.8 (7.7)	72.1 (20)	–	–
range	–	10.1–75.3 (2.8–20.9)	51.5–109.2 (14.3–30.3)	–	–

[a] In Stamford, service station samples were taken 4.6 metres (15 feet) away from the pump.
ND = not detectable; detection limit = 0.72 µg/m^3 (0.2 ppbv).

Kelly et al. (1993) performed 24-h ambient air sampling in the cities of Boston and Houston where MTBE was used nominally in gasoline (i.e. approximately < 5% by volume). Sampling took place approximately every 14 days from August 1990 to April 1991 and from June to August 1991. The Boston sampling site was categorized as being in an urban area of mixed industry and office buildings, with high traffic density, and the sampler was placed on a downtown fire department rooftop. Conversely, the Houston sampling site was located in a semi-rural area, on the roof of an air sampling station, and was expected to receive emissions from industrial and, to a lesser extent, urban sources. MTBE levels in ambient air at these sites ranged from < 0.72 to 1.8 μg/m³ (< 0.2 to 0.49 ppbv) and < 0.72 to 10.1 μg/m³ (< 0.2 to 2.8 ppbv), respectively (detection limit = 0.72 μg/m³ (0.2 ppbv). The median level from these data was < 2 ppbv for both Boston and Houston. MTBE was detected in several samples from Houston (n = 22; in 64 % of samples MTBE was non-detectable), but only at one site in Boston (n = 22; in 96% of samples MTBE was non-detectable).

Allen & Grande (1995) conducted an ambient air monitoring study in the city of Milwaukee as a result of public health complaints when MTBE was first introduced into Milwaukee reformulated gasoline (at approximately 11% by volume) in 1995. Eleven weekly 24-h samples collected at the Wisconsin Enhanced Ozone Monitoring Program air sampling station from January to March 1995 resulted in concentrations ranging from not detectable to 14.89 μg/m³ (4.13 ppbv) [n = 11; 45% non-detectable samples; detection limit 0.36 μg/m³ (0.1 ppbv)]. The median was determined to be 0.47 μg/m³ (0.13 ppbv). A control sample collected in each of the nearby cities of Madison and Green Bay, where reformulated gasoline use was not mandated, was found to be below the detection limit of 0.36 μg/m³ (0.1 ppbv).

In the same study, Allen & Grande (1995) collected 1- to 3-h roadside air samples at busy intersections and freeway interchanges where it was expected that there would be high concentrations of gasoline fumes. Mean levels of MTBE in air samples collected near a freeway interchange, a busy intersection and a roadway in Milwaukee were 1.9 μg/m³ (0.53 ppbv) (n = 3), 3.8 μg/m³ (1.06 ppbv) (n = 2) and 1.8 μg/m³ (0.50 ppbv) (n = 2), respectively. This particular choice of

roadside location is a more clear example of a roadside microenvironment and it may also be considered an ambient air sample.

The State of California mandated the year-round use of oxygenated fuels in the South Coast Air Basin in 1995 and throughout California by June 1996. As a result, MTBE was included in the California's ambient air monitoring programme in February 1996 for the cities of Burbank, Long Beach and Los Angeles and in June 1996 for Chico, Roseville and Fresno. The overall range of 24-h average concentrations was 1.4–44.7 $\mu g/m^3$ (0.4–12.4 ppbv) for the selected monitoring sites. The overall range of averages was closer to the Fairbanks data than to data from other cities in the continental USA. Averages ranged from 4.7 to 17.3 $\mu g/m^3$ (1.3 to 4.8 ppbv) with the highest averages occurring in the cities of Los Angeles and nearby Burbank. The following are average and ranges for each of the individual cities: Burbank 17.3, 4.7–31.7 $\mu g/m^3$ (4.8 ppbv, 1.3–8.8 ppbv), Long Beach 9.4, 3.2–21.6 $\mu g/m^3$ (2.6 ppbv, 0.9–6.0 ppbv), Los Angeles downtown 13.7, 4–24.1 $\mu g/m^3$ (3.8 ppbv, 1.1–6.9 ppbv), Chico 8.3, 3.6–27.8 $\mu g/m^3$ (2.3 ppbv, 1.0–7.7 ppbv), Fresno 9.4, 2.2–44.7 $\mu g/m^3$ (2.6 ppbv, 0.6–12.4 ppbv) and Roseville 4.7, 2.5–12.3 $\mu g/m^3$ (1.3 ppbv, 0.7–3.4 ppbv). The number of samples for each city ranged from 18 to 28 and the detection limit for MTBE was 0.72 $\mu g/m^3$ (0.2 ppbv) (M. Poore, personal communication).

Measurements of ambient air concentrations of MTBE at service stations are usually taken at the gasoline pump island and at the service station perimeter. The air levels of MTBE tend to be higher at the pump island and lower at the perimeter. In addition, service stations equipped with vapour recovery systems (Stage II) tend to have higher MTBE concentrations in both microenvironments. Furthermore, whereas the pump island data represents a particular microenvironment due to the presence of gasoline vapour coming from refuelling activities, the gasoline station perimeter data has been used to estimate potential community exposures and may be considered representative of upper end ambient air levels in neighbourhoods. Short-term peak samples of MTBE were not taken.

MTBE median concentrations generally ranged from 0.32 to 21.4 mg/m^3 (0.09–6 ppm) in breathing-zone samples as a result of

consumer refuelling. The values were measured over 2- to 15-min sampling periods and were highly variable but rarely exceeded 35.7 mg/m^3 (10 ppm). The range of median values measured at the pump islands ranged from 0.18 to 1.57 mg/m^3 (0.05–0.44 ppm) over a 4-h sampling period. The fenceline samples were lower and ranged from 0.004 to 0.5 mg/m^3 (0.001 to 0.14 ppm) with a collection period of 4 h. Generally, the concentrations were higher at service stations that did not have vapour recovery systems.

Allen & Grande (1995) collected 1- to 3-h MTBE area samples downwind of the gas pumps on the perimeter of four Wisconsin service station properties from 21 February 1995 to 9 March 1995. The average levels of MTBE at two service stations that dispensed reformulated gasoline and had Stage II vapour recovery[a] were 8.8 µg/m^3 (2.43 ppbv) (n = 2) and 2.7 µg/m^3 (0.75 ppbv) (n = 2). The level of MTBE at a station without vapour recovery was higher and was measured to be 16.5 µg/m^3 (4.58 ppbv) (n = 1). Finally, one air sample taken at a service station where reformulated gasoline was not mandated resulted in a lower concentration of MTBE i.e. 0.8 µg/m^3 (0.25 ppbv).

In addition, Zweidinger (1993) analysed a limited number of 8-h air samples taken in various microenvironments in Fairbanks (Phases I, II and III), Stamford and Albany for MTBE. Generally, micro-environmental air concentrations of MTBE decreased from Phase I or II to Phase III at the following locations: (1) service station pump island, (2) commercial vehicle interiors, (3) indoor – commercial garage service areas, (4) indoor – residential area and (5) indoor – public buildings near roadway (i.e. school, post office), due to the suspension of the oxyfuel programme. The median and range of MTBE concentrations for selected locations and phases are shown in Table 12. The air of one home with an attached garage was the exception to this tendency in that the indoor air samples contained levels of MTBE, benzene and other compounds associated with gasoline which were significantly higher than air samples measured

[a] Stage II is a vapour recovery system used to trap gasoline vapour during refuelling of consumer vehicles.

outside that home. This indicated that the residential garage may have had a source of evaporative emissions after parking the hot car in the garage or from gasoline stored in the garage.

Huber (1995) used a multizonal mass balance model to predict indoor air concentrations. Measured evaporative emissions of 0.5 g of MTBE emitted from an automobile at rest at 23.9 °C (a highly unrealistic estimate for Fairbanks in winter) during 4 h in a garage attached to a residential house resulted in modelled peak concentrations of 2.3 mg/m^3 (0.65 ppm) in the garage and 0.12 mg/m^3 (0.035 ppm) in the residence. Modelled 1-h average concentrations in the garage ranged from 2.5 to 4.3 mg/m^3 (0.7 to 1.22 ppm) while those in the residence ranged from 0.072 to 0.32 mg/m^3 (0.02 to 0.09 ppm). This was estimated to be a worst-case situation for evaporative emissions since a newer car or cold winter temperatures would probably have reduced evaporative emission rates resulting in lower concentrations (Huber, 1995). However, increased tailpipe vehicle emissions as a result of cold start (the first few minutes of running the engine before the catalytic converter starts to function) were not included in these estimations.

In the case of the Stamford microenvironment samples, the resulting 8-h average MTBE levels in indoor commercial garage service areas and indoor locations near a roadway were lower than those taken in Fairbanks even though the volume of MTBE present in Stamford gasoline was higher than the volume used in Fairbanks during Phases II and III. It is important to note that the service station pump island samples were not strictly comparable since they were taken 4.5 m away from the pump. When MTBE was only used as an octane enhancer, as was the case for Albany and Fairbanks Phase III, levels of MTBE in service station pump island air were found to be much higher in Albany.

Air measurements in the parking garage microenvironment have been conducted in two studies. MTBE concentrations measured in two 8-h air samples in a Stamford partially open parking lot (i.e. open-sided with an office building directly above) in April 1993 were 70.4 µg/m^3 (20.1 ppbv) and 177 µg/m^3 (49.0 ppbv) with a mean of 124.7 µg/m^3 (34.6 ppbv) (RB Zweidinger, personal communication). Allen

& Grande (1995) conducted measurements at an enclosed parking ramp in Milwaukee in February 1995 in order to show ambient levels during cold starts. One- to three-hour air samples showed MTBE levels of less than 72.1 μg/m³ (20 ppbv) with mean levels of 7.4 μg/m³ (2.05 ppbv) (n = 8). The highest level occurred at a point when a large number of vehicles were making cold starts in a short period of time.

Air samples were taken by Lioy et al. (1994) inside the vehicle cabin microenvironment for (1) activities surrounding refuelling, and (2) during suburban commutes before and after refuelling. The study took place in April 1993 in New Jersey, New York and Connecticut where gasoline containing 10 to 15% by volume MTBE was sold. The experiment protocol consisted of a 60-min commuter run that included a 5-min refuelling stop at full- and self-service stations with or without Stage II vapour recovery. Resulting in-cabin levels of MTBE taken immediately before, during and after refuelling ranged from 23.8 to 108 μg/m³ (6.6 to 30 ppbv), 133.4 to 313.5 μg/m³ (37 to 87 ppbv) and 31.4 to 151.4 μg/m³ (8.7 to 42 ppbv), respectively, for three different cars, with average concentrations of 55.3 μg/m³ (14.8 ppbv), 190.2 μg/m³ (55 ppbv) and 72.1 μg/m³ (20 ppbv). Short-term peak concentrations occurred during refuelling. In addition, post-refuelling in-cabin concentrations were slightly higher than pre-refuelling, although the increase was not statistically significant. It was noted that the highest of the levels that diffused into the cabin during refuelling occurred with an older vehicle, which had an abnormally high evaporative emissions rate. There did not seem to be a statistically significant difference in in-cabin levels between the various types of service stations, although the sample size was too small to be able to make this conclusions. Microenvironmental in-cabin air concentrations of MTBE measured during 60-min suburban stop/go commutes ranged from 3.6 μg/m³ (1 ppbv) to 576.6 μg/m³ (160 ppbv) with a geometric mean of 21.6 μg/m³ (6 ppbv) (n = 40). Most values were less than 19.8 μg/m³ (5.5 ppbv). It was noted that the higher values were associated with the use of the high-emission vehicle discussed previously.

Area monitoring was conducted in an indoor commercial garage service area in Fairbanks, Alaska (Buchta 1993a). Three air samples were taken over a 6- to 7-h period in February 1993 when MTBE use was limited to purposes of octane enhancement. MTBE was non-

detectable in the three areas (service area, parts department, shop wall) but the minimum detection limit was high (144.2 μg/m³, 40 ppbv). This is comparable to the Zweidinger (1993) 8-h indoor commercial garage air samples that were measured with more sensitive equipment and resulted in a median concentration for MTBE of 114.4 μg/m³ (31.75 ppbv). The higher levels in the latter study may have been the result of gasoline spills.

Ambient air levels of MTBE have been measured near three refineries in the USA. At one refinery a 24-h MTBE level of 20 μg/m³ was reported for one out of nine downwind samples taken at the perimeter of a rural refinery, which was stated to release approximately 33 tonnes of MTBE emissions in air per year. MTBE was not detected in the 26 other downwind and upwind samples taken at the refinery during the same period. MTBE was not detected in another 54 24-h samples taken at two other refineries: annual MTBE air emission release data were not provided for these refineries. It should be noted that the detection limit for these air samples was high (more than 20 or 30 μg/m³), but more sensitive canister samples taken for 24 h also resulted in non-detectable concentrations (detection limit = 6 μg/m³) (API, 1989b).

c) Finland

Vainiotalo et al. (1996) reported the concentration of MTBE at the perimeter and pump island of two self-service stations in Finland (one urban roadside and one simple roadside) both with Stage I[a] vapour recovery systems where gasoline containing 11% MTBE by volume was sold. The investigations were conducted during May/June and October 1995. The average 24-h perimeter concentrations for each of the 4-day sampling periods were generally higher for the urban roadside service station samples: 12.4 μg/m³ (June) and 14.1 μg/m³ (October), with 35–36 measurements collected at each side on each occasion. Several factors such as the volume of gasoline sold, mean wind speed and number of deliveries of gasoline to the station were

[a] In the USA, Stage I is a vapour recovery system used during loading and unloading of gasoline from delivery tankers. Since this is a Finnish Study, this definition may or may not be equivalent.

higher for the former and resulted in data with higher variability during the fall sampling. The overall range of perimeter air samples for both service stations was from 0.5 to 120.5 μg MTBE/m^3. Highest daily concentrations were usually obtained at the downwind sampling points. No seasonal influence was discernable. Mean 24-h concentrations measured in the centre of the pump island ranged from 247 to 1347 μg/m^3 (n = 15). The detection limit was not specified in the study.

5.1.1.2 *Dermal exposure*

Dermal exposure and absorption may occur from MTBE-blended gasoline at self-service refuelling or from its use as a solvent. It may also occur from MTBE-contaminated household water during washing, bathing or showering. There are, however, no data available to estimate dermal exposure to MTBE.

5.1.1.3 *Estimation of total personal exposure*

Exposure is a function of concentration and time. Thus, the time spent in various activities involving different concentrations and degrees of contact will affect human exposures to MTBE. Huber (1995) generated "worst-case scenario" estimates of long-term exposure to MTBE based on population activity patterns and available microenvironmental and ambient concentration data (generally rounded up to the next order of magnitude of 10). His intentionally high estimates were updated and slightly revised to indicate that an annual time-weighted average exposure might be as high as about 0.11 mg/m^3 (0.03 ppm), assuming that gasoline contained 15% MTBE by volume for 6 months and approximately 10% for the remainder of the year (US Interagency Assessment, 1997). This upper-end exposure estimate is highly uncertain, given the lack of adequate data to describe the distribution of actual personal exposure levels.

5.1.1.4 *Other pollutants*

There was an increase in indoor air levels of benzene after MTBE reformulated fuel use was discontinued (Gordian & Guay, 1995). Both ambient outdoor and specific indoor environment (garages, vehicles, workplace, school, post office and residence) samples, as well as blood

samples, were collected in Fairbanks during and after the oxygenated programme. In addition to MTBE, other volatile compounds, such as benzene and formaldehyde, were evaluated. In indoor samples, there was a statistically significant increase of benzene in garages and non-garages after MTBE was discontinued. In garages, the mean benzene concentration increased from 0.30 mg/m^3 (94.02 ppb) in December to 0.61 mg/m^3 (191.62 ppb) in February, and in the school, post office and residence from 0.02 mg/m^3 (5.89 ppb) to 0.06 mg/m^3 (20.22 ppb). The NIOSH-recommended exposure limit for benzene is 0.3 mg/m^3 (0.1 ppm). In vehicles the data were difficult to interpret because different vehicles were tested in December and in February. The same pattern, although not statistically significant, was seen in the outdoor samples.

5.2 Occupational exposure

5.2.1 *Industrial operations – manufacturing and blending*

MTBE can be encountered in solution and as vapour during its manufacturing at chemical plants and refineries, during blending into gasoline, transportation, distribution, and handling at service stations. Some industrial hygiene monitoring data are available (Table 13).

At the MTBE unit at the Neches Chemical West Plant in the USA, the TWA values ranged from less than 0.07 to 120.3 mg/m^3 (0.02 to 33.41 ppm) for operations and maintenance personnel (Simer, 1986).

Exposure monitoring in a manufacturing plant showed that all exposures to MTBE greater than 3.6 mg/m^3 occurred during quality control sampling procedures (ARCO, 1987). Two out of 46 short-term samples indicated exposures to MTBE at concentrations of 22 mg/m^3 and 6.5 mg/m^3 (6.1 ppm and 1.8 ppm, respectively); 91% of the full shift monitoring indicated exposure levels of less than 3.6 mg/m^3.

Texaco (1993) presented results from a short-term monitoring for MTBE conducted at a refinery in Guatemala in order to evaluate the adequacy of current work procedures. No details of ambient temperature were given. Air concentrations associated with transfer of neat

Table 13. Occupational exposure to MTBE in the petroleum industry (adapted from HEI, 1996)

Occupational exposure category	Sampling time[a]	Detection frequency[b]	Detection limit (ppm)	Range of MTBE concentrations (ppm)	Median MTBE[c] concentration	References[d]
MTBE manufacturing						
Occupational exposure of oil refinery and chemical plant personnel handling neat MTBE during:						
Routine operations	<30 min	14/27	0.16–1.00	0.16–7.8	1.00	API, 1995b
	6–9 h TWA	38/76	0.01–0.03	0.01–248.7	0.03	API, 1995b
	>9 h TWA	2/2	Not given	0.16–0.17	0.17	API, 1995b
Routine maintenance	<30 min	7/8	0.05	0.05–7.19	0.90	API, 1995b
	30 min–6 h[e]	1/1	Not given	0.20	0.20	API, 1995b
	6–9 h TWA	4/4	Not given	0.04–0.7	0.11	API, 1995b
	>9 h TWA	2/2	Not given	0.16–0.2	0.18	API, 1995b
Routine operations and maintenance	8–12 h TWA	8/21	0.02–0.06	<0.02–33.41	1.06	Simer, 1986
	20 min	0/1	[1.0]	<1.0–1.0	<1.0	ARCO, 1987
	4–6 h	1/11	[1.0]	<1.0–6.1	<1.0	ARCO, 1987
	12 h TWA	2/23	[1.0]	0.8–2.2	Not given	ARCO, 1987
QA/QC sampling of MTBE	12–36 min	3/16	[1.0]	<1.0–12.2	<1.0	ARCO, 1987

Table 13 (contd).

MTBE blending						
Occupational exposure of personnel involved in fuel-blending activities involving:						
Neat MTBE	<30 min	34/35	<0.005	0–97.0	2.90	API, 1995b
	30 min–6 h	12/13	0.21	0.21–72.0	1.03	API 1995b
	6–9 h TWA	7/12	0.04–1.80	0.04–87.97	2.24	API, 1995b
	>9 h TWA	0/9	0.23–0.34	0.23–0.34	0.30	API, 1995b
Fuel mixtures	<30 min	51/98	0.02–0.23	0.02–100	0.30	API, 1995b
	30 min–6 h	5/19	0.03–0.33	0.03–1.98	0.05	API, 1995b
	6–9 h TWA	34/112	0.02–0.20	0.02–14	0.04	API, 1995b
	>9 h TWA	9/22	<0.005–0.02	0–0.27	0.02	API, 1995b
MTBE transport						
Occupational exposure of marine barge, pipeline and rail car personnel to:						
Neat MTBE (trucking personnel included only for transport of neat MTBE)	<30 min	62/66	0.30–0.60	0.30–1050	13.83	API, 1995b
	30 min–6 h	23/27	0.04–0.36	0.04–700	2.20	API, 1995b
	6–9 h TWA	9/10	0.03	0.03–711.9	0.18	API, 1995b
	>9 h TWA	1/1	Not given	0.32	0.32	API, 1995b
	15 min TWA	4/4	Not given	90–150	110.00	Texaco, 1993

Table 13 (contd).

Occupational exposure category	Sampling time[a]	Detection frequency[b]	Detection limit (ppm)	Range of MTBE concentrations (ppm)	Median MTBE[c] concentration	References[d]
Fuel mixtures	<30 min	60/64	0.001–0.14	0.001–507.87	2.44	API, 1995b
	30 min–6 h	64/92	0.02–0.04	0.02–59.4	0.42	API, 1995b
	6–9 h TWA	28/42	0.007–0.04	0.01–26.24	0.14	API, 1995b
	>9 h TWA	8/8	Not given	0.19–4.51	1.49	API, 1995b
MTBE distribution						
Occupational exposures of marketing terminal and trucking personnel involved in the handling of Gasoline-MTBE mixtures	<30 min	93/129	<0.005–0.08	0–14.0	0.75	API, 1995b
	30 min–6 h	9/10	0.26	0.26–4.05	0.98	API, 1995b
	6–9 h TWA	62/87	0.01–0.05	0.01–2.2	0.11	API, 1995b
	>9 h TWA	46/47	0.06	0.06–6.2	0.71	API, 1995b
	15 min TWA[e]	½	0.2	<0.2–0.94	0.48	Hebert, 1993
	10–12 h TWA[e]	2/2	Not given	0.08–0.08	0.08	Hebert, 1993
	15 min TWA[f]	4/4	Not given	0.05–0.16	0.14	Gillie, 1993
	15 min TWA[g]	3/3	Not given	1.9–3.6	2.80	Gillie, 1993
	12 h TWA[g]	5/5	Not given	0.24–0.92	0.45	Gillie, 1993
	15–40 min[f]	(n=6)	0.2	2.8–42	13 (mean)	Hakkola & Saarinen, 1996

Table 13 (contd).

	10–30 min[a]	(n=4)	0.2	20–226	91 (mean)	Haakola & Saarinen, 1996
	22–44 min[a]	(n=5)	0.2	4.3–27	16 (mean)	Haakola & Saarinen, 1996
	10–37 min[a]	(n=6)	0.2	10.0–98.0	71 (mean)	Haakola & Saarinen, 1996

[a] Duration was task-related.
[b] Number of samples in which MTBE was detected divided by total number of samples.
[c] In the case of "non-detectable" samples the detection limit was used to calculate the median.
[d] The API (1995b) measurements used different sampling and analytical techniques on both personal breathing zone and area air samples.
[e] Loading of trucks with vapour recovery.
[f] Bottom loading of trucks with vapour recovery.
[g] Truck unloading at service station with vapour recovery.
[h] Top loading without vapour recovery.
[i] Truck unloading at service station without vapour recovery - Northern Finland.
[j] Truck unloading at service station without vapour recovery - Southern Finland.

MTBE from tank cars to a storage tank ranged from 324 to 540 mg/m^3 (90–150 ppm).

Hinton (1993) performed an occupational exposure study of MTBE employees designed to determine the amount of MTBE exposure during manufacturing, blending MTBE into gasoline, transportation, distribution and handling at service stations. The study included 2038 exposure measurements during an 11-year period. Occasionally the TWA exposure value exceeded 360 mg/m^3 (100 ppm) and the short-term (less than 30 min) exposure 1080 mg/m^3 (300 ppm), generally during non-routine or extraordinary tasks. The maximum short-term value sampled for less than 30 min, 3780 mg/m^3 (1050 ppm), was recorded during transportation of neat MTBE. The maximum TWA level was 2563 mg/m^3 (712 ppm) for the same activity. Usually, the TWA levels were less than 7.2 mg/m^3 (2 ppm) and the short-term levels were less than 36 mg/m^3 (10 ppm). Exposures in blending operations were less than 360 mg/m^3, and generally less than 36 mg/m^3. In distribution, MTBE levels were less than 3.6 mg/m^3, and for service station attendants levels were less than 10.8 mg/m^3 (3 ppm).

5.2.2 *Transportation*

An exposure assessment for MTBE vapour concentrations conducted on two gasoline truck drivers in New Jersey showed an average exposure concentration of 0.29 mg/m^3 (0.08 ppm) on a full shift (10–12 h) basis. The short-term 15-min TWA exposure was 2.05 mg/m^3 (0.57 ppm) (Hebert, 1993).

Monitoring has been made for workplace concentration levels for seven gasoline truck operators to assess exposure potentials during loading operations and during full unloading at service stations (Gillie, 1993). The 12-h TWA ranged from 0.86 to 3.31 mg/m^3 (0.24–0.92 ppm). Short-term exposure (5–23 min) during truck loading operations ranged from 0.18 to 0.58 mg/m^3 (0.05–0.16 ppm) and during fuel unloading from 3.24 to 12.96 mg/m^3 (0.9–3.6 ppm).

The occupational exposure of road tanker drivers to gasoline and some of its components, including MTBE, has been measured in

Finland in two depots and 11 service stations during loading and delivery (Hakkola & Saarinen, 1996). In Finland, unleaded gasoline contains 10–15% MTBE in liquid phase. The monitoring was made during the summer, and the temperatures ranged from 4 to 22 °C. In the south of Finland, four measurements were carried out during top loading and six measurements during delivery at service stations. In the north of Finland, six measurements were performed during bottom loading and five measurements at service stations during delivery. The mean short-term exposures of road tanker drivers to MTBE during loading and delivery were between 13 and 91 mg/m^3. The differences in exposure during bottom (2.8–42.0 mg/m^3, mean 13 mg/m^3) and top loading without vapour recovery (20–226 mg/m^3, mean 91 mg/m^3) were statistically significant ($p<0.02$). There also was a statistically significant difference ($p<0.03$) during delivery in northern (4.3–27.0 mg/m^3, mean 16.0 mg/m^3) and southern Finland (10–98 mg/m^3, mean 71 mg/m^3). The exposure time for loading was 25–35 min and for delivering 30–40 min per load.

5.2.3 Service station attendants and garage mechanics

An exposure assessment for MTBE vapour concentrations conducted on six full-service gas attendants in New Jersey showed an average exposure of 1.76 mg/m^3 (0.49 ppm) on an 8-h TWA basis (Hebert, 1993). For the short-term 15-min TWA, the average exposure was 2.16 mg/m^3 (0.60 ppm).

In an evaluation of exposure among service station attendants and operators, Hartle (1993) compared the exposure potential at three categories of service stations. Two facilities in Cincinnati, Ohio, represented service stations that did not use MTBE or used it only as an octane enhancer. In Phoenix, Arizona, two high-volume stations were selected, and in Los Angeles two service stations with advanced vapour recovery were selected. In Phoenix, where the MTBE content averaged 12.5–13% by liquid volume, the exposure measurements (41 samples) ranged from 0.14 to 13.97 mg/m^3 (0.04–3.88 ppm) with an average of 1.08 mg/m^3 (0.3 ppm). The Los Angeles exposure ranged from 0.07 to 2.63 mg/m^3 (0.02–0.73 ppm), averaging 0.50 mg/m^3 (0.14 ppm). In Cincinnati, only one of 32 samples was above the analytical limit of detection, i.e. 0.58 mg/m^3 (0.16 ppm).

Giacomello (1996) measured personal exposure of "full service" attendants to MTBE in 58 Italian service stations. The study included a number of geographical locations throughout the country and was conducted in the summer and winter in 1992 and 1995. An overall geometric mean of 0.71 mg/m^3 (1992) or 0.26 mg/m ^{3}(1995) was recorded in the summer, and 0.37 mg/m^3 in winter (latter data only for 1992).

Three NIOSH studies were performed in workers potentially exposed to gasoline and exhaust emissions during their work day (Almaguer, 1993; Buchta, 1993a,b). Breathing zone air samples were collected from workers exposed to MTBE and other gasoline components (benzene, toluene, and xylene, and, in one study, carbon monoxide) in several maintenance facilities for motor vehicles located in Fairbanks, Alaska (Buchta 1993a), in Stamford, Connecticut (Buchta, 1993b), and in Albany, New York (Almaguer, 1993). In two of the cities (Fairbanks and Albany), MTBE was only used as an octane enhancer (generally less than 1% of the fuel) during the study period. In Stamford, however, the MTBE content of the fuel ranged from 13 to 17% with an average of 14.2% by volume. The highest workplace exposure level concentrations were less than 0.50 mg/m^3 (0.14 ppm) in Albany and less than 1.6 mg/m^3 (0.45 ppm) in Fairbanks. In Stamford, the MTBE exposure levels ranged from 0.1 to 44.6 mg/m^3 (0.03 to 12.04 ppm). The cause for the highest value was unknown, and the next highest exposure value was 7.56 mg/m^3 (2.1 ppm). In all of the studies, the highest concentrations were measured on mechanics. The sampling was, however, conducted in late spring, and dilution ventilation (open windows and doors) may have affected the results.

5.2.4 Occupational exposure limit values

In the USA, the American Conference of Governmental Industrial Hygienists (ACGIH, 1994) has recommended a TWA of 144 mg/m^3 (40 ppm). In Sweden, the occupational air exposure TWA limit is 180 mg/m^3 (50 ppm) and the 15-min short-term exposure limit (STEL) 250 mg/m^3 (75 ppm) (AFS, 1994). The Dutch Expert Committee on Occupational Standards recommended a health-based occupational 8-h TWA exposure limit of 180 mg/m^3 (50 ppm) (DECOS, 1994).

5.3 Exposure via water

MTBE has been found in groundwater, storm water, reservoir water, and drinking-water in the USA (Garrett et al., 1986; Angle, 1991; Dey et al., 1991; Post, 1994; Squillace et al., 1995a,b, 1996; Delzer et al., 1996; Dale et al., 1997; US Interagency Assessment, 1997). Collectively, these references show that MTBE occurs in water, especially in areas where MTBE is extensively used, and where releases of MTBE to air, water and soil occur.

However, while there are some national monitoring data for ambient groundwater, monitoring data for MTBE in surface water and in drinking-water in the USA are very limited in scope. In an extensive review of MTBE in water in the USA, Zogorski et al. (1996) concluded that sufficient monitoring data were not available to characterize human exposure to MTBE by the consumption of drinking-water.

The following subsections summarize major findings for MTBE in: (a) snow and precipitation; (b) surface water; (c) groundwater; and (d) drinking-water.

5.3.1 *Snow and precipitation*

MTBE has been detected in snow at ground level in Denver, Colorado, USA, at very low (water equivalent) concentrations (Squillace et al., 1995b; Bruce & McMahon, 1996). There is no other published monitoring information on the presence or concentration of MTBE in snow or rainfall. Squillace et al. (1996) hypothesized that concentrations of MTBE in precipitation would be greater during winter months than warmer summer months due to the temperature effect on air-water partitioning.

5.3.2 *Surface water*

Information on MTBE in streams and rivers, in Long Island, New York and New Jersey, USA, has been reported by Stackelberg et al. (1997). For Long Island, at a reporting level of 0.5 µg/litre, MTBE was the second most frequently detected VOC, occurring in 29% of

the samples at concentrations ranging from 0.6 to 20 µg/litre, with an estimated median of 0.24 µg/litre. MTBE was detected more frequently in samples collected during winter months (33%) than summer months (26%). In New Jersey, a limited study was completed in spring 1994 along a ten-mile reach of the Hackensack River. Land use along this reach is highly urbanized, and numerous industries and municipal effluents are present. The study involved the collection of a single water sample at each of 14 sampling points just after a major snow melt. MTBE was detected in all samples at concentrations ranging from 2.6 to 30 µg/litre, with a median of 7.75 µg/litre (Stackelberg et al., 1997). Reconnaissance sampling of eight streams elsewhere in New Jersey in 1996 showed the presence of MTBE in water samples for seven of eight sites. The concentrations ranged from 0.2 to 4.9 µg/litre (Stackelberg et al., 1997). MTBE is used in reformulated gasoline at both Long Island, New York and in New Jersey, as part of a mandatory air abatement programme.

Measurable but low concentrations of MTBE were found in some of 592 stormwater samples (including samples from culverts, concrete pipes, lined ditches and channels) collected by the US Geological Survey in 16 cities and metropolitan areas from 1991 to 1995 (Delzer et al., 1996). MTBE was found in 6.9% of the samples (41 of 592 samples). When detected, concentrations ranged from 0.2 to 8.7 µg/litre, with a median below 1.0 µg/litre. Eighty-three percent of the detections occurred during the winter season (October to March) when oxygenated gasoline to abate CO pollution was expected to be used. A comparison of MTBE concentrations for samples collected during the summer and winter periods showed a statistically significant difference. Twenty-seven out of 148 stormwater samples contained both MTBE and BTEX compounds, indicating a common source for these samples.

The Metropolitan Water District of Southern California (MWDSC) relies, in part, on six lake-reservoirs for the storage of raw water to be used for drinking-water in Southern California. These reservoirs have varying degrees of recreational use. MWDSC began quarterly monitoring of these reservoirs for MTBE in the second quarter of 1996. MTBE was detected at the surface of Lake Perris, with confirmation in two subsequent samplings, at an average

concentration of 15 µg/litre. The following quarter MTBE was also detected at an average level of 19 µg/litre. No MTBE was detected above the study's reporting level of 1 µg/litre in any of the other reservoirs, which were sampled at outlet towers, where water is drawn from a lower depth (Dale et al., 1997).

5.3.3 Groundwater

Data from urban and agricultural areas show that MTBE occurs predominantly in shallow groundwater underlying urban areas, and, when present, occurs typically at low concentrations. In 1993–1994, the US Geological Survey measured the concentrations of MTBE and 59 other VOCs in 210 shallow wells (five drinking-water wells, 12 springs and 193 monitoring wells) in eight urban areas and 549 shallow groundwater wells from 21 agricultural areas, and deeper groundwater from 412 wells sampled in nine areas throughout the USA (Squillace et al., 1995a,b, 1996). MTBE occurred in 27% of the shallow urban wells and springs. Detectable levels of MTBE were found in 86% of the wells in industrial areas, 31% of the wells in commercial areas, 23% of the wells in residential areas, and 23% of the wells in areas of mixed urban land use, parks and recreation areas. MTBE was the second most frequently detected compound after trichloromethane (chloroform). In 73% of the 210 shallow urban wells, concentrations were less than the reporting level of 0.2 µg/litre. The estimated median value for urban areas was below 0.2 µg/litre (Squillace et al., 1996). Three percent of the wells had concentrations of MTBE above 20 µg/litre. No MTBE was detected in drinking-water wells in the urban areas. In the agricultural areas, 1.3% of the 549 shallow agricultural wells sampled had detectable concentrations of MTBE. MTBE was also detected in four of the 412 deeper groundwater samples from major aquifers. Three of these wells were used for domestic or municipal water supply. The measured maximum concentration of MTBE was 1.3 µg/litre. MTBE in groundwater was generally not found with BTEX compounds, which commonly are associated with point source spills of gasoline.

Bruce & McMahon (1996) measured MTBE concentrations in groundwater in the alluvial aquifer beneath Denver, Colorado, USA, as part of a survey of groundwater quality examining a range of

dissolved constituents. Thirty randomly selected alluvial wells were sampled. MTBE was the most frequently detected VOC (23 out of 29 wells). The maximum concentration was 23 mg/litre.

5.3.4 Drinking-water

Exposure to MTBE via drinking-water may involve more than direct ingestion of contaminated water. Household uses of water, such as in cooking, showering, bathing and washing, could result in exposure through inhalation and dermal absorption, even if ingestion of water was avoided.

Only limited monitoring data are available for MTBE in drinking-water sampled at the tap or from a municipal distribution system. Stern & Tardiff (1997) estimated that about 30% of the US population lives in areas where MTBE is in regular use; 95% of this population is unlikely to be exposed to MTBE in tap water at concentrations exceeding 2 µg/litre, most will be exposed to much lower or zero concentrations, but 5% could be exposed to higher concentrations due to fuel tank spills and leaks entering surface and groundwater. As part of the US Interagency Oxygenated Fuel Assessment in the USA (US Interagency Assessment, 1997), information on MTBE levels in drinking-water was sought from state drinking-water agencies on a voluntary basis by the US Environmental Protection Agency. Because monitoring for MTBE in drinking-water is not required by the US Federal Government, only a few states have information on MTBE in drinking-water. As such, it is not possible to describe levels of MTBE in drinking-water for the entire USA. Based on information provided by five states (New Jersey, Iowa, Illinois, Texas and Colorado), MTBE has been detected in the drinking-water of 51 public water systems. However, when detected, the concentration of MTBE was generally low and nearly always below 20 µg/litre (Zogorski et al., 1996). These data indicated that the consumption of drinking-water was not a major route of exposure for these few systems (Zogorski et al., 1996). No data on MTBE in drinking-water are available for other countries.

As noted previously, there have been a few instances in the USA where groundwater used for drinking-water, both private wells and public water systems, has become contaminated with levels of MTBE

in excess of 1000 µg/litre (Garrett et al., 1986; State of Connecticut, 1987; Zogorski et al., 1996). Many humans will probably detect MTBE in drinking-water when the concentration exceeds about 50–100 µg/litre owing to its low taste and odour threshold (see section 2.1 for taste and odour values). Some humans will detect MTBE in water at even lower concentrations. However, Du et al. (1998) considered that an MTBE concentration below 40 µg/litre in drinking-water would avoid any unpleasant taste or odour even for the most sensitive members of the population.

5.4 Soil and sediment

There are very limited data concerning levels of MTBE in the terrestrial environment. Trace amounts of MTBE have been found in sediment samples adjacent to motorways and centres of heavy urban road traffic density in the United Kingdom (Bianchi & Varney, 1989).

5.5 Biota

There are very limited data on MTBE levels in biota. In a study to detect organic and inorganic contaminants in shellfish in Nova Scotia, Canada, MTBE was not detected in any of the 21 samples assayed (detection limit = 0.01 µg/g) (Environment Canada, 1989).

6. KINETICS AND METABOLISM IN HUMANS AND LABORATORY ANIMALS

Kinetic data from human and animal studies are summarized in Table 14.

6.1 Human data

6.1.1 Controlled human studies

In an inhalation study two healthy young adult male and two healthy young adult female volunteers were exposed to MTBE at 6 mg/m^3 (1.7 ppm) in an environmental chamber for 1 h. The mean blood level rose from 0.83 ± 0.5 µg/litre (0.009 µmol/litre) preexposure to 17.1 ± 2.0 µg/litre (0.19 µmol/litre) at the end of the 1 h exposure period. One hour after the end of exposure the mean blood level fell to 6.3 ± 1.6 µg/litre (0.07 µmol/litre) after 1 h (Cain et al., 1996).

In a pharmacokinetics study, two volunteers (one healthy young adult male and one healthy young adult female) were exposed to 5 mg/m^3 (1.394 ppm) for 1 h in an environmental chamber (see also section 8.2). There was a rapid rise in blood MTBE concentration to 6.1 µg/litre (8.2 ppb) and 10.9 µg/litre (14.7 ppb), respectively, at 1 h from the start of exposure. Following the end of exposure, there was a rapid decline in blood MTBE concentration in both the male and female volunteer with half-lives of 36 and 37 min, respectively. By the end of the 7-h sampling period, blood MTBE concentration had fallen to 0.149 µg/litre (0.2 ppb) in the male volunteer and 0.447 µg/litre (0.6 ppb) in the female volunteer (Prah et al., 1994).

In another study, the area under the curve (AUC) values of MTBE and TBA were proportional to the MTBE exposure levels following short-term inhalation to 18, 90 or 180 mg/m^3 (5, 25 and 50 ppm), indicating linear kinetics up to at least 180 mg/m^3 (Johanson et al., 1995). Following exposure to 180 mg MTBE/m^3, the elimination of MTBE and TBA was complete within 24 and 48 h, respectively (Johanson et al., 1995).

Table 14. Summary of kinetic data for MTBE

Species and treatment	Absorption	Distribution	Metabolic transformation	Elimination and excretion	Reference
A. Human					
2 male, 2 female volunteers *Treatment:* 6 mg/m³ (1.7 ppm) for 1 h in inhalation chamber	rapid absorption from 0.003 µg/litre preexposure to 0.06 µg/litre after 1 h	mean MTBE blood concentrations rose steeply from 0.83 ±0.50 µg/litre preexposure to a peak blood level of 17.1±2.01 µg/litre by the end of exposure; rapid elimination, half-life of 40 min; the rapid elimination phase appeared to last approximately 1 h			Cain et al. (1996)
1 male, 1 female volunteer *Treatment:* 5 mg/m³ (1.39 ppm) as a 1-h exposure; blood samples up to 580 min after start	rapid rise in blood MTBE to 0.03 µg/litre (8.2 ppb) in the male and 0.05 mg/m³ (14.7 ppb) in the female		rapid decline observed in blood levels with a half-life of about 35 min and rapid metabolic transformation to TBA; TBA levels gradually increased and plateaued at 0.025–0.36 µg/litre (7–10 ppb) and maintained this concentration up to 7 h post-exposure		Prah et al. (1994)

Table 14 (contd).

Species and treatment	Absorption	Distribution	Metabolic transformation	Elimination and excretion	Reference
10 healthy adult male volunteers *Treatment*: exposed in chamber to 18, 90 and 180 mg/m^3 (5, 25 and 50 ppm) for 2 h on three occasions during light physical exercise (50W), observed up to 24 h and 48 h (only 180 mg/m^3) post-exposure	relative respiratory uptake was 32–42%; rapid absorption based upon blood concentration; by 2 h, peak blood concentrations of MTBE were 1.3, 6.3, and 12.2 µmol/litre at 18, 90, and 180 mg/m^3, respectively; TBA 5.7 and 0.7 µmol/litre at 90 and 180 mg/m^3, respectively; steady state was reached for TBA after 3–5 h, but was not reached during the 2 h exposure to MTBE		MTBE detected in expired air; both MTBE and TBA found in blood and urine	clearance of MTBE was 0.5 litre/h per kg; AUC values of MTBE and TBA were proportional to exposure levels, suggesting linear kinetics; elimination of MTBE in blood indicated three phases (6–7 min, 46–58 min and 6.2–7.2 h); in urine half-lives of 16–22 min and 3.0–3.1 h were identified; half-life of TBA in urine was 7.5–8.9 h; by 3.5 h post-dose, 20–30% of absorbed dose was eliminated in expired air; by 24 h, =0.1% MTBE and 0.5–0.8% TBA of absorbed dose was eliminated in urine	Johanson et al. (1995)

Table 14 (contd).

10 healthy adult male volunteers *Treatment*: exposed in chamber to 18, 90 and 180 mg/m³ (5, 25 and 50 ppm) for 2 h on three occasions during light physical exercise (50W); blood and urine collected during exposure and for 3 days post-exposure	respiratory uptake was 42–49%	mean concentrations in blood at the three exposure concentrations were 1.4, 6.5, and 13 µmol/litre respectively and were concentration-related	TBA was found in blood and urine	respiratory exhalation was 32–47%; elimination in blood was in four phases of 1 min, 10 min, 1.5 h, and 19 h; kinetics were linear up to the exposure concentration of 180 mg/h; elimination in urine was biphasic with mean half-lives of 20 min and 3 h; excretion was nearly complete 10 h after exposure; metabolic clearance was 0.34–0.52 litre/h per kg; renal clearance of TBA was 0.6–0.7 ml/h per kg and TBA was still present after 22 h	Nihlén et al. (1998a)

Table 14 (contd).

Species and treatment	Absorption	Distribution	Metabolic transformation	Elimination and excretion	Reference
B. Rodent					
i) Oral administration					
Species: Fischer-344 rats *Treatment*: 40 rats/sex/dose group received 40 or 400 mg/kg as single dose; observed (sacrificed) for various time-points until 36 h post-dose	rapid and extensive absorption of MTBE based upon peak plasma concentration within 15 min of dosing, lower plasma concentrations of MTBE in female rats compared to male rats; higher AUC values of MTBE and TBA with oral dosing compared to intravenous administration	apparent volume of distribution was 0.27 to 0.43 litre	in plasma, the major metabolite, TBA, peaked at 2 h; male rats had higher plasma concentrations than female rats; dose-unrelated plasma concentrations of MTBE and TBA indicate enzyme saturation	dose-related differences were observed for the plasma elimination half-time ($T_{½}$) of MTBE and TBA: $T_{½}$ of MTBE: 0.52–0.62 h (low dose) 0.74–0.88 h (high dose) $T_{½}$ of TBA: 0.95–1.0 h (low dose) 1.6–1.9 h (high dose) Plasma clearance (CL) of MTBE: male rats: 0.36–0.41 litre/h (both dose-groups) female rats: 0.48 litre/h (low dose) 0.29 litre/h (high-dose)	Ferdinandi et al. (1990a) Miller et al. (1997)

Table 14 (contd).

Species: Fischer-344 rats *Treatment:* 6 rats/sex/dose group received 40 or 400 mg/kg ^{14}C-MTBE as a single dose, observed for 48 h	by 48 h, 1.7–3% of administered radioactivity was recovered in carcass and tissues; 86 and 81% of administered radioactivity was recovered in lungs and kidneys at low and high dose, respectively	higher radioactivity was recovered in lungs at high oral dose and lower activity in kidneys suggesting enzyme saturation; most of the administered dose was exhaled as unchanged MTBE (predominating) and TBA (2.5–3.1% at low dose and 1.3–1.4% at high dose); in urine, the major radiolabelled species (from further oxidation of TBA) were 2-methyl-1,2-propanediol, α-hydroxyiso-butyric acid, and two minor unidentified components; no sex differences in biotransformation	slight sex difference in the route of elimination; by 48 h, recovery was 46–54% at low dose and 65–69% at high dose (highest in females); 29–36% was recovered in urine at low dose and 11–16% at high dose (highest in males) less than 1% was recovered in faeces	Ferdinandi et al. (1990b) Miller et al. (1997)

Table 14 (contd).

Species and treatment	Absorption	Distribution	Metabolic transformation	Elimination and excretion	Reference
ii) Inhalation					
Species: Wistar rats Treatment: 5 male rats/dose group were exposed to 180, 360 or 1080 mg/m³ (50, 100 or 300 ppm) vapour in exposure chambers 6 h/day, 5 days/ week for 2, 6, 10 or 15 weeks		dose-related concentrations of MTBE and TBA in blood after 2 weeks of exposure; the concentration of MTBE decreased after 6 weeks; the concentrations of TBA increased after 6 weeks of exposure and began to decrease after 10 weeks. Brain levels of MTBE and TBA followed a similar course. MTBE was also found in perirenal fat and at higher concentrations than in blood or brain. Concentrations of MTBE in the blood, brain and perirenal fat were directly related to the concentrations in the inspired air. The ratios of TBA/MTBE in blood increased from week 2 to week 15, indicating that MTBE had been oxidized to TBA, which was eliminated from the blood at a slower rate than MTBE	MTBE was metabolized at the ether bond. Two weeks of exposure caused transient increase of the microsomal UDP glucuronosyl-transferase activities in liver and kidney at all dose levels. After an initial decrease the muscle creatinine kinase activity gradually increased towards the end of the exposure. A minor induction of kidney cytochrome P-450 was noted. Almost no effect was found on hepatic cytochrome P-450 concentrations, brain succinate dehydrogenase, creatine kinase, or acetylcholinesterase activities		Savolainen et al. (1985)

Table 14 (contd).

Species: Fischer-344 rats *Treatment:* (T1) 52 rats/sex/dose group received 1440 or 28 800 mg/m^3 (400 or 8000 ppm) as a single 6-h dose. (T2) 40 rats/sex were exposed 6 h daily to 1440 mg/m^3 (400 ppm) for 15 days; observed (sacrificed) at various time-points until 12 h (T1) and 18 h (T2) post-dose	(T1) rapid absorption based upon plasma concentration; peak blood concentration was reached within 4–6 h for MTBE and 6.5 h for TBA; low but statistically significant difference in sexes of MTBE AUC values (low dose); TBA plasma concentration (AUC) was lower in female rats compared to male rats, statistically significant at high dose	(T1) apparent volume of distribution: low dose: 0.40 (females) and 0.52 litre (males) high dose: 0.25 (males) and 0.24 litre (females)	(T1) increased AUC values of MTBE 35-fold (males) and 37-fold (females) while the AUC values of TBA increased by 15-fold (males) and 7-fold (females); quotients of repeated and single dose AUC values (T2/T1) for MTBE were 0.64 (males) and 0.53 (females) and for TBA 1.1 (males) and 1.3 (females); a significant difference in plasma clearance between single doses 0.53 (males) and 0.57 (females) litre/h (low dose) and 0.30 (males) and 0.32 (females) litre/h (high dose); the plasma half-life of MTBE was 0.52–0.63 h (T1) and 0.48–0.51 h (T2); the (T1) half-lives of TBA were 2.8 (males) and 3.4 h (females) and (T2) 1.8 h (males) and 1.5 h (females)	Ferdinandi et al. (1990c) Miller et al. (1997)

Table 14 (contd)

Species and treatment	Absorption	Distribution	Metabolic transformation	Elimination and excretion	Reference
Species: Fischer-344 rats *Treatment:* (T1) 6 rats/sex/dose group received 1440 or 28 800 mg/m^3 (400 and 8000 ppm) of ^{14}C-MTBE as a single 6-h exposure (T2) 40 rats/sex were pretreated with 1440 mg/m^3 unlabelled MTBE 6 h a day for 14 days, followed by 6 h exposure for 1440 mg/ m^3 ^{14}C-MTBE on day 15, observed for 48 h post-dose	(T1&T2): rapid and extensive absorption as indicated by marked recovery of ^{14}C in urine by 24 h	by 48 h, 11–13% (low dose; T1&T2) and 4–5% (high dose) of administered radioactivity recovered in skin of some rats, probably due to contamination from urine (lower radioactivity recovered in urine); 0.6–1% in skin of remaining rats, 1–3% in carcass, and <1% in tissues	(T1&T2): radiolabelled species in expired air were MTBE and TBA; by 3 h post-dose, 30% (low dose) and 7–10% (high dose) of recovered radioactivity were correlated to TBA, while TBA was major radioactive component at 24 h post-dose (>90%, low dose); major radiolabelled species in urine from further oxidation of TBA were 2-methyl-1,2-propanediol, α-hydroxyisobutyric acid, two minor unidentified components, and minor detection of CO_2 (1% of the dose); no sex differences in biotransformation	rapid elimination in urine after low dose and in expired air at high dose, suggesting enzyme saturation at high dose; by 48 h, total recovery of radioactivity (^{14}C) in urine 65–71% (low dose, T1&T2) and 35–42% (high dose); in expired air 17–22% (low dose) and 54–59% (high dose) and <1% in faeces; no sex difference in rate and route of radioactivity elimination	Ferdinandi et al. (1990d) Miller et al. (1997)
iii) Intravenous administration					
Species: Fischer-344 rats *Treatment:* 40 rats/sex/group received 40 mg/kg as a single dose, observed (sacrificed) for various time-points until 36 h post-dose	a statistically significant difference in plasma concentrations (AUC) between sexes (lower in females)	apparent volume of distribution 0.27 to 0.31 litre	by 2 h, the major metabolite TBA was found in blood at peak concentration; male rats had higher blood concentration than female rats	half-life of MTBE (plasma) 0.45–0.62 h; half-life of TBA (plasma) 0.92–1.3 h; clearance from plasma of MTBE 0.36–0.41 litre/h (males) and 0.47 litre/h (females)	Ferdinandi et al. (1990a) Miller et al. (1997)

Table 14 (contd).

Species: rat, Fischer-344 *Treatment*: 6 rats/sex/group received 40 or 400 mg/kg ^{14}C-MTBE as a single dose; observed for 48 h		1.7–3% of administered radioactivity was recovered in tissues and carcass for each dose after 48 h	by 6 h, major radiolabelled species in expired air was MTBE, with a minor elimination of TBA (2.5–3.1% of administered dose); the major radiolabelled species in urine (from further oxidation of TBA) were 2-methyl-1,2-propanediol, α-hydroxyisobutyric acid, and two minor unidentified components; there were no sex differences in biotransformation	by 48 h, 71–73% of administered radioactivity was totally recovered: in exhaled air (42–46%), in urine (26%), and faeces (<1%); rapid elimination in lungs, 94% within 3 h	Ferdinandi et al. (1990b) Miller et al. (1997)
iv) Intraperitoneal					
Species: Charles River CD rats *Treatment*: 33 animals/sex/group received a single dose of approximately 60μCi ^{14}C-MTBE (about 232 mg MTBE/kg bw) in saline and were sacrificed at intervals of 5, 15, 30, and 45 min, and 1, 2, 3, 6, 12, 24 and 48 h post-treatment	rapid and extensive absorption based upon peak blood and plasma concentrations at 5 min post-treatment, averaging 92.04 ± 37.72 and 83.40 ± 20.48 μg ^{14}C-MTBE equivalents/ml blood for male and female rats, respectively. The half-life of ^{14}C-MTBE in blood was 59.8 min for male rats and 49 min for female rats. The half-life in plasma was 2.3 h for males and 1.3 h for females	the total cumulative ^{14}C activity in tissues averaged 3.39, 1.94 and 1.14% of administered dose at 15 min, 6 h, and 24 h post-treatment, respectively. At 15 min, the majority of the ^{14}C- radioactivity was found in mesenteric fat, liver and kidney; however, at 6 h and 24 h no ^{14}C was found in mesenteric fat	methanol and formic acid were found in plasma, liver and kidney	^{14}C activity was mainly eliminated in expired air, by 48 h, recovery was about 99.86% (≈92% as MTBE and ≈7.45% as CO_2); about 3% in urine and about 0.8% in faeces (male rats): ≈3% was excreted in urine and 0.8% (males) and 1.25% (females) in faeces. The ^{14}C activity in urine and faeces was mainly associated with ^{14}C-formic acid (a total of 3.08% of administered dose)	Biodynamics (1984)

Table 14 (contd).

Species and treatment	Absorption	Distribution	Metabolic transformation	Elimination and excretion	Reference
Species: mouse, ddY *Treatment*: 4 male mice/dose group were administered a single dose of 50, 100 or 500 mg/kg in corn oil solution; observed for 6 h				most of the administered MTBE was eliminated unchanged in the exhaled air; >90% of this amount was eliminated within 3 h. The pulmonary elimination showed an initial rapid decrease of the elimination ratio followed by a slow decrease at 100 and 500 mg/kg. The calculated half-lives were 45 and 80 min, respectively. The elimination ratios at the three different doses were 23.2, 37.6 and 69.0%, respectively	Yoshikawa et al. (1994)

Table 14 (contd).

C. *In vitro*			
Incubation of 5 or 14 mM MTBE with liver microsomes from phenobarbital- or acetone-pretreated or untreated Sprague-Dawley rats (3–5 males)		incubation of MTBE with liver microsomes from phenobarbital-pretreated rats resulted in TBA and formaldehyde in equimolar amounts. The V_{max} [a] value for demethylation of MTBE increased by 4-fold with acetone-induced and by 5.5-fold with phenobarbital-induced microsomes compared with the control V_{max} value. These results indicate that cytochrome P450 2B1 (inducible by phenobarbital) and cytochrome P450 2E1 (inducible by acetone) play a role in the demethylation of MTBE. Results after inclusion of monoclonal antibody against P450 2E1 indicated this enzyme only partially contributed to the demethylation. Microsomes pretreated with MTBE yielded a 47-fold induction of pentoxyresorufin *o*-dealkylase, with no change in *N*-nitrosodimethylamine demethylase activity. These results are consistent with an elevation of P450 2B1	Brady et al. (1990)

[a] V_{max} : the maximum velocity of the demethylation process.

Pekari et al. (1996) measured concentrations of MTBE in blood, urine and exhaled air from four volunteers exposed to 90 or 270 mg/m^3 (25 or 75 ppm) by inhalation for 4 h. A lung retention of around 40% was recorded, and blood levels of 11 µmol/litre (970 µg/litre) at 90 mg/m^3 or 29 µmol/litre (2556 µg/litre) at 270 mg/m^3 were achieved towards the end of the exposure period. Of the MTBE absorbed, the majority (about 58%) was excreted unchanged in expired air and small amounts (1.4%) unchanged in urine. The concentration of TBA in blood reached a peak of 16 or 34 µmol/litre (1419 or 2997 µg/litre) (following the low or high exposure, respectively) 15–45 min after exposure ceased. Trace amounts of TBA (1.2%) were found in urine, but none was detected in exhaled air. The terminal half-life for MTBE in blood was determined to be 5 h, while that for TBA was 11.9 h. The authors concluded that metabolism of MTBE was linear at exposures up to 268 mg/m^3 (75 ppm).

Nihlén et al. (1998a) studied the uptake, distribution, metabolism and elimination of MTBE in ten healthy male volunteers. The subjects were exposed on three different occasions for periods of 2 h in a chamber to MTBE concentrations of 18, 90 and 180 mg/m^3 (5, 25 and 50 ppm) while performing light physical exercise. MTBE (and its metabolite TBA) were monitored in exhaled air, blood and urine, the latter being collected up to 3 days after exposure. Respiratory uptake of MTBE was low (42–49%) and respiratory clearance was high (32–47%). The metabolic blood clearance was 0.34–0.52 litre/h per kg. The kinetics of MTBE were linear up to the highest exposure concentration of 180 mg/m^3 (50 ppm). The kinetic profile of MTBE in blood was described as having four phases, with average half-lives of 1 min, 10 min, 1.5 h and 19 h. In urine the post-exposure decay curve of MTBE had two linear phases with average half-lives of 20 min and 3 h. The urinary excretion of MTBE was less than 1% of the absorbed dose.

Biomarkers and partitioning of inhaled MTBE were studied in two (1 male, 1 female) volunteer subjects exposed for 1 h to a nominal concentration of 5 µg/m^3 (1.39 ppm), followed by clean air exposure for 7 h (Buckley et al., 1997). MTBE concentrations in expired air, venous blood and urine were monitored during and after exposure. The decay of MTBE was assessed by using a 2- or 3-exponential

model and yielded residence times of 2–3 min, 15–50 min, and 3–13 h in alveolar air, and 5 min, 1 h and 32 h in venous blood. Based on lower-than-expected blood and expired air MTBE concentrations during uptake and the decreasing blood-breath ratio during the post-exposure decay period, the authors hypothesized that the respiratory mucous membranes acted as a reservoir for MTBE, retaining 6–9% of the MTBE intake. Compartmental monitoring was used to estimate a blood-breath partition coefficient of approximately 18. The urinary concentration of MTBE ranged from 0.37 to 15 µg/litre and bore little relationship to the exposure: urinary elimination accounted for only a small fraction (<1%) of total MTBE elimination.

6.1.2 *Human exposure to oxygenated gasoline*

During an oxyfuels programme in Fairbanks, Alaska, there was a strong correlation between the workplace air levels ranging from 0.02 to 2.92 mg MTBE/m^3 and the difference in blood concentrations of MTBE between pre-shift and post-shift blood measurements ($p=0.0001$). The median pre-shift concentration of MTBE in the blood of 18 occupationally exposed workers was 1.15 µg/litre (range 0.1–27.8 µg/litre). The median post-shift blood MTBE level was 1.8 µg/litre (range 0.2–37.0 µg/litre) (Moolenar et al., 1994).

Breath samples were collected from a person pumping gasoline (containing 15% MTBE by volume) and a nearby observer (within 1 m), immediately prior to and an hour after refuelling (Lindstrom & Pleil, 1996). The MTBE concentration in the sample collected during refuelling was 412 µg/m^3. The ambient background level was approximately 25 µg/m^3 MTBE. Low concentrations of MTBE (7–10 µg/m^3) were detected in the exhaled breath before the refuelling that took 2 min and 8 seconds; 40 seconds after the exposure the concentrations had increased by factors of 35 for the observer and 100 for the person pumping gasoline (see also section 5).

6.2 Animal studies

Repeated exposure (2 to 15 weeks) to MTBE vapour by inhalation (6 h/day, 5 day/week) resulted in dose-dependent increases in MTBE levels in blood, brain and perirenal fat of Wistar male rats

(Savolainen et al., 1985). Very small differences were observed in blood MTBE levels following repeated exposure. TBA levels in blood increased with repeated MTBE exposure when comparing levels at 6, 10 and 15 weeks to levels following 2 weeks. Perirenal fat/blood MTBE concentration ratios ranged from 9.1 to 11.6 after 15 weeks of intermittent exposure. Blood and brain concentrations of TBA, the major main metabolite, were also dose-dependent. TBA was, however, not found in quantifiable amounts in the perirenal fat.

A series of studies on the kinetics of MTBE was conducted by Bio-Research Laboratories (Ferdinandi et al., 1990a–d). These data have been further published by Miller et al. (1997).

Miller et al. (1997) and Ferdinandi et al. (1990a–d) described the pharmacokinetics and disposition of MTBE in male and female Fischer-344 rats following i.v. (40 mg/kg), oral (40 and 400 mg/kg) and dermal (40 and 400 mg/kg in occluded chambers) administration and (nose-only) inhalation exposure for 6 h either for a single exposure or repeated exposure (15 days). The details of these studies are presented in Table 15. Miller et al. (1997) found that the elimination of radiolabelled MTBE in rats was rapid and mainly occurred through lungs and kidneys irrespective of administration route. The elimination was virtually complete 48 h post-dosing. The renal elimination was, however, slowest after dermal exposure. Twelve hours post-dosing, the radiolabelled recovery in urine was 14–26% of the dermal dose, 41–50% of the oral dose and 25–37% of the intravenously injected dose. The recovery was 75–94% 36 h post-dosing, irrespective of dose and administration route. A minor difference in excretion route was observed between the sexes. Collectively these studies demonstrated that MTBE is rapidly eliminated from blood (half-life = 0.5 h) by exhalation and metabolism to TBA (see Table 15). The major metabolites recovered in urine were 2-methyl-1,2-propanediol and α-hydroxyisobutyric acid. Dose-related differences in the AUC for plasma concentrations of MTBE and TBA were observed in rats exposed to 1440 or 28 800 mg MTBE/m^3 (400 or 8000 ppm) by inhalation (Ferdinandi et al., 1990a–d; Miller et al., 1997). Miller et al. (1997) further showed that increasing doses of MTBE (by inhalation and, to a lesser extent, oral administration) to Fischer-344 rats decreased the recoveries of radioactivity in urine and increased the

Table 15. Pharmacokinetic parameters of MTBE and TBA calculated from mean plasma concentrations of male F-344 rats exposed to MTBE (Miller et al., 1997)

Exposure route	Dose	MTBE				TBA	
		AUC (µg/h per ml)	Half-life (h)	CL (ml/h)	V/F or V_{ss}[d] (litre)	$AUC_{zero\ to\ infinity}$ (µg/h per ml)	Half-life (h)
Intravenous	40 mg kg	10.7	0.45	413	0.27	26.7	0.92
Oral	40 mg kg	17.0	0.52	392	0.29	39.0	0.95
	400 mg kg	230	0.79	358	0.41	304	1.6
Dermal	40 mg kg	7.9	2.3[a]	389	3.9	26.3	2.1[a]
	400 mg kg	46.9	1.8[a]	364	1.4	93.9	1.9[a]
Inhalation	low single	84.3	0.52	531	0.40	404	3.3
	high single	2960	0.57	299	0.25	6010	3.4
	low repeated	6.7[b]	0.51	[c]	[c]	127[b]	1.8

[a] Calculated from the alpha-phase of a two-compartment model. Half-lives of MTBE from 12 to 45 h post-dose curve at low and high doses were 92 and 37 h, respectively. Half-lives of TBA from 12 to 45 h post-dose were 170 (low dose) and 31 h (high dose).
[b] $AUC_{zero\ to\ infinity}$ on 15th day of exposure.
[c] Values were not calculated because plasma was not collected during exposure.
[d] V_{ss} = apparent volume of distribution at steady state after repeated inhalation.

recovery in expired air. This indicates a saturation of the oxidative metabolic pathway of MTBE at inhalation levels above 28 800 mg/m^3 (8000 ppm) or at oral administration levels above 400 mg/kg. There were no significant sex- or route-dependent differences in the pharmacokinetics and disposition of MTBE.

Following intraperitoneal administration of ^{14}C-MTBE to rats, the highest radioactivity was recovered in the expired air (Biodynamics, 1984). The radioactivity was also distributed throughout the animal tissues. The amount retained in tissues was less than 2% of the total dose of MTBE intraperitoneally administered to rats at 6 and 24 h post-treatment. Distribution of the radioactivity was primarily to the liver and secondarily to the kidney. Approximately 92% of MTBE was exhaled as the parent compound and approximately 7.5% as CO_2 in 48 h. Another 3% was excreted in urine and up to 0.8% in faeces. The ^{14}C-activity in urine and faeces was mainly associated with ^{14}C-formic acid. Peak blood levels were observed in male and female rats 5 min following intraperitoneal dosing of ^{14}C-MTBE. Peak levels of ^{14}C activity in the plasma occurred at 5 min post-treatment in male rats and at 15 min post-treatment in females rats. The radioactivity decreased sharply during 1 h and thereafter gradually during the study period (48 h). The half-time of radiolabelled MTBE in whole blood was 59.8 min for male rats and 49 min for female rats. The half-life of MTBE in plasma was 2.3 h for male rats and 1.3 h for female rats (Biodynamics, 1984).

In a study of MTBE distribution in male and female rats following inhalation exposure to 10 710 mg/m^3 (3000 ppm) for 6 h, it was reported that MTBE levels in the liver and brain were comparable in males and females but were higher in male kidneys than in those of females: MTBE was still detectable in male kidneys 18 h after exposure (Borghoff et al., 1998). The authors considered that this may have been due to the interaction of MTBE with α2u-globulin in the male rat kidney.

6.3 *In vitro* studies

In vitro measurement of liquid/air partition coefficients of MTBE at 37 °C, using a vial equilibration technique, showed a human blood/

air partition coefficient of 17.7 (confidence limits: 17.0–18.4), water/air 15.2 (CL: 14.9–15.5), and oil/air 120 (CL: 114–125) (Nihlén et al., 1995). There was no significant difference in partition coefficient for blood/air between the sexes. Liquid/air partition coefficients for MTBE between different media and air were also determined by Imbriani et al. (1997). The values were: blood/air = 20.0; urine/air = 15.6; saline/air =15.3; fat/air = 142.0; and olive oil/air = 138.0.

MTBE partition coefficients measured in rat tissues demonstrated a higher solubility of MTBE in fat (115.6) compared to blood (11.5) and other tissues such as liver (14.5) (Borghoff et al., 1996). The partition coefficient of MTBE in the male rat kidney was approximately five times higher than the value measured in female rat kidneys. This high uptake of MTBE into the male rat kidney was found to be due to an interaction with the male rat specific protein α2u-globulin (Borghoff et al., 1995; Poet & Borghoff, 1997).

In rats, MTBE is demethylated by hepatic microsomal enzymes to form TBA and formaldehyde (FA) (Savolainen et al., 1985; Brady et al., 1990). When using rat liver microsomes, the V_{max} for demethylation of MTBE to FA increased after pretreatment with acetone or phenobarbital (Savolainen et al., 1985; Brady et al., 1990). The results of Brady et al. (1990) indicated that both cytochromes P450 2BI and P450 2E1 are implicated in the metabolism of MTBE. *In vitro*, TBA has been shown to be oxidatively demethylated using rat liver microsomes to yield FA (Cederbaum & Cohen, 1980).

Hong et al. (1997) demonstrated that human liver microsomes metabolize MTBE to TBA. The activity of 125 ± 11 pmol TBA/min per mg protein was approximately 50% of the activity in rat and mouse liver microsomes. The metabolism of MTBE to TBA in human liver microsomes was NADPH-dependent and was inhibited by carbon monoxide, an inhibitor of cytochrome P450 (CYP) enzymes, suggesting that CYP enzymes play a critical role in human metabolism of MTBE. Human CYP2A6 and CYP2E1 cDNAs were each co-expressed with human cytochrome P450 reductase by a baculovirus expression system and the expressed enzymes used to metabolize MTBE. CYP2A6 was more active than CYP2E1 (activity 6.1 and 0.7 nmol TBA/min per nmol P450, respectively).

The role of the cytochrome P450 enzyme CYP2E1 in metabolizing MTBE (and other gasoline ethers) was examined in 2E1 knock-out mice, which lack demethylation capability. Liver microsomes metabolized MTBE with an activity level of 0.67 ± 0.1 nmol/min per mg. However, there were no significant differences in activity levels in microsome preparations from two 2E1+/+ strains of mice, demonstrating that CYP2E1 is not important in the metabolism of MTBE in mouse livers (Hong et al., 1998).

The probable metabolic pathway is presented in Fig. 2.

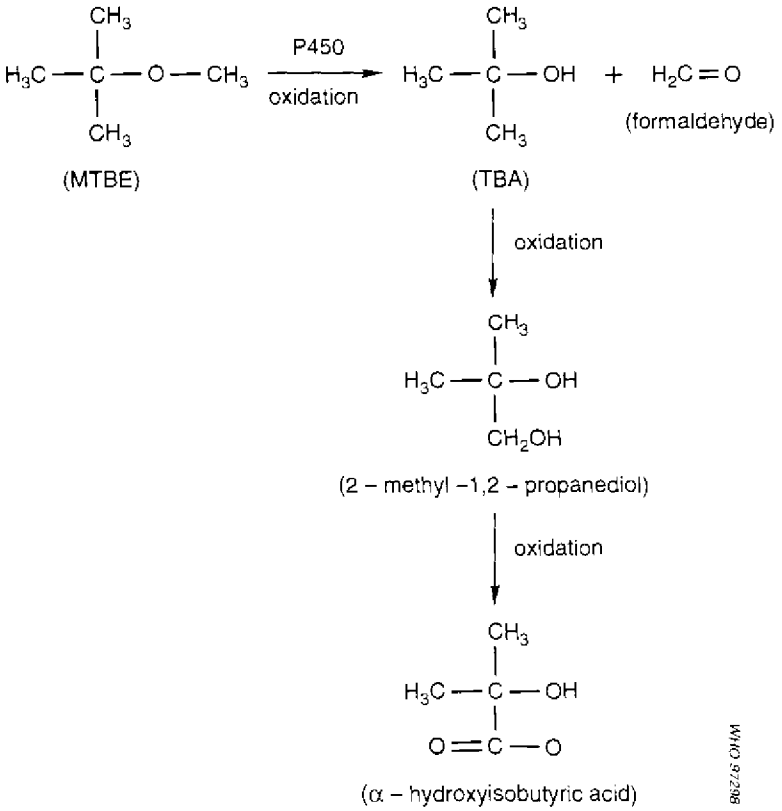


Fig. 2. Metabolic pathways for MTBE based on metabolites identified in studies presented in the EHC monograph (Miller et al., 1997).

6.4 Physiologically based pharmacokinetic modelling

A physiologically based pharmacokinetic model (PBPK) to describe the dosimetry of MTBE in rats has been developed (Borghoff et al., 1996). Using this PBPK model, MTBE blood levels following different routes of exposure and various exposure concentrations were predicted. When human anatomical parameters are used in this model and the metabolism is scaled allometrically, the model predicts the level of MTBE in blood (concentrations ranging from 0.03 to 17.1 µg/litre) during and following exposure of people to 6 mg MTBE/m^3 (1.7 ppm) (Borghoff et al., 1996; Cain et al., 1996). The human PBPK model was further expanded to include brain as a target tissue and an exposure model for bathing and showering. Model simulations of a bathing and showering MTBE exposure scenario in humans at water levels from 0.64 to 1.0 mg/litre and air levels from 5 to 5.7 mg/m^3 (1.4 to 1.6 ppm) predicted maximum brain levels to range from 0.015 to 0.02 mg MTBE/litre and 0.006 to 0.019 mg TBA/litre (Rao & Ginsberg, 1997).

7. EFFECTS ON LABORATORY MAMMALS AND *IN VITRO* SYSTEMS

Owing to the limited therapeutic use of MTBE in the dissolution of cholesterol gallstones in humans, there have been a number of studies in which effects have been examined following single or repeated exposure by direct instillation into the gallbladder. Reported effects at therapeutic doses were mild clinical signs and inflammatory changes in the gallbladder (Allen et al., 1985a; McGahan et al., 1988; Adam et al., 1990; Esch et al., 1992a,b; Chen et al., 1995).

7.1 Single exposure

The acute toxicity of MTBE has been studied in several animal species; the results are summarized in Tables 16 and 17. Studies by routes most relevant to human exposure are described here. The oral LD_{50} value for rats is about 3800 mg/kg bw (ARCO, 1987). Signs of intoxication after single oral lethal doses consist of CNS depression, ataxia, laboured respiration and death (ARCO, 1987). When the dose was non-lethal, recovery was complete.

The acute dermal LD_{50} is >10 200 mg/kg bw for rabbits (ARCO, 1987). Adverse local effects included erythema, oedema, fissuring and necrosis at dermal application.

In rats, the LC_{50} value for inhalation exposure to MTBE is about 142 000 mg/m^3 air (39 460 ppm) (ARCO, 1987). Reported LC_{50} values in mice are 141 000 mg/m^3 (1.6 mmol/litre) for 15 min of inhalation exposure (Marsh & Leake, 1950) and 658 000 mg/m^3 (18% v/v) for 10 min of inhalation exposure (Snamprogetti, 1980). Signs noted in rats following inhalation exposure included eye irritation, incoordination and loss of righting reflex (ARCO, 1987). Surviving animals appeared to recover within 24 h.

Table 16. Acute toxicity of MTBE in experimental animals

Species	Administration route	Dose	LD_{50} (mg/kg bw) (unless stated otherwise)	Observation	Reference
Rat: Charles River, 5 male, 5 female/ dose level	oral (gavage)	2000, 3000, 4600, 6800, or 10 200 mg/kg bw	3800	hypoactivity, muscular weakness, hyperpnoea, lacrimation, prostration and death; the symptoms were reversible at sublethal doses. Inflammation of the stomach and/or small intestine in animals that died	Industrial Bio-Test Laboratories (1969)
Rat: (strain and number not stated)	oral (gavage)		3866	CNS depression, ataxia, laboured respiration and death	ARCO (1987)
Rabbit: New Zealand White 2 male, 2 female/ dose level	dermal	6.8 or 10.2 g/kg bw, occlusive dressing, for 24 h; 14-day observation	>10 200	no deaths; no gross pathological alterations other than necrosis at application site	Industrial Bio-Test Laboratories (1969)
Rabbit: (strain and number not stated)	dermal		10 000	erythema, oedema, scaling, fissuring, and blanching hyperaemia in animals that died	ARCO (1987)
Rat: (strain and sex not stated)	inhalation		LC_{50} = 142 000 mg/m³ (39 460 ppm)	eye irritation, incoordination, tachypnoea, loss of righting reflex and death	ARCO (1987)

Table 16 (contd)

Species	Administration route	Dose	LD_{50} (mg/kg bw) (if not stated otherwise)	Observation	Reference
Mouse: White (strain and sex not stated), 20 mice/exposure group	inhalation (whole body exposure)	exposure for 15 min	LC_{50} = 141 000 mg/m^3 (1.6 mmol/litre)	the median concentration for anaesthesia (AC_{50}) = 106 mg/litre (1.2 mmol/litre)	Marsh & Leake (1950)
Mouse: Swiss, 4 males/exposure group	inhalation (whole body exposure)	exposure for 5 min; observation for following 48 h	400 000 mg/m^3 (260-600 mg/litre)	median effective concentration for anaesthesia (EC_{50}) = 200 mg/litre air (130–300 mg/litre); convulsive hyperventilation, hyperactivity, ataxia, loss of righting reflex, clonic, and sporadic convulsive seizures	Industrial Bio-Test Laboratories (1969)
Mouse: Swiss, I. 40 males/exposure group II. 20 males per group	inhalation (whole body exposure)	I. 20% v/v in air for 3, 4, 5, 6, 9 or 12 min II 8, 12, 17, 20, 22 or 26% v/v MTBE in air for 10 min	LT_{50}[a] = 5.6 min LC_{50} = 658 mg/litre (18% v/v) death occurred within 1 h		Snamprogetti (1980)

Table 16 (contd).

Skin and eye irritancy				
Rabbit: New Zealand White, 3 male, 3 female	skin application (occluded)	0.5 ml	moderate erythema and oedema	Cuthbert (1979)
New Zealand White, 3 male, 3 female	conjunctival instillation	0.1 ml	moderate conjunctival response; no corneal or iris involvement	
New Zealand White I. 6 (sex not stated)	conjunctival instillation	0.1 ml	conjunctival redness for 48 h, no chemosis or discharge, slightly more marked effects with temporary corneal opacity for 24 h	Hazleton Laboratories (1979)
II. 3 (sex not stated)	conjunctival instillation; washout with water 30 secs later	0.1 ml		
Rabbit Both sexes (strain and number not stated)	conjunctival instillation	0.05 ml or 0.1 ml	conjunctival congestion, thickening and lacrimation; more marked at high dose; reversible	Snamprogetti (1980)

[a] LT_{50} =exposure time which causes death in 50% of treated animals.

Table 17. Acute toxicity of MTBE following parenteral injection

Species	Injection route/site	Dose	LD_{50}	Comments	Reference
Rat: Wistar, 8 males/dose group	subcutaneous	3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0 or 10.0 mg/kg bw	6.7 ml/kg bw (5.75–7.76 ml/kg)		Snamprogetti (1980)
Mouse: Swiss, 8 males/dose group	subcutaneous	1.0, 2.0, 3.0, 4.0, 4.5, 5.0 or 5.5 ml/kg bw	3.6 ml/kg bw (2.93–3.57 ml/kg)		Snamprogetti (1980)
Rat: Wistar, 16 males/dose group	intravenous	0.1, 0.2, 0.3, 0.5, 0.75, 1.25 or 1.50 mg/kg bw	0.56 ml/kg bw	in lethal doses: nervous depression, sometimes followed by short clonic convulsions, autonomic activity (hypersalivation, urination, defaecation), and respiratory disorders; death occurred within 30 min. Surviving animals: no toxic symptoms or signs of nervous depression lasting more than 15–20 min	Snamprogetti (1980)

Table 17 (contd).

Rat: Sprague-Dawley, 7 males dosed intravenously 10 males dosed intraperitoneally	hepatic parenchyma, inferior vena cava, tail vein or peritoneal cavity		0.2 ml/kg bw	intracaval injection caused 100% mortality (pulmonary injury); intrahepatic injection caused 59% mortality and peripheral vein injection 17% mortality; the pulmonary injury included congestion, haemorrhage, and interstitial oedema	Akimoto et al. (1992)
Mouse: Swiss, 8 males/dose group	intraperitoneal	1.5, 2.0, 2.5, 3.0, 3.5, 4.0, or 5.0 ml/kg bw	1.4 ml/kg bw		Snamprogetti (1980)
Mouse: ddy 10 males/dose group	intraperitoneal	0, 50, 200, or 500 mg/kg bw	830 mg/kg bw (784–878 mg/kg)		Arashidani et al. (1993)

Results of studies in which neurological effects following single exposures were examined are reported in section 7.3.

7.2 Skin, eye, and respiratory tract irritation; skin sensitization

7.2.1 Skin irritation

Moderate erythema and oedema were reported by Cuthbert (1979) following application of 0.5 ml undiluted MTBE to the intact and abraded skin of six rabbits (applied under occlusion for 24 h). A primary irritation index of 3.36 was reported. Effects were slightly more pronounced on abraded skin:

	24 h		72 h	
	intact	abraded	intact	abraded
erythema	1.7	2.2	1.1	2.0
oedema	1.7	2.0	1.0	1.8

MTBE was considered to be a moderate skin irritant.

7.2.2 Eye irritation

Instillation of 0.05 or 0.1 ml of MTBE into the conjunctival area of albino rabbits (both sexes) caused reversible eye irritation (congestion of the conjunctiva, palpebral thickening and lacrimation, more marked at the high dose) (Snamprogetti, 1980).

Moderate erythema and slight chemosis and discharge, persisting for 3 days, were noted in another study after instillation of 0.1 ml MTBE into the conjunctival area of New Zealand white rabbits (Cuthbert, 1979):

	24 h	48 h	72 h	7 days
redness	2.2	1.7	1	0.2
chemosis	1.3	1.2	1	0.1
discharge	0.9	0.6	0.2	0

The reactions had largely resolved by one week post-treatment). The author concluded that MTBE was irritant to the rabbit eye.

Hazleton Laboratories (1979) conducted a study on nine New Zealand White rabbits (sex not stated) in which six rabbits had 0.1 ml MTBE instilled into one eye, the other acting as control, and three rabbits had the same treatment followed by eye washout with water 30 seconds later. There was slight irritation (mean score for redness 1.5 and 1.0 at 24 and 48 h, negligible chemosis or discharge) in six rabbits that did not have the eye washout, but slightly more marked effects, including corneal opacity lasting for 24 h, in the three rabbits with eye washout. The effects were all reversible.

Exposure to MTBE vapour in inhalation chambers also resulted in eye irritation. In Fischer-344 rats exposed to MTBE vapour concentrations of 14 300 or 28 600 mg/m^3 (4000 or 8000 ppm) for 6 h, lacrimation was noted 1 h post-exposure (Gill, 1989).

7.2.3 *Respiratory tract irritation*

A test of lung irritancy was used by Tepper et al. (1994) to evaluate the effects of 1-h exposures of Swiss-Webster mice (four males per dose group) to 300, 1000, 3000, 10 000 and 30 000 mg MTBE/m^3 in inhalation chambers. An almost immediate decrease in frequency of breathing was observed in all dose groups. The animals served as their own controls with baseline frequency of breathing and respiration waveform morphology being obtained by exposure to filtered air for 15 min. The severity of the irritant response was dose-related, ranging from "slight" (13% decrease in respiration rate) to "severe" at 30 000 mg/m^3. During the exposures, breathing rate returned to baseline after about 15 min, except for the highest dose group, in which the rate gradually decreased for another 40 min. There was a return to baseline frequency 15 min after end of exposure. Lung injury could not be confirmed at the 30 000 mg/m^3 dose level. Lung lavage about 20 h post-exposure indicated only a marginal increase of total protein and lactate dehydrogenase, both measures of lung cell damage; however, these results were comparable to those of similarly treated mice, exposed to filtered air, in a previous study.

In a single 6-h exposure vapour neurotoxicity inhalation study (see also section 7.3) in Fischer-344 rats at target concentrations of 14 400 or 28 800 mg/m^3 (4000 and 8000 ppm), survivors killed at the end of a 14-day observation period had slight to mild lung hyperaemia (Gill, 1989).

7.2.4 Skin sensitization

The sensitization potential of MTBE was assessed in guinea-pigs using a Magnusson and Kligman procedure (Cuthbert, 1979). No evidence of sensitization was reported in any of the 20 test animals following induction and challenge with 1% MTBE. Dermal sensitization has also been investigated using a Landsteiner technique (Litton Bionetics, 1980). Guinea-pigs were induced using intradermal injection (initial treatment 0.5 ml of a 1% aqueous solution, followed by 9 injections of 0.1 ml over 3 weeks). No sensitization reactions were recorded at challenge 2 weeks later (0.05 ml of a 0.01% solution of MTBE in water).

7.3 Neurotoxicity

Following a single MTBE vapour exposure, reversible alterations in central and peripheral nervous system function were observed (Gill, 1989; Daughtrey et al., 1997). Groups of Fischer-344 rats (22 of each sex per dose level) were exposed for 6 h in inhalation chambers at target MTBE concentrations of 0, 2860, 14 300 or 28 600 mg/m^3 (0, 800, 4000 or 8000 ppm). No mortality or clinical signs of toxicity were observed at any concentration. Behavioural evaluations performed 1, 6 and 24 h post-exposure included a screen for behavioural function using a functional observational battery (FOB) and analysis of motor activity prior to and following exposure. At 1 h post-exposure, concentration-related increases in the incidence and severity of ataxia and duck-walk gait appeared in both sexes of the mid- and high-dose groups. In high-dose males, lacrimation, decreased muscle tone, decreased rectal temperature, decreased performance time on the tread mill, and increased hind limb splay were also observed. The alterations in the FOB were significantly ($p<0.01$) different from the control group. An increased incidence of laboured respiration (not statistically significant) was also found in the high-dose male rats.

Additionally, piloerection was observed for all males in the high-dose group. However, piloerection was also observed in some male rats in the control group and in low- and mid-dose males.

Similar concentration-related findings were found in mid- and high-dose female rats (increased incidence of lacrimation, piloerection, ataxia and duck-walk gait, decreased rectal temperature, and decreased hind limb grip strength). Additional exposure-related findings for females in the high-dose group included a significantly ($p<0.01$) increased incidence of laboured respiration and latency to rotate on the inclined screen. Exposure-related alterations of motor activity were detected for both male and female rats during the initial 90 min of the test session. The mean activity was increased during the entire test period in low-dose males and decreased in high-dose males compared to the control group. However, in high-dose males, an initial 10-min decrease in activity was followed by increased activity during a 20-min interval and decreased thereafter. Males in the mid-dose group only showed an increased activity initially. For females, the mean activity for the entire test session was not different from the control group. No MTBE-related alterations were observed during the 6-h or 24-h post-exposure evaluation.

7.4 Short-term repeated dose studies

The short-term repeated dose toxicity of MTBE has been studied in rats, mice and pigs. Typically, effects of irritation and reversible central nervous system effects, including hypoactivity, ataxia, and anaesthesia, were noted.

7.4.1 Oral studies

Sprague-Dawley rats (10 males and 10 females per dose group) administered 0 (corn oil), 357, 714, 1071 or 1428 mg MTBE (99.95% pure)/kg bw daily by gavage (in corn oil) for 14 days exhibited transient anaesthesia at 1428 mg/kg and irritation of the pharyngeal mucosa at the highest dose levels (Robinson et al., 1990). Diarrhoea and reduced body weight gain were observed in all treatment groups. Six animals (four from the high-dose group) died during treatment due to difficulties associated with the gavage procedure, including

pharyngeal irritation in the high-dose animals. Absolute and relative lung weights were significantly ($p \leq 0.001$) lower in all exposed female rats. The mean absolute kidney weights were increased in dosed male rats and the relative kidney weights were significantly ($p \leq 0.05$ and $p \leq 0.001$) increased over controls in the mid- and high-dose group, respectively. The cholesterol levels were significantly ($p \leq 0.05$) increased in high-dose males and the two mid-dose groups of females. The blood-urea nitrogen (BUN) and creatinine were significantly ($p \leq 0.05$) decreased in high-dose females. The incidence of renal tubular disease (hyaline droplet nephropathy) was moderately increased in dosed male rats. Increased hyaline (protein) droplets within the cytoplasm of proximal tubular epithelial cells were noted in seven of eight (88%) of the males in the highest dose group as compared with two of five (40%) of the controls.

In a 28-day oral study, Sprague-Dawley rats (10/sex/group) were administered 0, 90, 440 or 1750 mg undiluted MTBE (purity not specified)/kg bw daily by gavage for a total of 20 h (IITRI, 1992). Seven rats (one low-dose female, one high-dose male, and five high-dose females) died accidentally during dosing. This was attributed to difficulties in dosing the animals owing to the strong odour, the irritating nature, and high volatility of MTBE. Clinical observations during the study period included transitory salivation in all treated groups and transitory hypoactivity and/or ataxia in mid- and high-dose animals. There were no significant effects on body weight or body weight gain. The only significant treatment-related change in haematological or clinical chemistry parameters was an increase in cholesterol in high-dose males and females.

No treatment-related gross necropsy observations were noted. The relative liver weights were significantly ($p<0.05$) increased in males and females in the high-dose group. In the high-dose males there was also a significant ($p<0.05$) increase in relative adrenal weight. Absolute kidney and relative kidney weights showed a dose-related increase in both males and females, but achieved statistical significance (corrected for multiple comparisons) only for relative weights in males at the mid- and high-doses and in females at the low and high doses. Histopathology showed hyaline droplet formation in

the proximal convoluted tubules in the kidneys of the mid- and high-dose males.

In a 90-day study, groups of Sprague-Dawley rats (ten males and ten females in each test group) were gavaged 0 (corn oil), 100, 300, 900 or 1 200 mg/kg bw of undiluted MTBE (≥99.95% pure) daily for 90 days (Robinson et al., 1990). The most pronounced clinical effect of MTBE was the profound anaesthetic effect at 1200 mg/kg bw; the animals recovered in about 2 h. In female rats, a significant ($p \leq 0.001$) treatment-related decreased BUN level and elevated cholesterol level were observed at all levels of exposure. In male rats, the mean absolute kidney weights were significantly ($p \leq 0.05$) elevated at 900 and 1200 mg/kg bw, respectively. The increase in the relative kidney weights was statistically significant ($p \leq 0.001$) at the two highest dose levels and also the relative liver weights ($p \leq 0.05$ at 900 mg/kg and $p \leq 0.001$ at 1200 mg/kg). In females, the relative kidney weights were significantly ($p \leq 0.05$) increased at and above 300 mg/kg bw and the relative liver, thymic and cardiac weights showed a statistically significant ($p \leq 0.05$) dose-related increase at 900 mg/kg. Microscopic findings included chronic nephropathy in both control and high-dose male rats, which was more severe in MTBE-treated rats. At the highest dose level, granular casts were found, and there was also a slight increase of cytoplasmic hyaline droplets in proximal tubular epithelial cells.

In a comparison study on the effects of inhalation exposure (see section 7.3.2), two groups of female B6C3F$_1$ mice (8/group) were given MTBE by gavage in corn oil (5 ml/kg/bw) at doses of 0 or 1800 mg/kg bw per day for 3 days and then killed around 18 h after the last dose (Moser et al., 1996a). Body weight and liver weight were not affected by treatment. MTBE induced a 37% increase in hepatic cytochrome P450 content ($P < 0.05$), a 9-fold increase in hepatic 7-pentoxy resorufin-*O*-dealkylase activity (PROD, a CYP2B marker) and a 2-fold increase in hepatic 7-ethoxy-resorufin-*O*-deethylase activity (EROD, a CAPE marker). MTBE also induced a 2-5-fold increase in the hepatic cell labelling index (as estimated from the incorporation of 5-bromo-2-deoxyuridine delivered by an implanted osmotic mini pump) in the absence of hepatotoxicity, judged by the absence of any change in serum alanine aminotransferase (ALAT) or histological signs of necrosis (Moser et al., 1996a).

7.4.2 Inhalation studies

Female B6C3F$_1$ mice (five or more/group) were exposed by inhalation to 0 or 27 900 mg/m^3 (7814 ppm) MTBE (>99.95% pure) for 3 or 21 days (6 h per day, 5 days per week) (Moser et al., 1996a). The exposure resulted in abnormal gait, hypoactivity, decreased muscle tone and increased lacrimation during exposure and immediately after termination of exposure to MTBE. The mice recovered quickly following termination of exposure. There was no significant change in body weight. The relative liver weights were increased 20% ($p<0.05$) as compared to controls at 3 days of exposure but the difference was not significant at 21 days. MTBE exposure significantly ($p<0.05$) decreased relative uterine weight to 48% of the control at 3 days, with a further significant ($p<0.05$) decrease to 65% at 21 days. The relative ovarian weight was decreased to 69% ($p<0.05$) at 21 days of exposure. Histopathological examination showed mild centrilobular to midzonal hepatocyte swelling at 3 days. At 21 days there were no microscopic exposure-related changes. The total hepatic microsomal cytochrome P450 content was elevated 40% at 3 days and approximately 200% at 21 days. After 3 days and 21 days of MTBE exposure, respectively, hepatic PROD activity increased 5-fold and 14-fold, while hepatic EROD activity increased 1.8-fold and 3.2-fold. There was a non-significant change in hepatic cell labelling index to a 2.5-fold higher value at 3 days, but at 21 days the MTBE group showed a significant reduction to 0.7% in comparison with the control value of 2.3% ($p<0.05$). There were no histological signs of hepatoxicity and serum ALAT was unaffected.

Information on the repeated dose toxicity of MTBE (>99.95% pure) is also available from a study comparing the short-term hepatic effects on female B6C3F$_1$ and CD-1 mice (Moser et al., 1996b). Groups of six female mice were exposed in inhalation chambers to particulate-free control air containing 0 mg/m^3 or a target concentration of 27 900 mg/m^3 (7800 ppm) 6 h per day, 5 days per week for 3 or 21 days. Clinical signs included abnormal gait, hypoactivity, decreased muscle tone and increased lacrimation during exposure and immediately after termination of exposure. The animals recovered quickly after termination of each daily exposure. There was a decrease of body weight ($p<0.05$) in CD-1 mice, but not in B6C3F$_1$ mice, after

21 days. Statistically significant ($p<0.05$) increases were seen in absolute and relative liver weight in both strains of mice at both time points. Histopathological examination showed slight centrilobular hypertrophy in both $B6C3F_1$ mice and CD-1 mice at 3 days as compared to controls. At 21 days there was no indication of hepatotoxicity or necrosis. Serum ALAT showed no increased activity at either 3 or 21 days. In the CD-1 mice, after 3 and 21 days, respectively, total hepatic microsomal cytochrome P450 content increased 2.3-fold ($p<0.05$) and 1.8-fold ($p<0.05$), PROD increased 5-fold ($p<0.05$) and 5-fold ($p<0.05$), and EROD increased 2.3-fold ($p<0.05$) and 3-fold ($p<0.05$). Corresponding data for the $B6C3F_1$ mice are described below. The hepatic cell labelling indices were, in contrast to $B6C3F_1$ mice, increased in CD-1 mice at both time points; the increases were 3-fold and 5-fold, respectively, at 3 and 21 days (Moser et al., 1996b). A slightly decreased survival relative to control was noted in female $B6C3F_1$ mice following 16 weeks exposure to 28 450 mg/m^3 (7969 ppm) (100% versus 92% survival, respectively). After 32 weeks of exposure, survival was 96% for controls and 88% for MTBE-exposed mice. Body weight was significantly decreased ($p<0.05$) at both time points. PROD activity was increased 4.9 fold, and EROD activity 1.9 fold, after 16 weeks treatment. While MTBE exposure produced mild centrilobular to midzonal hypertrophy, there was no indication of cytotoxicity or hepatic necrosis, or alteration in serum ALAT (Moser et al., 1996b).

Sprague-Dawley rats (10/sex/group) showed increasing depth of anaesthesia with increasing concentrations of MTBE when exposed to MTBE vapour in exposure chambers at concentrations of 0, 900, 1800 or 3600 mg/m^3 (0, 250, 500 and 1000 ppm, respectively) 6 h per day, 5 days per week for 13 weeks (Greenough et al., 1980). The haematological analyses revealed an increase in haemoglobin levels during week 13 in male rats exposed to 3600 mg/m^3. At autopsy, a slight reduction in relative and absolute lung weight was detected in female rats at the same exposure level. There were no other gross or histopathological effects reported.

In a range-finding study, Fischer-344 rats and CD-1 mice were exposed to MTBE vapour in inhalation chambers 6 h per day for 13 consecutive days (Dodd & Kintigh, 1989). The target concentrations

were 0, 7150, 14 300 and 28 600 mg/m^3 (0, 2000, 4000 and 8000 ppm, respectively). The measured mean concentrations were 7200, 13 750 and 28 330 mg/m^3 (2018, 3850 and 7936 ppm, respectively). No mortality occurred during the study period. Clinical signs included hypoactivity, ataxia, and periocular irritation in both rats and mice, primarily in the high-dose groups during exposure. Reversible neurobehavioural alterations (ataxia) were observed immediately after exposure in high-dose rats (mice were not observed). Body weight gain was depressed in rats (but not in mice) in the mid- and high-dose groups (statistically significant for male rats). In female mice, both absolute and relative liver weights were significantly increased at all levels of exposure. In the mid-dose rats, both absolute and relative liver weights were significantly increased in females; in males, there was an increase in relative kidney and liver weights. In rats at the highest dose, males had an increase in relative weight of liver, kidney and adrenal. Females had an increase in both absolute and relative weights of liver and adrenal, and absolute weight of kidneys was increased.

In a 13-week vapour inhalation study that included neurotoxicity evaluation, Fischer-344 rats were exposed to target concentrations of 0, 2860, 14 300 and 28 600 mg MTBE/m^3 (0, 800, 4000 and 8000 ppm) 6 h per day, 5 days per week (Dodd & Kintigh, 1989; Lington et al., 1997). No mortality occurred. Major findings included motor activity changes and reversible changes in body temperature in mid- and high-dose rats, ataxia, and depressed body weight gain and food consumption. Only mild haematological changes (e.g., decreased erythrocyte counts and increased reticulocyte counts) were observed, primarily in male rats. The corticosterone levels were significantly increased in both male and female rats at the highest exposure level. No treatment-related gross lesions were found at necropsy. The relative weight of liver and kidney were significantly increased in all male groups and in females in the two highest exposure groups. Relative weight of adrenal was significantly increased in males and females at the two highest doses. There were, however, no treatment-related microscopic changes in these organs. It is probable that there is an association between the liver enlargement and the high serum corticosterone levels. (Although this was reported by the authors, the Task Group considered that it was more likely that the increase in

adrenal weight was associated with the high serum corticosterone levels). The only treatment-related microscopic findings were found in males at the highest dose level and included a statistically significant increase in lymphoid hyperplasia in the submandibular lymph nodes, an increase (not statistically significant) in the degree of haemosiderosis in the spleen, and a mild increase of hyalin droplets in the renal proximal tubules. Proximal tubule necrosis and protein droplet accumulation were observed in kidneys from male, but not female, rats exposed to 5400 and 10 760 mg/m^3 (1516 and 3013 ppm) for 6 h/day for 10 consecutive days (Prescott-Mathews et al., 1997). Alpha-2u-globulin immunoreactivity was present in and confined to protein droplets in male rat kidney. A mild dose-related increase in alpha-2u concentration in the male rat kidney correlated with an exposure-related increase in cell proliferation. No significant differences were observed in female rats for any of these responses.

7.4.3 Intraperitoneal administration

Katoh et al. (1993) reported that MTBE administered to mice (500 mg/kg bw as a single dose, or 200 mg/kg bw as repeated doses) caused lipid peroxidation, as demonstrated by increased levels of lipid peroxide in liver homogenates, and an induction of hepatic microsomal cytochrome P450 content. Repeated treatment with 200 mg/kg bw for 4 weeks did not affect glutathione content or glutathione-S-transferase (details on pattern and period of administration were not provided).

7.5 Neurotoxicity studies

A single 6-h inhalation exposure of Fischer-344 rats to MTBE vapour at target concentrations of 0, 2880, 14 400 or 28 800 mg/m^3 (0, 800, 4000 or 8000 ppm) induced reversible alterations in central and peripheral nervous system function (Gill, 1989). Group of 8 male and 8 female rats were used at each concentration for behavioural evaluation and 14 males and 14 females for motor activity observations. Motor activity changes appeared within 10 min of exposure to 28 800 mg/m^3 (8000 ppm) in both male and female rats. For male rats, motor activity changes were also observed at 2880 and 14 400 mg/m^3). Behavioural evaluation (functional observational battery, FOB) was

performed 1, 6 and 24 h post-exposure. At 1 h post-exposure there were concentration-related behavioural alterations at 14 400 mg/m^3 and 28 800 mg/m^3 but these were not found at 6 or 24 h post-exposure.

In a pilot study for a 13-week exposure study (see also section 7.3), Fischer-344 rats and CD-1 mice (five per sex and species) were exposed to target MTBE concentrations of 0, 7150, 14 300 and 28 600 mg/m^3 (0, 2000, 4000 and 8000 ppm) 6 h per day for 13 consecutive days (Dodd & Kintigh, 1989). Hypoactivity was observed at all dose levels and ataxia at the two highest dose levels in both rats and mice during exposure. In high-dose rats, ataxia, decreased startle and pain reflexes, and decreased muscular tone were also observed immediately after exposure. Recovery was complete within 1 h. The NOAEL was determined to be 7200 mg/m^3 in both rats and mice.

The subsequent 13-week study with neurotoxic evaluation included testing for inhalation toxicity, FOB, motor activity and neuropathology (Dodd & Kintigh, 1989). Fischer-344 rats (25 rats of each sex per dose level) were exposed to MTBE vapour at target concentrations of 0, 2860, 14 300 and 28 600 mg/m^3 (0, 800, 4000 and 8000 ppm) 6 h per day, 5 days per week (see also section 7.4.2). Clinical findings included hypoactivity in the mid- and high-dose groups and ataxia in the high-dose group immediately following the daily exposure. The exposure resulted in minor changes in the FOB including elevated body temperature (in high-dose male rats and in mid- and high-dose female rats) and decreased hind limb grip strength (in mid-dose males). Decreased motor activity for males in the high-dose group and increased motor activity for females in the low- and mid-dose groups were reported. Additional findings are reported in section 7.3. Necropsy revealed no treatment-related gross lesions. There were no treatment-related microscopic changes in the central and peripheral nervous system tissues.

7.6 Reproductive and developmental toxicity

Protocols and results of reproductive/developmental studies are presented in Table 18 These include one- and two-generation inhalation studies in rats and four developmental studies (inhalation) in rats, rabbits and mice. In these investigations, MTBE did not induce

Table 18. Reproductive studies with MTBE in laboratory animals

Species	Route of exposure	Number of animals	Dosage	Time of treatment	Results	Reference
One- and two-generation studies						
Rat, Sprague-Dawley	inhalation	15 males and 30 females/group	0, 1070, 4640 and 12 140 mg/m^3 (0, 300, 1300 and 3400 ppm)	one generation, two litter study (F_{1a}, F_{1b})	slightly decreased pup viability ($p<0.05$) in $F1_b$ 12 140 mg/m^3	Biles et al. (1987)
Rat, Sprague-Dawley	inhalation	25 males and 25 females/group	0, 1430, 10 700, and 28 600 mg/m^3 (0, 400, 3000 and 8000 ppm)	two generation study	1430 mg/m^3: no adverse effects; $\geq$ 10 700 mg/m^3: reduced bw, bw gain and food consumption in parental animals (mainly in males), clinical signs and neurotoxic effects, reduced pup bw and bw gain postnatally. NOEL for general toxicity 1430 mg/m^3; NOEL for reproductive effects >28 600 mg/m^3; LOEL for adults and offspring $\geq$ 10 700 mg/m^3	Neeper-Bradley (1991)

Table 18 (contd)

Species	Route of exposure	Number of animals	Dosage	Time of treatment	Results	Reference
Developmental studies						
Rat, Sprague-Dawley	inhalation	25 rats per dose level	0, 900, 3600 and 9000 mg/m^3 (0, 250, 1000 and 2500 ppm)	gestation days 6–15	reduced food consumption in treated groups during the day 9–12 interval; no significant developmental toxicity	Conaway et al. (1985)
Mouse, CD-1	inhalation	25 mice per dose level	0, 900, 3600 and 9000 mg/m^3 (0, 250, 1000 and 2500 ppm)	gestation days 6–15	a slight (not statistically significant), dose-related decrease in food and water consumption; no significant developmental effects	Conaway et al. (1985)

Table 18 (contd).

Mouse, CD-1	inhalation	30 mice per dose level	0, 3600, 14 300 and 28 600 mg/m^3 (0, 1000, 4000 and 8000 ppm)	gestation days 6–15	≥ 14 300 mg/m^3: clinical signs of toxicity and reduced fetal bw; 28 600 mg/m^3: reduced bw, bw gain, and food consumption; increased number of non-viable implantations, reduced number of viable implantations and % male fetuses, and increased incidence of cleft palate. NOEL for maternal and developmental toxicity 3600 mg/m^3	Tyl & Neeper-Bradley (1989)
Rabbit, New Zealand White	inhalation	8 females per dose level	0, 7150, 14 300 and 28 600 mg/m^3 (0, 2000, 4000 and 8000 ppm)	gestation days 6–18	≥ 7150 mg/m^3: reduced food consumption in all dosed groups; increased incidence of lung foci; 28 600 mg/m^3: reduced bw gain, audible respiration, and slightly lower fetal weights	Tyl (1989)

Table 18 (contd).

Species	Route of exposure	Number of animals	Dosage	Time of treatment	Results	Reference
Rabbit, New Zealand White	inhalation	15 females per dose level	0, 3600, 14 300 and 28 600 mg/m^3 (0, 1000, 4000 and 8000 ppm)	gestation days 6–18	≥14 300 mg/m^3: reduced bw gain and food consumption; 28 600 mg/m^3: hypoactivity, ataxia, increased relative liver weight, decreased corrected gestational weight change and gravid uterine weight. No significant developmental effects; NOEL for maternal toxicity 3600 mg/m^3; NOEL for developmental toxicity ≥28 600 mg/m^3	Tyl (1989)

specific adverse reproductive effects; developmental effects were observed only at dose levels that were maternally toxic. At very high dose levels (28 000 mg/m^3) decreased relative uterine weight was observed in one study.

7.6.1 Reproductive toxicity

Biles et al. (1987) conducted a two-litter, one-generation inhalation study of reproductive effects in CD Sprague-Dawley rats. Target concentrations were 0, 890, 3600 and 8925 mg/m^3 (0, 250, 1000 and 2500 ppm). Corresponding measured concentrations were, respectively, 1070, 4430 and 10 640 mg/m^3 (300, 1240 and 2980 ppm) for females and 1030, 4210 and 10 210 mg/m^3 (290, 1180 and 2860 ppm) for males. Fifteen males exposed for 12 weeks were mated to thirty females exposed for 3 weeks. Exposures continued throughout the mating period, during gestation and through days 5–21 of lactation. A second litter (F_{1b}) was produced under the same mating and post-mating exposure regimen. In the mid- and high-dose groups of the F_{1b} generation, there was a slight statistically significant ($p<0.05$) decrease in pup viability. The authors felt that this was in large part attributable to the high viability (99%) in the control group.

There were no treatment-related differences between control and exposed animals based upon examination of clinical signs, gross post-mortem examination and histopathological examination of the gonads of exposed adults, mating or fertility indices, pregnancy rates, mean gestational length and number of pups at birth, litter survival indices or pup weight. (The NOEL was above 8925 mg/m^3 (> 2500 ppm) in both parents and offspring).

In a two-generation reproductive and fertility inhalation study, CD Sprague-Dawley rats were exposed to MTBE at concentrations of 0, 1430, 10 700 or 28 600 mg/m^3 (0, 400, 3000 or 8000 ppm) (Neeper-Bradley, 1991; Bevan et al., 1997). There was parental toxicity at the target concentrations of 28 600 mg/m^3 and 10 700 mg/m^3. Concomitant perinatal toxicity was also observed at these concentrations. There were no treatment-related effects on reproductive indices at any concentration and no adverse effects on the offspring at concentrations that were not toxic to the parents. (NOEL = 1430 mg/m^3 (400 ppm);

hypoactivity, lack of startle reflex and blepharospasm in parents at 10 700 mg/m^3 (3000 ppm); NOEL for reproductive effects >28 600 mg/m^3 (8000 ppm).

Inhalation exposure to 28 800 mg/m^3 MTBE (99.95% pure) resulted in significantly decreased relative uterine weight in B6C3F$_1$ mice at 3 (48%) and 21 days (65%) of exposure as compared to controls (Moser et al., 1996a) (see also section 7.4.2). The relative ovarian weight was significantly ($p<0.05$) decreased at 21 days of exposure. There were no exposure-related microscopic findings in ovaries, adrenals and pituitary, and no effects on adrenal and pituitary weight. Moser et al. (1996a) investigated if the decreased uterine weights were due to an increased rate of estrogen metabolism by measuring the rate of conversion of 3H-17B-oestradiol to water-soluble metabolites in hepatocytes from MTBE-treated female mice. MTBE was found to increase the oestrogen metabolism by 2.1-fold.

Ward et al. (1994) studied the toxicity of MTBE to germ cells in CD-1 male and female mice. Groups of 10 mice were given 1, 10, 100 or 1000 mg/kg bw MTBE in corn oil by gavage 5 days per week for 3 weeks; a negative control group received corn oil only. At the end of treatment the mice were killed and one testis from each male and both ovaries from each female were sectioned for cytological evaluation. In males, sperm number, Sertoli cells, spermatogonia, spermatocytes and capped spermatids were evaluated, and, in females, oocyte quality. There were no effects of MTBE on any of the cell types examined.

7.6.2 Developmental toxicity

The results of four inhalation studies on the developmental toxicity of MTBE are summarized in Table 18.

There was a significant decrease in food consumption on days 9–12 of gestation in pregnant rats exposed to as much as 9000 mg/m^3 (2500 ppm) but no other effects that the authors considered to be maternally toxic, embryotoxic or teratogenic (Conaway et al., 1985). The NOEL for offspring and parents was >9000 mg/m^3 (2500 ppm).

Two different studies were conducted in the same strain of mice exposed to various concentrations of MTBE for 6 h/day on days 6–15 of gestation (Conaway et al., 1985; Tyl & Neeper-Bradley, 1989). No significant maternal toxicity or developmental effects were observed when groups of 30 pregnant females were exposed to 1000, 3960 or 9675 mg/m^3 (280, 1110 or 2710 ppm), though the incidence of lacrimation was increased in exposed mothers and there was a slight increase in the incidence of fused sternebrae in the high-dose group (Conaway et al., 1985). The NOAEL of parents and offspring was 9000 mg/m^3 (2500 ppm). Tyl & Neeper-Bradley (1989) concluded that 14 300 mg/m^3 (4000 ppm) was maternally toxic, based on observed hypoactivity and ataxia. There were significant decreases ($p<0.01$) in body weight, body weight gain and food consumption at 28 600 mg/m^3 (8000 ppm). At 14 300 mg/m^3 (4000 ppm) or more, there were significant reductions in fetal body weight per litter ($p<0.01$) and increased skeletal variation. The proportion of male fetuses was significantly reduced ($p<0.01$) at the highest dose level in the Tyl & Neeper-Bradley (1989) study, but this has not been observed in other studies with mice, rats or rabbits. At 28 600 mg/m^3 (8000 ppm), the number of non-viable implantations per litter and incidence of cleft palate was also increased (LOAEL in parents and offspring = 14 300 mg/m^3 (4000 ppm). The NOAEL in this study was 3570 mg/m^3 (1000 ppm).

Maternal toxicity was observed at the two highest concentrations in rabbits exposed to 3570, 14 300 and 28 600 mg/m^3 (1000, 4000 and 8000 ppm) during days 6–18 of gestation (Tyl, 1989). No developmental effects were observed at any exposure level [NOAEL in offspring = 28 600 mg/m^3 (8000 ppm); NOAEL in parents = 3570 mg/m^3 (1000 ppm); LOAEL in parents = 14 300 mg/m^3 (4000 ppm)].

7.7 Mutagenicity and related end-points

Genotoxicity study results with MTBE are generally negative. However, there are indications that MTBE may have some genotoxic potential in the presence of metabolic activation. Genotoxicity data for MTBE are compiled in Table 19.

In studies on reverse mutation in *Salmonella typhimurium*, MTBE was found to be non-mutagenic in tester strains TA1535, TA1537,

Table 19. Genotoxicity studies with MTBE

Species	Strain/cells	Measured end-point	Test conditions	Activation	Result	Reference
Bacterial systems						
S. typhimurium	TA1535 TA 1537 TA1538 TA98 TA100	reverse mutation	625, 1250, 2500, 5000, 10 000 µg/plate	+ -	- -	Cinelli & Seeberg (1989)
S. typhimurium	TA98 TA100	reverse mutation	exhaust particle extracts from gasoline containing 7% by volume MTBE; five concentrations ranging from 1 to 100 µg/plate; duplicate plates	+ +	nd ±	Clark et al. (1984)
Non-mammalian eukaryotic systems						
Drosophila melanogaster	wild type Oregon-R, males	sex-linked recessive lethal test	Basc test; 0.03, 0.15 or 0.3% MTBE; adult feeding for 24 h		-	Sernau (1989)
***In vitro* mammalian systems**						
Mouse	lymphoma cell line L5178Y/TK	forward mutation	1.0, 2.0, 3.0, 4.0 µl/ml	+	+	Mobil Oil Corporation (1993)
Rat	primary hepatocytes	UDS	3.16, 10.0, 31.6, 100, 316, 1000, 3160, 10 000 µg/ml		-	Seeberg (1989)

Table 19 (contd).

In vivo - in vitro					
Mouse, CD-1	primary hepatocytes	UDS	vapour exposure: 0, 1440, 10 800, 28 800 mg/m^3, 6 h/day for 2 consecutive days	-	Vergnes & Chun (1994)
***In vivo* mammalian systems**					
Rat, Fischer -344	bone marrow cells	chromosome aberrations	vapour exposure: 0, 2800, 14 400, 28 800 mg/m^3, 6 h/day for 5 days	-	Vergnes & Morabit (1989)
Mouse, CD-1	spleen lymphocytes	chromosome aberrations	oral administration, 1.0, 10, 100 or 1000 mg/kg bw for 3 weeks	a slight inverse dose-response relationship in male mice but not in female mice	Ward et al. (1994)
Mouse, CD-1	spleen lymphocytes	mutations at *hprt* locus	oral administration, 1.0, 10, 100 or 1000 mg/kg bw for 3 weeks	-	Ward et al. (1994)
Mouse, CD-1	bone marrow cells	chromosome damage	vapour exposure: 0, 1440, 10 800, 28 800 mg/m^3, 6 h/day for 2 consecutive days	-	Vergnes & Kintigh (1993)

TA1538, TA98 and TA100, with and without S9 (liver enzyme homogenates from induced Sprague-Dawley male rats) metabolic activation, at doses up to 10 mg/plate (Cinelli & Seeberg, 1989).

No significant increase in the frequency of recessive lethal mutations in the X-chromosome could be established after feeding MTBE (99.14% pure) (0.03, 0.15 or 0.3% MTBE in 5% aqueous sucrose) to adult *Drosophila melanogaster* (wild-type Oregon-R males) for 24 h (Sernau, 1989).

In the presence of a liver-derived metabolic system (liver S9 from Arochlor 1254-induced male Sprague-Dawley rats) MTBE (>99% pure; 1.0, 2.0, 3.0 or 4.0 ml/ml) induced forward mutations *in vitro* at the thymidine kinase locus of mouse lymphoma cell line L5178Y/ TK+/- (Mackerer et al., 1996). The observed mutagenicity was dose-dependent.

Other experimental data, using a test system developed to determine if the mutagenicity of a material is the result of the presence or release of formaldehyde, had indicated that the mutagenicity was due to the metabolism of MTBE to formaldehyde (Blackburn et al., 1991). To establish if formaldehyde, derived from MTBE in the presence of S9, was responsible for the observed mutagenicity, Mackerer et al. (1996) used a modified mouse lymphoma assay. In this assay formaldehyde dehydrogenase and its co-factor NAD^+ were added during the exposure period so that any formaldehyde produced would be converted to formic acid, which is non-genotoxic. An MTBE dose-related increase in the frequency of mutant lymphoma cells occurred without the presence of formaldehyde dehydrogenase and NAD^+, but not when these were present, indicating that formaldehyde was responsible for the mutations.

In two independent *in vitro* experiments MTBE (purity not specified) did not induce unscheduled DNA synthesis (UDS) in primary rat hepatocytes at concentrations up to 10 mg/ml (Seeberg, 1989).

In an *in vivo-in vitro* hepatocyte UDS assay, ten male and ten female CD-1 mice were assigned to each dose group and an air-only

control group and, in addition, five of each sex to a positive control group (DMN) (Vergnes & Chun, 1994). The animals were exposed to MTBE (purity not specified) in inhalation chambers 6 h a day for two consecutive days. The target concentrations were 0, 1440, 10 800 and 28 800 mg/m^3 (0, 400, 3000 8000 ppm). The animals were sacrificed and hepatocytes were sampled 18 h after the second exposure day (for the positive control group after approximately 2 h). No dose-related increase in the DNA repair activity could be established. The UDS assay is used to indicate primary DNA damage; this is, however, transient in nature and it is necessary to analyse cells for damage as soon as possible after cessation of treatment. Since the half-life of MTBE in the animal body is quite short (1–3 h) and DNA repair is relatively rapid, the study should have been designed accordingly.

MTBE (purity not specified) was considered nonclastogenic to Fischer-344 rats in an *in vivo* test system (Vergnes & Morabit, 1989). No concentration-related or significant increase in the incidence of chromosome aberrations in rat bone marrow cells was found in either males or females following whole body exposure to MTBE 6 h per day for five consecutive days. The target concentrations were 0, 2860, 14 300 and 28 600 mg/m^3 (0, 800, 4000 and 8000 ppm, respectively).

MTBE did not induce micronuclei *in vivo* in mouse bone marrow cells (Vergnes & Kintigh, 1993). CD-1 mice were exposed to MTBE (purity not specified) vapour in inhalation chambers (five animals per sex per dose level) at concentrations of 0, 1430, 10 710 or 28 600 mg/m^3 (0, 400, 3000 or 8000 ppm) 6 h a day for two consecutive days. Bone marrow cells were collected 24 and 48 h after the second exposure day. No significant, exposure-related increase in the frequency of micronuclei could be established at any dose level and sampling time in either sex in this study.

Ward et al. (1994) examined the frequency of somatic cell mutations in spleen lymphocytes after administration by gavage 5 days per week for 3 weeks with MTBE (99.8% pure) in corn oil to CD-1 male and female mice (ten animals per dose group). Ethyl-nitrosourea was used as a positive control. The doses were 1, 10, 100 and 1000 mg/kg bw. The frequency of mutations at the hypoxanthine-guanine phosphoribosyl transferase (*hprt*) locus was determined 3 weeks after

the cessation of exposure. There was no indication that MTBE produced a mutagenic effect at the tested dose levels. Ward et al. (1994) also analysed chromosome aberrations in spleen lymphocytes. This was performed on the first day after the termination of exposure in 13 male mice and on the second day in the remaining mice. A slight, but not statistically significant, inverse dose-relationship was seen in male mice; this was not seen in the females.

7.8 Carcinogenicity

Three bioassays are available on the oncogenicity of MTBE in both sexes of rats and mice. These include two inhalation studies, one in Fischer-344 rats and one in CD-1 mice, and one oral study in Sprague-Dawley rats (Table 20). At high inhalation exposure levels, MTBE increased the incidence of renal cell carcinomas in male rats and liver tumours in female mice. Oral administration increased the incidence of lymphomas and leukaemias in female rats. The studies also resulted in testicular tumours in both strains of rats following exposure either by inhalation or oral administration.

Fischer-344 rats (50 of each sex per dose level) were exposed to MTBE (99% pure) vapour in inhalation chambers at target concentrations of 0, 1430, 10 700 or 28 600 mg/m^3 (0, 400, 3000 and 8000 ppm, respectively) 6 h per day, 5 days per week (Chun et al., 1992; Bird et al., 1997). The control group was exposed to filtered air. Increased mortality and decreased mean survival time were observed for male rats from all exposure groups. Owing to the high mortality rate, surviving males, six from the mid-dose group and nine from the high-dose group, were killed at weeks 97 and 82, respectively. The numbers of surviving males at the end of the study were 13, 6, 6 and 9 at 0, 1430, 10 700 and 20 600 mg/m^3, respectively. Mean survival times were 632, 617 ($p<0.05$), 587 ($p<0.01$) and 516 ($p<0.01$) days, respectively. Low-dose males and all females were killed during weeks 104 and 105.

Various clinical signs of toxicity (blepharospasm, hypoactivity, ataxia, lack of startle reflex, swollen periocular tissue and salivation) were observed in both sexes at the two highest dose levels. No clinical signs were noticed at the lowest dose level. Significantly ($p<0.01$)

Table 20. Carcinogenicity studies with MTBE

Species	Exposure	Tumour	Reference
Mouse (CD1)	Male:	Liver, adenoma:	Burleigh-Flayer et al. (1992)
	control	11/49	Bird et al. (1997)
	1430 mg/m^3 (400 ppm)	11/50	
	10 710 mg/m^3 (3000 ppm)	9/50	
	28 600 mg/m^3 (8000 ppm)	12/49	
	Male:	Liver, carcinoma:	
	control	2/49	
	1430 mg/m^3 (400 ppm)	4/50	
	10 710 mg/m^3 (3000 ppm)	3/50	
	28 600 mg/m^3 (8000 ppm)	8/49	
	Male:	Liver, adenoma and carcinoma:	
	control	12/49	
	1430 mg/m^3 (400 ppm)	12/50	
	10 710 mg/m^3 (3000 ppm)	12/50	
	28 600 mg/m^3 (8000 ppm)	16/49	
	Female:	Liver, adenoma:	
	control	2/50	
	1430 mg/m^3 (400 ppm)	1/50	
	10 710 mg/m^3 (3000 ppm)	2/50	
	28 600 mg/m^3 (8000 ppm)	10/50 ($p<0.05$)	
	Female:	Liver, carcinoma:	
	control	0/50	
	1430 mg/m^3 (400 ppm)	1/50	
	10 710 mg/m^3 (3000 ppm)	0/50	
	28 600 mg/m^3 (8000 ppm)	1/50	

Table 20 (contd).

Species	Exposure	Tumour	Reference
	Female: control 1430 mg/m^3 (400 ppm) 10 710 mg/m^3 (3000 ppm) 28 600 mg/m^3 (8000 ppm)	Liver, adenoma and carcinoma: 2/50 2/50 2/50 11/50	
Rat (F344)	Male: control 1430 mg/m^3 (400 ppm) 10 710 mg/m^3 (3000 ppm) 28 600 mg/m^3 (8000 ppm)	Killed at: 104 weeks 104 weeks 97 weeks 82 weeks	Chun et al. (1992) Bird et al. (1997)
	Male: control 1430 mg/m^3 (400 ppm) 10 710 mg/m^3 (3000 ppm) 28 600 mg/m^3 (8000 ppm)	Kidney, adenoma: 1/50 0/50 5/50 3/50	
	Male: control 1430 mg/m^3 (400 ppm) 10 710 mg/m^3 (3000 ppm) 28 600 mg/m^3 (8000 ppm)	Kidney, carcinoma: 0/50 0/50 3/50 0/50	
	Male: control 1430 mg/m^3 (400 ppm) 10 710 mg/m^3 (3000 ppm) 28 600 mg/m^3 (8000 ppm)	Kidney, adenoma and carcinoma: 1/50 0/50 8/50 3/50	

Table 20 (contd).

	Male: control 1430 mg/m^3 (400 ppm) 10 710 mg/m^3 (3000 ppm) 28 600 mg/m^3 (8000 ppm)	Testes: 32/50 35/50 41/50 47/50	
	Male: control 1430 mg/m^3 (400 ppm) 10 710 mg/m^3 (3000 ppm) 28 600 mg/m^3 (8000 ppm)	Pituitary tumours, week 104: 6/50 5/50 0/50 0/50	
	Female: control 1430 mg/m^3 (400 ppm) 10 710 mg/m^3 (3000 ppm) 28 600 mg/m^3 (8000 ppm)	Kidney, adenoma: 0/50 0/28 1/39 0/50	
Rat (Sprague-Dawley)	Male: control 250 mg/kg 1000 mg/kg	Testicular adenoma (denominator is total number in group): 2/60 2/60 11/60	Belpoggi et al. (1995)
	Male: control 250 mg/kg 1000 mg/kg	Testicular adenoma (denominator is number of animals surviving at the time this tumour first appeared): 2/26 2/25 11/32 ($p<0.05$)	

Table 20 (contd).

Species	Exposure	Tumour	Reference
	Female:	Lymphomas or leukaemia (denominator is total number in group):	
	control	2/60	
	250 mg/kg	6/60	
	1000 mg/kg	12/60	
	Female:	Lymphomas or leukaemias (denominator is number of animals surviving at the time this tumour first appeared):	
	control	2/58	
	250 mg/kg	6/51	
	1000 mg/kg	12/47 ($p<0.01$)	

reduced body weight and body weight gain were recorded at week 81 for the high-dose rats. For low- and mid-dose male rats, body weight and body weight gain were slightly to significantly ($p<0.05$) increased during the first 70 to 80 weeks. Thereafter, there were no clear dose-related changes. In females, there was a slight, but not exposure-related, decrease at the two lower exposure levels. High-dose male rats also showed a significantly ($p<0.05$) decreased corticosterone level at week 81. A trend toward increases in liver and kidney weights relative to final body weight was recorded for the mid-dose male rats. In female rats, concentration-related increases in liver and kidney weight (absolute and relative to body or brain weight) were observed at the two highest dose levels. There was also a trend toward an increased adrenal gland weight relative to final body weight for high-dose males. However, only the organ weight data from the control and the low-dose group were statistically evaluated due to the different sacrifice periods for the mid- and high-dose groups.

Non-neoplastic effects of treatment included an increased incidence and severity of chronic progressive nephropathy in male rats from all dose groups and in female rats from the mid- and high-dose groups. Treated males were more severely affected than the females, which usually showed only slight changes. Chronic progressive nephropathy was diagnosed as the cause of morbidity or death for 3/37, 16/44, 26/44 and 39/41 male rats and for 0/20, 0/23, 4/27 and 6/25 female rats in the control, low-, mid- and high-dose groups, respectively. The incidences of nephropathy, with interstitial fibrosis, in the control, low-, mid- and high-dose groups were 19/37 (51%), 29/44, (66%), 37/44 (84%) and 40/41 (98%), respectively (significance not specified). Histologically, the chronic progressive nephropathy included an exposure-related increase in severity for glomerulosclerosis, tubular proteinosis, interstitial nephritis and interstitial fibrosis in both male and female rats from the mid- and high-dose groups. The chronic nephropathy was also associated with secondary lesions such as fibrous osteodystrophy, hyperplasia within the parathyroid glands, and mineralization within numerous tissues. An increased incidence of renal tubular cell adenomas and carcinomas was noted in mid- and high-dose male rats. The incidence was 8/50 and 3/50 for the mid- and high-dose groups, respectively, and 1/50 for the control group. The renal tubular cell carcinomas were only noted

in the mid-dose group (3/50). One renal cell adenoma was found in a mid-dose female.

In mid- and high-dose males, there was also a dose-related increase of interstitial cell (Leydig cell) adenomas of the testes. The incidence was 32/50, 35/50, 41/50 and 47/50 (64%, 70%, 82% and 94% for the control, low-, mid- and high-dose groups, respectively. In high-dose males, there was also an exposure-related decrease in the frequency of pituitary adenomas. The incidences were 27/47, 29/48, 27/47 and 2/48 in the control, low-, mid- and high-dose groups of males, respectively. A treatment-related decrease of large granular lymphocyte (LGL) leukaemia was also noted. The incidence of LGL in males was 33/50, 22/50, 20/50 and 3/50 and in females 22/50, 14/50, 15/50 and 16/50 for control, low-, mid- and high-dose rats, respectively. LGL leukaemia, which is age-dependent and generally does not appear until 20 months of age, was the main cause of death in the control and low-dose males. The lymphoid hyperplasia of the submandibular lymph node observed in a 13-week inhalation study with Fischer-344 rats at a dose level of 28 600 mg/m^3 was not observed in the present study using the same strain of rats and the same dose level. No NOEL could be determined for male rats due to a slight increase of nephropathy at the lowest dose level. For female rats, the NOEL for toxicity was 1440 mg/m^3.

A number of points regarding this study can be made:

a) The tumour incidence values were analysed using methods that are not appropriate when there are marked inter-group differences in survival.

b) Testicular adenomas are quite common in untreated aging male F-344 rats (Haseman et al., 1990), with a spontaneous incidence in the range 64–98% for animals contemporaneous with those used here. On this basis, it appears that this tumour type may have been under-represented in the concurrent controls, influencing the slope of the dose-response curve. In the Fischer-344 rats used in this laboratory, the average historical control incidence of Leydig cell tumours was 88% (Bird et al., 1997). Thus, in comparison with historical control data, there was no

increased incidence in this tumour in the dosed groups. However, concurrent control comparisons are always more appropriate, unless it is known that there had been a particular problem with the study, e.g., inappropriate randomisation.

c) Neoplasm incidence decreases were observed for pituitary adenomas in the high-dose males and for large granular lymphocyte leukaemia in males and females at all dose levels. Decreases in the high-dose rats might be related to body weight gain restrictions in this group and to increased mortality rate in males. Alternatively, the concurrent control values for these neoplasms may be particularly high in this study.

An oncogenicity study was also carried out on CD-1 mice exposed to MTBE (99% pure) vapour in inhalation chambers (Burleigh-Flayer et al., 1992; Bird et al., 1997). Groups of 50 male and 50 female mice were exposed to target concentrations of 0, 1430, 10 700 and 28 600 mg/m^3 (0, 400, 3000 and 8000 ppm, respectively) 6 h per day, five days per week for 18 months. The control group was exposed to filtered air. The mortality rates for male mice (including those sacrificed moribund but excluding procedural and accidental deaths) in the control, low-, mid- and high-dose groups were 33%, 22%, 35% and 49%, respectively. The corresponding values for females were 27%, 18%, 23% and 33%, respectively. The authors reported that increased mortality rate (significance not reported) and decreased survival time were observed for male mice from the high-dose group only. This was considered as a probable result of a slightly increased frequency of obstructive uropathy (distended urinary bladder and/or obstruction of the urethra). Clinical signs, i.e. ataxia, blepharospasm, hypoactivity, prostration, and lack of a startle reflex (in the high-dose group prostration also and in the mid-dose group stereotypic behaviour also) were observed in both male and female mice at the two high-dose levels. Ataxia, observed in most male and female mice from the highest dose group throughout the study, was the only clinical finding considered to be exposure related. Body weight and body weight gain were decreased for both male and female mice from the high-dose group. At the end of the study, body weight gain was decreased 15% ($p < 0.01$) for the males and 24% ($p<0.01$) for the females from the high-dose group.

Necropsy showed that the liver was the target organ for toxicity. There was a dose-related increase in liver weight, both absolute and relative to body weight, in both sexes (increase in absolute weight in males significant at all dose levels). A slight (significant), although not concentration-related, increase in kidney weight was noted for male mice from all exposure groups and in female mice from the high-dose group. Decreases, although not statistically significant, in absolute brain and spleen weight were also noted for high-dose male and female mice. In addition, an increase in serum corticosterone levels was observed in both male and female mice from the high-dose group at week 79. The increase was significant ($p<0.05$) only for male mice. A slight decrease in urinary pH and increases in urine gamma globulin were observed for both male and female mice at the high-dose level.

For male mice that were found dead in the high-dose group (7/25), a slightly increased frequency of urinary bladder dilation/ distension was noted at autopsy as compared to controls (3/18). In addition, the incidence of the number of liver masses was increased in the high-dose male mice (13/50 compared to 7/50 for the control group). The only exposure-related lesion in female mice found at necropsy was an increased incidence of liver masses in the high-dose group (9/50) when compared to the controls (0/50). Histopathology showed an exposure-related increase in hepatocellular hypertrophy in high-dose male mice (15/49) when compared to controls (5/49). This lesion also showed an increased, although not statistically significant, incidence in mid-dose male mice (10/50) and in female mice from the high-dose group (9/50 as compared to 4/50 in the control group). Exposure to MTBE did not, however, cause hepatocellular necrosis or degeneration. In high-dose male and female mice, mineralization within the brain was decreased. In addition, there was a dose-related decrease in the incidence of cystic endometrial hyperplasia for female mice.

An increased frequency (not statistically significant) of hepatic adenomas and carcinomas was observed in male mice at the high-dose level (16/49 as compared to 12/49 in the control group). The increase (not statistically significant) was due to a slightly increased frequency of hepatocellular carcinomas in the high-dose group (8/49) when compared to the controls (2/49). The analysis for the combined

incidence of hepatocellular adenomas and carcinomas did not, however, include statistical methods that adjusted for difference in survival between the control and exposure groups. In female mice, there was a significant increase in the incidence of hepatocellular adenomas at the high-dose level (10/50 as compared to 2/50 from the control group). The induced incidences were modest and occurred in the group in which hepatocellular hypertrophy also occurred. There was no exposure-related increase in the incidence of hepatocellular carcinomas in female mice. The NOEL for toxicity in mice exposed to MTBE for 18 months was 1440 mg/m^3.

In an oral exposure study, male and female Sprague-Dawley rats (60 per sex and dose group) were administered 0, 250 or 1000 mg/kg bw MTBE (>99% pure) in 1 ml extra virgin olive oil by gavage four times a week for 104 weeks on a weekly schedule of 2 days dosing, 1 day without dosing, 2 days dosing, followed by 2 days without dosing (Belpoggi et al., 1995). There were no treatment-related differences in mean body weights of treated groups compared to control groups. The animals were kept under observation until natural death. High-dose male rats showed a higher survival than controls at treatment week 80 and thereafter. At week 80, survival was approximately 56% in control and exposed groups; at 112 weeks, it was approximately 10% in controls and the low-dose group, but 35% in the high-dose group. In female rats, a dose-related decrease in survival was observed from treatment-week 16. It was reported that there were no evident behavioural changes; at week 72, survival in the high-dose group was about 65%; at week 120, it was less than 20%; at week 136, it was less than 5%. The authors reported no evident behavioural effects; however, the extent of examination of behavioural effects was not specified. No relevant non-neoplastic changes (including renal) were detected at autopsy and histopathology. No specific data were, however, reported. In male rats, there was a dose-related increase in the incidence of testicular Leydig cell (interstitial cell) tumours (2/60, 2/60 and 11/60), statistically significant at the highest dose ($p<0.05$). In female rats, there was a dose-related increase in lymphomas and leukaemias combined (2/60, 6/60 and 12/60), marginally significant at the low-dose level and highly significant at the high-dose level ($p<0.01$). There also was an increase in dysplastic proliferation of lymphoreticular tissue in female rats at both dose levels, but the

incidence was higher in the low-dose group. Dose-related decreases in mammary fibromas and fibroadenomas, and in pituitary adenomas and tumours of adrenal glands were observed in dosed females. Since these tumours and the testicular interstitial cell tumours are age-dependent, these effects were probably at least partly due to the dose-related early mortality and the prolonged observational period in the surviving animals.

A number of points regarding this study should be made:

a) there is limited description of the results, particularly the histopathological findings;

b) diagnostic criteria are not given for the distinction between Leydig cell tumours and hyperplasia (the latter were not reported at all, which is unusual for old Sprague-Dawley rats showing Leydig cell tumours);

c) diagnostic criteria are not given for the distinction between dysplastic hyperplasia and lymphoma;

d) lymphomas and leukaemias are pooled; specific tumour type and incidences were not reported;

e) historical control data might aid the evaluation of lymphomas and leukaemias, particularly if they are available for these rats within different age ranges;

f) chronic progressive nephropathy was not observed in these Sprague-Dawley rats, although these lesions might be expected, on the basis of data from a number of other studies with this strain of rat.

7.8.1 Initiation-promotion protocol

In a study to investigate if MTBE exhibited hepatic tumour-promoting activity, 12-day-old female B6C3F$_1$ mice were initiated with a single intraperitoneal injection of the mutagen diethylnitrosamine (DEN) or saline and then exposed subsequently to 0 or

28 800 mg/m^3 (8000 ppm) MTBE (>99.95% pure) from 8 weeks of age for 16 or 32 weeks (Moser et al., 1996b). Liver weight was significantly ($p<0.05$) increased at both time points in both saline-treated and DEN-initiated mice after exposure to MTBE, and was associated with mild centrilobular to midzonal hypertrophy in both groups. There was no significant difference in the percentage of microscopic lesions classified as hepatic foci (86%), hepatocellular adenomas (10%), or hepatocellular carcinomas (4%) in DEN/MTBE mice as compared to DEN/control mice. However, the absolute number of microscopic hepatic lesions was 50% less in the DEN/MTBE group than in DEN/control mice. MTBE appeared inactive in this tumour initiation-promotion assay.

7.9 Metabolites of MTBE

Animal carcinogenicity experiments have been conducted with the metabolites *tertiary*-butyl alcohol (TBA) and formaldehyde (FA). TBA administered in drinking-water caused increased incidences of renal tubular adenoma and carcinoma in male Fischer-344 rats and increased severity of chronic progressive nephropathy (Cirvello et al., 1995). In female B6C3F$_1$ mice, TBA produced thyroid follicular cell adenoma and hyperplasia, and, in both male and female mice, inflammation and hyperplasia of the urinary bladder (Cirvello et al., 1995). FA has caused nasal squamous cell carcinoma in both Fischer-344 and Sprague-Dawley rats and in B6C3F$_1$ mice, and also increases of cancers of the nasopharynx, nasal cavity and sinus in humans (Grindstaff et al., 1991).

7.10 Mode of action

7.10.1 Kidney tumours

A number of chemicals cause both protein droplet nephropathy and, with chronic exposure, renal cancer in male rats only (Borghoff et al., 1990). The proposed mechanism by which these chemicals cause renal tumours in male rats is based on their ability to cause protein droplet nephropathy by accumulating α2u-globulin, a male-rat-specific protein of low relative molecular mass. Evidence suggests that chemical binding to α2u-globulin makes the protein more resistant to

hydrolysis, which accounts for its accumulation in the renal lysosomes in the form of protein droplets. The chemically induced accumulation of α2u-globulin is thought to be responsible for cytolethality, which in turn stimulates cell division as the kidney attempts to repair itself. Chronic chemical exposure with repeated cycles of cytolethality and reparative replication is probably the cause of the renal tumours in male rats (Borghoff et al., 1990; Hard et al., 1993). A protein similar to α2u-globulin has not been detected in human kidneys (Borghoff & Lagarde, 1993).

MTBE causes male-rat-specific renal tumours with chronic exposure (Bird et al., 1997). MTBE also causes the accumulation of protein droplets in male but not female rats following exposure ranging from 10 days to 13 weeks (Dodd & Kintigh, 1989; Chun & Kintigh, 1993; Prescott-Mathews et al., 1997). Similar results have been observed with TBA, a metabolite of MTBE (Lindamood et al., 1992).

α2u-Globulin immunoreactivity was present in and confined to protein droplets in the kidneys of male rats exposed to MTBE in these studies (Dodd & Kintigh, 1989; Chun & Kintigh, 1993; Prescott-Mathews et al., 1997). Although a slight increase in α2u-globulin-positive staining was observed in male rats exposed to MTBE, as compared to controls, a linear exposure-related increase was not observed in any of these studies. α2u-Globulin-positive proteinaceous casts at the junction of the proximal tubules and the thin limb of Henle were not observed (Swenberg & Dietrich, 1991). MTBE caused an exposure-dependent mild increase in the renal concentration of α2u-globulin measured in male rats (Prescott-Mathews et al., 1997). Immunohistochemical staining of α2u-globulin is probably not as sensitive as actually quantifying the α2u-globulin levels with a mild increase in this protein. Further analysis of the kidney protein profile from control and MTBE-treated male rats confirmed the accumulation of α2u-globulin with no other protein detected (Prescott-Mathews et al., 1997).

MTBE-induced kidney lesions, characterized by tubular necrosis and protein droplet accumulation, were mild, especially when compared with strong inducers of α2u-globulin nephropathy.

Additionally, granular casts, considered characteristic for α2u-globulin nephropathy, were not observed in all studies. In the case of the 10-day MTBE inhalation exposure, however, there was a concentration-dependent increase in kidney necrosis with minimal sloughing of epithelial cells in male rat kidney following exposure to 10 710 mg/m^3 (3000 ppm) (Prescott-Mathews et al., 1997).

In male and female rats exposed to MTBE vapour for 10 and 28 days, MTBE caused enhanced cell proliferation in male, but not female, rat kidneys (Chun & Kintigh, 1993; Prescott-Mathews et al., 1997). A strong positive correlation was observed between the cell proliferative response and the concentration of α2u-globulin in the kidneys of MTBE-exposed male rats.

With many of the chemicals that cause α2u-globulin nephropathy, either the chemical or a metabolite has been found to bind reversibly to α2u-globulin. *In vitro*, a high uptake of MTBE into male rat kidney homogenate could be predicted using a two-compartment model system when the binding of MTBE to α2u-globulin was described using a dissociation constant of 10^{-4} M (Poet & Borghoff, 1997). This estimated dissociation constant for MTBE binding to α2u-globulin was found to be similar to the dissociation constant previously measured for 1,4-dichlorobenzene, a known inducer of α2u-globulin nephropathy and a chemical identified as bound to α2u-globulin following treatment of male rats with 1,4-dichlorobenzene (Charbonneau et al., 1989). Together these findings indicate that MTBE interacts, although weakly, with α2u-globulin and induces α2u-globulin nephropathy and renal cell proliferation in male, but not female, rats.

MTBE increases the severity of chronic progressive nephropathy in both male and female rats, but does not cause renal necrosis, enhanced cell proliferation or renal cancer in female rats. Chronic progressive nephropathy alone is not associated with increased incidence of renal tumours.

7.10.2 Liver tumours

It has been hypothesized that liver tumours in female mice can be promoted by interfering with the estrogen-mediated suppression of preneoplastic foci. In this regard, both unleaded gasoline and MTBE induce cytochrome P450 activity and estrogen metabolism in mouse hepatocytes, induce a mitogenic response in mouse liver, and decrease uterine and ovarian weight in exposed mice. Additionally, unleaded gasoline promotes DEN-initiated female mouse liver tumours, but this response has not been observed with MTBE (Standeven & Goldsworthy, 1993; Moser et al., 1996b). Therefore, the relevance of this hypothesis to an interpretation of the MTBE-induced mouse liver tumours is currently unclear.

8. EFFECTS ON HUMANS

As explained in chapter 3, two separate fuel programmes in the USA legally require the use of oxygenate in gasoline to address ambient air quality objectives. Although no specific oxygenate is required, MTBE has dominated the USA market place and is used at 15% (by volume) to meet a 2.7% (by weight) oxygen requirement for oxygenated gasoline in the cold-weather season in areas with excessive carbon monoxide levels and at 11% (by volume) to meet a 2.0% (by weight) oxygen requirement for reformulated gasoline sold year-round in areas with excessive ozone levels. In the fall of 1992, shortly after the introduction of oxygenated gasoline containing 15% MTBE in Alaska, consumer complaints were registered about health effects such as headaches, eye irritation and cough in Fairbanks (Beller & Middaugh, 1992) and Anchorage (Chandler & Middaugh, 1992). Subsequently, residents in other places in the USA also reported health complaints associated with the introduction of cold-season oxygenated fuel. Somewhat similar public concerns were raised in Milwaukee, Wisconsin, with the introduction of reformulated gasoline, some of which contained 11% (by volume) MTBE, in January 1995 (Anderson, 1993; Anderson et al., 1995). Health complaints have also been registered by some occupationally exposed individuals, such as tank truck drivers handling bulk MTBE (Gillie, 1993).

These "outbreaks" of health complaints prompted several field and experimental studies as well as other assessments (e.g., HEI, 1996; US Interagency Assessment, 1997) of available data and information generated by these studies. In this section epidemiological studies will be described first, followed by controlled chamber studies of human volunteers. Because non-occupationally as well as occupationally exposed populations were investigated in the epidemiological studies, these studies will be discussed in one section rather than two separate sections devoted to general population and occupational population exposures.

8.1 Population studies

In December 1992, Moolenar et al. (1994) undertook a pilot study in Fairbanks, Alaska, to investigate the possible relationship between

MTBE exposure and health complaints. In Phase I of the study, exposure was evaluated by air sampling and by analysing blood samples for MTBE and TBA in 18 workers heavily exposed to gasoline fumes and exhaust in their workplace (e.g., service station workers, mechanics, meter readers). A questionnaire administered to the workers asked about 15 symptoms: seven that had been most frequently reported to a local telephone hotline the previous month (headache, eye irritation, burning of the nose or throat, cough, nausea or vomiting, dizziness, and a sensation of spaciness or disorientation), and eight other symptoms (fatigue, fever, sweats or chills, diarrhoea, fainting or black-out spells, skin irritation or redness, muscle aches, and difficulty breathing). Phase II of the study was conducted in February 1993, after the oxygenated gasoline programme was suspended, and included 28 (12 of the original) occupationally exposed subjects. Four workers whose post-shift blood MTBE levels were in the top quartile (>9.6 µg/litre) all had one or more of the seven key health complaints, compared with 9 of 14 workers whose levels were in the lower three quartiles. This finding was not statistically significant, but the study may not have had adequate statistical power to detect a relationship, owing to the small sample size. In Phase II, only one worker reported a health complaint (nausea). Exposures to MTBE, as well as complaints of both workers and non-occupationally exposed residents of Fairbanks, declined significantly after the termination of the oxygenated gasoline programme (CDC, 1993), but interpretation of these events is possibly confounded by several factors, including a lack of representative sampling and changes in the cost of gasoline that may have contributed to public attitudes.

Mohr et al. (1994) conducted a cross-sectional cohort study that included 237 garage workers exposed to high and low MTBE concentrations: 115 workers exposed in northern New Jersey during the wintertime oxyfuel programme and 122 workers in southern New Jersey 10 weeks after the phase-out date for the programme. Both groups of workers reported feeling significantly worse at the end of the work day, but there was no difference between the groups across the work shift. Active air sampling and passive sampling devices confirmed the higher exposure levels of the workers in northern New Jersey. No significant differences were found in either the cross-sectional reporting of symptoms or the pre- and post-shift analyses.

A study performed in Stamford, Connecticut, in April 1993 near the end of the oxygenated gasoline season there, investigated exposure to MTBE in oxygenated gasoline and symptom prevalence in occupationally and non-occupationally exposed subjects (White et al., 1995). The study included 37 workers and 14 commuters. The prevalence of symptoms was highest among people who worked in car repair-shops or around traffic. The eight workers with the highest levels of MTBE in blood (>3.8 µg/litre) reported one or more key symptoms (OR = 21.0, 95% CI = 1.8-539.0) such as headache, irritated eyes, burning of the nose and throat, cough, dizziness, spaciousness, disorientation, and nausea. There were no reports of diarrhoea, difficulty in breathing, skin irritation, fever, sweats or chills, or fainting.

In response to health concerns raised by the public following the introduction of the reformulated gasoline (RFG) programme in the Milwaukee, Wisconsin area, the Wisconsin Department of Health initiated a random digit-dial telephone survey designed to assess the prevalence and scope of health complaints (Anderson et al., 1995). A questionnaire was administered to approximately 1500 persons: 527 residents of the Milwaukee, where RFG was sold and numerous complaints about the fuel had been registered; 485 residents of Chicago, where essentially the same fuels were sold but few complaints had been registered; and 501 residents of the remainder of Wisconsin, where RFG had not been required. Overall, there was a significantly higher prevalence rate for "unusual symptoms" in Milwaukee (23%) than in Chicago and the rest of Wisconsin (6% each). The fact that symptom prevalence in the Chicago RFG area was so similar to that in non-RFG areas of Wisconsin suggested that factors other than RFG use contributed to the difference between Milwaukee and the other two areas. Although the prevalence of colds and flu was the same in the three areas, Milwaukee residents were more likely to report unusual symptoms if they had experienced a cold or the flu, smoked cigarettes, or were aware that they had purchased RFG. The authors concluded that many symptoms reported by Milwaukee residents may have actually been due to colds or flu rather than RFG exposure. Also, individuals who reported purchasing RFG were more likely to report symptoms than individuals who said they had not purchased or did not know whether they had purchased RFG, which

suggested that knowledge about RFG may have increased awareness of an individual's health status and resulted in the assumption that any health symptoms experienced were unusual and attributable to gasoline exposure. This study and its conclusions were reviewed by a panel of independent experts who concluded that "The study does not support a conclusion that exposure to RFG is associated with widespread or serious acute adverse health effects." This evaluation of the study was later endorsed by another, independent peer review group (HEI, 1996).

Anderson et al. (1995) followed up on 1280 Milwaukee residents who had initially contacted governmental agencies about their health complaints. These self-identified individuals were interviewed by telephone to determine the types of complaints and risk factors that could be associated with symptoms. Results of the study indicated that the strongest predictors were age, allergies, and colds or flu since November 1994. The purchase of RFG, a surrogate for exposure, did not correlate with self-reported health symptoms.

A cross-sectional study was conducted in Finland to investigate the occurrence of neurophysiological symptoms in tanker drivers exposed to gasoline containing approximately 10% MTBE (Hakkola et al., 1996). A reference group of milk delivery drivers was selected from the same areas. A total of 201 male drivers participated in the study, including 101 tanker drivers and 100 milk delivery drivers. The occurrence of symptoms and Profile on Mood States (POMS) scales showed an association with age, chronic diseases, and the perceived health of the drivers in both the exposed and the unexposed group. Although there were more sensory and motor symptoms in tank drivers, there was no evidence of any statistically significant difference in the occurrence of symptoms between the two groups. Duration of work as a driver, shift schedule and length of the working week had no statistical connection with symptoms and the modified POMS scales.

8.2 Controlled studies

To determine if 1-h exposures to MTBE at 6 mg/m^3 (1.7 ppm) in an inhalation chamber could result in similar symptoms as those reported in the field, Cain et al. (1996) performed a controlled study

in 22 male and 21 female subjects (ages 18 to 34 years). Both objective and subjective indices of behavioural and physiological effects were studied. A control exposure to air and a control exposure to a 17-component mixture of volatile organic compounds (VOCs) (19 mg/m^3) were also included. The selected MTBE concentration and duration were based upon preliminary results from exposure studies in commuters (Lioy et al., 1994). The effects of MTBE exposure on discomfort, symptoms and possible objective correlates of symptoms were investigated by using questionnaires, various ocular and nasal inflammation parameters, and neurobehavioural testing. Repeated blood samples were obtained from a subset of subjects to relate the exposure to the body burden and toxicokinetics of MTBE (see section 6.1.1). The exposure produced a mean peak blood MTBE level of 17 µg/litre. Subjective reactions, such as irritation, fatigue and headache, typically showed greater sensitivity than objective indices. There was a differential effect of gender on rated odour, intensity and pleasantness. Females found odour intensity greater, pleasantness worse, and air quality worse. Ocular measurements indicated a mild tendency for eye irritation during exposure; this was, however, not statistically significant. MTBE caused no objective inflammatory changes in the nasal mucosa. Aside from odour, no significant reactions were found.

In another controlled study, conducted by Prah et al. (1994), 20 male and 20 female volunteer subjects (healthy and non-smokers) were exposed in an inhalation chamber to MTBE at 5 mg/m^3 (1.39 ppm) for 1 h. Symptom questionnaires, cognitive testing, and objective measures of ocular and nasal irritation were obtained before and at the end of the exposure. In addition, the odour threshold of MTBE and some pharmacokinetic data were obtained from two additional subjects, one male and one female (see section 6.1.1). No increase in the reporting of symptoms such as headache, nasal irritation, cough or eye irritation was found, apart from a gender effect in reporting of air quality. Females rated the air quality in the chamber with MTBE exposure slightly poorer when compared to the clean air exposure. There were no changes in objective indicators in either the eye or the nose.

Johanson et al. (1995) and Nihlén et al. (1998b) reported similar results at much higher concentrations. Ten healthy male volunteers

were exposed to MTBE vapour at 18, 90 or 180 mg/m^3 (5, 25 or 50 ppm) for 2-h periods while performing light physical exercise (see also section 6.1.1). All the subjects reported the strong smell of MTBE on entering the chamber but their rating of the smell decreased with time. On the basis of subjective assessment there was no irritation of the ocular, nasal or pharyngeal mucosae. The MTBE exposure induced essentially no effects on eye and mucous membrane irritation.

Riihimaki et al. (1996) assessed a number of subjective (e.g., irritant sensations, mood state) and objective (simple reaction time, postural sway) end-points in 13 male volunteers exposed to 0, 90 or 268 mg/m^3 (0, 25 or 75 ppm) MTBE for 1 or 3 h. The authors concluded that only "mild symptoms, mainly a feeling of heaviness in the head and, to a smaller extent, of mild mucous membrane irritation, were reported". The frequency of symptoms was related to the level of MTBE exposure and reached statistical significance at 268 mg/m^3 (75 ppm) after 3 h of exposure. There was no effect on reaction time or postural sway.

8.3 Subpopulations at special risk

There are no data by which to identify any subpopulations (e.g., the elderly, pregnant women, children or people with allergy or asthma) who might be at special risk to MTBE exposure.

8.4 Special studies

8.4.1 *Organoleptic properties*

For many people, MTBE has a quite distinctive odour. Odour detection thresholds have been reported to average around 0.1 to 0.2 mg/m^3 (0.03–0.05 ppm), with average recognition (identification) thresholds in a range from 0.2 to 0.5 mg/m^3 (0.06–0.13 ppm) for neat MTBE vapour (TRC, 1993; Smith & Duffy, 1995). For gasoline containing 15% (by volume) MTBE in the USA, average odour detection thresholds ranged from approximately 0.3 to 3 mg/m^3 (0.08–0.9 ppm), with recognition thresholds ranging from 0.7 to 2.5 mg/m^3 (0.2–0.7 ppm). Odour thresholds for MTBE-oxygenated gasoline may vary considerably, depending in part on the aromatic and other

constituents of the gasoline and the sensitivity of the individuals who inhale the vapours. The addition of MTBE to gasoline has been found to reduce the detection threshold (i.e. increase "detectability") for gasoline by as much as 80% (HEI, 1996).

8.4.2 Immunological effects

In a study to assess the effects of MTBE on the immune system, interleukin levels were measured in blood plasma of 22 volunteers at several different locations around Fairbanks exposed to auto emissions derived from oxyfuel (Duffy, 1994). The study was performed during a 4-week period in late November and early December 1992. During this period, the mean daily temperature ranged from about -1.5 °C (35 °F) to about -37 °C (-38 °F). Plasma interleukin 1 β (IL-1 β) and interleukin 6 (IL-6) levels were measured at the beginning and at the end of an 8 h work day. The results showed no difference between the morning mean levels (2.50 pg/ml ± 2.4 SD and the evening mean levels (2.53 pg/ml ± 2.6 SD). There were, however, 14 out of 22 individuals who showed slight increases at the end of the work day. IL-1, which was measured in 10 individuals, was below the detection limit.

9. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

9.1 Laboratory experiments

9.1.1 Algae

The effect of MTBE on the growth of the unicellular algae *Selenastrum capricornutum* (Chlorophyta), *Navicula pelliculosa* (Bacillariophyta) and *Synechococcus leopoliensis* (Cyanobacteria), representing three taxonomic groups, was investigated under laboratory conditions (Rousch & Sommerfeld, 1998). The growth of *N. pelliculosa* and *S. leopoliensis* was inhibited at a nominal MTBE concentration of 2400 mg/litre in the growth medium, whereas *S. capricornutum* growth was increased at 600 mg/litre and decreased at 4800 mg/litre. The authors suggested that the differential sensitivity of these representative species implies that MTBE could alter algal community composition in the environment.

9.1.2 Aquatic animal species

The results of aquatic toxicity tests are presented in Table 21.

Experimental data on acute toxicity are available for four species of invertebrates, four species of fish, and one species of amphibian. The experimental data ranged from a 96-h LC_{50} of 553 mg/litre for the crustacean *Chaetogammam marinum* (Adema, 1982), to a 96-h LC_{50} of >10 000 mg/litre for a copepod *Nitocra spinipes* (Tarkpea & Svanberg, 1982).

Acute toxicities were determined by Tarkpea & Svanberg (1982) for MTBE alone, MTBE combined with a base fuel at a concentration of 5%, and the base fuel alone. The acute toxicity tests were conducted on the harpacticoid copepod *Nitocra spinipes* under static conditions for 96 h at 21 °C. The test solutions were not aerated. A 96-h LC_{50} greater than 10 000 mg/litre was reported for MTBE alone. The 96-h LC_{50} values were 242 mg/litre for MTBE in a base fuel and 201 mg/litre for the base fuel alone. The results of the tests show that the acute toxicity of base fuel to aquatic organisms is not increased by the addition of 5% MTBE.

Table 21. Aquatic toxicity testing results for MTBE

Species	Parameter	Temperature (°C)	Concentration (mg/litre)	Reference
Invertebrates				
Ceriodaphnia	LC_{50} (48-h)	18–21 °C	841	THE, 1989
Daphnia magna	LC_{50} (96-h)		>1000	Gupta & Lin, 1995
Copepod (*Nitocra spinipes*)	LC_{50} (96-h)		>10 000	Tarkpea & Svanberg, 1982
Copepod (*Nitocra spinipes*)	LC_{50} (96-h)		>1000	Bengtsson & Tarkpea, 1983
Gammarid (*Chaetogammarus marinus*)	LC_{10} (96-h)	15 °C	553	Adema, 1982
Fish				
Bleak (*Alburnus alburnus*)	LC_{50} (24-h)	10 °C	1700–1800	Tarkpea & Svanberg, 1982
Bleak (*Alburnus alburnus*)	LC_{50} (96-h)		>1000	Bengtsson & Tarkpea, 1983
Fathead minnow (*Pimephales promelas*)	LC_{50} (96-h)	25 °C	706	Veith et al., 1983
Fathead minnow (*Pimephales promelas*)	LC_{50} (96-h)		672	Geiger et al., 1988
Rainbow trout (*Oncorhynchus mykiss*)	LC_{50} (96-h)		1300	Environment Canada, 1993
Rainbow trout (*Oncorhynchus mykiss*)	LC_{50} (96-h)		1483	Environment Canada, 1993

Table 21 (contd).

Species	Parameter	Temperature (°C)	Concentration (mg/litre)	Reference
Amphibians				
European frog tadpole (*Rana temporaria*)	LC_0 (48-h)		≤2000	Paulov, 1987
European frog-tadpole (*Rana temporaria*)	LC_{50} (48-h)		2500	Paulov, 1987
European frog-tadpole (*Rana temporaria*)	LC_{100} (48-h)		≤3000	Paulov, 1987

Tarkpea & Svanberg (1982) also determined the 24-h LC_{50} of MTBE on a shoal fish, the bleak *Alburnus alburnus* in a closed, static system at 10 °C. The LC_{50} was between 1700 and 1800 mg/litre. When the bleaks were introduced into the test media, several sublethal effects were observed, including disturbed balance, surface swimming and overturning. The sublethal effects were short-lived, as several of the individual test subjects had recovered when the test was completed. The environmental significance of these results was not discussed by the authors.

When European frog tadpoles (*Rana temporaria*) were exposed to concentrations of MTBE in water ranging from 100 to 2500 mg/litre, various effects were observed. An increase in body weight of frogs and tadpoles that had undergone metamorphosis was observed at 100 mg/litre, as compared with the controls. At sublethal concentrations (<2500 mg/m^3) in water, accelerated development of the tadpole was observed and metamorphosis occurred two days earlier than in controls (Paulov, 1987). The environmental significance of these results was not discussed by the author.

No data on chronic aquatic toxicity were found in the literature.

Data on the toxicity of MTBE to terrestrial animals, terrestrial plants or soil biota were not found in the literature, other than information from mammalian toxicology studies.

9.2 Field experiments

Data on field experiments on MTBE were not found in the literature.

10. EVALUATION OF HUMAN HEALTH RISKS AND EFFECTS ON THE ENVIRONMENT

10.1 Evaluation of human health risks

10.1.1 Exposure

Total exposure of human populations to MTBE may involve more than one environmental pathway and route of intake. Populations may be exposed to MTBE in air in areas where it is used in gasoline, though available data on environmental levels and human exposure are limited. In several studies, median concentrations of MTBE in ambient air ranged from 0.47 to 14.4 μg/m^3 (0.00013 to 0.004 ppm) where MTBE is used in oxygenated gasoline, and non-detectable to 26.4 μg/m^3 (0.0073 ppm) in urban air of cities where MTBE is used as an octane enhancer. Concentrations near industrial facilities range up to 35.7 mg/m^3 (10 ppm). Median 1- to 2-min exposure levels gathered in the breathing zone of service station attendants and consumers while refuelling were highly variable, ranging from 1.0 to 21.4 mg/m^3 (0.03 to 6 ppm) and occasionally exceeding 35.7 mg/m^3 (10 ppm).

Monitoring data for MTBE are too limited to characterize adequately its occurrence in drinking-water. The intake of MTBE in drinking-water is generally expected to be negligible, although drinking-water may be polluted from point sources such as accidental spills of large amounts of MTBE in gasoline. Exposure could also occur through dermal absorption or inhalation of MTBE vapour from household water used for bathing, cooking and laundering.

Potentially exposed workers include those involved in the production, handling and use of MTBE and MTBE-containing gasoline, including mechanics and service station attendants. Occupational exposure of workers transporting MTBE is highest, with an average short-term median concentration of 140 mg/m^3 (39 ppm). Long-term average median levels for this group of workers were about 2.85 mg/m^3 (0.8 ppm). Median long-term exposure of service station attendants averaged 1.79 mg/m^3 (0.5 ppm). The long-term median value for mechanics was 0.36 mg/m^3 (0.1 ppm).

10.1.2 Human health effects

Consumers in some areas of the USA have complained about acute health symptoms such as headache, eye and nose irritation, cough, nausea, dizziness and disorientation associated with the use of oxygenated fuels such as gasoline containing MTBE. Epidemiological studies of human populations exposed under occupational and non-occupational conditions, as well as experimental studies of human volunteers exposed under controlled conditions, have not been able to identify a basis for these complaints. Results of community studies conducted in Alaska, New Jersey, Connecticut and Wisconsin, USA, have been mixed and provided limited or no evidence of an association between MTBE exposure and the prevalence of health complaints. In addition, independently conducted experimental studies of volunteers exposed in inhalation chambers to MTBE concentrations ranging from 5.0 mg/m^3 (1.4 ppm) in one study to 180 mg/m^3 (50 ppm) for 2 h in another study have shown no evident effects in terms of either subjective reports of symptoms or objective indicators of irritation or other effects. Based on the collective evidence, it appears unlikely that MTBE alone induces adverse acute health effects in the general population under common inhalation exposure conditions. However, the potential effects of mixtures of gasoline and MTBE, as well as the manner in which most people are exposed to MTBE in conjunction with the use of oxygenated fuels, have not been examined experimentally or through prospective epidemiological methods. Moreover, the role of factors such as awareness of MTBE, due in part to its distinctive odour, for example, has not been investigated.

In studies on animals, MTBE is "moderately" acutely toxic, with an oral LD_{50} in rats of approximately 3800 mg/kg bw and LC_{50} value (15 min) of about 141 000 mg/m^3 air in mice. Signs of intoxication include CNS depression, ataxia and laboured respiration. The LD_{50} for dermal toxicity in rabbits is >10 200 mg/kg bw.

MTBE is considered to be a mild skin and eye irritant but does not induce skin sensitization.

Repeated exposure results primarily in increases in organ weights and histopathological effects in the kidney of rats and the liver of mice. Effect levels are compiled in Tables 22 and 23. Concentrations

or doses that induced significant increases in organ weights, for which histopathological effects were observed at higher levels, were considered LOELs. Doses at which histopathological effects were observed were considered LOAELs (Tables 22 and 23).

Lowest reported effect levels for nephrotoxicity following ingestion in subchronic studies were 440 mg/kg bw per day (increases in relative kidney weight and hyaline droplet formation in Sprague-Dawley rats). At 2860 mg/m^3 (800 ppm), in a 90-day inhalation study, there were increases in kidney weight associated at higher concentrations with a mild increase in hyaline droplets in the proximal tubules in Fischer-344 rats. At 1430 mg/m^3 (400 ppm), in inhalation oncogenicity studies, there was an increase in absolute liver weight, which correlated with increased severity of hepatocellular hypertrophy at higher concentrations and an increase in relative kidney weight in male mice; in rats, incidence and severity of chronic progressive nephropathy were increased at this level.

Exposure to MTBE also results in reversible central nervous system effects including sedation, hypoactivity, ataxia and anaesthesia at higher concentrations, and biphasic effects on motor activity at lower concentrations. In a single 6-h inhalation exposure study in rats, dose levels from 2860 mg/m^3 (800 ppm) produced reversible, non-monotonically dose-related changes in motor activity. These effects were transient and not observed in longer-term studies.

Specific adverse effects on reproduction have not been observed in rats at concentrations up to 28 600 mg/m^3 (8000 ppm). MTBE has not induced developmental effects in rats, mice or rabbits at concentrations less than those that were toxic to the mothers. Decreases in uterine weight and increases in estrogen metabolism have been observed at 28 600 mg/m^3.

The weight of evidence indicates that MTBE is not genotoxic. Identified oncogenicity studies include an inhalation study in rats and mice and an oral study (gavage) in rats. In these investigations, MTBE induced testicular (Leydig cell) tumours in male rats (Fischer-344 and Sprague-Dawley), renal tumours in male rats (Fischer-344) liver

Table 22. MTBE levels for non-neoplastic effects following oral exposure

Species	Protocol	Effect Level (mg/kg bw/day)	Basis of Effect Level	Reference
Sprague-Dawley rats	28-day gavage (undiluted)	LOAEL 440 NOAEL 90	males: increase in relative kidney weight; hyaline droplet formation in convoluted tubules	IITRI (1992)
Sprague-Dawley rats	90-day gavage in corn oil	LOEL 900 NOAEL 300	increase in male absolute and relative kidney weight; chronic nephropathy and increase in hyaline droplets in proximal tubular cells at the next higher dose (1200 mg/kg bw/day)	Robinson et al. (1990)
Sprague-Dawley rats	104 weeks gavage in olive oil; maintained until death	NOEL 1000	no effects at any dose	Belpoggi et al. (1995)

Table 23. MTBE levels for non-neoplastic effects following inhalation exposure

Species	Protocol	Effect level	Basis for effect level	Reference
Fischer-344 rats	single exposure	LOEL for reversible neurological effects = 2860 mg/m^3 (800 ppm)	biphasic changes in motor activity in females	Gill (1989); Daughtrey et al. (1997)
Fischer-344 rats	13 week study	LOEL 2860 mg/m^3 (800 ppm)	males: increase in relative weight of liver and kidney;	Dodd & Kintigh (1989); Daughtrey et al. (1997)
		no NOAEL	males: at 28 600 mg/m^3, increase in lymphoid hyperplasia in submandibular lymph nodes; mild increase in hyaline droplets in renal proximal tubules	
Fischer-344 rats	up to 104 weeks	LOAEL 10 700 mg/m^3 (3000 ppm) LOEL 1430 mg/m^3 (400 ppm)	males: increased mortality and decreased survival time at 10 700 mg/m^3; chronic progressive nephropathy was the major cause of death at 10 700 mg/m^3; increased incidence and severity of chronic progressive nephropathy at all doses (significance not specified)	Chun et al. (1992); Bird et al. (1997)
CD1 mice	up to 18 months	LOEL 1430 mg/m^3 (400 ppm)	increase in absolute liver weight in male mice which correlated with increased severity of hepatocellular hypertrophy at higher concentrations; increase in relative kidney weight in males	Chun et al. (1992) Bird et al. (1997)

tumours in female mice (CD-1) and lymphomas and leukaemias (combined) in female (Sprague-Dawley) rats.

All investigations on nephrotoxicity are consistent with the renal tumours observed in Fischer-344 rats being related to α2u-globulin nephropathy. α2u-Globulin nephropathy is considered an effect specific to male rats and, therefore, these tumours are of questionable relevance to humans.

Leydig cell tumours have been induced by MTBE in two strains of rats. This type of tumour has been reported to be induced by non-genotoxic carcinogens that disturb the hormonal balance of testosterone, luteinizing hormone and luteinizing hormone releasing factor in rats. Owing to differences between rats and humans in the regulation of gonadotropins, it is questionable that a similar effect will occur in humans. Although such a mechanism may be relevant, this is not substantiated by experimental evidence, since these hormones were not determined in any of the studies with MTBE.

Liver tumours have been induced by MTBE in female mice and possibly in male mice (the data on male mice were not corrected for increased mortality). The effect was modest and occurred only at 28 600 mg/m^3 (8000 ppm) and in association with hepatocellular hypertrophy (indicating enzyme induction) and altered estrogen metabolism. The relevance of these mouse liver tumours for human risk estimation is considered to be questionable.

In a single oral study in SD rats, the frequency of lymphomas and leukaemias (combined) were increased in the high-dose group. This observation was not supported by any indications of relevant (preneoplastic) effects on the lymphoid system in other studies. Moreover, the description of the study made it difficult to evaluate adequately the results. However, since the effect observed appears to be rather pronounced, it is not justified to neglect this finding, based on presumed experimental deficiencies. For a proper evaluation, additional information is required.

On the basis of these data, MTBE should be considered a rodent carcinogen. MTBE is not genotoxic and the carcinogenic response is

only evident at high levels of exposure that also induce other adverse effects. The available data are inconclusive and prohibit their use for human carcinogenic risk assessment until outstanding complications in their interpretation have been addressed.[a]

10.2 Evaluation of effects on the environment

MTBE emissions and leakages can be widespread in the environment in areas where MTBE is used as an octane improver and oxygenate in oxygenated gasoline.

MTBE is predominately emitted into air; however, it can be released into the water and soil compartments. Ambient concentrations in air are low. There are no terrestrial toxicity data for exposure to MTBE in air; however, this appears not to be of concern to an environmental evaluation since ambient air concentrations are low and its half-life is relatively short.

Owing to its physical and chemical properties, MTBE can persist longer in water and soil than in air. There are very limited data on concentrations in ambient surface water. The biodegradation of MTBE in water and soil is not well understood but is believed to be relatively slow. MTBE in soil can leach into groundwater and persist there, due to its lack of removal. MTBE has not been generally detected in deeper groundwater or in shallow groundwater in agricultural areas. It is more frequently found in shallower groundwater in urban areas where MTBE is most extensively used.

Data available for ecotoxicological assessment refer almost exclusively to MTBE in water. It can be classified as relatively non-toxic for aquatic biota, with a lowest acute effect for several aquatic organisms of more than 100 mg/litre. No long-term aquatic toxicity

[a] MTBE was reviewed by an International Agency for Research on Cancer (IARC) Working Group in October 1998. The conclusions were that there was inadequate evidence for the carcinogenicity in humans of MTBE, limited evidence for its carcinogenicity in experimental animals, and the overall evaluation was that MTBE was not classifiable as to its carcinogenicity for humans (Group 3).

tests at low concentrations have been identified. However, the limited data on concentrations of MTBE in ambient surface water have shown that concentrations range from non-detectable to 30 µg/litre. The maximum concentration is several orders of magnitude below the effect level of the most sensitive organism tested to date. It does not appear that the concentrations of MTBE in ambient water are toxic to aquatic organisms, except during spills when very high levels of MTBE may be found.

There are no data on concentrations of MTBE in soil or on terrestrial toxicity. However, concentrations in this medium are expected to be low except in the case of spills.

11. RECOMMENDATIONS

To provide quantitative guidance on relevant limits of exposure and to estimate risk, it is recommended that additional data be acquired in the following areas:

a) additional information to evaluate the induction of lymphomas/ leukaemias in Sprague-Dawley rats;

b) mechanistic data on the induction of Leydig cell tumours and sex specificity of liver tumours in mice;

c) controlled exposure studies to characterize the dose-response in humans for MTBE and MTBE-containing mixtures;

d) monitoring data for better characterization of human exposure, with particular attention to microenvironments;

e) potentiation studies of MTBE with BTX components of gasoline;

f) monitoring of environmental concentrations of MTBE in soil and biota in areas adjacent to major sources and ambient areas in order to verify theoretical values;

g) long-term toxicity tests in aquatic and possibly terrestrial organisms;

h) field degradation tests to determine how persistent MTBE can be in soil and groundwater under a range of redox conditions.

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RÉSUMÉ

Le méthyltertiobutyléther (MTBE) est actuellement le plus utilisé des éthers que l'on peut employer comme additifs de l'essence. L'éthyltertiobutyléther (ETBE), le tertioamylméthyléther (TAME), le tertioamyléthyléther (TAEE) et le diisopropyléther (DIPE), entre autres, peuvent être ajoutés ou substitués au MTBE afin d'améliorer l'oxygénation et l'indice d'octane, aussi peut-on en trouver à côté du MTBE.

1. Identité, propriétés physiques et chimiques et méthodes d'analyse

Le MTBE est un composé volatil et incolore, à l'odeur terpénique, qui est liquide à la température ambiante. Sa viscosité est faible et son point d'ébullition est de 55,2 °C. Son point de congélation est de -109 °C. Sa densité est de 0,7404 à 20 °C. Sa tension de vapeur est relativement élevée: 33 500 Pa à 25 °C. C'est une substance inflammable qui peut en outre former des mélanges explosifs avec l'air. Il est très soluble dans les autres éthers et dans l'alcool. Miscible à l'essence, il est également soluble dans l'eau (42 000 g/m^3 à 19,8 °C). Son coefficient de partage entre l'octanol et l'eau (log K_{ow}) est de 0,94–1,3. Il est instable en solution acide.

La recherche et le dosage du MTBE se font dans tous types de matrices par chromatographie en phase gazeuse au moyen de détecteurs et de colonnes capillaires adaptés à la matrice en cause. On a également recours à la chromatographie liquide à phases inversées pour l'analyse des échantillons d'essence. On utilise aussi, pour la préparation des échantillons d'air, d'eau et de sédiments ou encore des échantillons biologiques, divers systèmes de purge et de piégeage, la sorption/désorption et des méthodes basées sur l'espace de tête.

2. Sources d'exposition humaine et environnementale

Autant qu'on sache, le MTBE n'existe pas à l'état naturel. Dans l'industrie, on l'obtient par l'action du méthanol sur l'isobutylène en présence d'un catalyseur. Un certain nombre de pays le produisent en quantités croissantes depuis la fin des années 70. Il compte actuellement parmi les 50 produits chimiques dont le volume de production est le plus élevé. En 1996, la capacité de production des Etats-Unis était

de 10,6 millions de tonnes et on estime que la demande de MTBE va encore augmenter. Environ 25% de l'essence vendue aux Etats-Unis est additionnée de MTBE. On l'utilise presque exclusivement pour améliorer l'indice d'octane et accroître la teneur de l'essence en oxygène. On en ajoute à l'essence jusqu'à 17% en volume.

3. Transport, distribution et transformation dans l'environnement

Une fois libéré dans l'air, le MTBE y reste en majeure partie avec seulement de petites quantités qui passent dans le sol et dans l'eau. Le MTBE présent dans l'atmosphère peut passer en partie dans l'eau de pluie, mais la proportion qui s'élimine ainsi reste faible. Dans l'atmosphère, l'action des radicaux hydroxyle entraîne la formation d'un certain nombre de composés et en particulier de formiate de tertiobutyle, photochimiquement stable, et de 2-méthoxy-2-méthylpropanol, qui doit réagir énergiquement avec les radicaux hydroxyles pour donner du CO_2, du formaldéhyde, de l'acétone et de l'eau. Lorsque du MTBE est libéré dans l'eau, il se dissout partiellement, une partie passant dans l'air. Les quantités qui passent dans les biotes et les sédiments sont faibles. Les épreuves classiques indiquent une faible biodégradabilité. On pense que d'une façon générale, la biodégradation est lente dans l'environnement. Lorsque du MTBE est libéré dans le sol, il passe dans l'air par volatilisation, dans les eaux de surface par entraînement et dans les eaux souterraines par lessivage. Le MTBE peut persister dans les eaux souterraines.

4. Concentrations dans l'environnement et exposition humaine

Les données relatives aux concentrations dans l'environnement et à l'exposition humaine sont peu nombreuses.

Dans des études portant sur l'air de certaines villes où les véhicules utilisaient de l'essence oxygénée contenant 15% de MTBE, on a relevé des concentrations ambiantes allant de "non décelable" à 100,9 $\mu g/m^3$ (0,028 ppm), avec plusieurs concentrations médianes allant de 0,47 à 14,4 $\mu g/m^3$ (0,00013 à 0,004 ppm). Dans l'air de quelques villes où le MBTE était utilisé à plus faible teneur pour augmenter l'indice d'octane, la concentration de ce composé allait de non décelable à 26,4 $\mu g/m^3$ (0,0073).

Au niveau du sol ou à proximité de raffineries de pétrole, la concentration allait de 15 à 281 µg/m³. Dans l'air urbain, à proximité d'ateliers où l'on procédait au mélange de cet additif à l'essence, la concentration était de 1508 µg/m³ (0,419 ppm), avec des valeurs extrêmes de 216–35 615 µg/m³ (0,06–9,8 ppm).

Dans les stations service situées dans des zones où l'on utilisait de l'essence oxygénée à 10–15% de MTBE, c'est dans la zone de respiration des consommateurs, au moment des pleins, que la concentration de l'additif était la plus forte (300 à 136 000 µg/m³, soit 0,09 à 38 ppm), les valeurs dépassant toutefois rarement 3600 µg/m³ (10 ppm) et tombant un peu plus bas au niveau des pompes (de non décelable à 5700 µg/m³, soit 1,6 ppm). Les valeurs les plus faibles ont été relevées sur le périmètre de la station (de non décelable à 500 µg/m³, soit 0,14 ppm). Les concentrations relevées dans les stations services dépourvues de système de récupération des vapeurs étaient généralement plus élevées.

A l'intérieur d'une automobile, on a relevé des valeurs de 7 à 60 µg/m³ (0,002 à 0,017 ppm) au cours de navettes et de 20 610 µg/m³ (0,006 à 0,172 ppm) lors des pleins.

D'après des données de surveillance qui se limitent presqu'exclusivement aux Etats-Unis, la présence de MTBE a été décelée dans de la neige, des eaux d'orage, des eaux de surface (ruisseaux, rivières et retenues), des eaux souterraines et dans de l'eau de boisson. Les valeurs relevées dans les eaux d'orage allaient de 0,2 à 8,7 µg/litre avec une valeur médiane inférieure à 1,0 µg/litre. Dans le cas des ruisseaux, rivières et retenues, les concentrations s'étageaient entre 0,2 et 30 µg/litre, les valeurs médianes obtenues dans diverses études allant de 0,24 à 7,75 µg/litre.

La présence de MTBE n'a généralement pas été décelée dans les eaux souterraines profondes ou non des zones agricoles. Lorsqu'on en a trouvé, la concentration était inférieure à 2,0 µg/litre. La présence de MTBE est plus fréquente dans eaux souterraines de faible profondeur des régions urbanisées (dans les premiers 1,5 à 3 m des nappes phréatiques). On trouve alors des concentrations de moins de 0,2 µg/litre à 23 µg/litre, avec une valeur médiane de moins de 0,2 µg/litre.

On trouve rarement du MTBE dans l'eau des réseaux d'adduction qui est pompée dans les nappes souterraines. Sur 51 réseaux contrôlés sauf 3, la concentration était inférieure ou égale à 20 µg/litre. Il est difficile de donner des valeurs caractéristiques pour l'eau d'adduction captée en surface car les données sont insuffisantes. On a trouvé de fortes concentrations de MTBE dans quelques puits privés utilisés comme source d'eau potable (soit >1000 µg/m³). On peut toutefois douter que de l'eau contenant plus de 50 à 100 µg/litre de MTBE soit encore buvable, car le seuil organoleptique du MTBE est bas.

Parmi les travailleurs exposés au MTBE, on peut citer ceux qui produisent, distribuent ou utilisent ce composé ou de l'essence qui en contient, y compris les pompistes et les mécaniciens des stations service.

En ce qui concerne l'exposition de courte durée (<30 min) lors d'opérations habituelles de production ou de stockage de MTBE pur, les chiffres vont de 715 à 43 000 µg/m³ (0,2 à 12 ppm), avec une valeur médiane moyenne de 3400 µg/m³ (0,95 ppm). Pour l'exposition de plus longue durée (30 min à 8 h), les valeurs vont de 360 à 890 000 µg/m³ (0,01 à 250 ppm), avec une valeur médiane d'environ 540 µg/m³ (0,15 ppm). Chez les ouvriers qui mélangent l'additif à l'essence, les valeurs de l'exposition de courte durée vont de non décelable à 360 000 µg/m³ (100 ppm), la médiane se situant à environ 5700 µg/m³ (1,6 ppm). Dans le cas d'une exposition de plus longue durée, les valeurs obtenues vont de non décelable à 257 000 µg/m³ (72 ppm), avec une valeur médiane moyenne d'environ 2000 µg/m³ (0,6 ppm).

C'est lors du transport de MTBE pur ou en mélange avec des carburants, dans des canalisations, sur des péniches, des wagons de chemin de fer ou des camions (MTBE pur seulement) que l'on a enregistré les expositions les plus fortes, avec des valeurs à court terme allant de 3750 mg/m³ (0,001 à 1050 ppm) et une valeur médiane moyenne de 140 mg/m³ (39 ppm). Dans le cas d'expositions à long terme, les valeurs allaient de 0,036 à 2540 mg/m³ (0,01 à 712 ppm), la valeur médiane moyenne se situant à 2,85 mg/m³ (0,8 ppm). Lors de la distribution (c'est-à-dire du chargement de mélanges carburant-MTBE sur des camions et de leur livraison et déchargement dans des stations service), on a relevé des valeurs à court terme allant de non décelable à 225 mg/m³ (63 ppm), les valeurs médianes moyennes se

situant autour de 21 mg/m^3 (6 ppm). Les valeurs à long terme allaient de 0,036 à 22 mg/m^3 (0,01 à 6,2 ppm), avec une valeur médiane moyenne de 1,79 mg/m^3 (0,5 ppm).

L'exposition médiane moyenne à court terme des pompistes de stations service allait, selon certaines mesures, généralement de 1,071 à 21,42 mg/m^3 (0,3 à 6 ppm) et dépassait rarement 35,7 mg/m^3 (10 ppm). Dans le cas de l'exposition médiane à long terme, on a obtenu la valeur de 1,79 mg/m^3 (0,5 ppm). L'exposition médiane des mécaniciens est restée inférieure au seuil de détection dans une étude à court terme; dans le cas de l'exposition à long terme, la valeur était d'environ 360 µg/m^3 (0,1 ppm).

5. Cinétique et métabolisme

Les données toxicocinétiques relatives aux effets du MTBE sur l'Homme proviennent essentiellement d'études contrôlées pratiquées sur des volontaires adultes ou sur une population exposée à de l'essence oxygénée. Après inhalation, le MTBE passe rapidement dans le courant sanguin. Chez des volontaires humains en bonne santé exposés par voie respiratoire, on constate que la cinétique est linéaire jusqu'à la concentration de 268 mg/m^3 (75 ppm). On a procédé au dosage de l'alcool tertiobutylique (en abrégé TBA, un métabolite du MTBE) dans le sang et les urines. Chez des sujets humains exposés à des concentrations de MTBE allant de 5,0 à 178,5 mg/m^3 (1,4 à 50 ppm), la concentration maximale de MTBE et de TBA allait respectivement de 17,2 à 1144 µg/litre et de 7,8 à 925 µg/litre. En utilisant un modèle monocompartimental, on a pu constater qu'intervenaient dans la demi-vie globale du MTBE des constituants à demi-vie brève (36–90 min) et des constituants à demi-vie longue (19 h).

Chez les rongeurs, le MTBE est bien résorbé et réparti après administration *per os* ou exposition par la voie respiratoire. L'absorption est moindre par voie percutanée. A la dose de 400 mg/kg *per os* et de 28 800 mg/m^3 (8000 ppm) par inhalation, la proportion de la dose totale absorbée qui était éliminée dans l'air expiré augmentait à mesure que diminuait la proportion éliminée dans les urines, ce qui est le signe d'une saturation du métabolisme. On n'a pas mis en évidence de TBA dans l'urine des rats exposés. La présence de 2-méthyl-1,2-propanediol et d'acide α-hydroxyisobutyrique dans l'urine indique que le TBA est également métabolisé. Les études *in vitro*

montrent que le MTBE est métabolisé en TBA, formaldéhyde et acétone.

6. Effets sur les animaux de laboratoire et les systèmes d'épreuve *in vitro*

Chez le rat, la dose létale médiane aiguë par voie buccale (DL_{50}) est égale à environ 3 800 mg/kg de poids corporel. La concentration létale médiane aiguë (CL_{50}) pour une exposition de 15 minutes par inhalation se situe aux environs de 141 000 mg/m^3 d'air chez la souris. Parmi les signes d'intoxication on peut citer une dépression du SNC, une ataxie et des difficultés respiratoires. Aux doses non létales, la récupération a été complète. Par voie percutanée, la DL_{50} est >10 200 mg/kg de poids corporel chez le lapin.

On n'a trouvé qu'une seule étude où il soit question d'un effet "modérément" irritant pour la peau, l'irritation consistant en un érythème et un oedème modérés après application sur la peau de lapins. Chez ce même animal, le MTBE s'est également révélé irritant pour la muqueuse oculaire, les effets produits étant bénins et réversibles. Dans la seule étude retrouvée, le MTBE a provoqué une irritation légère à forte des voies respiratoires lors de l'exposition de souris à des doses de 300 à 30 000 mg/m^3. Il n'a pas produit de sensibilisation cutanée chez le cobaye.

L'expérimentation sur des rats et des souris montre que des expositions réitérées conduisent principalement à une augmentation du poids des organes et ont des effets histopathologiques sur le rein (rat) et sur le foie (souris). Une étude d'ingestion de 90 jours a montré que la limite inférieure d'apparition d'effets néphrotoxiques se situe à 440 mg/kg p.c. par jour (augmentation du poids des reins et dégénérescence hyaline chez des rats Sprague-Dawley). En exposant des rats Fischer-344 par inhalation à une concentration de 2880 mg/m^3 (800 ppm) de MTBE, on a obtenu une augmentation du poids rénal accompagnée, lorsqu'on accroissait la concentration, d'une augmentation modérée de la dégénérescence hyaline au niveau des tubules proximaux. Lors d'études d'oncogénicité comportant l'exposition des animaux par inhalation, on a observé à la dose de 1440 mg/m^3 (400 ppm), un accroissement de la fréquence et de la gravité des néphropathies progressives chroniques chez les rats mâles, alors que chez les souris mâles, il y avait à cette même dose augmentation du

poids absolu du foie (corrélée avec une augmentation des hypertrophies hépatocellulaires à plus forte concentration) et du poids relatif des reins.

L'exposition au MTBE provoque également des effets irréversibles sur le système nerveux central (SNC) consistant notamment en sédation, diminution de l'activité, ataxie et anesthésie à forte concentration. Des effets biphasiques s'observent également sur l'activité motrice à plus faible concentration. Lors d'une étude sur des rats comportant une exposition de 6 h par inhalation, on a constaté qu'à la dose de 2880 mg/m^3 (800 ppm), il se produisait, chez les animaux d'un des deux sexes, des modifications réversibles et liées à la dose de l'activité motrice. Ces effets étaient passagers et n'apparaissaient plus guère lors des études à long terme.

On a pu retrouver des études de reproduction portant sur une ou deux générations de rats ainsi que quatre études relatives au développement de rats, de souris et de lapins exposés à du MTBE. Ces études n'ont pas permis de mettre en évidence d'effets spécifiques sur la reproduction des rats à des concentrations allant jusqu'à 28 800 mg/m^3. En outre, aux concentrations inférieures à celles qui se révélaient toxiques pour les mères, le MTBE n'a pas eu non plus d'effets sur le développement de la progéniture. A la dose de 28 800 mg/m^3, on a constaté, chez la souris, une augmentation du poids de l'utérus et un accroissement du métabolisme des estrogènes.

Le MTBE a fait l'objet d'un grand nombre d'épreuves valables de mutagénicité et autres études de génotoxicité. Les résultats obtenus montrent que le composé n'est pas génotoxique, même si un résultat positif a été obtenu dans l'épreuve de mutation portant sur le locus tk des cellules lymphomateuses. Ce résultat s'explique en effet par la métabolisation du MTBE en formaldéhyde.

Pour les études de cancérogénicité, on a exposé par inhalation des rats Fischer-344 et des souris CD-1 ou gavé des rats Sprague-Dawley avec une nourriture contenant du MTBE. Dans aucune des études d'exposition par inhalation on a procédé à une correction statistique pour tenir compte des différences de survie. Dans les trois études, on a constaté une augmentation sensible de l'incidence des tumeurs, localisées, chez les rats mâles Fischer-344, au niveau des tubules rénaux et des cellules de Leydig, chez les rats mâles Sprague-Dawley,

au niveau des cellules de Leydig (lymphomes et leucémies chez les femelles) et chez les souris femelles CD-1, au niveau du foie. Les tumeurs des tubules rénaux et les leucémies/lymphomes n'ont donc pas été observées systématiquement chez le rat lors des différentes études. En outre, les tumeurs rénales sexospécifiques étaient associées à une néphropathie également sexospécifique mettant en jeu l'α2u-globuline, qui a été observée dans plusieurs études de courte durée. L'augmentation des tumeurs des cellules de Leydig a été observée à la dose la plus élevée chez les rats Sprague-Dawley (1000 mg/kg p.c.), mais chez les rats Fischer-344, l'interprétation de cet accroissement est rendu délicate par la très forte incidence tumorale également observée chez les témoins concomitants et les témoins historiques. Les tumeurs hépatiques ont été observées dans les groupes témoins et à la dose de 28 800 mg/m^3 (8000 ppm) dans les groupes exposés avec des incidences respectives de 2/50 et 10/50 chez les femelles et de 12/49 et 16/49 chez les mâles. L'accroissement d'incidence était modeste et s'accompagnait d'une hypertrophie hépatocellulaire.

7. Effets sur l'Homme

Après la mise sur le marché, aux Etats-Unis, de deux types d'essence nécessitant l'utilisation d'additifs d'oxygénation (pas obligatoirement du MTBE), on a constaté que les usagers se plaignaient de symptômes aigus tels que maux de tête, irritation des yeux et du nez, toux, nausées, vertiges et désorientation. Les études épidémiologiques effectuées sur des populations humaines en milieu professionnel ou non, de même que les études expérimentales sur volontaires humains exposés dans des conditions contrôlées, n'ont pas permis de découvrir si ces plaintes étaient fondées. Des études intracommunautaires menées en Alaska, au New Jersey, dans le Connecticut et dans le Wisconsin ont, avec des résultats divers il est vrai, montré qu'il n'y avait guère de relation entre l'exposition au MTBE et les symptômes dont la population se plaignait.

Des volontaires adultes ont été placés, dans le cadre d'études expérimentales contrôlées, dans des chambres d'inhalation où on leur a fait respirer du MTBE à des concentrations allant de 5,0 mg/m^3 (1,4 ppm) à 270 mg/m^3 (75 ppm). Aucun effet patent n'a été relevé, qu'il s'agisse de la relation subjective de symptômes ou d'indicateurs objectifs tels qu'une irritation ou d'autres signes, à des concentrations allant jusqu'à 180 mg/m^3 (50 ppm) et pendant une durée pouvant

atteindre 2 h. A en juger d'après ces résultats, il est peu probable que le MTBE puisse à lui seul exercer des effets toxiques aigus sur la population générale dans les conditions habituelles d'exposition par la voie respiratoire. Il est cependant à noter que les effets potentiels d'essences additionnées de MTBE, dans les conditions où la plupart des gens sont exposés à cet additif lorsqu'ils utilisent des carburants oxygénés, n'ont été étudiés ni expérimentalement, ni par le biais de méthodes épidémiologiques prospectives. Par ailleurs, le rôle de facteurs tels que la perception de la présence de MTBE, explicable en partie par l'odeur particulière de ce composé, n'a pas été étudié non plus.

8. Effets sur les autres êtres vivants au laboratoire et dans leur milieu naturel

Expérimentalement, la toxicité aiguë (exprimée par la CL_{50}) du MTBE pour les poissons, les amphibiens et les crustacés se révèle supérieure à 100 mg/litre. On ne possède pas de données sur la toxicité chronique ou subléthale de ce composé pour les organismes aquatiques, ni sur sa toxicité pour les organismes terrestres.

9. Evaluation des risques pour la santé humaine et des effets sur l'environnement

A en juger par les données collectives, il semble peu probable que le MTBE puisse à lui seul et dans les conditions usuelles d'exposition, provoquer des effets toxiques aigus dans la population générale.

D'après les études effectuées sur l'animal, le MTBE possède une toxicité aiguë "modérée" et il provoque une légère irritation cutanée et oculaire, mais pas de sensibilisation. Des expositions répétées entraînent des effets essentiellement localisés au rein chez le rat et au foie chez la souris, la dose nocive la plus faible étant de 440 mg/kg p.c. par jour chez le rat après ingestion et de 1440 mg/m^3 (400 ppm) après inhalation. Aux concentrations inférieures au seuil de toxicité parentale, le MTBE n'a pas eu d'effets nocifs sur la reproduction ou le développement.

Le MTBE n'est pas génotoxique mais il peut provoquer la formation de tumeurs chez les rongeurs, surtout aux concentrations suffisamment élevées pour avoir d'autres effets toxiques. On considère

actuellement que ces données ne sont pas suffisantes pour que l'on puisse en tirer une évaluation du risque cancérogène chez l'Homme. Le Groupe spécial a conclu que, pour être en mesure de donner des indications quantitatives concernant les limites d'exposition et d'évaluer le risque, il fallait obtenir des données supplémentaires sur un certain nombre de points.

Il ne semble pas que le MTBE, aux concentrations auxquelles il se trouve dans l'eau, puisse être toxique pour les organismes aquatiques, sauf en cas de déversement. On ne possède pas de données sur la toxicité du MTBE pour les organismes terrestres mais il n'y a vraisemblablement pas lieu de s'alarmer, étant donné que sa concentration est faible dans l'air ambiant et que sa demi-vie est relativement brève.

RESUMEN

El éter metil-*terciario*-butílico (MTBE) es uno de los distintos éteres que pueden utilizarse como aditivos de combustibles y en la actualidad es con gran diferencia el más usado. El éter etil-*terciario*-butílico (ETBE), el éter *terciario*-amil-metílico (TAME), el éter *terciario*-amil-etílico (TAEE) y el éter diisopropílico (DIPE), entre otros, pueden ser suplementos del MTBE o sustituirlo para fines de oxigenación o mejora de los octanos y, en consecuencia, pueden hallarse en asociación con el MTBE.

1. Identidad, propiedades físicas y químicas y métodos analíticos

El MTBE es un líquido volátil e incoloro a la temperatura ambiente, de olor parecido al terpeno. Su viscosidad es baja y tiene un punto de ebullición de 55,2 °C. El punto de congelación es de -109 °C. La densidad es de 0,7404 a 20 °C. La presión de vapor es relativamente alta: 33 500 Pa a 25 °C. El MTBE es inflamable y puede formar mezclas explosivas con el aire. Es muy soluble en otros éteres y alcohol. Se mezcla con la gasolina y es soluble en agua (42 000 g/m^3 a 19,8 °C). El coeficiente de partición log *n*-octanol/agua es de 0,94–1,3. Es inestable en solución ácida.

El MTBE se analiza en todas las matrices en general por cromatografía de gases, utilizando una gama de columnas capilares y sistemas detectores que son apropiados para la matriz específica. También se ha utilizado la cromatografía inversa en fase líquida para el análisis de las muestras de gasolina. Se han empleado sistemas de sorción-desorción, incluidos sistemas de purga y captación, así como procedimientos de recámara, a fin de preparar muestras de aire, agua, sedimento y biológicas para el análisis.

2. Fuentes de exposición humana y ambiental

No se conoce la presencia natural de MTBE en el medio ambiente. En la industria deriva de la reacción catalítica del metanol y el isobutileno, y en varios países se ha producido en volúmenes crecientes desde los últimos años setenta. El MTBE figura actualmente

entre los 50 productos químicos de mayor producción en volumen. En 1996, la capacidad estadounidense de producción fue aproximadamente de 10,6 millones de toneladas, previéndose un constante aumento del uso de MTBE. El 25% aproximadamente de la gasolina en los EE.UU está mezclada con MTBE. El MTBE se utiliza casi exclusivamente para el refuerzo de los octanos y para aumentar el contenido de la gasolina en oxígeno. El MTBE se ha añadido a la gasolina en concentraciones de hasta el 17% en volumen.

3. Transporte, distribución y transformación en el medio ambiente

Tras su eliminación en el aire, el MTBE permanecerá en gran parte en este medio, penetrando cantidades menores en el suelo y el agua. En la atmósfera, el MTBE puede ser arrastrado por la lluvia. Sin embargo, sólo una pequeña cantidad es eliminada de la atmósfera de este modo. La transformación atmosférica por radicales hidroxilos produce varios productos, entre los que figuran el formato *terciario*-butílico (TBF) estable y el 2-metoxi-2-metilpropanol, que se supone que son muy reactivos con los radicales hidroxilos, dando CO_2, formaldehido, acetona y agua. Cuando el MTBE pasa al agua se disuelve una cantidad significativa, con cierta proporción en el aire. La proporción que pasa a los biota y el sedimento es escasa. La biodegradabilidad en ensayos convencionales es limitada. Se cree que por lo general es lenta en el medio ambiente. Cuando el MTBE pasa al suelo, es transportado al aire por volatilización, al agua superficial por escurrimiento y al agua subterránea como resultado de la lixiviación. El MTBE puede persistir en el agua subterránea.

4. Niveles medioambientales y exposición humana

Se dispone de escasos datos sobre los niveles medioambientales y la exposición humana.

En los estudios sobre el MTBE en el aire de algunas ciudades que utilizan gasolina oxigenada con MTBE al 15%, las concentraciones ambientales iban del nivel indetectable a 100,9 $\mu g/m^3$ (0,028 ppm), con varias concentraciones medianas de 0,47 a 14,4 $\mu g/m^3$ (0,00013 a 0,004 ppm). Las concentraciones de MTBE en el aire de algunas

ciudades en donde se utiliza MTBE como reforzador de octanos en concentraciones inferiores van del nivel no detectable a 26,4 μg/m³ (0,0073 ppm).

Las concentraciones a nivel del suelo o cerca de las refinerías eran de 15 a 281 μg/m³. Los niveles medianos en el aire urbano cerca de instalaciones de mezclado eran de 1508 μg/m³ (0,419 ppm), con gamas de 216–35 615 μg/m³ (0,06 a 9,8 ppm).

En las estaciones de servicio situadas en zonas en donde la gasolina oxigenada contiene el 10–15% de MTBE, las concentraciones alcanzaban el nivel máximo en la zona de respiración durante el llenado de los depósitos por los consumidores (gama de 300 a 136 000 μg/m³ (0,09 a 38 ppm)), con niveles que rara vez pasaban de 3600 μg/m³ (10 ppm), siendo ligeramente inferiores en la zona de bombas (indetectables a 5700 μg/m³ (1,6 ppm)) y mínimos en el perímetro de la estación (indetectables a 550 μg/m³ (0,14 ppm)). En general las concentraciones eran superiores en las estaciones de servicio sin sistemas de recuperación de vapores.

En la cabina del automóvil, las concentraciones eran de 7 a 60 μg/m³ (0,002 a 0,017 ppm) durante la conducción y de 20 a 610 μg/m³ (0,006 a 0,172 ppm) al llenar el depósito.

Basándose en operaciones limitadas de vigilancia realizadas casi exclusivamente en los EE.UU., se ha detectado el MTBE en la nieve, el agua de tormenta, las aguas superficiales (riachuelos, ríos y embalses), las aguas subterráneas y el agua de beber. Las concentraciones de MTBE detectadas en el agua de tormenta iban de 0,02 a 8,7 μg/litro, con un valor mediano de menos de 1,0 μg/litro. En los riachuelos, ríos y embalses, la gama de detección era de 0,2 a 30 μg/litro y la gama de valores medianos en varios estudios era de 0,24 a 7,75 μg/litro.

En general no se ha detectado el MTBE en las aguas subterráneas profundas o cercanas a la superficie en zonas agrícolas. Cuando se ha detectado, la concentración era inferior a 2,0 μg/litro. El MTBE se halla con más frecuencia en las aguas subterráneas cercanas a la superficie (1,6 a 3,2 metros de estos acuíferos) de las zonas urbanas.

En este entorno, las concentraciones van de menos de 0,2 µg/litro a 2 mg/litro, con un valor mediano inferior a 0,2 µg/litro.

El MTBE se halla poco frecuentemente en sistemas de abastecimiento público de agua procedente de capas freáticas. Entre 51 sistemas estudiados, en 48 la concentración era de ≤20 µg/litro. Son insuficientes los datos disponibles para caracterizar la concentración de MTBE en los sistemas de abastecimiento público de agua procedentes de aguas superficiales. El MTBE se ha hallado en concentraciones altas (esto es, >1000 µg/litro) en algunos pozos privados utilizados para obtener agua de beber. Sin embargo, es dudoso que las personas puedan consumir agua con concentraciones de MTBE superiores a unos 50–100 µg/litro debido al bajo umbral de su gusto y olor.

Entre los trabajadores con posible exposición al MTBE figuran los ocupados en la producción, distribución y uso de MTBE y de gasolina con MTBE, que incluye el personal de estaciones de servicio y los mecánicos.

La exposición a corto plazo (<30 min) en operaciones corrientes de fabricación y mantenimiento de MTBE puro iba de 715 a 43 000 µg/m^3 (0,2 a 12 ppm), siendo el promedio de los valores medianos de 3400 µg/m^3 aproximadamente (0,95 ppm). La exposición a largo plazo (30 min a 8 h) era de 360 a 890 000 µg/m^3 (0,01 ppm a 250 ppm), con valores medianos de aproximadamente 540 µg/m^3 (0,15 ppm). En el caso de los trabajadores de operaciones de mezclado, los valores a corto plazo oscilaban entre niveles indetectables y 360 000 µg/m^3 (100 ppm), siendo el promedio de los valores medianos de 5700 µg/m^3 aproximadamente (1,6 ppm). Los valores a largo plazo comprendían desde niveles indetectables hasta 257 000 µg/m^3 (72 ppm), siendo el promedio de los valores medianos de 2000 µg/m^3 aproximadamente (0,6 ppm).

La exposición alcanzó el nivel máximo durante el transporte de MTBE puro y de mezclas de combustible en oleoductos, barcazas, vagones de ferrocarril y camiones (sólo MTBE puro), variando los valores a corto plazo entre 4 y 3750 mg/m^3 (0,001 a 1050 ppm), con un promedio de los valores medianos de 140 mg/m^3 (39 ppm). Los

valores a largo plazo fueron de 0,036 a 2540 mg/m^3 (0,01 a 712 ppm), con un promedio de los valores medianos de 2,85 mg/m^3 (0,8 ppm). En las operaciones de distribución (esto es, carga de mezclas de combustible y MTBE en camiones y entrega y descarga en las estaciones de servicio), los valores a corto plazo oscilaron entre niveles indetectables y 225 mg/m^3 (63 ppm), siendo el promedio de los valores medianos de 21 mg/m^3 aproximadamente (6 ppm). Los valores a largo plazo fueron de 0,036 a 22 mg/m^3 (0,01 a 6,2 ppm), siendo el promedio de los valores medianos de 1,79 mg/m^3 (0,5 ppm).

Los valores medianos de la exposición a corto plazo de operarios de estaciones de servicio fueron en general de 1,071 a 21,42 mg/m^3 (0,3 a 6 ppm), excediendo rara vez de 35,7 mg/m^3 (10 ppm). Los valores medianos de la exposición a largo plazo en operarios de estaciones de servicio presentaron un promedio de 1,79 mg/m^3 (0,5 ppm). Los valores medianos de la exposición de mecánicos estaban por debajo de los niveles de detección en un estudio a corto plazo; el promedio de los valores medianos para la exposición a largo plazo fue aproximadamente de 360 µg/m^3 (0,1 ppm).

5. Cinética y metabolismo

Los datos toxicocinéticos sobre el MTBE en personas proceden principalmente de estudios controlados en voluntarios adultos sanos y en una población expuesta a la gasolina oxigenada. El MTBE pasa rápidamente a la circulación después de la exposición por inhalación. En voluntarios sanos expuestos a la inhalación, la cinética del MTBE era lineal hasta concentraciones de 268 mg/m^3 (75 ppm). Se midió en la sangre y orina de personas expuestas el alcohol *terciario*-butílico, metabolito del MTBE. Las concentraciones sanguíneas máximas del MTBE y el alcohol *terciario*-butílico fueron de 17,2 a 1144 µg/m^3 y de 7,8 a 925 µg/m^3, respectivamente, en personas expuestas a 5,0 a 178,5 mg/m^3 (1,4 a 50 ppm) de MTBE. Basándose en un modelo de monocompartimiento se identificaron componentes rápidos (36–90 min) y lentos (19 h) de la semivida del MTBE.

En los roedores, el MTBE se absorbe y distribuye bien después de la administración oral y la exposición por inhalación, con menor absorción cutánea. En la administración oral de 400 mg/kg y en la

inhalación de 28 800 mg/m^3 (8000 ppm) aumentó el porcentaje de la dosis absorbida total eliminado en el aire espirado, con un descenso correspondiente del porcentaje eliminado por la orina, indicando la saturación metabólica. No se identificó la presencia de alcohol *terciario*-butílico (TBA) en la orina de ratas expuestas. Hubo indicios de un metabolismo adicional del TBA, basados en la identificación de 2-metil-1,2-propanodiol y de ácido α-hidroxiisobutírico eliminado por la orina. Los estudios *in vitro* prueban que el MTBE se metaboliza hasta TBA, formaldehido y acetona.

6. Efectos en los animales de laboratorio y en los sistemas *in vitro*

En las ratas, la dosis letal oral mediana aguda (DL_{50}) es aproximadamente de 3800 mg/kg de peso corporal. La concentración letal mediana aguda (CL_{50}) para una exposición por inhalación de 15 minutos es de aproximadamente 141 000 mg/m^3 de aire en ratones. Entre los signos de intoxicación figuran la depresión del SNC, la ataxia y la respiración laboriosa. Si la dosis no es letal, la recuperación es completa. La DL_{50} para la toxicidad cutánea en conejos es de >10 200 mg/kg de peso corporal.

En un solo estudio identificado, el MTBE resultó "moderadamente" irritante para la piel, produciendo eritema moderado y edema después de la aplicación cutánea en conejos. También resultó irritante para los ojos de los conejos, produciendo lesiones leves y reversibles. En el único estudio identificado, el MTBE produjo irritación respiratoria ligera a intensa después de la exposición de ratones a 300 y 30 000 mg/m^3, respectivamente. No causó sensibilización cutánea en estudios en cobayos.

La exposición repetida produce fundamentalmente aumentos del peso de los órganos y lesiones histopatológicas en el riñón de ratas y en el hígado de ratones. Los niveles de mínimo efecto señalado de nefrotoxicidad tras la ingestión en estudios de 90 días fueron de 400 mg/kg de peso corporal por día (aumentos del peso renal relativo y formación de gotas hialinas en ratas Sprague-Dawley). En la exposición por inhalación a 2880 mg/m^3 (800 ppm) se produjeron aumentos del peso del riñón asociados a las concentraciones más altas,

con moderado aumento de las gotas hialinas en los túbulos proximales en ratas Fischer-344. En estudios de oncogenicidad por inhalación en dosis de 1440 mg/m^3 (400 ppm), la incidencia y la gravedad de la nefropatía progresiva crónica aumentó en ratas machos; en esta concentración, en ratones machos se observó un aumento del peso absoluto del hígado (que guardaba correlación con el aumento de la hipertrofia hepatocelular en concentraciones superiores) y un aumento del peso renal relativo.

La exposición al MTBE también produjo lesiones reversibles del sistema nervioso central (SNC), incluidas sedación, hipoactividad, ataxia y anestesia en concentraciones superiores y efectos bifásicos sobre la actividad motriz en concentraciones inferiores. En un estudio de una sola exposición de 6 horas en ratas, las concentraciones de 2880 mg/m^3 (800 ppm) produjeron cambios reversibles de la actividad motriz relacionados con la dosis en sexos separados. Esos efectos fueron transitorios y no se pusieron de manifiesto en estudios a largo plazo.

Se han efectuado estudios reproductivos por inhalación de una y dos generaciones y estudios de cuatro generaciones en ratas, ratones y conejos. En esos estudios no se hallaron efectos reproductivos específicos en ratas en concentraciones de hasta 28 800 mg/m^3. El MTBE no ha producido efectos en el desarrollo en concentraciones inferiores a las que resultaron tóxicas en las madres. Se han observado disminuciones del peso del útero y aumentos del metabolismo estrogénico en ratonas con dosis de 28 000 mg/m^3.

El MTBE ha sido sometido a pruebas apropiadas en una amplia gama de ensayos de mutagenicidad y de genotoxicidad. Los resultados muestran que el MTBE no es genotóxico, aunque resultó positiva una prueba de mutación del locus tk en células linfomatosas de ratón debido al paso metabólico de MTBE a formaldehído.

Se han realizado estudios de carcinogenicidad que comprendieron la exposición por inhalación de ratas Fischer-344 y de ratones CD-1 y el cebado de ratas Sprague-Dawley. En ninguno de los dos estudios de inhalación se utilizaron métodos de análisis estadístico que efectuaran el reajuste de las diferencias de supervivencia. En los tres

estudios se produjeron aumentos significativos de la incidencia de tumores, esto es, tumores de células tubulares renales y tumores de células de Leydig en ratas Fischer-344 machos, tumores de células de Leydig en ratas Sprague-Dawley machos y linfomas-leucemias (combinadas) en ratas hembras de la misma especie, y tumores de células hepáticas en ratones CD-1 hembras. Así pues, no se observaron constantemente tumores de células tubulares renales ni leucemias-linfomas en los distintos estudios en ratas. Además, los tumores renales específicos del sexo se asociaron a la nefropatía de la α2u-globulina específica del sexo, observada en varios estudios de breve duración. Se observaron aumentos de los tumores de células de Leydig con la dosis más alta (1000 mg/kg de peso corporal) en la ratas Sprague-Dawley, pero la interpretación de los aumentos registrados en las ratas Fischer-344 resultó compleja por las incidencias muy altas concurrentes y de los testigos históricos. En los ratones, las incidencias de los tumores hepáticos fueron en los testigos y en los grupos expuestos a 28 800 mg/m^3 (8000 ppm), respectivamente, de 2/50 y 10/50 en las hembras y de 12/49 y 16/49 en los machos. Los aumentos fueron moderados y acompañados de hipertrofia hepatocelular.

7. Efectos en el ser humano

Tras la introducción de dos programas separados relativos a los combustibles en los EE.UU., que requieren el empleo de productos de oxigenación de la gasolina (no necesariamente MTBE), los consumidores de algunas zonas se han quejado de trastornos agudos de la salud, como dolor de cabeza, irritación de los ojos y la nariz, tos, náuseas, mareos y desorientación. Los estudios epidemiológicos de poblaciones humanas expuestas en condiciones profesionales o no profesionales, así como los estudios experimentales de voluntarios expuestos en condiciones controladas, no han podido identificar la base de esos trastornos. Aunque los resultados son variados, los estudios comunitarios efectuados en Alaska, New Jersey, Connecticut y Wisconsin (EE.UU.) no han proporcionado indicios, o éstos han sido limitados, de la asociación entre la exposición al MTBE y la prevalencia de trastornos de la salud.

En estudios experimentales controlados en voluntarios humanos expuestos en cámaras de inhalación al MTBE en concentraciones de

5,0 mg/m^3 (1,4 ppm) a 270 mg/m ^{3}(75 ppm) no hubo efectos manifiestos en términos de presencia subjetiva de síntomas o de indicadores objetivos de irritación u otros efectos en concentraciones de hasta 180 mg/m^3 (50 ppm) durante dos horas. Partiendo de esos datos parece improbable que el MTBE por sí solo produzca efectos agudos adversos en la salud en la población general en las condiciones corrientes de exposición por inhalación. Sin embargo, los posibles efectos de las mezclas de gasolina y MTBE y el modo de exposición de la mayor parte de las personas al MTBE en asociación con el empleo de combustibles oxigenados, no se han examinado experimentalmente ni por métodos epidemiológicos prospectivos. Por otra parte, no se ha investigado, por ejemplo, la función de factores tales como la percepción del MTBE, debida en parte a su olor distintivo.

8. Efectos en otros organismos en el laboratorio y sobre el terreno

La toxicidad aguda experimental (CL_{50}) del MTBE en los peces, los anfibios y los crustáceos es >100 mg/litro. No existen datos sobre la toxicidad crónica o subletal para las especies acuáticas ni la toxicidad para los organismos terrestres.

9. Evaluación de los riesgos para la salud humana y efectos en el medio ambiente

Basándose en datos de observación colectiva, parece improbable que el MTBE por sí solo induzca efectos agudos adversos en la salud de la población general en las condiciones corrientes de exposición.

En estudios en animales, el MTBE es "moderadamente" tóxico en forma aguda y produce irritación cutánea y ocular moderada, pero no sensibilización. La exposición repetida afecta fundamentalmente al riñón de ratas y al hígado de ratones, observándose los efectos adversos mínimos con concentraciones de 440 mg/kg de peso corporal por día en ratas después de la ingestión y de 1400 mg/m^3 (400 ppm) después de la inhalación. El MTBE no ha inducido efectos adversos en la reproducción o el desarrollo en concentraciones inferiores a las que eran tóxicas para los padres.

El MTBE no es genotóxico, pero ha producido tumores en roedores, principalmente con concentraciones altas, que también inducen otros efectos adversos. Esos datos se consideran en la actualidad insuficientes para la evaluación del riesgo carcinogénico en seres humanos. El Grupo Especial llegó a la conclusión de que para proporcionar orientación cuantitativa sobre los límites pertinentes de exposición y para estimar el riesgo se necesita adquirir datos adicionales en distintos sectores.

No parece que las concentraciones de MTBE en el agua ambiental sean tóxicas para los organismos acuáticos, excepto en caso de escapes. Aunque no hay datos sobre la toxicidad terrestre del MTBE, parece que no es preocupante ya que las concentraciones en el aire ambiental son bajas y la semivida del MTBE es relativamente breve.

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