European Chemicals Bureau

Institute for Health and Consumer Protection

European Chemicals Bureau

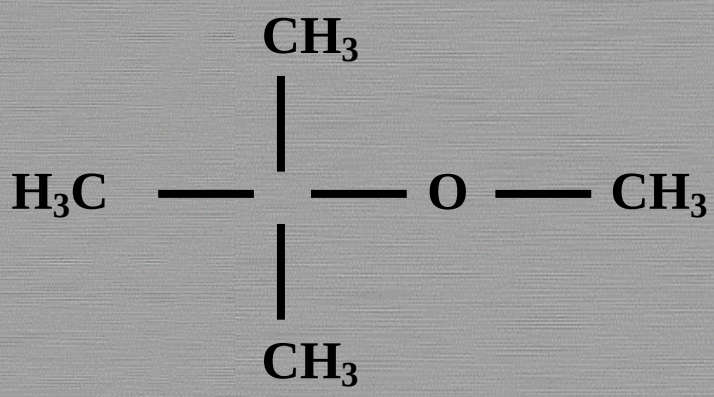
Existing Substances

European Union Risk Assessment Report

CAS No: 1634-04-4

EINECS No: 216-653-1

tert-butyl methyl ether



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RISK ASSESSMENT

Cataloguing data can be found at the end of this publication

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RISK ASSESSMENT

Final Report, 2002

Finland

The rapporteur for the risk assessment report on MTBE is the Finnish Environment Institute, in co-operation with the National Product Control Agency for Welfare and Health.

The scientific work on this report has been prepared by the Finnish Environment Institute, the National Product Control Agency for Welfare and Health and the Finnish Institute of Occupational Health.

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Date of Last Literature Search :	**2001**
Review of report by MS Technical Experts finalised:	**2001**
Final report:	**2002**

Foreword

We are pleased to present this Risk Assessment Report which is the result of in-depth work carried out by experts in one Member State, working in co-operation with their counterparts in the other Member States, the Commission Services, Industry and public interest groups.

The Risk Assessment was carried out in accordance with Council Regulation (EEC) 793/93[1] on the evaluation and control of the risks of "existing" substances. "Existing" substances are chemical substances in use within the European Community before September 1981 and listed in the European Inventory of Existing Commercial Chemical Substances. Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of these substances if they are produced or imported into the Community in volumes above 10 tonnes per year.

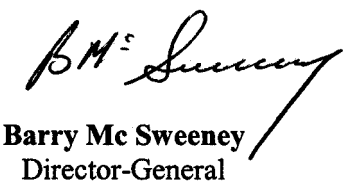
There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each substance on a priority list, a Member State volunteers to act as "Rapporteur", undertaking the in-depth Risk Assessment and recommending a strategy to limit the risks of exposure to the substance, if necessary.

The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94[2], which is supported by a technical guidance document[3]. Normally, the "Rapporteur" and individual companies producing, importing and/or using the chemicals work closely together to develop a draft Risk Assessment Report, which is then presented at a Meeting of Member State technical experts for endorsement. The Risk Assessment Report is then peer-reviewed by the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) which gives its opinion to the European Commission on the quality of the risk assessment.

If a Risk Assessment Report concludes that measures to reduce the risks of exposure to the substances are needed, beyond any measures which may already be in place, the next step in the process is for the "Rapporteur" to develop a proposal for a strategy to limit those risks.

The Risk Assessment Report is also presented to the Organisation for Economic Co-operation and Development as a contribution to the Chapter 19, Agenda 21 goals for evaluating chemicals, agreed at the United Nations Conference on Environment and Development, held in Rio de Janeiro in 1992.

This Risk Assessment improves our knowledge about the risks to human health and the environment from exposure to chemicals. We hope you will agree that the results of this in-depth study and intensive co-operation will make a worthwhile contribution to the Community objective of reducing the overall risks from exposure to chemicals.



Barry Mc Sweeney
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[1] O.J. No L 084, 05/04/199 p.0001 – 0075

[2] O.J. No L 161, 29/06/1994 p. 0003 – 0011

[3] Technical Guidance Document, Part I – V, ISBN 92-827-801 [1234]

0 OVERALL RESULTS OF THE RISK ASSESSMENT

CAS Number: 1634-04-4
EINECS Number: 216-653-1
IUPAC Name: Propane, 2-methoxy-2-methyl

Environment

Results of risk characterisation for the aquatic environment

Conclusion (i) There is a need for further information and/or testing.

This conclusion is reached because there is a need for better information to adequately characterise the risks to the aquatic ecosystem regarding the emission of the substance to surface water.

The information and test requirements are: a tiered testing approach for investigation of avoidance behaviour in fish and if necessary in other wildlife animals related to water contaminated with the substance.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

This conclusion applies to production, production/formulation, formulation and processing sites; to transport, storage and delivery except for intermittent release to surface water from terminal site storage tank bottom waters; to road traffic (runoff) and to boating (exhaust).

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

This conclusion applies to intermittent release to surface water from terminal site storage tank bottom waters.

Results of risk characterisation for microorganisms in wastewater treatment plants

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

This conclusion applies to production, production/formulation, formulation and processing sites.

Results of risk characterisation for the atmospheric compartment

Conclusion (ii) There is at present no need for further information or testing or risk reduction measures beyond those which are being applied already.

Results of risk characterisation for soil

Conclusion (ii) There is at present no need for further information or testing or risk reduction measures beyond those which are being applied already.

This conclusion applies to production, formulation, processing and runoff infiltrated.

Results of risk characterisation for groundwater

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account

This conclusion applies to overall quality of groundwater. The risks are mainly related to leaking underground storage tanks and spillage from overfilling of the storage tanks.

Human health

Human health (toxicity)

Workers

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

This conclusion applies for maintenance and automotive repair scenarios, due to the long-term local effects to skin.

Consumers

Conclusion (ii) There is at present no need for further information or testing or risk reduction measures beyond those which are being applied already.

Humans exposed via the environment

Conclusion (ii) There is at present no need for further information or testing or risk reduction measures beyond those which are being applied already.

Combined exposure

Conclusion (ii) There is at present no need for further information or testing or risk reduction measures beyond those which are being applied already.

Human health (risks from physico-chemical properties)

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account

This conclusion is reached for humans exposed via the environment due to concerns for the potability of drinking water in respect of taste and odour as a consequence of exposure arising from leaking underground storage tanks and spillage from overfilling of the storage tanks.

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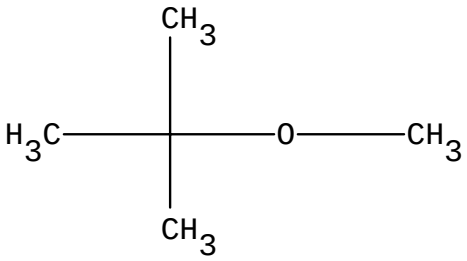
TABLES

FIGURES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS No.: 1634-04-4
EINECS No.: 216-653-1
IUPAC Name: Propane, 2-methoxy-2-methyl-
Molecular Weight: 88.15
Molecular Formula: $C_5H_{12}O$
Structural formula:



Smiles notation: O(C(C)(C)C)C
Synonyms: tert-Butyl methyl ether, Methyl-1,1-dimethylethylether, 1,1,1-Trimethyl-dimethyl ether, Methyl-tertiary

1.2 PURITY/IMPURITIES, ADDITIVES

Methyl tertiary-butyl ether (in further assessment called MTBE) is chemically stable. It does not polymerise, nor decompose under normal conditions of temperature. Unlike most ethers, MTBE does not tend to form peroxides during storage (Product Safety Bulletin, ARCO Chemical Company). The degree of purity of the produced/imported MTBE within the EU is from >95% w/w up to >99.8% w/w. MTBE does not contain any additives (IUCLID, 1996).

Table 1.1 Impurities in MTBE and their maximum percentage contents (Data submitted by the producers)

CAS-No:	EINECS-No:	Name:	Contents:
		C4-olefins	<1% w/w
		Aromatics	<1% w/w
		Tert-amyl methyl ether	<0.2% w/w
		C_{4-6}-parafins	<1% w/w
67-56-1	200-659-6	Methanol	<1.5% w/w
75-65-0	200-889-7	2-methylpropan-2-ol	<1.5% w/w
107-39-1	203-486-4	2,4,4-trimethylpent-1-ene	<1% w/w
115-11-7	204-066-3	Isobutene	<1% w/w
	---------	Di-isobutene (C_8H_{16} isomers)	<1% w/w
7756-94-7	----------	Tri-isobutene ($C_{12}H_{24}$ isomers)	<0.5% w/w
25167-70-8	246-690-9	2,4,4-trimethylpentene	1% w/w
25167-70-8	246-690-9	2,4,4-trimethylpentene	<1% w/w
		Water	<0.1% w/w

1.3 PHYSICO-CHEMICAL PROPERTIES

Pure MTBE is at 20°C and 1013 hPa a colourless volatile liquid. It is soluble in most organic solvents and it is also quite soluble in water. MTBE is flammable and combustible. Physico-chemical data on MTBE are summarised in a number of references. Some of these references are from secondary sources such as handbooks (Merck Index, CRC Handbook and Product Safety Data Sheets of producers) and hence are not validated by original data. The basic physico-chemical data are presented in **Table 1.2.** Below the table there are further explanations of the data and their validity.

Table 1.2 Physico-chemical properties of MTBE

Property	Value	Reference
Melting temperature	- 108°C	Iuclid data, Merck Index (1989)
Boiling temperature	55.2-55.3°C	MTBE Iuclid data
Density	0.741 g/cm^3 at 20°C	IUCLID, (CRC, 1996)
Vapour pressure	270 hPa at 20°C 330 hPa at 25°C	IUCLID, (CRC, 1996)
Surface tension	20 mN/m at 20°C	Scholz et al. (1990)
Log Kow	1.06 at 25°C	Hansch et al. (1968); Huels AG (1989)
Water solubility	42 g/l at 20°C	Stephenson (1992)
Henry's law constant:	43.8 Pa m^3/mol at 20^{o}C	Robbins et al. (1993)
Flash point	-28.2°C – closed cup method	Daubert et al. (1989)
Auto flammability	460^{o}C	Ullmann's (1997)
Explosive properties	No explosive properties	Structural reasons
Oxidising properties	No oxidising properties at NTP	Structural reasons

Melting temperature

The melting temperature -108.6 - -109°C (Daubert et al., 1989; Scholz et al., 1990; Howard, 1990; Merck Index, 1989). Only handbook data or values from MTBE are available. The values are consistent and differ only very slightly from each other.

Boiling temperature

The boiling temperature submitted by producers (IUCLID-Data) is given as 55.3°C. It is consistent with the values found in the literature 55.2-55.3°C (Scholz et al., 1990; Howard, 1990; Daubert et al., 1989).

Density

0.741 at 20°C relative to water at 4°C (IUCLID, 1996; Merck Index, 1989).

Vapour pressure

Values presented in IUCLID are summarised in **Table 1.3**.

Table 1.3 MTBE vapour pressure at different temperatures

Pressure hPa	Temperature °C	Reference
268	20	MABANAFT GmbH (1994)
268-270	20	Huels AG Safety Data Sheet (04/10/1993)
330	25	REPSOL PETROLEO, S.A. MADRID (1985)
335	25	Ambrose et al. (1976)
408	30	ARCO (1989)
482.1-551.7	38	ARCO (June 1993)
599	40	ARCO (1989) (DIPPR Database)
605	40	ARCO (1989)

Sources: ARCO Chemical Company, Methyl Tertiary Butyl Ether Product.
Safety Bulletin (1989) and (1993) Based on DIPPR Database (1989). Huels AG Safety Data Sheet, 04/10/1993.
Iuclid Data sets: MABANAFT GmbH, REPSOL PETROLEO, S.A.

Log K_{ow}

A range of values 0.94 - 1.43 can be found in literature and databases. A measured value Log K_{ow} 1.06 will be used in the further assessment since it is a measured value using accepted methods (OECD Guide-line 107 and GLP) The measured log K_{ow} is 1.06 (stand-dev. 0.98-1.13) (Huels AG, 1989). Similar measured value 1.06 is cited in IUCLID from a GLP study, method according to Directive 84/449/EEC, A.8 cited in IUCLID by MABANAFT GmbH Hamburg (original study not located).

Lowest reported value 0.94 is from Funasaki et al. (1985) (cited in IUCLID). Measured K_{ow} value 17.2-17.5 (Fujiwara et al., 1984) gives log K_{ow} 1.24. In addition value 1.3 is in IUCLID from Veith et al. (1983).

There are also calculated values in IUCLID: 1.06 (Hanch et al., (1968) and 1.24 by REPSOL PETROLEO, S.A. These values are close to the measured ones.

Water solubility

Data on water solubility are variable, see **Table 1.4**.

Table 1.4 MTBE in weight- % in aqueous phase at different temperatures

Temperature °C	% wt [a]	% wt [b]	g/l [c]	g/l [d]
30		2.2	31	
25	5.16			26
20	5.83	3.3	42	
15	6.55			
10	7.30	5.0	51	
0	9.12	7.3	83	

a) Bennett et al. (1928)
b) Scholz et al. (1990)
c) Stephenson (1992)
d) MABANAFT GmbH Hamburg (IUCLID data GLP)

Measured vales seem to confirm the fact that solubility of MTBE decreases as temperature increases, thus MTBE is more soluble in cold water. The solubility value of 42 g/l at 20°C, will be chosen and used in the further calculations (Stephenson, 1992).

Flammability

The flammability limits in the air are: lower 1.26, upper: 8.0 (% vol. in air) (lower: 40.8, upper: 258 in units mg/dm^3) (method: ASTM E681-85). Saturation concentration in air is 32.9 mol % (correspondent to 59.9 wt-%) at 25^{o}C. The vapour density is 3.1 (air=1) Safety Data Sheet, Neste Oy, (1997).

Auto flammability

A value of 460^{o}C is given for auto flammability in the IUCLID data sets (Method DIN 51794). Ullmans Encyclopaedia refers to a value of 460°C (Method DIN 51794) (Ullmann's, 1997).

Flash point

- 28 and -29°C closed cup method (IUCLID), -28.2°C (Daubert et al., 1989).

Explosive properties

Not explosive for structural reasons.

Henry's law constant

Values from different sources are tabled below.

Table 1.5 Henry's Law Constants for MTBE

H (m^3 atm/mol)	H (Pa m^3/mol)	Temp (^{o}C)	Reference
0.00045	45.6	20	Neste Co. Safety Data Sheet
0.000433	43.8	20	Measured (Robbins et al., 1993)
0.000528	53.5	25	Measured (Robbins et al., 1993)
0.000587	59.8		Howard (1990)
0.000546	55.3	20	Calculated (FEI 1999)

Conversion Factors

1 ppm = 3.57 mg/m^3; at 25^{o}C
1 mg/m^3 = 0.28 ppm; at 25^{o}C (WHO, 1998)

Odour Threshold in air

Detection (average) 0.053 ppm (0.19 mg/m^3)(Vetrano et al., 1993)
Recognition (average) 0.08 ppm (0.29 mg/m^3) (Vetrano et al., 1993)

Odour and Taste Threshold in water

Individual variability in sensitivity to taste and odour makes it difficult to identify point thresholds for MTBE. According to Keller et al. (1998), the taste and odour thresholds for MTBE range from 2.5 μg/l to 680 μg/l, and 2.5 μg/l to 190 μg/l, respectively (Keller et al., 1998). Even if the threshold for taste and odour occurs as low of 2.5 μg/l, studies in the literature suggest most persons would have a somewhat higher threshold. Typically the odour of MTBE can be detected at concentrations slightly lower than those that can be detected by taste, but there are exceptions (API, 1994).

Difference between the thresholds observed in laboratory studies could be due for example to sensitivity and training of panellists, water hardness and temperature. In true world conditions thresholds may be more or less site and case specific, high chlorination or other contaminants of the water may have influence on detection. Consequently, the concentration level at which the taste or odour makes water unacceptable for the consumers may vary. As a conclusion, it can however be assumed, according to studies referred in Section 4.2.3.3, that the range of concentration unacceptable for consumers in most cases may be some tens of micrograms per litre at maximum in water otherwise of good quality.

In individual studies, Young et al. (1996) found that geometric mean odour and taste threshold were 34 and 48 μg/l, respectively. The lowest concentration, at which the odour and taste were detected, were 15 and 40 μg/l. The Oxygenated Fuels Association in the US commissioned an extensive test on the taste and odour properties of MTBE in water (Pirnie, 1998) using an odour panel of 57 participants. The results of the study supported the setting of a Secondary Maximum Contaminant Limit (SMCL – an advisory guideline set for aesthetic, non-health effect parameters by the USEPA) of 15 μg/l for taste and odour in drinking. Also in the USA, the California EPA has recently adopted an SMCL of 5 μg/l (OEHHA, 1999). In a recent Danish study odour detection threshold 7.4 μg/l and taste detection threshold 7.3 μg/l were determined. The drinking water tested was typical non chlorinated Danish drinking water (at 25^{o}C, method ISO 4120, ISO 5495, 8 panellists, analytical concentration control). The lowest detections were 3 μg/l (Danish EPA, 2000b).

For the present assessment 15 μg/l is used as the organoleptic threshold of MTBE in drinking water for human exposure assessment (Section 4.1.1.3) although it is recognised that the variability of values is high. Certain investigations indicate that the threshold value in drinking water maybe lower than 15 μg/l for a sensitive fraction of the human population.

Odour detection threshold in water	15 μg/l (2.5 - 190 μg/l variable sources).
Taste detection threshold in water	40 μg/l (2.5 - 680 μg/l variable sources).

Odour:

Terpene-like

1.4 CLASSIFICATION

Currently not in Annex 1. Foreseen to be adopted at the 29th ATP of Directive 67/548/EEC[4]:

Classification:	(provisional)		
	F; R11	Highly flammable	
	Xi, R38	Irritant; Irritating to skin	
Labelling:	(provisional)		
	F;Xi	R: 11-38	S: (2-) 9-16-24

Environmental classification: No environmental classification.

[4] The classification of the substance is established by Commission Directive 2001/32/EC of 19 May 2000 adapting to technical progress for the 26th time Council Directive 67/548 on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances (OJ L 136, 8.6.2000, p.1).

2 GENERAL INFORMATION ON EXPOSURE

2.1 NATURAL OCCURRENCE

MTBE is an anthropogenic chemical and there are no known naturally occurring sources of the substance.

2.2 PRODUCTION

Commercial production of MTBE started in Europe in 1973 and in the USA in 1979. Total worldwide production capacity in 1994 was 20.6 million tonnes (ECETOC, 1997).

MTBE is typically manufactured in petroleum refineries but also in plants manufacturing industrial organic chemicals. MTBE is prepared principally by reacting isobutene with methanol over an acidic ion-exchange resin catalyst at 38-93^{o}C and 100-200 psi. It can also be prepared from methanol, *tert*-butyl alcohol (TBA) and diazomethane (WHO, 1998).

Feed materials to the MTBE synthesis are produced in different kinds of cracking units. There are four different sources for the isobutene (1-4) (Newenham, 1997):

- Field butanes. Mixed butanes are isomerised and dehydrogenated to yield isobutene. These plants are only viable on a large scale and tend to have capacities in excess of 500,000 t/a.

- Propylene oxide. In this process propylene reacts with isobutane to produce propylene oxide and tertiary butyl alcohol, which is dehydrated to isobutylene. These plants may have capacities in excess of 500,000 t/a.

- Steam cracker C4s. This route is much simpler than the previous two since the isobutene is merely extracted as a by-product from steam cracker. Plant capacity is determined by feed constrains but sizes of 50,000- -220,000 t/a (information submitted by industry) are typical.

- Fluid cat cracker (FCC) C4s. This route is very similar to the steam cracker route, only the isobutene is extracted from the FCC overheads. Capacity is determined by feed availability, but many plants are in the range 20,000-70,000 t/a.

Of the total worldwide production capacity of 20.6 million tonnes of MTBE in 1994, 23% was produced by steam cracker, 31.5% from fluid liquid cracker and 32.5% from dehydrogenation operations. The remaining 13% was formed by dehydration processes. Most recent growth is based on butane hydrogenation and fluid catalytic cracker units (ECETOC, 1997).

Total worldwide annual production 1995 was about 15 million tonnes (DeWitt & Company Inc, 1996); (WHO, 1998) and about 21 million tonnes in 1999 (DeWitt & Company Inc, 2000).

There were 29 companies producing MTBE at 37 facilities in the EU in 1995. In 1997, the number of companies was 25 and the amount of facilities was 35. Appendix **Table A.1** lists EU producers, plant locations, and plant capacities in 2000.

The types of plants producing MTBE are:

- Refinery-based plants using Fluidized Catalytic Cracking Unit (FCCU) (Isobutylene FCCU). The capacity was approximately 1,200,000 tonnes/year in 1997.

- Refinery-based plants using FCCU and raffinate feed. The capacity was approximately 400,000 tonnes/year in 1997.

- Merchant plants using raffinate feed. The capacity was approximately 900,000 tonnes/year in 1997.

- Merchant plants using TBA from propylene oxide production. The capacity was approximately 1,100,000 tonnes/year in 1997.

The total production capacity of MTBE in 1997 was 3,545,000 tonnes/year but the actual volume produced was 3,030,000 tonnes (Dewitt & Company Inc., 1998). The capacities, production, export and use in separate EU countries are summarised in **Table 2.1**.

The Netherlands with the produced amount of 903,500 tonnes/year is used as a regional environment in the EUSES calculations. The production in the Netherlands is relatively high and it is considered to be relatively close to a Technical Guidance Document (TGD) definition of a densely populated area of 200 · 200 km with 20 million inhabitants.

Table 2.1 MTBE balance (excluding import) in the EU in 1997 (tonnes/year) (Dewitt & Company Inc., 1998)

Country	Capacity	Produced [1)]	Export	Consumed
Austria	48,200	41,000		60,400
Belgium	140,600	126,600	17,400	105,700
Denmark				4,300
Finland	120,500	102,400	11,000	211,400
France	638,900	543,000	240,800	198,400
Germany	455,200	387,000	1,800	349,400
Italy	315,400	283,900		509,000
Netherlands	1,069,800	903,500	471,400	99,200
Portugal	50,200	42,700	93,600	
Spain	355,600	302,200	16,000	347,200
Sweden	49,200	41,800		60,400
Switzerland			(8,600)	(8,600)
United Kingdom	301,300	256,100	51,800	138,000
Total	3,545,000	3,030,200	903,800	2,126,400

[1)] t-Amyl methyl ether (TAME) included (information submitted by industry)

In addition to two large PO/TBA plants in France and in the Netherlands there are only few companies selling merchant MTBE which are not part of the oil industry.

2.3 USE

The annual production volume of MTBE in the year 1997 in the EU was 3,030,000 tonnes. About 187,000 tonnes was imported (Fortum, 2000a) and about 904,000 tonnes was exported outside the EU in the year 1997 (Dewitt & Company Inc., 1998). The majority of the exported volume (>83%) was exported to the USA and Canada. The majority of exported volume (>80%)

was transported as non-blended MTBE and minority as a component of petrol (blended). The annual consumption of MTBE within the EU was hence 2,313,000 tonnes in the year 1997 (**Table 2.2**).

Table 2.2 Production, import, export and consumption in the EU in 1997 (tonnes/year)

Production	Import into the EU	Export outside the EU	Consumption in the EU
3,030,000 [1)]	187,000 [2)]	904,000 [1)]	2,313,000

[1)] Dewitt & Company Inc. (1998)
[2)] Fortum (2000a)

Trends in MTBE production, export, import and use volumes can be seen in **Table 2.3**. The trend seems to be a slight increase in production, use, export and import.

The future consumption of MTBE is expected to increase in Europe mainly as an octane booster. In the new European petrol quality requirements (EC Directive 98/70/EC) decreased overall aromatics concentration is required leading to lower octane ratings. Therefore, there is increasing need for high octane blend components in the coming years.

Table 2.3 Trends in MTBE production, export, import and use (tonnes/year)

	1994	1995	1996	1997	1998[(2]	1999[(2]
Capacity	3,126,000	3,260,000	3,394,000	3,485,000	-	-
Production	2,496,000	2,877,000	2,959,000	3,030,000	2,880,000	3,290,000
Use	2,289,000	2,150,000	2,105,000	2,127,000	2,301,000	2,646,000
Export	207,000	727,000	854,000	904,000	848,000	935,000
Import [1)]	317,000	307,000	203,000	187,000	269,000	291,000

Dewitt & Company Inc. (1998) [1)] Fortum (2000a) [2)] data submitted by industry

Annual consumption volume of MTBE per use pattern within the EU is presented in **Table 2.4.** The reference year is 1997.

Table 2.4 Volumes of MTBE consumed in the EU in 1997

Use	Tonnes	Percentage
Fuel additive	2,278,000 [1,2)]	98.5
Production of isobutylene	29,000 [2) 3)]	1.2
Solvent	6,000 [2) 3)]	0.3
Total	2,313,000 [(1]	100

[1)] Dewitt & Company Inc. (1998) [2)] data submitted by industry [3)] 1996

2.3.1 Use as a petrol additive

The main use of MTBE is as an additive/component in petrol. This usage covers more than 98% of the total quantity produced in the EU. MTBE is the most commonly used fuel oxygenate.

Oxygenates are used widely as a component of unleaded petrol. MTBE is the dominant petrol oxygenate used in the EU. In addition, several small ETBE (ethyl *tert*-butyl ether) plants are operating in France and Spain (DeWitt & Company Inc, 1996). Besides ETBE also TAME (*tert*-

amyl methyl ether) and next-TAME (C4-C7 tertiary alkyl methyl ethers) are used as oxygenates solely or in combination with MTBE.

According to directive 98/70/EEC, the legal maximum concentration of MTBE is 15% volume in automotive petrol. The European average oxygenate concentration in petrol is about 2.5%-wt, but the concentration varies widely from country to country and from refiner to refiner. (MTBE conversion ratio volume % to weight % in petrol is very close to 1 (at 15°C) in typical European commercial petrol grades (Fortum, 2000b). Some countries have special grades of petrol which require oxygenates to be added, for example, reformulated petrol (RFG) in Finland which requires 2.0–2.7%-wt oxygen. This would be equivalent of 11 to 15% vol MTBE, but other oxygenates such as alcohols and other ethers may also be used to provide this oxygen, therefore the concentration of MTBE may be lower than this (data submitted by industry). MTBE is not used in aviation petrol (CONCAWE, 1997b).

MTBE has been added to petrol blends since second half of the 1970's, initially at low levels (2-5% w/w) to boost the octane rating of unleaded premium or high performance grades. More recently MTBE has been added at higher levels (11-15%-vol) to promote more efficient combustion of the petrol. Blends meeting the latter specifications are widely used in North America and parts of Europe to improve air quality (oxygenated petrol) (ECETOC, 1997). Regionally the use of MTBE has been variable within the EU. **Table 2.5** illustrates annual motor petrol consumption volumes and MTBE consumption at the EU member state level in the year 1997.

Table 2.5 Motor Petrol and MTBE Consumption in the European Union in 1997 (Fortum Oil & Gas Oy)

Country	Motor Petrol Net Consumption, 1,000 metric tonnes	MTBE Consumption, 1,000 metric tonnes	Average MTBE wt%	Note
Austria	2,094	60	2.9%	
Belgium	2,535	100	3.9%	
Denmark	1,975	4	0.2%	
Finland	1,882	160	8.5%	1
France	13,067	200	1.5%	
Germany	29,996	350	1.2%	
Greece	3,056			
Ireland	1,173			
Italy	17,149	500	2.9%	
Luxembourg	542			
Netherlands	4,145	100	2.4%	
Portugal	1,931	50	2.6%	2
Spain	9,100	340	3.7%	
Sweden	4,126	60	1.5%	
United Kingdom	22,288	140	0.6%	
European Union	115,059	2,130	1.9%	3

Sources: Gasoline: International Energy Agency: Oil, Gas, Coal & Electricity, Quarterly Statistics, Third Quarter 1998.
MTBE: DeWitt & Co.: MTBE Annuals (some figures may include other ethers also).
Notes:
1) MTBE only; based on Fortum's usage and estimate of imports by other oil companies
2) Minimum estimated MTBE consumption
3) MTBE total consumption based on the conference paper by Patrick Henshall, DeWitt & Co., Prague, June 17, 1999
Additional information: The MTBE production volume in Norway was 35,000 tonnes (1997) and consumption volume ca. 8,000 tonnes giving 0.5% average MTBE concentration in petrol (SFT, 2000).

Average MTBE wt-% values in the table above are just calculated from the total consumption figures. It does not indicate MTBE concentrations in commercial petrol specifications. In practice, concentration is highly variable, from 0 to 15%, depending on petrol grade, oil company and country. For instance 98-99 RON (Research Octane Number) petrol grade ("high performance", "super","super plus") may typically contain 5-13% and 92-95 RON grade ("premium") 0,5-8% of MTBE.

Taken as whole the Western Europe is the second largest market for motor petrol in the world. In 1997, the region consumed about 40% of the volume consumed in US market.

In recent years, European petrol use has been more or less stagnant. Between 1988 and 1992, overall demand increased by about 1.8% per year (DeWitt & Company Inc, 1996). From 1993 to 1995, demand shrunk each year by about 1.0 to 1.5%. 1996 and 1997 saw a small reversal of this trend with little or no chance from 1995. For the future industry predicts that there will be a more steady growth at 0.5% or more (Dewitt & Company Inc., 1998). In Europe, production of MTBE started already in the year 1973 in Italy. In general, introduction of MTBE into petrol in the EU was done later than in the USA. Neither there has been any minimum requirements for MTBE in any of the EU member states.

MTBE has been used as an octane enhancer in the USA since the late 1970s. The United States 1990 Clean Air Act Amendments require fuel oxygenates, such as MTBE or ethanol, to be added to petrol used in some metropolitan areas to reduce atmospheric concentrations of carbon monoxide (CO) or ozone (O_3). Areas that exceed the national ambient air-quality standard for carbon monoxide were required to use oxygenated fuels by November 1, 1992. The Clean Air Act Amendments also require oxygenated fuels during winter when the concentrations of carbon monoxide are largest. Petrol must contain no less than 2.7 percent oxygen by weight, which is equal to 15 percent MTBE by volume, to meet this oxygen requirement. Nine US metropolitan areas that have the most severe ozone pollution were required to use a special blend of petrol called reformulated gasoline (RFG) year round beginning in January 1995. Reformulated gasoline must contain at least 2.0 percent oxygen by weight, a maximum of 1.0 percent benzene and 25 percent aromatic hydrocarbon by volume. Reformulated gasoline would contain 11 percent MTBE by volume to meet this oxygen requirement.

Recently there have been restrictions on the use of MTBE in States of California and Connecticut in the USA. Monitoring data from the USA show that the use of MTBE has resulted in growing detections of MTBE in drinking water because of leaking underground petrol tanks, with between 5-10 percent of community drinking water supplies in high oxygenate use areas showing detectable amounts of MTBE, with approximately one percent rising to levels above 20 µg/l (US EPA, 1999).

Future consumption of MTBE in the EU

The EU Fuels Directive 98/70/EC (EC 1998) set new mandatory specifications on petrol. From 1 January 2000, new limits on aromatic 42% v/v were set and no later than 1 January 2005, the total aromatics shall not exceed 35% v/v. Because high intrinsic octane rating of aromatics, decrease in aromatics leads to loss of octane rating in base petrol. The chance in aromatics concentration in petrol, ca. 7% v/v drop in five years, means a remarkable loss in octane number. Even 7-8 million tonnes of aromatics has to be replaced with non-aromatic, high octane blending components. Theoretically, MTBE could be the sole substitute for aromatics. That would mean substantial increase in annual consumption volume compared to current ca. 3 million tonnes (1999).

The maximum concentration of MTBE, expressed in Directive 98/70/EC as "Ethers containing 5 or more carbon atoms per molecule" is 15% vol. However, EU legislation does not mandate to oxygenate use. MTBE is fairly expensive blending component just for octane boost. It is unlikely that remarkable proportion of petrol on the market would comprise the maximum content. Generally, there are numerous alternatives available and it is at least partly an open question how this will be solved in individual oil companies.

DeWitt Co. has made long-range prospects for MTBE consumption trends in the EU until the end of year 2005. Annual consumption in the year 2000 is ca. 3 Mt. They saw realistic, that until the end of the year 2005 ca. 4 Mt of MTBE will be used annually, amongst other blending substances, to cover octane loss and meet 98/70/EC requirements concerning total aromatics in EU countries. They believe that MTBE would play the major role in this aromatics reduction (DeWitt & Company Inc, 2000; Dewitt & Company Inc., 1998). Current annual production capacity of MTBE within the EU is about 4 Mt (at February 2000) (ECETOC, 2000). In this light, DeWitt's estimate of 4 Mt indicates, that there would not be need to built additional production capacity at once. Decreasing trend in export to the USA is expected in coming years leaving extra capacity for EU consumption. Remarkable export in 90s to the USA may turn to nett import as well. Demand for high octane blending compounds may increase also in non-EU Eastern Europe countries as lead substitute. This may have influence on EU production volumes and capacity building as well.

2.3.2 Other use patterns

MTBE is also used as a chemical intermediate to produce high purity isobutylene. Approximately 29,000 tonnes were used for this purpose in 1996 (data submitted by industry).

High purity MTBE is being used as a process reaction solvent in the pharmaceuticals industry (ECETOC, 1997). About 6,000 tonnes were used as a solvent in 1996 (data submitted by industry).

Minor use patterns are use as chromatographic eluent and use as a therapeutic agent for *in vivo* dissolution of cholesterol gallstones in humans (WHO, 1998). More detailed figures on use as an eluent or therapeutic agent are currently not available.

Known misuses of petrol (and MTBE as a component) include use as a solvent, a cleaning agent and petrol sniffing (solvent abuse) (CONCAWE, 1997b). Exposure from misuses is not covered by this assessment.

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

3.1.1 General discussion

Environmental emissions of MTBE are closely related to petrol, its storage, distribution and use. Approximately half of the anthropogenic VOC (Volatile Organic Carbon) emissions are caused by traffic and result from engine combustion processes as well as from the distribution of highly volatile petrol (storage, turnover, refuelling) (BUA, 1996), (McInnes, 1996), (CORINAIR, 1995).

A major source of MTBE in ambient air is automobile exhaust gases. Environmental emission/exposure estimate uses statistical data of the years 1995 and 1997. The consumption of MTBE has increased remarkably between the years 1995-99 in Europe (23%). However, despite of increased consumption volumes of MTBE, fleet turnover may have resulted at least regionally, if not at continental level, so that emissions of MTBE into air have not increased.

Emissions from use patterns other than fuel additive/component are minor in terms of emitted volumes. This is mainly because of the low amounts used and the manner of use, being primarely non-dispersive industrial applications (industrial point sources).

Because MTBE is widely used as a fuel component, there are monitoring data available from different kind of environmental samples. However, much of the data are from particularly contaminated environments, while measurements of background levels in many compartments are still limited. A large part of the monitoring data comes from the USA.

Hydrocarbons (HC) from motor vehicles are regulated pollutants in the EU and historically emissions standards have been addressed only the mass of total hydrocarbons (THC) or non-methane hydrocarbons (NMHC). A primary reason for these regulations is that vehicular HC emissions are major contributor to the formation of tropospheric ozone. As a group, all HC (except methane) are considered ozone precursors. Because of rather high vapour pressure of MTBE, it is one of the major VOC components in oxygenated European petrol.

3.1.1.1 Existing control on MTBE

This chapter lists the most important EU directives concerning the composition of petrol and the emission control from its distribution and use. Various national legislative at member state level are not covered.

Petrol Composition

Directive 98/70/EC: Based on the results of the Auto/Oil programme, 98/70/EC regulates maximum content of MTBE as “ethers containing 5 or more carbon atoms per molecule” to 15% v/v. In addition, leaded petrol to be phased out by year 2000 and new improved petrol quality standards from 1 January 2000: restrictions on volatility (Reid Vapour Pressure summer max. 60.0 kPa) and maximum content of sulphur (150 mg/kg) olefins (18% v/v), aromatics (42% v/v) and benzene (1% v/v). In addition, no later than 1 January 2005, total aromatics shall not exceed 35% v/v and maximum content of sulphur 50 mg/kg.

Petrol storage

Directive 96/82/EC: "Seveso II" is aimed at the prevention of major accidents which involve dangerous substances, and the limitation of their consequences for man and the environment. The Directive shall apply to establishments where dangerous substances are present in quantities equal to or in excess of the quantities listed in annexes of the directive. Minimum quantities for application of Seveso II for petrol, presence of "Automotive petrol and other petroleum spirits", are 5,000 tonnes, thus 96/82/EC comprises predominantly large size establishments, marketing depots and terminals.

National legislation: Regulations on technical specifications and control of underground tanks are not harmonised in the EU. Existing regulations are established on national and/or county/regional basis. The national legal requirements which are incorporated into the service stations building and operation permits may include, for instance the guidelines for monitoring leaks, technical requirements and periodical examination for tanks.

Emission Control

Directive 91/441/EEC: the so-called "EURO 1" standards limits exhaust and evaporative emissions of petrol hydrocarbons from passenger cars. As a consequence of these changes in the legislation, it was necessary for all new petrol cars to be equipped with closed-loop three way catalysts and with carbon canisters for evaporative emission control, and thus these technologies first entered widespread use in the EU from the beginning of 1993.

Directive 92/55/EEC determines in service HC emission standard for petrol fuelled passenger cars at two idle conditions (low and high idling).

Directive 93/59/EEC introduced limits on light commercial vehicles, of equivalent stringency to those in 91/441/EEC for passenger cars.

Directive 94/12/EC sets "EURO 2" emission standards for passenger cars. Standards are valid until the end of year 2000.

Directive 94/63/EC (1994): "Stage 1 & 2" is for limiting emissions of volatile organic compounds (VOC-emissions) during the storage of petrol and its distribution from the delivery centres to the service stations (refuelling stations). The requirements of the directive limits the annual total loss of petrol during filling and storage of tanks (throughput) to 0.1 kg/t loss of petrol in delivery depots, 0.05 kg/t loss during filling and emptying of mobile tanks in delivery depots and 0.1 kg/t during filling of the storage tanks of gas stations. At the Stage I stations, during unloading from tank truck to station tank, vaporised petrol is collected, which reduces the release to the air. At the Stage 2 stations, vaporised petrol is collected also during refuelling by an inlet which is attached to the petrol pistol.

Directive 96/69/EEC sets EURO 2 emission limits for Light Duty petrol fuelled vehicles.

Directive 97/24/EC sets limits on the emissions from new motorcycles. Two stage standards are included as 3.0 (g/km) HC+NOX June 1999 and 1.2 (g/km) HC+NOX in June 2000.

Directive (98/69/EC) introduces new mandatory (gradually tightening) limit values on emissions from new cars and light commercial vehicles. From year 2000, hydrocarbon exhaust emission limit for petrol-fuelled cars is 200 mg/km. On board diagnostics are required on petrol vehicles from 2000. The driving cycle test procedure is modified to include a cold start at - 7^{o}C.

Short history of the emission control stages

Until 1971 passenger car exhaust emissions were uncontrolled (PRE ECE) and thereafter gradual control actions have taken place: 70/220 & 74/290/EEC (ECE 15 00 & 01 controls) years 1972-1977, 77/102/EEC (ECE 15 02) years 1978-1980, 78/665/EEC (ECE 15 03) years 1981-85, 83/351/EEC (ECE 15 04) years 1985-92, Improved Conventional, Open loop catalyst, (1991→) 91/441/EEC (EURO I), 94/12/EEC (EURO II), *EURO III (2000-2005) EURO IV (2005-)*.

Until 1996 2-wheeled vehicles (<50cm^3) were controlled by ECE R 47, 1997-1998 COM(93)449 Stage 1, after 1999 COM(93)449 Stage 2, >50 cm 2- stroke until 1996 ECE R 40.01 after 1997 COM(93)449, >50 cm^3 4-stroke until 1996 ECE R 40.01 after 1997 COM(93)449.

3.1.2 Release scenarios

The environmental emission/exposure stages during life-cycle of MTBE used in the assessment are as follows:

- Production of MTBE
- Formulation: petrol blending with MTBE (on site and off site)
- Processing 1: storage, transport and delivery of petrol
- Private use: consumer use of petrol
- Processing 2: MTBE used as intermediate for isobutylene production
- Processing 3: MTBE used as solvent in pharmaceuticals industry

The environmental exposure assessments combine the relevant exposure scenarios for MTBE and apply recommended assessment methods for deriving PEC local and regional according to Technical Guidance Document (TGD, 1996) and European Union System for the Evaluation of Substances (EUSES model ver. 1.0 (1997)) if applicable.

The use of petrol is extensive and wide. Therefore, there are specific information on use and emissions available which will be used in the exposure assessment. Emissions of MTBE to air from use of petrol have been calculated manually using emission factors (EF's) from specific exhaust and evaporative emission measurements, legislative emission limit values and other relevant sources.

In this report, organic compounds in the gas phase, excluding particular matter, are referred as VOCs, TOCs or HCs and mean the same (cited as it is in original reference). If methane is excluded, abbreviation "NMVOC" is used.

Production

MTBE is produced in closed systems in either wet or dry processes. Atmospheric emissions are expected from both types of processes and release to water primarily from the wet process. Typically, production of MTBE in EU is part of oil industry except mainly for two large plants which produce merchant MTBE in the chemicals industry branch.

In the wet process of manufacturing MTBE, water is used to wash a hydrocarbon-methanol stream to extract the methanol from the hydrocarbon stream and recycle it. In the dry process, there is no water wash used to extract the methanol. The excess methanol is extracted by other means and recycled to the feed.

During the manufacturing process of MTBE, the product is never in direct contact with water. Water is used in some processes (the so called wet processes) to wash the methanol from the methanol-hydrocarbon stream. The MTBE product is extracted before the wash. However, some traces of MTBE can be present in the MeOH-HC stream. To avoid concentration of the water stream, a very small side stream is extracted from the water stream and led to the wastewater unit. This stream can contain MTBE in small amounts (<0.1 ppm) but these traces are removed in the wastewater unit to levels below detection.

The default emission factors from the Technical Guidance Document for mineral oil and fuel industry (category 1b) are replaced by specific data regarding emissions to air and wastewater (**Table 3.2**).

Formulation

Formulation of MTBE covers the blending of petrol with MTBE. Emissions into environment are mainly atmospheric.

There are two formulation techniques for blending petrol with MTBE, in-line blending and batch blending. In in-line blending the petrol components (including MTBE) are pumped from their storage tanks to a common line and pumped further through the common line to the product storage tank. The components are blended both during the pumping through the common line and in the product tank. In batch blending the petrol components are pumped through separate lines to the storage tank. The blending of the components hence takes place only in the product tank.

When MTBE is blended in to petrol outside the refineries, e.g. in commercial terminals, both techniques can be used for the blending. Batch blending is however usually more used. There are 4-8 commercial terminals within the EU that do blending of petrol. Approximately 5% or less of the MTBE used in Europe are blended outside the refineries (Fortum, 2000a). It is expected that the MTBE emissions in these terminals should not differ from the emissions from blending activities in the refineries since the techniques used are similar.

The default emission factors from the Technical Guidance Document for mineral oil and fuel industry (category 1b) are replaced by specific data regarding emissions to air and wastewater. The default fraction of the main source is also replaced by specific data (**Table 3.2**).

Processing scenario 1

Emission scenario processing 1 covers emissions from transportation, storage and delivery of MTBE and blended petrol during storage, loading/reloading, transportation and finally delivery of petrol at service stations. Emissions to all environmental compartments are possible.

Emissions to air are predominantly fugitive emissions directed to air during storage of petrol in tanks and during loading/emptying phases. Emission from distribution is not only restricted to the consumed volume but emission during export (e.g. border terminals) are also included in the estimation. Petrol is a mixture and evaporative emissions are dependent on the composition of petrol. The vapour pressure and density of pure MTBE is close to the typical European grades of commercial petrol. A specific evaporative emission (VOC) factor for petrol is used (3 kg/t) and assuming linearity of MTBE evaporation over concentration range 1-15% emission calculation is carried out for the total produced and consumed MTBE tonnage **Table 3.9** (imaginary blended as 10%-wt for emission calculation and emission factor 0.3 kg/t consequently).

The assumption of linear emission needs some clarification. According to the studies where specific MTBE emission has been measured, with variable concentration of MTBE in petrol, rather linear relationship has been observed between the concentration of MTBE in petrol and emitted levels (evaporative and exhaust).

The published gas-chromatographic analytical data show the composition of 10 European premium grade fuels from 8 countries taking into account the summer and winter quality of the years 1984/85 and the corresponding vapours. The average volume concentration of hydrocarbons in the vapour was ca. 90% for C3-C5-alkanes and ca. 2% for aromatic hydrocarbons. In contrast, average mass concentration of hydrocarbons in petrol liquid was about 26% for C3-C5-alkanes and about 43% for aromatics. An average mass concentration of 5.4% of MTBE in petrol liquid led to a mean volume concentration of 5.4% in the vapour phase (BUA, 1996). More recent analytical data on GC headspace analysis showed similar results of MTBE volatility. The concentration of MTBE in the gas phase (headspace) seems to be directly proportional on the concentration in petrol. In a GC study where MTBE volatilisation from petrol containing 2,2% 10,8% or 16,6% were measured, the linearity of MTBE volatilisation was good in relation to initial concentration of MTBE in petrol (r^2 = 0.9998) (FORTUM, 1999). 12%-wt MTBE in summer time quality Finnish RFG petrol led to a mean mass concentration of 10.5%-wt in the vapour phase (FEI, 1999). Therefore, it can be expected that evaporative VOC gases from petrol would contain on average approximately 8.5-9.5%-wt of MTBE if the liquid petrol originally contained for instance 10%-wt of MTBE (0.85-0.95%-wt of MTBE in VOC per 1 wt-% of MTBE in petrol assuming linearity).

Release to aquatic environment may occur during transportation of petrol/MTBE through waterways and refuelling of watercrafts in boat service stations. Intermittent releases to aquatic environment, to wastewater and surface water, arise from the storage tanks bottom waters (local PEC calculation, Section 3.1.5.1). Otherwise, the default emission factor from the Technical Guidance for mineral oil and fuel industry (A3.8) is used (see **Table 3.1** and **3.2**).

Release to soil during storage and transportation is assumed low compared to emissions directed to air. However, these emissions exist and soil in refuelling station and depot areas are more or less contaminated with petrol based hydrocarbons. Serious soil and groundwater pollution may happen in the case of leaking underground storage tanks or piping. However, no specific local PECs are derived for leaking tanks. The default emission factor from the Technical Guidance for mineral oil and fuel industry (A3.8) is used (see. **Table 3.1** and **Table 3.2**).

Private use scenario

Private use scenario covers emissions from the use of petrol as a fuel in spark ignition engines (cars, boats, stationary engines, etc.). Emissions to all environmental compartments are possible although emissions into environment are mainly atmospheric.

Emissions to air from the use of petrol are the main source of MTBE released to the environment. It covers the majority of the total emitted mass volume. Emissions are divided into two main categories: evaporative emissions and exhaust emissions.

The total continental exhaust emission of MTBE is calculated (**Table 3.9**) using statistical data on annual driven mileage and fuel consumption within EU as well as MTBE as a component in exhaust HC- emission gases per different vehicle fleet classes. Finally, the emission factor, MTBE emission to air for the petrol consumption, is calculated as a ratio of total emitted/consumed tonnage. As a result, EF 0.025 is used in further exposure assessment.

Release to surface water happens from motor boating and related activities and via road and urban runoff. Specific information is available for boating and runoff, and these are used later in the report to calculate local PECs. Otherwise, the default emission factor from the Technical Guidance for mineral oil and fuel industry (private use category) is used (**Table 3.1** and **Table 3.2**).

Direct release to soil occurs for instance because of malfunctioning fuel systems in vehicles and engines. No specific information is available and the default emission factor from the Technical Guidance for mineral oil and fuel industry (private use category) is used (**Table 3.1** and **Table 3.2**).

Processing scenario 2

Industrial use covers emissions from the use of MTBE as an intermediate in transformation of MTBE into isobutene. Emissions into environment are mainly atmospheric.

The default emission factors from the Technical Guidance Document for Chemical industry; chemicals used in synthesis, are replaced by specific data regarding emissions to wastewater. The default fraction of the main source is also replaced by specific data (**Table 3.2**).

Processing scenario 3

This scenario covers MTBE used as an extraction solvent in pharmaceuticals industry. Pharmaceuticals industry is the only industry branch using MTBE as solvent.

High purity MTBE is used for the production of intermediates for pharmaceutical active ingredients because of technical advantages to other solvents. The main advantage of MTBE in comparison with other solvents is the stability against oxidation processes and nearly no formation of peroxides. So, MTBE is used as a specialist solvent for closed special processes.

The extraction solvent is recycled after usage. Only a small amount of the overall amount of MTBE is disposed to wastewater or burned in waste incineration plants. Exhaust air is typically treated in exhaust air burning facilities.

The default emission factors from the Technical Guidance Document for Chemical industry; basic chemicals (IC2, UC48) are replaced by specific data regarding emissions to wastewater (**Table 3.2**).

Recovery/waste disposal

This stage covers wasted material which may contain MTBE. Materials may be produced in any of the earlier life stages.

The production waste is spent catalyst, which can be landfilled or incinerated. MTBE concentrations are expected to be very low due to the treatment of the catalyst (information submitted by the industry).

Emissions cannot be excluded from private and professional vehicle and other engine fuel system maintenance and repairing. However, emission data from these sources are not available. But, it can be concluded that emitted amounts during maintenance and repairing are usually low compared to the total emissions during the life cycle of the vehicles and engines. However, these emissions may not be without local importance as point sources.

Used engine lubrication oil (crank case oil) contains petrol. Depending on the technical condition of the engine and the driving conditions, the amount of petrol in oil varies from trace amounts

even to tens of volume percentiles. In this assessment, it is assumed that used motor oils are disposed adequately (according to Directive 75/439/EEC on waste oils) and no additional environmental releases of MTBE occur. In addition, the relative volume of oil to overall fuel use is very low.

Soil and groundwater in petrol retail and storage sites may often be contaminated with petrol hydrocarbons. In connection to remediation activities, discharges of MTBE contaminated groundwtaerater takes place to municipal sewage system or directly to surface water. This situation is rather common and because of high volumes of often just slightly contaminated water, there is a frequent wish for permission of discharge of contaminated water to surface water. Remediation is normally managed by local or regional pollution control authorities and decisions for permissions are decided on the case-by-case basis. More detailed qualitative or quantitative risk characterisation has not been carried out in this risk assessment concerning above-mentioned recovery/waste disposal issues.

Summary for emission scenarios

Tables 3.1 and **3.2** summarise emission scenario characteristics and detailed parameters used in this risk assessment.

Table 3.1 Main Categories, industrial and use categories (according to the TGD)

Local scenario	Industry category	Use category	Main category	A-Table [1)]	B-Table [2)]	Fraction of tonnage %	Fraction of chemical in formulation, %
Production	9	28	Ib	A1.1	B1.4	98.5	
Formulation 1 Petrol formulation (blending)	9	28	Ib	A2.1	B2.6	98.5	1-15 vol%
Processing 1 (storage, transportation, delivery)	9	28	IV	A3.8 [3)]	B3.7	98.5	1-15 vol%
Private Use, use as engine fuel	9	28	IV	A4.2 [3)]	B4.1	98.5	1-15 vol%
Processing 2, Production of isobutylene, processed on site	3	33	III	A3.3	B3.2	1.2	100%
Processing 3. Solvent in pharmaceuticals industry	2	48	III	A3.2	B3.2	0.3	100%
Export (released volume is added to Processing 1 scenario)	9	28	III	[3)]		Exported Volume [4)]	3-100%

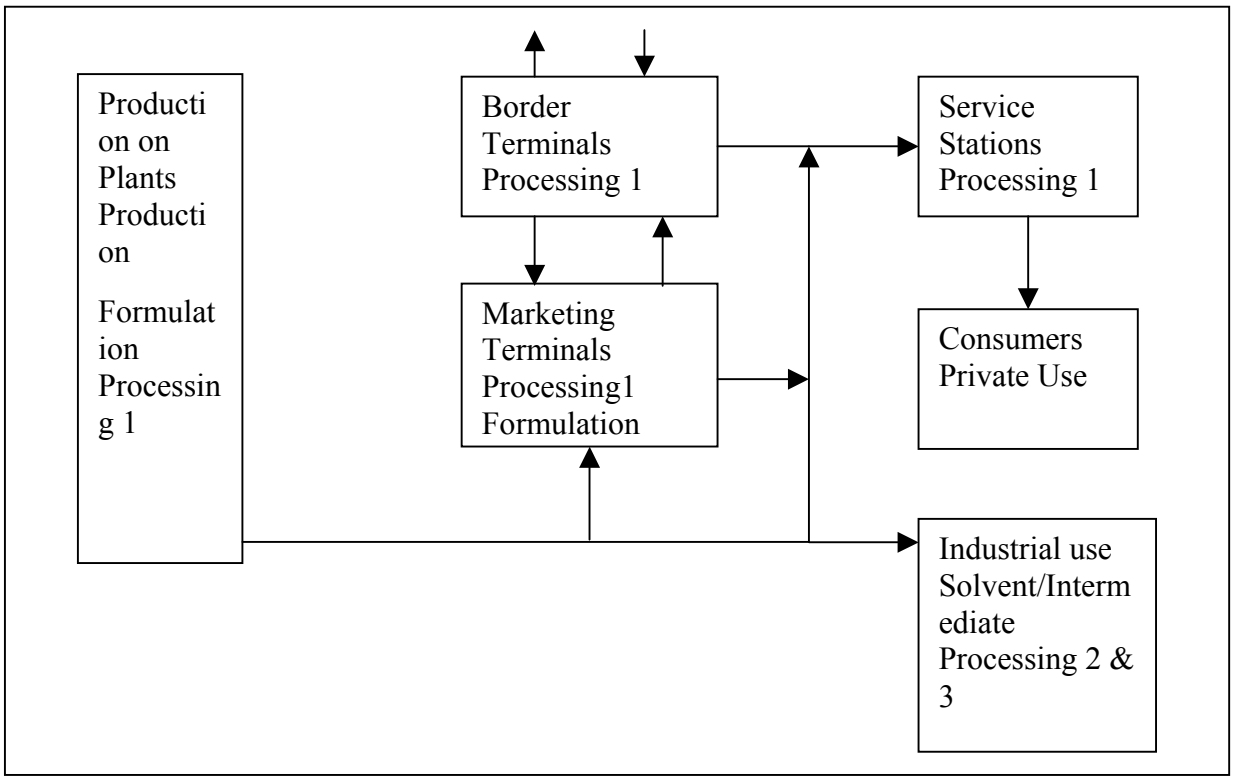
[1)] To select emission factors.
[2)] To select f-value and emission days.
[3)] Specific data emission scenario tables only partly used.
[4)] It covers also the transportation of non-blended (100%) within EU countries.

Table 3.2 Emission calculation parameters used in emission estimation

	Production 1	Formulation 1	Processing 1	Private use 1	Processing 2	Processing 3
Emission factors Air Wastewater Surface water Industrial soil	c 0.001 (s) 0.0003 (s) 0 0.0001	A2.1 (1b) 0.001 (s) 0.0003 (s) 0 0.0001	A3.8 0.003 (1) 0.0005 0 0.001	A4.2 0.025 (2) 0.0005 0.0001 0.0001	A3.3 0.05 0.000008 (s) 0 0.0001	A3.2 0.25 0.01 (s) 0 0.001
B-table Fraction of the main source	B1.4 0.4	B2.6 0.05 (s)	B3.7 0.02	B4.1 0.000002 (s)	B3.2 1.0 (s)	B3.2 0.4
Emission days	300	300	350	365	300	60

(s) means specific data, mostly measured data presented later in the report
(1) 0.0035 is used in EUSES calculation (see Section 3.1.3.3)
(2) specific data (see Section 3.1.3.3.)

Figure 1 Basic MTBE material flowchart (emission flows omitted)



3.1.3 Releases to the environment

The structure of this Section 3.1.3 may be divided under three main items. These items focus on:

- Describing selection of specific emission factors for Processing 1 and Private Use (Sections 3.1.3.1-3.1.3.2).
- Calculating continental emission rates/volumes to the environment and summed total emission factors to air for Processing 1 and Private Use (Section 3.1.3.3).
- Emission summary and selections for regional assesment, regional tonnages of petrol and average MTBE concentrations (Section 3.1.3.4.)

The default emission factors as well as some specific factors used in emission estimation are summarised in **Table 3.2**. The continental (EU totals) emission estimation focuses on the MTBE/petrol consumption tonnage and vehicle fleet composition and driving mileage statistics of the years 1995-1997.

In the emission calculation the total exhaust and evaporative HC is used as surrogate in MTBE emission calculation and average MTBE concentration in petrol (10 %-wt) in calculations does not reflect average EU MTBE concentration in petrol but the total consumed MTBE tonnage is the basis for emission calculations.

3.1.3.1 Emission factors for processing 1 scenario

Emission factor for petrol transportation, storage and delivery

MTBE is stored and transported as such, non-blended (pre formulation stage) and as a component of petrol. This emission scenario tries to calculate emissions from both of these basic source types.

Petrol distribution starts at the refinery tank farm from where the petrol is either pumped into pipelines or loaded into trucks, rail tank cars or waterborne craft. Petrol is transported either to downstream depots, from where further distribution takes place, or directly to customers (mainly refuelling stations). In the case of sea-going tankers, the product may be shipped to overseas refineries or terminals, from where the downstream distribution continues.

It is estimated/monitored that total average petrol emission in Western Europe during operations: Refinery→ Tank barge/rail tank car →Intermediate depot → Road tanker → Gas station was 1.42 kg/t (BUA, 1996).

ECE-CORINAIR inventory emission factor for refinery dispatch station is 0.31 kg/t and transport + depot is 0.74 kg/t and service station 2.88 kg/t (tank + refuelling emissions), in total 3.93 kg/t when refuelling of cars is included.

Directive 94/63/EU (1994) is for limiting emissions of volatile organic compounds (VOC-emissions) during the storage of petrol and its distribution from the delivery centres to the gas stations to 0.25 kg/t (goal).

Emission factors for refuelling

During the refuelling of motor vehicles at gas stations, a fuel-air mixture is displaced from the fuel tank (refuelling and displacement emission) (BUA, 1996). Displacement emission is estimated to be 1.4 kg/t and total emission 1.54 kg/t petrol (leaking 10% of displacement 0.14 kg/t) (CONCAWE, 1978).

About 70-90% of the displacement emissions can be prevented by equipping gas stations with vapour recovery systems (BUA, 1996).

Table 3.3 Emissions factors of petrol based hydrocarbons during turnover and storage of petrol and refuelling of vehicles

Operation	Emission kg/t
Filling	
Tank barges or rail tank cars	0.49
Road tankers	0.44
Mobile refuelling vessels	0.0002
Intermediate storage tanks	1.12
Gas station tanks	1..4
Gas station tanks, with gas balancing	0.14
Breathing	
Intermediate storage tanks	0.16
Gas station tanks	0.08
Refuelling of vehicles	
Displacement emission, without gas recovery	1.4 – 1.48
Displacement emission, gas recovery (80% efficiency)	0.31
Leaking (refuelling)	0.14-0.08

Sources: Gasoline /GDCh Advisory Committee on Existing Chemicals of Environmental Relevance. BUA report 1996.
EMEP/CORINAIR Atmospheric Emission Inventory Guidebook. European Environment Agency 1996.

Conclusion

Taking into account filling and breathing emissions from intermediate storage tank (1.12 + 0.16 kg/t) and gas station tanks (1.4 + 0.08kg/t) and refuelling emissions (1.48 kg/t) The data presented in **Table 3.3** assume the average turnover and storage VOC emission factor for petrol about 4.5 kg/tonnes (without gas recovery, no Stage1 or Stage 2 controls).

A great deal of petrol is transported directly from refinery depot to service stations and there are no emissions from unloading/loading and storing phases in intermediate depots leading to lowered total emissions. Similar lowered trend is achieved, as the gas recovery equipment is becoming more common in refinery and intermediate depot dispatch stations and service stations (Stage 1 controls). Refuelling gas recovery is also common in service stations in some of the EU member states (Stage 2 controls) cutting emissions to air by 80-90%. The proportion of the Stage 2 stations is 38-90% in six most advanced European countries in late 90's. In Finland, the proportion of Stage 2 stations was only 5% in the year 1998 (Hakkola et al., 1998b). A great deal of ships and barges transporting MTBE and petrol are not equipped with gas recovery equipment or equipment can not be used on board because lack of equal devices at the terminal harbours (FORTUM, 1999).

Taking into account data in **Table 3.3**, different emission control stage implementation in different member states, and the fact that emission estimation is focused on the years 1995-97 (Stage 1 & 2 controls common in some EU countries with high petrol consumption), an average EF 3 kg/t is used in further emission calculation.

As a conclusion, the TGD defaults are used in the further (processing 1) emission estimation for soil and wastewater and specific emission factor 3.0 kg/t for air.

Table 3.4 Emission factors (EF) for petrol per tonne for processing 1: transportation, storage and refuelling

	EF petrol
Air total	3 kg/t
Soil	1 kg/t
Wastewater	0.5 kg/t

3.1.3.2 Emission factors for private use scenario

This emission scenario deals with emissions from the use of petrol and is divided into two main sectors: 1) evaporative emissions and 2) exhaust emissions. Emission estimation is focused on to the atmospheric emission estimation. The intention is to derive realistic emission factors for different classes of vehicles and engines and thereafter calculate total annual emission of MTBE in the air at continental level. Finally, total emission factor to air for private use scenario is calculated as a ratio of total emitted/consumed tonnage.

3.1.3.2.1 Evaporative emission from vehicles/engines

Evaporative losses contribute substantially to total road transport related VOC emissions. Depending on the operation- and ambient temperature (evaporation emission), hydrocarbons are emitted from the motor vehicle tank and fuel system during the operation and standstill of the motor vehicle.

There are three primary sources of evaporative emissions:

- Diurnal (daily) emissions,
- Hot soak emissions,
- Running losses.

Hot soak emissions occur when the vehicle is stationary and the engine is hot and diurnal emissions occur when the vehicle is stationary and subject to day/night temperature changes. The hydrocarbon composition of hot soak emissions is more representative of the whole liquid fuel whereas diurnal emissions are enriched in the more volatile components (headspace components). Running losses are the result of vapour generated in petrol tanks during vehicle operation.

Since evaporative emissions are very sensitive to temperature, emissions are highly dependent on the time of the year. All three types of evaporative emissions are significantly affected by the volatility of the petrol being used, the absolute ambient temperature and temperature changes, and vehicle design characteristics. For hot soak emissions and running losses the driving pattern is also of importance.

Until 1993, evaporative losses of petrol passenger cars were not controlled in the EU. Since 1993 Directive 91/441/EEC requires the application of an on board carbon canister, which adsorbs petrol vapours and desorbs them to the engine under appropriate conditions. The overall efficiency of these canisters is of the order of 90% (McInnes, 1996).

Hydrocarbons are emitted from the motor vehicle tank and fuel system during the standstill of the motor vehicle. Heine and Baretti estimated, about ten years ago, before the emission control actions, VOC evaporative emission factor per tonnage petrol (Heine and Baretti cited in BUA,

1995). They got total emission factor 10.9 kg/tonne (after turning off hot and cold 6.4 kg, for standing motor vehicle 2.5 kg, diffusion from plastic containers 2.0 kg).

More recently, controlled and uncontrolled emission factors have been reviewed by Samaras et al. (1997). See **Table 3.5**.

Table 3.5 Evaporative emission factors for uncontrolled and controlled passenger cars

Type of Evaporative Emission	Uncontrolled	Controlled (carbo-canister efficiency 92-97%)
DIURNAL (g/day)	2.5 (January) 5-15 (June)	0.1-1
HOT SOAK (g/procedure)	11-22	0.3-0.8
WARM SOAK (g/procedure	1-7	0.2-0.8
HOT RUNNING (g/km)	0.02 (January) 0.1 (June)	0 (January) 0.01(June)
WARM RUNNING (g/km)	0,02 (January) 0,08(June)	0.002 (January) 0.01 (June)
Total Evap. Emissions (g/day)	34 (January) 47 (June) 40.5 (average)	1,8 (January) 2,8 (June) 2.3 (average)

Data Source: CORINAIR, RWTÜV in (Samaras et al., 1997)

Data from the above table can be used to get an evaporative EF (per tonne fuel) for uncontrolled and controlled passenger cars. If we assume 1,000 kg petrol consumed in a passenger car with average petrol consumption 8 l/100km (6kg/100km), it correspond 16 670 km driving. Correspondent evaporative VOC emission per 1000 kg petrol for a car driving at least once every day throughout the year would be 40.5 g/day ·365 days = 14.8 kg for uncontrolled older car and 2.3 g/day · 365 days = 0.84 kg for a controlled new car.

In the further assessment, a bulk-evaporative emission factor 0.01 (10 kg/t) is used for all types of uncontrolled on-road vehicles, off-road vehicles and petrol-fuelled engines. Emission factor 0.001 (1 kg/t) is used for controlled on road vehicles (EURO 1&2 controls).

Table 3.6 Evaporative VOC and MTBE emission factors for vehicles and engines (kg/t)

	EFpetrol	EF MTBE
Uncontrolled on-road and off-road vehicles and engines	10 kg/t	1 kg/t
Controlled on-road vehicles (EURO 1)	1 kg/t	0.1 kg/t

3.1.3.2.2 Exhaust emission factors and annual mileage

Exhaust hydrocarbons

Total organic carbon emission data (TOC) from dynamometer studies and on road tunnel studies and remote sensing studies are used as a surrogate to calculate the total MTBE emissions at the continental/regional level.

Tunnel studies

The proportion of unburned MTBE in exhaust TOC gases has been measured in real world driving conditions. In a tunnel study (1,100 m long Caldecott tunnel in California) Kirchstetter et al. (1996) measured 3.3 wt-% (+/- 0.3%) MTBE in total exhaust TOCs. Average oxygen content in petrol was 2.0% and traffic flow in this tunnel study was steady and cars were “temperature

balanced" so the results are valid for highway driving. The measured TOCs include emissions from evaporative losses also. Information on cold start's emission and stop and go emissions are not gathered from the tunnel study. The proportion of methane in exhaust gases were 11 +/- 3.5 wt-%. In NMVOC (Non-Methane Volatile Organic Carbon) emission MTBE concentration was 3.7 +/- 0.3.

The direct comparison of the emission factors of tunnel studies in the USA is restricted because of major differences in vehicle fleet in Europe and the USA. As the vehicles without catalyst strongly dominate the emissions in Europe whereas in the USA older catalyst types are also installed (John et al., 1999).

In a Gubrist–tunnel study in Switzerland, VOC emission of total 18,560 petrol-fuelled passenger cars, vans and motorcycles (73% catalyser models) were measured by in the year 1993. Average total-VOC emission per individual petrol-fuelled vehicle 456 (± 42) mg/km at average speed 92 km/h was measured. Driving conditions were representing highway driving (Staehelin et al., 1998). John et al. (1999) compared emission factors from this tunnel study to relevant emission factors from dynamometer studies. They found that considering the EF for all vehicles results were in a quite good agreement although EFs from the tunnel study were slightly higher for certain classes of vehicles.

Remote sensing studies

The remote sensing technology (Infra Red based) provides practical approach to routinely characterise real-world, on-road automobile HC exhaust emissions. It was used to measure the exhaust emissions of more than 1,000,000 vehicles in many locations around the world (Zhang et al., 1995). One important conclusion was that the absolute emissions differences between well- and badly maintained vehicles of any age were considerably larger than observable effects of emission control technology and vehicle age.

On-road remote sensing VOC emissions of 11,298 petrol-fuelled vehicles were measured in Switzerland. 50% of the VOC-emissions were caused by only 9.3% of these vehicles. However only about 25% of high emitters did not meet the exhaust gas standards (even some very new cars suffered from malfunctioning of the catalytic converter), and typically these "legal" 75% high emitters are older cars without catalyst (Maly and Sherrer, 1995; John et al., 1999).

Dynamometric measurements are accurate and well standardised methods in measuring emissions from on-road vehicles. A major drawback of dynamometer testing is that it does not accurately reflect the range of real-world driving conditions. Furthermore, the vehicles selected for testing may not be reflective of the actual on-road fleet of vehicles, e.g. the tested vehicles are generally in good operating condition and therefore under-represent emissions from malfunctioning vehicles. However, dynamometer studies (and legislative control levels) give good basic emission level standards for emission estimates. Appendix **Tables A.2 and A.3** present hydrocarbon exhaust emission levels for certain classes of vehicles.

<u>On-road vehicle fleet in the EU</u>

Passenger cars are by far the most abundant vehicle type, representing 80% of all vehicles in the EU. Light goods vehicles make up another 6.5%, of which some two thirds have diesel engines and the remainder petrol, heavy duty vehicles (effectively all diesel) comprise 3% of the fleet as HGVs and 0.25% as buses and coaches. Mopeds and motorcycles make up the remaining 10% (Hickman et al., 1999).

The distribution of the vehicles within the various emission categories is closely related to their age (since the various emission standards were introduced on a fixed time scale in most Member States). The average age of passenger cars is between 7 and 8 years. There are again variations from country to country: the oldest cars are in Finland where the average age is about 11 years, while the youngest fleet is in Luxembourg, with an average age of about 4 years (Hickman et al., 1999).

The number of passenger cars equipped with a catalyser is very different in different EU member countries. In 1997 lowest proportions of cars equipped with a three way catalyser (TWC)* were in Spain, Portugal, France and Finland (between 25-35 %) and highest proportions in Austria and the Netherlands (between 65-75%) (ÖKKL, 1999). Compared with passenger cars catalyser are more rare in delivery cars ("vans") and nonexisting in two wheelers.

Annual mileage and petrol consumption

Estimated traffic volume distribution (driven kilometres) by vehicles categories show that passenger cars represents within the EU member states from 75 to 90% of the total traffic volume, goods transport 8 to 20%, while bus and two-wheeler traffic are limited to 1 to 2% each (Andre et al., 1999).

Individual vehicles used for commercial purposes (light goods vehicles, heavy goods vehicles, buses and coaches) tend to be used much more than passenger cars. Compared with an overall annual mileage of about 12,000 km for cars, light goods vehicles cover approximately 20,000. Conversely, two-wheel vehicles cover considerably smaller annual mileage. Those less than 50 cc engine capacity, which are used mainly in urban areas for relatively short journeys, average 3,000 km/year while larger motorcycles have an average annual mileage of about 5,500 km/year (Hickman et al., 1999).

Table 3.7 shows %-ratio of average annual petrol consumption per vehicle class of the total consumption in EU. The total petrol consumption has been rather stagnant, about 115-120 million tonnes in the 90's.

Table 3.7 Annual mileage and petrol consumption % of total in EC-15 states per vehicle/engine Class, Reference year 1995

Petrol Consumer/Emission Classes *)	Total annual mileage (km/yr) per vehicle class (1995)	Estimated petrol consumption % of total in the EU
On-Road Vehicles		
4. Cars Pre ECE	$8.4 \cdot 10^8$	0.05
4. Cars ECE 15-00/01	$2.6 \cdot 10^{10}$	1.7
4. Cars ECE 15-02	$4.0 \cdot 10^{10}$	2.5
3. Cars ECE 15-03	$1.7 \cdot 10^{11}$	11.3
2. Cars ECE 15-04	$4.5 \cdot 10^{11}$	29.0
2. Cars Improved conventional	$3.5 \cdot 10^{10}$	1.7
2. Cars Open loop	$2.4 \cdot 10^{10}$	1.0
1. Cars EURO 1&2 (1991->)	$7.9 \cdot 10^{11}$	41.5
5. High Emitters (maintenance problems)	?	?
4. Light goods vehicles Uncontrolled	$1.6 \cdot 10^{11}$	7.2
1. Light goods vehicles EURO 1&2	$9.9 \cdot 10^9$	0.5
6. Cars 2-stroke	$3.2 \cdot 10^7$	0.002
6. Motor Cycles 2-stroke < 50 ccm	$3.6 \cdot 10^9$	0.85
6. Motor Cycles 2-stroke > 50 ccm	$1.7 \cdot 10^9$	0.20
4. Motor Cycles 4-stroke	$1.5 \cdot 10^{10}$	1.80
On-Road Vehicles TOTAL		ca. 99
Off-Road Vehicles and Engines	-	+ ca. 1% of total **)
6.Off-Road vehicles and Engines 2-stroke	-	
7.Off-Road vehicles and Engines 4-stroke	-	

Source: Data derived for MTBE RAR using original statistical data from Hickman et al. (1999)
*) Vehicles with equal heading numbers belong to the same emission category. Categories are used in further emission calculation.
**) The off-road consumption of petrol is ca. 1% of total (McInnes, 1996).

Hydrocarbon and MTBE exhaust emissions

In general, there is a close relationship between the fuel and the resultant exhaust composition (Duffy et al., 1999). Higher proportion of MTBE in petrol normally leads to higher concentration of unburned MTBE in exhaust gases and visa versa.

Using dynamometric driving cycle emission data and other relevant data sources average emission factors for TOC and MTBE has been derived. These emission factors will be used in further continental emission calculation. Average emission levels for different classes of vehicles are presented in Appendix **Tables A.2 and A.3** and emission factors in **Table 3.8** in the next page.

Unburned MTBE is one of the components of the emitted unburned and partly burned hydrocarbons. Dynamometric studies, where specific substances have been measured from the exhaust stream, allow to make estimates what is the %-proportion of MTBE in exhaust gases versus MTBE %-proportion in the original fuel. There are direct proportionality and good

enough linearity, between petrol composition and exhaust composition, and we can use "normalised" 10-% MTBE blend in continental emission calculations for each of the emission classes. So, without taking into account the actual high variety of MTBE blends used within the EU, the emission calculation assumes that all the annually consumed MTBE (>2 million tonnes) is blended and used as 10-% wt blend. The actual petrol tonnage in calculations is therefore more than 20 million tonnes. (Correspondingly, if "normalised" blend were 5-% the total petrol, tonnage in calculations would be doubled to more than 40 million tonnes).

Emission factors for different vehicle classes

Emission factors used in the continental/regional atmospheric emission estimation concerning petrol distribution and use are aggregated bulk factors, which tries to represent realistic average TOC emission level from different vehicle/engine class and MTBE as its component. The characterisation of the corresponding driving and operating conditions, trip characteristics, parking conditions, load factors, gradient and thermal operating conditions has not been taken into account in this simplified emission estimation.

Vehicle fleet (and petrol fuelled off road vehicles and engines) is divided in 5-6 main categories according to basic exhaust TOC emission level. Categorisation is made according to age of the vehicle (legislative control stage) or other reasons like engine type (2-stroke) or functionality level of the engine (maintenance problems) Exhaust emission categories and EF's for TOC and MTBE (weight -% in exhaust TOC) are presented in **Table 3.8**.

Table 3.8 TOC/MTBE exhaust emission categories and coarse emission factors

Exhaust Emission Category	Mean EF-TOC TOC emission kg/t petrol	Mean EF-MTBE %-wt MTBE in TOC
1. Passenger cars and vans with EURO1 & 2 Emission Control	7 kg/t	2% in TOC
2. Passenger cars and vans, Emission Control: ECE 15-04, Improved Conventional, Open Loop	30 kg/t	4% in TOC
3. Passenger cars and vans ECE 15-03	40 kg/t	5% in TOC
4. Passenger cars and vans, motor bikes (4-stroke) Emission Control: PRE ECE, ECE 15-00/01, ECE 15-02	60 kg/t	6% in TOC
5. High emitters cars, vans, etc. (maintenance problems)	250 kg/t	8% in TOC
6. 2-stroke vehicles and engines	250kg/t	8% in TOC
7. Off road vehicles and engines 4-stroke	40 kg/t	5 % in TOC

Key: PRE ECE (-->1971), ECE 15-00/01 (1972-1977), ECE 15-02 (1978-1980), ECE 15-03 (1981-85), ECE 15-04 (1985-92), Improved Conventional, Open Loop, EURO 1 (1991-94) &2 (1995-->)

Emission factors listed in table above are used in MTBE exhaust emission estimation in Section 3.1.3.3. (summary in Appendix **Table A.3**). The mean EF-TOC emission factors for different emission classes are coarse bulk EF's. Basic TOC emissions (g/t) for most of the emission classes are presented in Appendix **Table A.4** (emission control stage, engine capacity, speed, fuel consumption and TOC exhaust emission). In addition, emission degradation due to vehicle age for each emission class has been taken into account in some extent by multiplying basic TOC emission (kg/t) by factor 1.4-3.0. In **Table 3.8** the EF-petrol (X) as well as petrol use (Z) for class 5. High emitters class maintenance problems" is just assumption, supported by remote-sensing studies, that engines having for instance firing problems in one or several cylinders or

engines running fuel rich may have exceptionally high emissions. In addition if the fuel is passed into the exhaust gases almost unburned (maintenance problems) the concentration of MTBE in exhaust gases is expected to be close to concentration found in original fuel (Y-value in **Table 3.8**).

Although the emission estimation method does not take into account different driving patterns, geographic and fleet differences between member states etc. it is believed that these simplified EF's and the calculation method gives a reasonable good approximation of total exhaust emissions of MTBE into air.

3.1.3.3 Continental emission calculation of MTBE into air from the processing 1 and private use

In the year 1997 in EU-15 countries 2.28 million tonnes of MTBE was consumed as fuel. In manual emission calculations (**Table 3.9**) it is assumed that all the MTBE consumed as engine fuel is petrol which contains 10%- wt MTBE (as described previously in Section 3.1.2).

The main reason to this simplification is to make regional/continental emission estimation and calculations easier and avoid excess complexity. Secondary reason to this shortcut is lack of accurate statistical data on actual concentrations of MTBE (especially at low end <5%) and marketed volumes in different member states. However, just only the annual total consumed volume of MTBE is taken into account in emission calculations, not more.

This assumption is not in contradiction to the fact that actual petrol blends on the market may contain <1-15%-vol of MTBE or are MTBE free. Typically, high-octane (98-99) blends contain 8-14%-vol (ca. 8-14%-wt) MTBE and lower octane blends less.

In the emission calculation of transportation of non-blended MTBE, the amount of non-blended MTBE (925,000 tonnes) exported in 1997 has been taken into account. In addition, all MTBE produced in the chemicals industry branch (propylene-oxide process) is expected to formulated off-site in the EU or exported as non-blended MTBE. Emission factor 0.001 to air will be used for transportation of non-blended MTBE. The total amount of non-blended MTBE transported is estimated to be 1,300,000 tonnes (1997).

Table 3.11 calculates and summarises MTBE emission to air from storage, distribution and use of petrol (Processing 1 and Private Use emission scenarios).

The calculated total MTBE emission to air from storage and distribution of petrol is **8,140** tonnes and from the use of petrol **56,052** tonnes.

Finally the total emission factors are:

Processing 1: EF= emission/total tonnage = 8,140/2,280,000 = **0.0035**

Private Use: EF= emission/total tonnage = 56,052/2,280,000 = **0.025**

Note: MTBE consumption data of the year 1997 are used in this assessment. However, statistical data on annual mileage and vehicle fleet (**Table 3.7**) for the year 1995 are used in emission calculation (year 96-97 statistics were not available) leading to higher emissions.

However the actual effect of this contradiction has only very slight effect on the final emission factor EF=0.025 used for the private use scenario. Refinement of the EF is possible as soon as new statistics are available.

The true emission to air from Processing and Private use is obviously lower in the year 1997 than 1995 of two reasons.

Firstly, the consumed volume of MTBE was slightly lower 1997 than 1995 (on the other hand 1998 consumption figures seems to be higher than -95 or -97). Secondly, higher proportion of petrol was consumed in new lower emission vehicles in 1997 compared to 1995.

Table 3.9 Continental (EU totals) emission to air calculation Processing 1 and Private Use

Operation or Emission class	X=EF-petrol [1]	Y=EF-MTBE [2]	Z=MTBE/ petrol use [3]	Emission to Air Total (tonnes)
PETROL DISTRIBUTION (Processing 1 Scenario)			**22,800,000 t [4]**	
Blended MTBE (10%):				
Transportation of blended petrol: Refinery→ Tank barge/rail tank car → Intermediate depot → Road tanker → Gas station ---> Vehicle refuelling	0.003 (3 kg/t VOC) [5]	0.1	100%	6,840
Non blended MTBE (100%):				
Transportation of nonblended MTBE (export+import+off-site formulation)	-----	0.001 MTBE [6]	1,300,000 t	1,300
TOTAL emission to air Processing1				**8,140**
PETROL USE (Private Use scenario)				
Evaporative Emissions:				
Evaporative emissions: EURO1 controlled vehicles	0.001 (1 kg/t VOC)	0.1	0.41(41%)	935
Evaporative emissions: non EURO1 vehicles and engines	0.01 (10 kg/t VOC)	0.1	0.59 (59%)	13,452
Exhaust Emissions:				
1. Exhaust emission EURO1 vehicles with TWC (10 wt-% MTBE)	0.007 (7 kg/t TOC)[7]	0.02 (2% in TOC)	0.41 (41%)	1,309
2. Exhaust emission CARs Emission Control: ECE 15-04, Improved Conventional or Open Loop	0.030 (30 kg/t TOC)[7]	0.04 (4% in TOC)	0.31 (31%)	8,482
3. Exhaust emission CARs and vans, Emission Control: ECE 15-03,	0.040 (40 kg/t TOC)	0.05 (5% in TOC)	0.1 (10%)	5,016
4. Exhaust emission CARs, vans, Motorbikes 4-stroke Emis. Control PRE ECE, ECE 15-00/01, ECE 15-02	0.060 (60 kg/t TOC)	0.06 (6% in TOC)	0.12 (12%)	10,670
5. Exhaust em. High emitters cars, vans, etc. (maintenance problems)	0.250 (250 kg/t TOC)	0.08 (8% in TOC)	0.02 (2%)	9,120
6. Exhaust em. All On-Road and Off Road vehicles and engines 2-stroke	0.250 (250 kg/t TOC)	0.09 (8% in TOC)	0.015 (1.5%)	6,840
7. Exhaust em. Off Road vehicles and stationary engines 4-stroke	0.040 (40 kg/t TOC)	0.05 (5% in TOC)	0.005 (0.5%)	223
TOTAL emission to air from use of petrol				**56,052**

Key: Emission (tonnes) = X * Y * Z * 22,800,000 t

1) EF-petrol describes VOC emissions by weight from different life stage of petrol

2) EF-MTBE describes the proportion of MTBE in X, emissions from petrol by weight from different life stages of petrol.

3) Fraction (or tonnage) of main consumed per operation or emission class

4) Total EU consumption of MTBE in fuel (1997) blended as 10 wt-%.petrol

5) CONCAWE data

6) Non Blended Estimated emission 1 kg/t --> Emission (tonnes) = Y * Z

7) FTP-75 test data

3.1.3.4 Emission summary

Regional and continental as well as local emission estimate results to all environment compartments from all of the emission scenarios (1-6) are summarised in this Section. Results are calculated using EUSES model or calculated manually (see **Table 3.9**) and the results are summarised in **Table 3.10**.

Regional consumption

On average, petrol consumption within the EU was about 310 kt per million inhabitants in 1997. True consumption was lowest in Portugal 193 kt and highest in Sweden 458 kt (The tonnages are calculated from the data in **Table 2.5** and actually the highest but omitted "consumption" was in Luxembourg 1,355 kt per million inhabitants because of high "export"). Assuming the average value 310 kt for 20 million inhabitant (in 40,000 km^2) the regional consumption of petrol would be 6.2 Mt. If 6.2 Mt petrol are blended with 223,000 t MTBE (TGD 10% rule) the average regional concentration is 3.6%.

Actually the consumption of MTBE is remarkable more common in some member states than in others and therefore the actual realistic regional consumption of MTBE might be higher than 10% of the total EU consumption (TGD 10% rule). If the 6.2 Mt petrol is accepted as regional consumption of petrol the highest average percentage MTBE blend (8.5%) at member state level would comprise 527,000 tonnes MTBE which is ca. 24% of total annual EU consumption. MTBE blend (5%) would comprise 310,000 tonnes, which is ca. 14% of total annual EU consumption. In the further regional assessment the regional consumption of MTBE is 14% of the total EU consumption.

Table 3.10 MTBE emission summary table

	Production 1	Formulation 1	Processing 1	Private use 1	Processing 2	Processing 3	Total t/yr
Relevant tonnage for application (tonnes/year)	3,030,000		2,280,000		29,000	6,000	
Regional tonnage of substance (tonnes/year)	903,500		310,000 [1] specific data	310,000 [1] specific data	29,000 [3] specific data	600	
Continental tonnage of substance (tonnes/year)	2,130,000		1,970,000	1,970,000	0	5,400	
Emission factors Air Wastewater Surface water Industrial soil	A1.1 (1b) 0.001 [2] 0.0003 [2] 0 0.0001	A2.1 (1b) 0.001 [2] 0.0003 [2] 0 0.0001	A3.8 0.0035 [4] spec. data 0.0005 0 0.001	A4.2 0.025 [4] specific data 0.0005 0.0001 0.0001	A3.3 0.05 $8 \cdot 10^{-6}$ [2] 0 0.0001	A3.2 0.25 0.01 [2] 0 0.001	
Fraction of the main source	B1.4 0.4	B2.6 0.05 [8]	B3.7 0.02	B4.1 0.000002 [6] specific data	B3.2 1	B3.2 0.4	
Emission days	300	300	350	365	300	60	
Continental release Air Wastewater Surface water Industrial soil	 2,130 t/yr 638 t/yr 0 213 t/yr	 1,970 t/yr 590 t/yr 0 197 t/yr	 6,880 t/yr 983 t/yr 0 1,970 t/yr	 49,100 t/yr 983 t/yr 197 t/yr 197 t/yr	 0 0 0 0	 1,350t/yr 54 t/yr 0 5.4 t/yr	 $7.4 \cdot 10^{04}$ $2.3 \cdot 10^{03}$ $1.2 \cdot 10^{03}$ $2.6 \cdot 10^{03}$
Regional release Air Wastewater Surface water Industrial soil	 904 t/yr 271 t/yr 0 90.3 t/yr	 3.0 t/yr 93 t/yr 0 31 t/yr	 1,080 t/yr 155 t/yr 0 310 t/yr	 7,740 t/yr 155 t/yr 31 t/yr 31 t/yr	 1,450 t/yr 0.232 t/yr 0 2.9 t/yr	 150 t/yr 6 t/yr 0 0.6 t/yr	 $1.4 \cdot 10^{04}$ 476 235 465
Local emission to air during episode	1,200 kg/day	51.7 kg/day	62 kg/day	- [7]	4,830 kg/day	1,000 kg/day	
Local emission to wastewater during episode	361 kg/day	15.5 kg/day	8.8 kg/day	- [7]	0.773 kg/day	40 kg/day	
Local indirect emission to air from STP during episode	156 kg/day	6.68 kg/day	3.8 kg/day	- [7]	0.333 kg/day	17.2 kg/day	
Total Emissions (tonnes/year)	4,246 t/yr	2,884 t/yr	11,378t/yr	58,434 t/yr	1,453 t/yr	? t/yr	

[1] The regional use of MTBE 310,000 tonnes/year use of MTBE as a petrol additive [2] See sections on local PECs [3] Use volumes submitted by industry [4] specific factor see Section 3.1.3.3 [5] No release to wastewater expected [6] Fraction of emission per vehicle/engine assuming 0.5 million vehicles in use simultaneously [7] considered not relevant or no emission scenario available. [8] Only fraction of ca 5% of total consumed MTBE is formulated outside refineries.

3.1.4 Environmental distribution and fate

3.1.4.1 Partitioning

Henry's law constant can be estimated using the vapour pressure of 270 hPa at 20°C and water solubility 42,000 mg/l at 20°C, H = 56.7 Pa m^3/mol (log H = 1.74). The calculated H value indicates that MTBE volatises easily from water to air. There are also measured values available, 43.8 Pa m^3/mol (log H = 1.64) at 20°C and 53.5 Pa m^3/mol (log H = 1.73) at 25°C (Robbins et al., 1993). Calculated and measured values differ from each other only slightly. Measured value 43.8 Pa m^3/mol at 20°C will be used in further model calculations (20°C is closer to average environmental temperature than 25°C).

Log K_{ow}: Values 0.94 - 1.43 has been referred in literature and databases (see Chapter 1). A measured value Log K_{ow} 1.06 will be used in the further assessment (Huels AG, 1989). The same value 1.06 has also been calculated earlier by Hansh (Hansch et al., 1968).

Equilibrium partitioning: Using the fugacity model (level 1), the theoretical distribution of MTBE based on physico-chemical properties between four environmental compartments at equilibrium can be calculated. Results indicate that volatilisation may be expected from water and soil and adsorption to particulate matter is poor.

Table 3.11 Fugacity level 1. Equilibrium partitioning

Compartment	Distribution %
Air	93.9%
Water	6.045%
Soil	0.054%
Sediment	0.001%

At lower temperatures as the water solubility of MTBE increases and vapour pressure decreases the equilibrium partitioning is less in the air compartment side and higher proportion of the substance is in water phase.

Adsorption and desorption

Because of structural reasons (low molecular weight aliphatic ether), it can be concluded that physisorption is the predominant adsorption mechanism of MTBE (no chemisorption processes like covalent bond formation or ion exchange is expected). Some adsorption will always take place on minerals but adsorption of MTBE and related substances to soils free of organic matter is most often less pronounced compared to soils with organic matter (Lyman et al., 1990).

Physisorption occurs more at lower temperatures (McKay, 1996). This may lead to slightly higher adsorption of substances in cold groundwtaerater-soil systems. On the other hand, higher solubility of MTBE in cold water compared to solubility at 25°C (Scholz et al., 1990; Stephenson, 1992) may compensate for these slight changes in adsorption.

Various QSAR estimations give an organic carbon partitioning coefficients (K_{oc}) of 9-12. MTBE is expected to have high mobility in soil based on estimated K_{oc} of 12.3 (derived from water solubility data) and 10.96 (derived from K_{ow} data) and K_{oc} of 11.2 (Howard, 1990). MTBE is

expected to be highly mobile in soils, and leaching of the chemical into groundwtaerater is likely (Howard, 1990).

Calculating Koc for MTBE using TGD QSAR for predominantly hydrophobics (Log K_{oc} = 0.81 log K_{ow} + 0.10) gives the value K_{oc} = 9.1 (calculated as nonhydrophobics (Log K_{oc} = 0.52 log K_{ow} + 1.02) gives the value K_{oc} = 1.6).

It can be concluded that the adsorptivity of MTBE to the soil is poor and leaching with water is the predominant abiotic fate process in the subsurface ground. Monitoring data strongly support this assumption.

Water solubility of MTBE-oxygenated petrol

The high solubility of MTBE in water, combined with its high concentration in petrol, can result in high concentration of MTBE in surface water and groundwater contaminated by point sources of oxygenated petrol.

The partitioning of MTBE between water and petrol is affected in part by the solubility of MTBE in water. At a given temperature, the solubility of a pure organic liquid in water is a constant, represented as cs (mg/l). However, the solubility is reduced below cs when other organic compounds are present in the liquid organic phase (e.g. petrol). At a given temperature, the solubility of a compound from the organic mixture will be reduced from cs by the factor Xm, which is the mole fraction of the compound in the mixture (Squillace et al., 1997).

For petrol that is 10% by weight MTBE, equilibrium solubility in water at room temperature would be 4-5 g/l (assuming no depletion of the MTBE concentration in the petrol and solubility of pure MTBE 40-50 g/l) (Squillace et al., 1997).

The solubility of petrol was tested by Huttunen (1997) with non-oxygenated and oxygenated petrol. The total hydrocarbon water solubility for a non-oxygenated petrol poor in aromatics is generally about 90-120 mg/l and rich in aromatics 220-250 mg/l (at 20^{o}C). The water solubility of a reference fuel which was poor in aromatics but contained MTBE (11%) was determined to be 2,300 mg/l.

The high concentrations of MTBE that can occur in groundwater at petrol-release sites have raised the question as to whether MTBE could enhance the subsurface transport velocities of the BTEX (benzene, toluene, ethylbenzene, xylene) group through a co-solvency effect. In fact, research has indicated that co-solvency effects generally arise only when the co-solvent is present in water at 1% (10,000 mg/l) or more (Squillace et al., 1997).

3.1.4.2 Degradation

3.1.4.2.1 Biotic degradation

Biodegradation in water

Aerobic Standard Ready Tests

In a Closed bottle study (OECD 301D) with 2 mg/l of test substance, no degradation of MTBE was observed (0%) after 28 days (Huels AG, 1991e).

In a second study Closed bottle test (OECD 301D) with 2 mg/l of test substance, 1.8% degradation after 28 days was observed (RBM, 1996e).

From the results of these studies, it can be concluded that MTBE is not readily biodegradable in the aquatic environment.

Aerobic Standard Inherent Biodegradation Tests

There are no standard inherent test results available.

Non-standard Aerobic Biodegradation Tests

High mineralisation rates of MTBE were observed by Salanitro et al. (1994) in a study using high concentration of isolated adapted mixed bacterial culture. A special inoculum (120-200 mg/l) contained several bacterial species and MTBE as the sole carbon source. This test shows that certain microbes (probable nitrifying species) are able to degrade MTBE. The growth of the species responsible to degrade MTBE was found to be very slow (<0.01/day). This culture metabolised MTBE to CO_2 (40%) and cell mass (40%).

The test substance, pure MTBE, was radiolabelled on the methoxy group carbon. The primary intermediate degradation product was identified to be tertiary butyl alcohol (TBA). Degradation was concentration dependent. Highest degradation of MTBE (>80%) was observed with MTBE concentrations higher than 100 mg/l. Little or no degradation was observed when the concentration was lower than 20 mg/l other factors being constant.

High degradation rates were also observed by Sun et al. (1993). It was shown that MTBE can be aerobically degraded to low levels, usually below 1 mg/l. Complete mineralisation was accomplished without producing observable amounts of intermediates in the continuous units used in the experiment. When the conditions were favourable more than 99% MTBE removal through biodegradation was routinely accomplished with an adapted inoculum (1,000 mg/l) that can use MTBE as its sole carbon source. On the other hand, the culture is extremely slow growing and can be easily upset by environmental insults; such as anaerobic conditions or sudden changing in feed MTBE concentrations.

In an aerobic study by Mo et al. (1997), 7-8% (CO_2 evolution) of MTBE was degraded after one week using a pure bacterial culture inoculum. The pure cultures were isolated from activated sludge and fruit of Gingko tree and were classified to the genuses *Methylobacterium*, *Rhodococcus* and *Arthrobacter*. The growth of the inoculum on MTBE as the sole carbon source (200 mg/l test substance) was very slow compared with growth on a nutrient rich medium.

In an aerobic study by Steffan et al. (1997), several propane oxidising bacteria were tested for their ability to degrade MTBE. Both a laboratory strain and natural isolates were able to degrade MTBE in laboratory conditions after growth on propane. High degradation rates were achieved (60% mineralisation in 24 hours at 28^{o}C, 20 mg/l test substance, 70-100 mg/l inoculum). The initial oxidation of MTBE resulted in the production of *tert*-butyl alcohol (TBA). TBA was further oxidised to 2-methyl-2-hydroxy-1-propanol and then 2-hydroxy isobutyric acid, neither of these degradation products was an effective growth substrate for the propane oxidisers. Because propane oxidisers are widespread in nature, authors suggest that these bacteria may provide a basis for the development and implementation of biologically mediated treatment processes for petrol oxygenates.

High removal rates were measured in aerobic high biomass (ca. 1,000 mg/l biomass and 7-9 mg/l MTBE) comparative studies using continuous reactor systems (US EPA method 304a&b) and

batch reactor systems. First order degradation rate constants K_1 for MTBE on average 11-16 h^{-1} were reached. In comparison for toluene in the same test system K_1 was on average 169-268 h^{-1} and for 1,2-dichloro ethane, 0.02. Methods simulated continuous biological treatment systems and stripping and recirculation of the substances were allowed in the test methods (except the SBT "serum bottle test"). A two-months preadaptation phase of the biomass was reported (Cano et al., 1999).

Anaerobic biodegradation

In an anaerobic, static sediment/water microcosm study by Mormile et al. (1994), MTBE was only slowly degraded under all conditions tested. After 152 days of incubation in static sediment/water microcosms only one sample showed approximately 50% decrease in MTBE content (50 g of sediment and 75 ml water were mixed with 50 ppm MTBE). Sediments were collected from sites chronically contaminated with petroleum hydrocarbons. Inoculum was indigenous sedimentary microorganisms occurring under anoxic/anaerobic subsurface conditions. Both sulphate reducing and nitrate reducing metabolic pathways were explored using appropriate co-incubation factors. Metabolism under methanogenic conditions was also assessed.

After 249 days (<8 months) of incubation, MTBE did not biodegrade (0%) under the test conditions in anaerobic, sediment/water test system (Suflita et al., 1993).

Conclusions on biodegradation in aquatic compartment

MTBE is not readily biodegradable in aquatic environment according to the standardised aerobic ready-biodegradation tests.

As no test results from standard inherent test systems for aquatic biodegradation are available, conclusions are made according to the non-standard tests.

High degradation rates have been observed in non-standard tests using special types of inoculum, pure cultures and mixed cultures. These studies show that at least some microbial species are capable to degrade MTBE and to use it even as their sole carbon source.

It may be concluded that MTBE is inherently biodegradable under certain conditions in aquatic aerobic environment. However, the non-standard test data available indicate that MTBE degradation might not fulfil the test criteria (OECD 302) to be classified "inherently biodegradable". Therefore, in the EUSES model calculations the characterisation of biodegradability in aquatic environment is "Inherently biodegradable, not fulfilling criteria".

Biodegradation in soil

Aerobic and anaerobic degradation in soil

Yeh et al. (1994) studied anaerobic biodegradation of petrol oxygenates in soils. They observed that MTBE degradation occurred only in soils with low organic content and with pH of about 5.5. MTBE did not degrade in soils with high organic content. Addition of easily biodegradable organic compounds inhibited the biodegradation of MTBE in soils that otherwise could degrade MTBE. Soils were collected from diverse sites and included unsaturated clay, sandy loam, and silty loam. Soils from the sites had not been previously exposed to fuels. Concentrations of MTBE were monitored for more than 250 days. Three different kinds of soils from three sites were used. Soils were moderately acidic (pH 5.0-6.0). Substantial numbers of anaerobic microorganisms were found at these sites.

Three anaerobic metabolic processes were evaluated including 1) denitrification, 2) sulphate reduction and 3) anaerobic degradation. These processes were individually evaluated by adding nutrients that selectively encouraged their activity (i.e. nitrate, sulphate, and cysteine, respectively). MTBE was resistant to biodegradation in most sets of experiments. The addition of nitrate to promote the activity of denitrifiers did not enhance the degradation of MTBE. Degradation of MTBE was observed only on one of the three sites; on site 1 with low organic content and a microbial population two orders of magnitude lower than on sites where no degradation was observed. Addition of starch, nutrients and molybdate on site 1 enhanced degradation remarkable. The initial concentration of 100 mg/l of MTBE decreased to a level lower than 1 mg/l in 250 days. If no additives (starch etc.) were used no degradation was observed in any of the test soils. Degradation of tertiary butyl alcohol (TBA) and ethyl tertiary butyl alcohol (ETBE) was also studied and MTBE was the most recalcitrant (Yeh et al., 1994).

In a study by Allard et al. (1996), a special mixed culture did not degrade MTBE in aerobic conditions during six weeks. A single sample of hydrocarbon-contaminated soil was enriched under aerobic conditions in a mineral medium supplemented with t-butanol (1g/l) as sole carbon source, or methylamine (2g/l) as main carbon source and t-butanol (0.1 g/l) as co-substrate. The mixed cultures obtained after four serial transfers were used for further experiments. In a growth experiment, the concentration of t-butanol declined slowly after an initial lag phase. Cell suspensions of the mixed culture or of methylamine-grown cells incubated with MTBE showed no similar decline in substrate concentration during 6 weeks. As a conclusion; MTBE was undegraded under aerobic conditions during 6 weeks incubation with cell suspensions prepared from either t-butanol or methylamine-grown cells.

A recent study done by Bradley et al. (1999) showed remarkable aerobic mineralisation of MTBE by stream bed sediment microorganisms. Initial MTBE concentration was 150 µg/l and 400 µg/l. Laboratory microcosm studies (at room temperature) were conducted using bed sediments from two underground petrol spill sites. Up to 73% of MTBE were degraded to $^{14}CO_2$. under mixed aerobic/anaerobic conditions during 105 days. Result indicates that biodegradation may in some cases be a significant removal process of MTBE in aerobic soil. No significant mineralisation was observed under strictly anaerobic conditions.

Except for certain laboratory biodegradation studies proving MTBE biodegradation, limited empirical data are available from contaminated sites. Those that are available indicate that MTBE degrades very slowly, only degrades near the source, or is recalcitrant (Reisinger et al., 2000).

Conclusion on biodegradation in soil

Based on the studies available it may be concluded that rapid and reliable biodegradation of MTBE in soil can not be assumed in any normal environmental conditions indicating very slow degradation in soil. The biodegradability of MTBE in soil in aerobic and especially in anaerobic conditions seem to be very slow and favourable conditions for degradation are difficult to attain. In the further EUSES model calculations the characterisation of biodegradability in soil is "Not biodegradable" (half-life $1 \cdot 10^6$ day).

Table 3.12 Summary table; results of referred biodegradation tests for MTBE

no.	Type of test	Detection	Result	Day	Method	Conc. of TS	Conc. of inoc.	Ref.
1	Closed bottle	O_2 uptake	0%	28	(OECD 301D)	2 mg/l		Huels AG (1991)
2	Closed bottle	O_2 uptake	1.8%	28	(OECD 301D)	2 mg/l		RBM (1996)
3	Non standard aerobic	MTBE ^{14}C labelled	up to 99%	0.3	adapted mixed culture Microbial growth rate <0.01/day	variable	120-200 mg/l	Salanitro (1994)
4	Non standard aerobic		>99%		adapted inoculum		1,000 mg/l	Sun (1993)
5	Non standard aerobic	CO_2 evolution	7-8%	7	pure culture Methylobacterium, Rhodococcus and Arthrobacter	200 mg/l		Mo et al. (1997)
6	Non standard aerobic		60% minerali-sation	1	Special propane oxidising (28 °C)	20 mg/l	70-100 mg/l	Steffan et al. (1997)
7	Variable methods aerobic	GC analysis	>99%	1	adapted inoculum	7-9 mg/l	1,000 mg/l	Cano et al. (1999)
8	Non standard anaerobic, static sediment/water		0-50%	152	from petroleum contaminated sites			Mormile et al. (1994)
9	Anaerobic, sediment/water		0	249	from sites contaminated chronically with landfill leachate			Suflita et al. (1993)
10	Aerobic stream-bed sediment	$^{14}CO_2$	73	105	sediments from petrol spill sites	150-400µg/l		Bradley et al., 1999
11	Anaerobic stream-bed sediment	$^{14}CO_2$	~ 0		sediments from petrol spill sites	150-400µg/l		Bradley et al. (1999)

3.1.4.3 Abiotic degradation

3.1.4.3.1 Abiotic degradation in air

Direct photodegradation

Direct photolysis will not be an important removal process since aliphatic ethers do not absorb light at wavelengths >290 nm (Schumann et al., 1973; Howard, 1990; US EPA, 1994).

Indirect photodegradation

Under atmospheric conditions, MTBE reacts essentially solely with the OH-radicals (Tuazon et al., 1991). Reaction with O_3 , and reaction with NO_3 radicals are negligible slow compared to reaction with hydroxyl radicals (Howard, 1990; Wallington et al., 1989).

MTBE is susceptible to indirect photolysis by photochemical-oxidative degradation in the atmosphere. In ethers, it has been found that C-H bonds adjacent to the -O atom react more readily than the equivalent C-H bonds in hydrocarbons (Atkinson in Cox et al. (1982)).

There are two studies of the oxidation of MTBE under simulated atmospheric conditions. The first, by Cox et al. (1982), employed the photolysis of MTBE-HONO-air mixtures. In the second by Japar et al. (1990), three different chemical systems were investigated (MTBE-CH_3ONO-NO-air, MTBE-Cl_2-NO-air, MTBE-Cl_2-air). *Tert*-butyl formate (TBF) was observed to be the major degradation product in these studies.

In a relative rate study (Smith et al., 1991) hydroxyl radicals were generated by the photolysis of ethyl nitrate in air with nitric oxide present to preclude formation of ozone and NO3 radicals. The concentration of hydroxyl radicals was not specified in this paper. Rate constant 2.99 (±0.12) · 10-12 cm3/molecule-sec at 298°K was measured. Degradation was essentially complete under the conditions of the test. Chemical reaction products resulting from the indirect photolysis of MTBE were: t-butyl formate, methyl acetate, acetone, t-butyl alcohol, and formaldehyde. The first three compounds account for 95% of the photodegraded MTBE.

Table 3.13 Absolute rate parameters for the reactions of OH radicals with MTBE (OH + MTBE --> products)

k_1 10^{-12} cm^3 $molec^{-1}$ s^{-1}	Temp. K	$A_1 10^{-12}$ cm^3 $molec^{-1}$ s^{-1}	E_1 kJ/mol	Temp. range	Technique	Reference
2.5 (± 0.5)	295				RR	Cox & Goldstone (1982)
3.09 (± 0.15)	298	5.1 (±1.6)	1.3 (±0.8)	240-440	FP-RF	Wallington et al. (1988)
2.84	298	4.0 (± 1.3)	0.85 (± 0.59)	246-314	RR	Bennett et al. (1990)
3.09	298	5.2 (± 1.7)	1.3 (±0.8)	240-440	Evaluation	Bennett et al. (1990)
2.99 (±0.12)	298				RR	Smith et al. (1991)
2.98 (±0.11)	293			295-750	LIF	Arif et al. (1997)

Relative Rate (RR), Flash Photolysis (FP), Resonance Fluorescence (RF), Resonance Absorption (RA), Laser Photolysis (LP), Laser Induced Fluorescence (LIF)

The majority of the OH-radical attack (appr. 60%) leading to degradation occurs at the methoxy (O-CH3) group, leading to the formation of an alkoxy radical, which reacts with molecular oxygen to give the formate TBF and an HO_2 -radical (Japar et al., 1991).

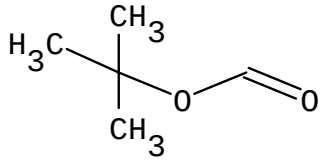


Figure 2 **TBF** the major primary degradation product of MTBE in the air

The further degradation rate constant (reaction with OH radicals) for *tert*-butylformate (TBF), in the air has been measured k=7.37 ±0.05 · 10^{-13} cm^3 $molecule^{-1}$ s^{-1} (at 25°C) (Smith et al., 1991).

Table 3.14 presents the main degradation products of MTBE in the air and the corresponding conversion percentages detected in the cited studies.

Table 3.14 MTBE degradation products identified in indirect photolysis studies in the air (% refers to molar proportion)

Degr. Product	MTBE converted to %	Study
t-butyl formate	major (62%±$^{12}_{5}$)	Cox et al. (1982); Tuazon et al. (1991); Smith et al. (1991) Japar et al. (1990)
Formaldehyde	major (40%±$^{13}_{5}$)	Tuazon et al. (1991); Smith et al. (1991)
Methyl acetate	major (17%±$^{2}_{5}$)	Tuazon et al. (1991); Smith et al. (1991); Japar et al. (1990)
Acetone	major to minor (down to 2%)	Cox et al. (1982); Tuazon et al. (1991); Smith et al. (1991)
t-butyl alcohol	minor (6%±$^{5}_{5}$)	Smith et al. (1991); Japar et al. (1990)
Acetaldehyde	Minor	Tuazon et al. (1991)

Conclusion on abiotic degradation in air

According to existing data, degradation half-life of MTBE in the air is 3-6 days depending on environmental conditions (predominantly OH-radical concentration).

Using degradation rate constant 2.84 · 10^{-12} cm^3/molecule s^{-1} and OH –radical conc. 5 · 10^{5} radicals/cm^3 a half-life 5.65 days is calculated. This half-life for degradation in air will be used in further assessment. Half-life 5.65 days represents degradation rate in non-polluted air, rather than polluted air where half-lives typically are shorter due to higher concentrations of reactive radical components in the air.

3.1.4.3.2 Abiotic degradation in water

Hydrolysis

MTBE is resistant to hydrolysis in environmentally relevant pH scale. Strong acids decompose MTBE but pH needed for decomposition is far below normally detected in natural soil and water.

Photolysis in water

Direct photolysis will not be an important removal process since aliphatic ethers do not absorb light at wavelengths >290 nm (Howard, 1990; Schumann et al., 1973). The UV-spectrum (max at 289 nm) indicates that direct photolysis in water may not occur.

Elimination in WWTPs

Based on the physico-chemical properties of MTBE and taking into account the degradation rate for biodegradation of 0 h-1, the elimination in WWTPs (as a result of distribution processes) can be determined using the Simple Treat 3.0 model in accordance with the TGD as follows:

Table 3.15 Simple Treat 3.0-model calculation for MTBE

Evaporation to air (%)	43.1
Release (dissolved) to water (%)	56.8
Adsorption to sewage sludge (%)	0.1
Degradation (%)	0
Total elimination from water (%)	43.2

3.1.4.4 Bioaccumulation

According to the (Q)SAR proposed in EC (1996), BCF of 1.6 can be estimated for fish (log BCF = 0.85 log K_{ow} - 0.70).

A calculated BCF of 2.7 for 28-d exposure of fathead minnows, is mentioned in WHO (1998) and Veith et al. (1983).

Whole-body bioconcentration factors (BCF) of 1.5 and 1.4 were reported for Japanese carp exposed to 10 and 80 mg/l MTBE in a flow-through system at 25 ^{o}C. Fish exposed for 28 days and then transferred to clean water eliminated almost all MTBE residues within 3 days (Fujiwara et al., 1984).

These calculated and tested BCFs indicate a low potential for bioconcentration. For the further assessment, **BCF 1.5** (measured value) is used.

3.1.5 Aquatic compartment

3.1.5.1 Local predicted environmental concentrations in the aquatic compartment

Local PECs for production sites, generic and site specific, are presented in Section 3.1.5.1. In addition there are PEC calculations or derivation in Sections 3.1.5.2-3.1.5.4 concerning:

- Intermittent release from storage tank bottom waters,
- Boating,
- Stormwater runoff.

3.1.5.1.1 Local PECs for production, formulation and processing sites – EUSES calculations

The PEC local for the aquatic compartment from industrial point sources is calculated according to the TGD (1996). Using the values from EUSES calculations the removal by volatilisation is 43%, if the substance is considered non degradable in an industrial sewage treatment plant (STP).

The concentration of MTBE in the WWTP- effluent is calculated with the following formula:

$$Clocal_{eff} = \frac{Elocal_{water} \cdot 10^6}{EFFLUENT_{stp}} \cdot Fstp_{water}$$

where $Elocal_{water}$ = local emission rate to (waste) water during episode (kg/day) (from **Table 3.10** MTBE emission summary table),
$EFFLUENT_{stp}$ = effluent discharge rate of STP (default 2,000,000 l/day),
$Fstp_{water}$ = fraction of emission directed to water by STP (0.57 i.e. 57.0%),
$C_{localeff}$ = concentration of the chemical in the STP-effluent (mg/l).

According to the TGD the local concentration of the substance in surface water is calculated as follows:

$$Clocal_{water} = \frac{Clocal_{eff}}{(1 + Kp_{susp} \cdot SUSP_{water}\ 10^{-6}) \cdot DILUTION}$$

where $Clocal_{eff}$ = concentration of the chemical in the STP-effluent (mg/l)
Kp_{susp} = solids-water partitioning coefficient of suspended matter (0.91 l/kg)
$SUSP_{water}$ = concentration of suspended matter in the river (default 15 mg/l)
DILUTION = dilution factor (default 10)
$Clocal_{water}$ = local concentration in surface water during emission episode (mg/l)

From the concentration of the substance in the surface water, the $PEClocal_{water}$ will be calculated by adding the regional concentration of the substance:

$$PEClocal_{water} = Clocal_{water} + PECregional_{water}$$

Table 3.16 Concentrations in waste and surface waters according to EUSES

	Concentration in untreated wastewater (mg/l)	Concentration in treated wastewater of WWTP ($Clocal_{eff}$) (mg/l)	Local concentration in surface water ($Clocal_{water}$) (mg/l)	Local PEC in surface water mg/l (regional = 0.0015 mg/l)
Production 1	181	103	10.3	10.3
Formulation 1	7.75	4.4	0.44	0.442
Processing 1	4.42	2.51	0.251	0.253
Processing 2	0.387	0.22	0.022	0.023
Processing 3	20	11.4	1.14	1.14

Some substances have an adverse impact on microbial activity. For the risk characterisation of a chemical upon microorganisms in the STP, ideally the concentration in the aeration tank should be used. Assuming homogeneous mixing in the aeration tank, the dissolved concentration of a substance there is equal to the effluent concentration:

$$PEC_{stp} = Clocal_{eff}$$

where $Clocal_{eff}$ = total concentration of chemical in STP effluent (mg/l)
PECstp = PEC for microorganisms in the STP (mg/l)

Consequently, the concentration of the substance in wastewater ($Clocal_{eff}$) is the concentration for which microorganisms are exposed and which is regarded as PEC for microorganisms.

For indirect human exposure and secondary poisoning, an annual average concentration in surface water is calculated:

$$Clocal_{water,ann} = Clocal_{water} \cdot \frac{T_{emission}}{365}$$

where $T_{emission}$ = number of days per year that the emission takes place (from **Table 3.10** MTBE emission summary table)
$Clocal_{water,ann}$ = annual average local concentration in surface water (mg/l)

Annual average predicted environmental concentration is calculated:

$$PEClocal_{water,ann} = Clocal_{water,ann} + PECregional_{water}$$

Table 3.17 Annual average local PECs in surface water

	($Clocal_{water,ann}$) = Annual average concentration in surface water (mg/l)	**($PEClocal_{water,ann}$) = Annual average local PEC in surface water (mg/l)**
Production 1	8.43	8.43
Formulation 1	0.362	0.363
Processing 1	0.241	0.242
Processing 2	0.018	0.019
Processing 3	0.187	0.188

PEC for sediment is calculated using PEC for water as follows:

$$PEClocal_{sed} = \frac{K_{susp\text{-}water}}{RHO_{susp}} \cdot PEClocal_{water} \cdot 1{,}000$$

where $PEClocal_{water}$ = concentration in surface water during emission episode (mg/l)
$K_{susp\text{-}water}$ = suspended matter – water partitioning coefficient (EUSES 1.13m^3/ m^3)
RHO_{susp} = bulk density of suspended matter (TGD 1,150 kg/m^3)
$PEClocal_{sed}$ = predicted environmental concentration in sediment (mg/kg)

Table 3.18 EUSES calculation PEC locals in sediments

MTBE Life Cycle	PEClocals in sediment, mg/kgwwt
Production 1	10.1
Formulation 1	0.433
Processing 1	0.248
Processing 2	0.023
Processing 3	1.11

3.1.5.1.2 Local PECs for production, formulation and processing sites – site-specific approach

All sites known to produce MTBE in theEU region are included in **Table 3.19**. All European MTBE plants in February 2000 are listed in Appendix **Table A.1**. There are 29 production and/or formulation sites, one production/processing 2 (isobutylene production) site and various processing 3 (use as pharmaceutical solvent) sites in the EU region. For some sites, there are no specific information on possible formulation on-site. If no information is available, it is assumed that all MTBE produced to be used as petrol additive is formulated on site. When actual emission or concentration data are available, it is assumed that formulation is included in the emission to the wastewater.

There are relevant emission data or measured concentrations reported from all but 1 production and/or formulation sites. These sites represent a production of about 3,150,000 tonnes/year, which is about 95% of the total production volume in the EU in 1999.

The emissions from sites that have informed only the volume of production/formulation are calculated using default emission factor derived from site-specific data. Calculation of the emission factor for production/formulation sites has succeeded in 23 cases, because some sites have not informed emissions to wastewater directly but e.g. concentrations in influent, effluent or receiving water. MTBE concentration being quite often below detection limit, the emission factors calculated from them are not accurate or in many cases even realistic.

Site 9 in **Table 3.20** is the only site which is using MTBE for isobutylene production. The emission factor from this site including both production and processing 2 is calculated from specific data. **Table 3.21** includes information from one site that is using MTBE as solvent in the production process of pharmaceutical active agents. Specific data are also used to calculate the emission factor for use as solvent in pharmaceutical industry.

Table 3.19 Site-specific local concentrations from production and production/formulation sites

Site code and activity	Process type	Emission factor	Local emission rate to wastewater $Elocal_{water}$ (kg/day)	WWTP	Effluent discharge of STP $EFFLUENT_{stp}$ (l/day)	Emission to surface water as WWTP effluent (kg/year)	Conc. in effluent $Clocal_{eff}$ (mg/l)	Dilution factor	Conc. in receiving water (mg/l)	$PEClocal_{water}$ (PECregional = 0.0015) (mg/l)	$PEClocal_{sed}$ (mg/kg)
Site 1 Production Formulation		0.000008		yes	**$2.9 \cdot 10^7$**		**<0.1 (detection limit)**	def 10	<0.01	<0.01	<0.01
Site 2 Production Formulation	wet closed	0.0001	39.4	yes	**$1.2 \cdot 10^7$**	**8,200** [5]	1.82	def 10	0.182	0.183	0.180
Site 3: no longer producing MTBE											
Site 4 Production	wet closed	-		yes	**$2.3 \cdot 10^{13}$**		**<1 (detection limit)** [5]	def 10	<0.1	<0.1	<0.1
Site 5 Production	wet closed	def 0.0003	41.1	yes (own + nearby)	$6 \cdot 10^6$		3.90	def 10	0.390	0.390	0.383
Site 6 Production Formulation	dry closed	0.0000005	**0.07**	yes	**$6.34 \cdot 10^6$**		**0.074** [5]	**120,000**	$6.0 \cdot 10^{-7}$	0.0015	0.0015
Site 7 Production	wet closed	0.000002 calc. with def $EFFLUENT_{stp}$		yes			**<1**	def 10	**<0.1** [5] **(detection limit)**	<0.1	<0.1
Site 8 Production	dry closed	0.0000001		yes	**$3.6 \cdot 10^7$**		**<0.0002** [5]	**22**	**<0.00003 (detection limit)**	<0.00003	<0.00003
Site 9: see Table 3.20											
Site 10 Production Formulation [1]	wet	-		yes	**$9.1 \cdot 10^6$**		**<25** [5] **(detection limit)**	def 10	<2.50	<2.50	<2.46

Table 3.19 continued overleaf

Table 3.19 continued Site-specific local concentrations from production and production/formulation sites

Site code and activity	Process type	Emission factor	Local emission rate to wastewater $Elocal_{water}$ (kg/day)	WWTP	Effluent discharge of STP $EFFLUENT_{stp}$ (l/day)	Emission to surface water as WWTP effluent (kg/year)	Conc. in effluent $Clocal_{eff}$ (mg/l)	Dilution factor	Conc. in receiving water (mg/l)	$PEClocal_{water}$ (PECregional = 0.0015) (mg/l)	$PEClocal_{sed}$ (mg/kg)
Site 11 Production Formulation		0.00009		yes			**0.190** [5] **(influent 6.53)**	def 10	0.019	0.020	0.020
Site 12		0.000003	**0.93**	yes	**$8.6 \cdot 10^7$**	**114**	**0.0036** [5] **(influent 0.011)**	**100**	0.00004	0.0015	0.0015
Site 13: no longer producing MTBE											
Site 14 Production Formulation [2]	dry closed	0.0000004		yes	**$6.0 \cdot 10^6$**		**<0.010 (detection limit) (influent 0.441)**	def 10	<0.001	<0.0025	<0.0025
Site 15 Production Formulation		0.00004		yes	**$2.4 \cdot 10^7$**		**0.167** [5] **(influent 0.866)**	def 10	0.017	0.018	0.018
Site 16 Production Formulation		0.00004 (0.0001 – $2 \cdot 10^{-8}$)	**6.85 (estimated)**	yes	**12,000**		**0.59** [5] **(influent 22.2)**	def 10	0.059	0.060	0.059
Site 17 Production Formulation	wet closed	0.0002		yes			**<2** [5]	def 10	<0.2	<0.2	<0.2
Site 18 Production Formulation	wet closed	0.0002		yes			**<2** [5]	def 10	<0.2	<0.2	<0.2
Site 19 Production Formulation	wet closed	0.0000007		yes	**$8.6 \cdot 10^6$**		**<0.02** [5] **(influent 0.03)**	**14,000**	<1.4 · 10-6	<0.0015	<0.0015

Table 3.19 continued overleaf

Table 3.19 continued Site-specific local concentrations from production and production/formulation sites

Site code and activity	Process type	Emission factor	Local emission rate to wastewater $Elocal_{water}$ (kg/day)	WWTP	Effluent discharge of STP $EFFLUENT_{stp}$ (l/day)	Emission to surface water as WWTP effluent (kg/year)	Conc. in effluent $C_{localeff}$ (mg/l)	Dilution factor	Conc. in receiving water (mg/l)	$PEClocal_{water}$ (PECregional = 0.0015) (mg/l)	$PEClocal_{sed}$ (mg/kg)
Site 20 Production Formulation	dry closed	0.0002	**<0.015**	yes	**$3.5 \cdot 10^7$**	**<5.5**	**<1**	def 10	<0.1	<0.01	<0.01
Site 21 Production Formulation		0.0001 calc. with def EFFLUENTstp		yes	def $2.0 \cdot 10^6$	**4** [5)]	**5.5**	def 10	0.55	0.55	0.54
Site 22 Production Formulation				yes	**$1.6 \cdot 10^7$**			**>1,000,000**	**<0.010** [5)]	<0.010	<0.01
Site 23 Production Formulation		0.000003	**0.97**	yes	**$1.5 \cdot 10^7$**	**27.6**	**0.005 (influent 0.064)**	def 10	0.0005	0.002	0.002
Site 24 Production Formulation		0.0003	**24.7**	yes	**$5.4 \cdot 10^6$**	**9.9**	**0.005** [(5] **(influent 4.54)**	**1,000,000**	**<0.010**	<0.010	<0.01
Site 25 Production Formulation		0.0002 calc. with def EFFLUENTstp		yes [3)]	def $2.0 \cdot 10^6$		9.98 **(influent 17.5)** [5)]	def 10	1.00	1.00	0.98
Site 26 Production Formulation		0.00001	**2.8**	yes	**$1.9 \cdot 10^7$**	**273.3**	**0.039** [5)] **(influent 0.147)**	**100**	**<0.010**	<0.010	<0.01
Site 27 Production Formulation		0.0001 (A) 0.00002 (B)	12.1 (A) 6.9 (B)	A B [4)]	**$1.2 \cdot 10^7$ (A) $6.9 \cdot 10^6$ (B)**	**221 (A) 252 (B)**	**0.050 (A) (5 0.100 (B) (influent 1.0 (A, B))**	**1,000,000**	**<0.010**	<0.010	<0.01

Table 3.19 continued overleaf

Table 3.19 continued Site-specific local concentrations from production and production/formulation sites

Site code and activity	Process type	Emission factor	Local emission rate to wastewater Elocalwater (kg/day)	WWTP	Effluent discharge of STP $EFFLUENT_{stp}$ (l/day)	Emission to surface water as WWTP effluent (kg/year)	Conc. in effluent $C_{localeff}$ (mg/l)	Dilution factor	Conc. in receiving water (mg/l)	$PEClocal_{water}$ (PECregional = 0.0015) mg/l)	$PEClocal_{sed}$ (mg/kg)
Site 28 Production Formulation		0.00001	0.7	Yes	**9.6 · 106**	**17.5**	**0.005** [5] **(influent 0.071)**	**1,000,000**	**<0.010**	<0.010	<0.01
Site 29 Production Formulation		0.00003	**2.6**	Yes	**5.2 · 106**	**52.5**	**0.030 (influent 0.196) spot samples**	**1,000,000**	**$3 \cdot 10^{-8}$**	0.0015	0.0015
Site 30 [2] Production Formulation		0.0000008	**0.172**	Yes	**3.6 · 107**		**<0.008**	**4,524**	**0.000002**	0.0015	0.0015
Site 31 [2] Production Formulation				Yes	**1.44 · 106**		**0.3 (hydrocarbons)**	def 10	~ 0.03 (hydrocarbons)	~ <0.03	~ <0.03
Site 32 [2] Production Formulation		-	-	Yes	**6.24 · 106**	-	**0.2 (hydrocarbons)**	def 10	~ 0.02 (hydrocarbons)	~ <0.02 +regional	~ <0.02

values received from industry written in bold

[1] running a project to change the unit to ETBE by the end of next year [2] more data should be coming [3] wastewater stream connected to a wwtp outside the refinery

[4] discontinuous discharge (about 500 h/year for wwtp b) [5] known to be based on various measurements

No EU legislation or Member State legal requirement exists with regard to MTBE sampling in water, air and soil. It was therefore agreed that MTBE producers would voluntarily set up a sampling programme predominantly for verification of MTBE concentrations in water and if possible for air sampling for risk assessment purposes. This sampling programme occurred during the summer 2000. Some of the producers have been monitoring MTBE concentrations in water and air since 1997.

The emission factor to wastewater from the production and production/formulation sites in **Table 3.19** ranges from 0.0000001 to 0.0003. The default emission factor according to the Technical Guidance Document is 0.003. Since there are site-specific information from 28 sites and emission factor could be calculated for 23 sites from the total of 29 sites, the highest emission factor 0.0003 will be used in stead of default in EUSES calculations and for the one site that has not delivered any emission data.

The concentration of MTBE in effluent ranges from 0.00003 mg/l to 9.98 mg/l (**Table 3.19**). In many cases the measured concentrations of MTBE are below the detection limit which ranges form 0.001 mg/l to <25 mg/l. In the cases where the detection limit is high, the calculation of the emission factor does not give a reasonable result. The default EUSES calculations using the site specific emission factor 0.0003 show concentrations of MTBE in effluent from production 103 mg/l and from formulation 4 .4 mg/l (**Table 3.16**).

The concentration in receiving water ranges from 0.00000008 mg/l to 0.55 mg/l when site-specific information is available (**Table 3.19**). Very often in the MTBE measurements the concentrations are below detection limit. The reported detection limit values range from <0.0005 mg/l to <1 mg/l but obviously there are methods which can detect MTBE in much lower concentrations. The default EUSES calculations using the site-specific emission factor 0.0003 show concentrations of MTBE in receiving water from production 10.3 mg/l and from formulation 0.44 mg/l (**Table 3.16**).

The predicted environmental concentrations in water from site-specific data range from <0.00003 mg/l to <2.5 mg/l and in sediment from <0.00003 mg/l to <2.46 mg/l (**Table 3.19**) whereas the default EUSES calculations using the site-specific emission factor 0.0003 show predicted environmental concentrations of MTBE in surface water of 10.3 mg/l from production and 0.442 mg/l from formulation and in sediment 10.1 and 0.433 mg/l, respectively (**Table 3.16**).

Table 3.20 Site-specific local concentrations in surface water and sediment from production and processing 2 (production of isobutylene)

Site code and activity	Process type	Emission factor	WWTP	Effluent discharge of STP EFF_{stp} (l/day)	Conc. in effluent $Clocal_{eff}$ (mg/l)	Dilution factor	Conc. in receiving water (mg/l)	$PEClocal_{water}$ ($PEC_{regional}$ = 0.0015) (mg/l)	$PEClocal_{sed}$ (mg/kg)
Site 9 Production Processing 2	wet closed	0.000008	yes	**$1.5 \cdot 10^7$**	**<0.1**	10	<0.01	<0.01	<0.01

values received from industry in bold

The emission factor for the Site 9 using MTBE for production of isobutylene is 0.000008 and concentration in effluent is <0.1 mg. Using the default dilution factor of 10, the concentration in receiving water and the predicted environmental concentration is <0.01 mg/l (**Table 3.20**).

There is only one company which has informed to use MTBE for production of isobutylene. There is also production in the same site. The emission factor to wastewater according to the Technical Guidance Document for this kind of activity is 0.007. Since this is the only site, the emission factor calculated for this site 0.000008 will be used in EUSES calculations.

The EUSES calculation with emission factor of 0.000008 give 0.22 mg/l for concentration in the effluent, 0.022 mg/l for concentration in surface water and 0.023 mg/l for predicted environmental concentration (**Table 3.16**).

Table 3.21 Site-specific local concentrations in surface water and sediment from processing 3 (solvent use)

Site code and activity	Emission factor	Local emission rate to wastewater $Elocal_{water}$ (kg/day)	WWTP	Conc. in effluent $Clocal_{eff}$ (mg/l)	Dilution factor	Conc. in receiving water (mg/l)	$PEClocal_{water}$ (mg/l) (PECregional = 0.0015)	$PEClocal_{sed}$ (mg/kg)
Site 33 (MTBE is used 330 days/year)	0.009	**2.4**	**yes**	**<0.1 (influent 2)**	**2,000**	0.00005	0.0016	0.0016

values received from industry in bold

The emission factor from Site 33 using MTBE as solvent in pharmaceuticals industry is 0.009 and the concentration in effluent is <0.1 mg/l. Using the dilution factor of 2,000 the concentration in receiving water is 0.00005 and the predicted environmental concentration is 0.0016 mg/l (**Table 3.21**).

The default value for emission factor to wastewater using MTBE as solvent in pharmaceuticals industry according to the TGD is 0.65. There is information from only one site from the estimated total around 60 sites in the EU region. According to industry information, all processes using MTBE as solvent are identical to this (see Section 3.1.2). Regarding this information emission factor 0.01 is used in EUSES calculations for this type of use. The EUSES calculation using emission factor of 0.01 give concentration in the effluent of 11.4 mg/l and both the concentration in receiving water and the predicted environmental concentration in surface water are 1.14 mg/l (**Table 3.16**).

3.1.5.1.3 Local PECs for processing 1

Emissions to surface water during transportation

Direct release to surface water is expected to be low or non-existing during transportation of petrol. Petrol and MTBE are, however, transported in barges and ships in inland waters and releases to water are possible for instance from leaking loading/unloading facilities. No quantitative estimation has been carried out.

Ship and barge ballasting water and/or tank wash water cause intermittent releases. Tanks which have previously contained petrol, are loaded with ballast water and emptied with variable amount of petrol components in the water. In modern ships, there are separate tanks for liquid bulk and ballasting water and therefore chemicals do not contaminate ballasting water. This kind of releases are regulated with international agreements (MARPOL 73/78) and more specifically with regional agreements and regulations and considered to be out of the scope of this risk assessment.

Release from the storage of petrol

In refinery, marketing and border depots petrol is stored in tanks of different construction, i.e., fixed roof tanks, fixed roof tank with internal floating covers or floating roof tanks as well as in some countries, also in underground manmade caverns in basement rock. The size of marketing and border terminal storage tanks is highly variable and typical size is 5,000-50,000 m^3.

Industry has submitted information on 17 sites handling with bulk storage and transfer operations of petrol and light oil (processing 1). The emissions of MTBE to water are presented in Appendix Table 4. The emission factor for bulk storage and transfer operations of petrol and light oil (processing 1) to wastewater ranges from 0.0000001 to 0.0006. The default emission factor according to the TGD is 0.0005. The measured concentrations in receiving water are range from < 0.010 mg/l (detection limit) to 0.1 mg/l. The calculated concentrations are somewhat higher but at all those sites the emission is going to a WWTP outside the bulk terminal or to a municipal sewer system when no data on actual dilution are available.

MTBE may pose a significant wastewater treatment problem especially at petrol product terminals. Few wastewater characterisation works have been done concerning MTBE concentration in waste streams. Petrol tank bottom water may contain MTBE at concentrations of 200 to 4,000 mg/l and product terminal wastewater from 30 to 500 mg/l (Sun et al., 1993).

During the storage and turnover of petrol in storage tanks water is condensed on the bottom of these tanks. Because of the high-water solubility of MTBE, tank bottom waters may typically have high concentration of MTBE. Bottom water problem is less pronounced in refinery storage tanks due to the "dryness" of refined new distillates. Marketing depots and border depots receive products with higher proportion of water. Time to time tank bottom water is removed and disposed either directly or via STP to surface water causing intermittent releases. Concerning the monitoring data (Appendix **Table A.4**) there is no knowledge of the frequency of the measurement cited in which makes it difficult e.g. to assess for instance the proportion and frequency of tank bottom waters in the effluent.

Bottom water problems are more difficult in cavern storage. Since much of Sweden's petrol is stored in underground caverns, there has been a significant problem with oxygenates. These caverns always have an oil-water interface, through which oxygenate migration would occur (Dewitt & Company Inc., 1998). Because of precautionary measures, MTBE added petrol is usually not stored in such caverns (SFT, 2000).

Aquatic PEC_{local}, intermittent release from tank bottom waters

Because there are large number of terminal sites in the EU storing and handling gasoline, a generic emission estimate is made for tank bottom waters. Some of the sites do not have actual wastewater treatment system for tank waters.

As a simplified realistic worst case, scenario it is assumed that storage tank bottom water is drained directly (via water/oil separator) to surface water. PEC_{local} for surface water is calculated for one operation of draining water (10 cm) from a medium to high size (30,000 m^3) cylindrical storage tank. Bottom area of a 10 m high tank is 3,000 m^2 and the volume of 10 cm thick bottom water layer is 300 m^3. If released directly to surface water (or via water/oil separator) as a realistic worst-case situation 1,200 kg of MTBE is released at once at the concentration 4,000 mg/l (in pure MTBE tank concentration can be even much higher reaching the maximum water solubility of the substance). SAMS, screening assessment model system (OECD 1992), can be used in crude estimation of PEC_{local} in recipient (TGD 2.3.8.3). SAMS – river is a 50-box steady state model for chemical transport in rivers. Flow rate, 20,000 m^3/d (0.232 m^3/s), was selected

for the river, which is 10 times TGD default STP flow. Other parameters were: 10 m wide, 0.5 m deep, 10 km long river with 100 g/m^3 suspended matter (4% organic C). Tank bottom water was released to the river in 6 hours and initial MTBE concentration was 4,000 mg/l. The amount of released water was 300 m^3 (0.0138 m^3/s) leading to an dilution factor of 16.8) As a result of SAMS calculation, concentration PEC_{local} was 59.48 mg/l at 400 m from the release point and still 45 mg/l at 10 km from the release point.

PEC local for surface water from depot tank bottom water PEC_{local} = 60 mg/l

For substances subject to intermittent releases to the aquatic compartment, a dedicated PNEC (Section 3.2.1.8) is used in the risk characterisation.

It is believed that terminal site tank bottom waters are the most pronounced source of MTBE to surface waters from these sites in terms of emitted volumes and high peak concentrations.

In large depot areas with many tanks, bottom water releases may happen weekly or more often or even continuously like in cavern storage. In these cases it is not appropriate to regard emissions as intermittent but rather continuous and PNEC derived from long-term tests have to be used in deriving the PEC/PNEC ratio.

Table 3.22 Emissions from tank bottom waters (data submitted by industry)

Site	Emission from petrol storage tanks (kg/day)	Concentration in tank bottom waters (mg/l)	Influent concentration
Site 11		# 150	
Site17	max 35	12 000	1-3 ppm in influent to WWTP
Site 18	max 35		1-3 ppm in influent to WWTP
Site 19: tank bottom waters to WWTP			
Site 28		40 – 700	
Site 39		83	
Site 40		3	
Site 50		1067	

3.1.5.1.4 Local PECs from road traffic

Because of the extensive and wide use of petrol as a fuel in road traffic, direct releases to surface water from road traffic are likely. Direct releases may take place especially from bridges, ferry boards etc. in connection with malfunctioning petrol distribution systems in vehicles like leaking carburettors, piping etc. Runoff from roads after rain may also contain trace amounts of petrol components.

Stormwater runoff in 16 US cities and metropolitan areas was monitored in 592 samples from 1991 through 1995. Concentrations of 62 VOCs, including MTBE, were analysed. MTBE was the seventh most frequently detected VOC in urban stormwater, following toluene, total xylene, chloroform, total trimethylbenzene, tetrachlorethene and naphthalene. MTBE was detected in 6.9 percent (41 of 592) of the samples collected. When detected, concentrations of MTBE ranged from 0.2 to 8.7 µg/l, with a median of 1.5 µg/l (Delzer et al., 1996).

As a realistic worst-case situation, the PEC for MTBE can be estimated in a small stream receiving drainage from a long stretch of motorway. According to existing studies the PEC of MTBE is most probably less than 10 µg/l and the influence of other road traffic based contaminants (BTEX, PAH, heavy metals) in terms of aquatic toxicity potential or concentration

exceeds that of MTBE's. Based on the referred monitoring data, the mean concentration value was 1.5 µg/l when detected. If additional dilution in receiving surface water is not taken into account the PEClocal $_{\text{aquatic, road runoff}}$ is:

$$\mathbf{PEC_{local\ aquatic,\ road\ runoff} = 1.5\ \mu g/l}$$

3.1.5.1.5 Local PEC from petrol fuelled watercrafts

Motorboating and comparable activities lead to direct emissions of petrol to the aquatic environment through spills and exhaust gases.

Certain types of watercrafts (most outboard motors and jet skis) direct their exhaust gases directly under the water surface. This technique is used for lowering exhaust noise. The basic technique for releasing exhaust gases under water is similar in most petrol-fuelled boats regardless weather the type of the motor is two- or four-stroke. Exhaust TOC emissions from four-stroke engines (and injection fuelled two-stroke engines) are normally far lower than from traditional two-stroke engines.

Two cycle engines commonly used on recreational watercrafts are particularly inefficient in their use of fuel. Even >>25% of the fuel is passed through properly functioning engines and into the water via exhausts.

MTBE may comprise 11-15% of petrol by volume and consequently, on heavily used lakes a significant amount of MTBE is passed into the water column (Johnson et al., 1998).

A minor part of the substances in exhaust gas bubbles distributed into the water will be dissolved to water. The diffusion time of the substances is rather limited and the major part of the substances is released to atmosphere as the exhaust bubbles enter the water/air interface. Test results of MTBE partitioning are available. When petrol is released from normal operation of a motorboat, approximately 40% of the MTBE is retained in the water, while 60% is immediately lost to the atmosphere over the short time course of these tests (Keller et al., 1998).

Petrol can be spilled directly into the surface water while switching or loading of petrol tanks and carburettor overflow while tilting the motor. This release is estimated to be less than 0.1% of total fuel consumption and very low compared to exhaust emissions.

Monitoring data

There are existing monitoring data from boating available. Monitoring of lakes indicates that during the boating season MTBE is found in the water column at concentrations that range from 2-3 µg/l to 20-30 µg/l, depending on the relative amount of boat traffic within the previous few days. These monitoring studies indicate that most of the MTBE is found within the epilimnion (Johnson et al., 1998). In Helsinki during summer 1999, the concentration of MTBE in brackish seawater in boat marinas and boat waterways varied between 0.4-6.13 µg/l (n=17) and the average value was 2.6 µg/l (Helsinki, 2000). Surface water concentrations after organised boating or jet ski events can be considerably higher. Even 100 µg/l has been measured (OEHHA, 1998).

A one year study in Donner Lake (USA) showed that recreational boating was clearly the most important source of MTBE in the lake water, and it appeared that engine exhaust and not spills was the major factor. Neither urban runoff nor precipitation contributed significantly. Analysis of fresh snowfall indicated that in all samples MTBE was less than 0.1 µg/l. MTBE

concentration in lakewater ranged from <0.1 µg/l to 12.1 µg/l (n=470, dl=0.1µg/l). Beginning in early May, and coincident with the onset of the summer boating season, MTBE concentrations in the surface waters increased from a low value of 0.1 µg/l on April 24th to approximately 2 µg/l just prior to the 4th of July weekend. Between July 1-7, 1997, total lake MTBE rose dramatically, 2 µg/l to 12 µg/l, from 115 kg to 365 kg because of intense boating. By the following January, levels declined to a minimum of 15 kg suggesting little, if any, persistence between years. The major loss of MTBE from Donner Lake appeared to be volatilisation at the air-water interface. During the boating season, and following the seasonal maximum, total lake MTBE declined at a rate of 1.2 kg.d-1 (193 day half-life). However, once boating drastically declined at the end of the summer recreation season, MTBE loss increased to 8.1 kg.d-1 (14 day half-life). The influence of mean daily wind speed on the seasonal distribution of MTBE was minimal. The density gradient in the lake produced by thermal stratification was an effective barrier against MTBE transport to deeper depths (Reuter et al., 1998).

Average measured concentrations of MTBE in surface water where boating is the major source of MTBE are <0.1-12 µg/l. Depending on local conditions "moderate" boat traffic seems to cause 2-3 µg/l and high traffic even >10 µg/l concentration. Maximum measured values 100 µg/l are considered as short-term peak values. Assuming that high traffic period average concentration (Donner Lake study) represents realistic local high concentrations, thus:

$PEC_{\text{local surface water boating}}$ = 12 µg/l

3.1.5.2 Regional and continental predicted aquatic concentrations

From the EUSES model, the following $PEC_{regional}$ and $PEC_{continental}$ MTBE concentrations have been calculated for the surface water and sediment. The regional values are considered as calculated background values.

Regional PEC in surface water (dissolved)	1.5 µg/l
Regional PEC in sediment (total)	1.12 µg/kgwwt
Continental PEC in surface water (dissolved)	0.1µg/l
Continental PEC in sediment (total)	0.08 µg/kgwwt

3.1.5.3 Surface water and rainwater monitoring data

General points

Obtained measurement data on MTBE in European aquatic environments are rather scarce, particularly from background areas (see **Table 3.23**).

Table 3.23 Summary statistics of MTBE concentrations (ng/l) in the aquatic environment.

Environment	n	Min	Med	Max	Information source
Rivers, D	6	7	67	140	Achten & Puettmann
Rivers, UK	5			200	Wrc (unpubl.)
River, FI	1		193		City of Helsinki Environ. Centre (1999)
Rivers, USA	112		420	760	Reiser & O'Brien, ref. Achten & Puettmann
Creeks (urban), FI	4	340		620	City of Helsinki Environ. Centre (1999)
Lakes, DK	4	<		590	Miljostyrelsen (1998)
Lake, City of Marl, D	1		100		Oxeno Gmbh (unpubl.)
Rain water (urban), D	3	<10		70	Achten & Puettmann
Sea (boat harbors), FI	17	390		6,130	City of Helsinki Environ. Centre (1999)
Urban wastewater, FI	1		910		City of Helsinki Environ. Centre (1999)
Urban stormwater, USA	592	200		8,700	Zogorsky et al., ref. Achten & Puettmann

The measurement data are commented below by type of aquatic environment. The relevance and significance of the data for the assessment are further evaluated in connection with comparisons of modelled and measured data in Section 3.1.5.4.

Rivers and brooks

Recently, concentrations of 7-160 ng l^{-1} have been measured by novel pre-treatment methods in the German rivers Elbe, Oder, Rhein and Main (Achten and Puettmann, in press). The median value is ca. 6 times below that in surface waters in the USA. The difference may be explained by monitoring methodologies (e.g. sampling focus), MTBE use volumes and (areal) patterns, amounts released (depending on e.g. the technical standard of storage and treatment), and dilution (due e.g. to area of the country per amount of MTBE released).

In Helsinki, Finland, average concentrations of 420 to 480 ng/l were measured in two urban creeks subject to diverse emissions e.g. from stormwater (Helsinki, 2000). In the river Vantaanjoki, a concentration of 193 ng/l was measured in a downstream sampling point in Helsinki. This value is higher that in the German rivers but lower than those in creeks in the same area, which may reflect different intensities of emissions in relation to catchment area.

In Germany, concentrations were below the detection limit 30 ng/l in river Lippe in the Ruhr area (written unpublished information by Oxeno Olefinchemie GmbH).

In a UK survey, concentrations in upland and lowland rivers were below the detection limit of 100 ng/l except for one sample which had a level of 200 ng/l (WRc, 1996).

In the USA, higher concentrations have been reported in an investigation of 7 rivers which had values ranging from 150 to 760 ng/l, with a detection frequency of 78% and a median of 420 ng/l (Reiser et al., 1998; Achten et al., 2000).

Lakes

Data have been found on Danish lakes used as potable water (near points of extraction); the concentrations have ranged from below detection limits to 590 ng l^{-1} (Miljöstyrelsen, 1998). The loading and natural characteristics of these lake environments are nor known. The same applies

to the lake of the city of Marl in Germany, where a concentration of 100 ng/l has been measured (information by Oxeno Olefinchemie GmbH).

Sea

In Finland, concentrations ranging from 390 to 6,130 ng/l have been measured in seawater at 17 boat harbours in Helsinki (Helsinki, 2000). The sampling points include inner-harbour areas subject to various emissions as well as recreational shores of higher water exchange rates and predominantly leisure boat impacts.

Precipitation

The first few reported measurements of MTBE concentrations in precipitation, from downtown Frankfurt am Main (Achten and Puettmann, in press) reveal a range of up to 70 ng/l, the highest value having been obtained in December (as was expected based on theoretical temperature dependence of atmospheric behaviour). The values are below the median value calculated for precipitation based on atmospheric data from the USA (Zogorski et al., 1998, ref. Achten & Puettmann, in press).

Wastewater

Concentrations in wastewater discharges from European MTBE producing industries have ranged to 1,000 µg/l, while some plants have reported concentrations below detection limits (WRC, unpublished). For example, concentrations in wastewaters of a MTBE plant in Germany were reported to have been under the detection limit which was as high as 1,000 ng/l (1 µg/kg) for these samples (information by Oxeno Olefinchemie GmbH).

In a wastewater sample from urban sewer network subject to mixed emissions from MTBE use, a concentration of 910 ng/l was found in Helsinki, Finland (Helsinki, 2000).

In the USA, urban stormwater has been extensively analysed, yielding a concentration range of 200 – 8,700 ng/l and a mean value of 1,500 ng/l in the 41 samples (7% of all samples) with detectable levels (Zogorsky et al., ref. WRC unpublished).

Sewage sludge

No data on concentrations in sewage sludge from wastewater treatment have been found.

3.1.5.4 Comparison of modelled and monitored concentrations in aquatic environment

In general, the regional surface water concentration seems to be in reasonable agreement with measured concentrations. The calculated regional concentration in surface water is 1.5 µg/l, which is well a realistic or even low value for lakes and rivers having motor-boating. Background concentrations in non-boating areas may typically be 3-10 times less than the calculated value and closer to the calculated continental concentration 0.1 µg/l. However, higher concentrations are found in areas with high boat traffic density.

3.1.6 Atmosphere

3.1.6.1 Local predicted environmental concentrations in the atmosphere

Local predicted environmental concentration in the atmosphere (PEC local air) and deposition fluxes have been derived for point sources: production, formulation and processing. Results are presented in **Table 3.24** and **Table 3.25** (EUSES output data). Site-specific data are also presented from production plants if it is available.

In addition, PEC in local air has been calculated for the vicinity (100 m) of a service station. Traffic based concentration of MTBE in urban air has not been modelled. It is assumed that there are enough existing monitoring data from urban air (streets, parking halls etc.) and it could be used rather than modelling results for instance in human exposure assessment.

3.1.6.1.1 Local PECs in the atmosphere - EUSES calculations

The concentration of the substance in air is estimated according to the TGD at a distance of 100 m from a point source. In the calculation of PEC_{local} for air, both emissions from a point source as well as the emissions from a STP are taken into account. However, the maximum from the two concentrations is used as the PEC_{local}.

$$Clocal_{air} = \max (Elocal_{air}, E_{stp,air}) \cdot C_{std,air}$$

where $Clocal_{air}$ = local concentration in air during emission episode, mg/m^3
$Elocal_{air}$ = local direct emission rate to air during episode (kg/d) (**Table 3.10**)
$E_{stp,air}$ = local indirect emissions to air from STP during episode (kg/d) (**Table 3.10**)
$C_{std,air}$ = concentration in air at source strength of 1 kg/d ($2.78 \cdot 10^{-4}$)

Annual average concentration in air is calculated as:

$$Clocal_{air,ann} = Clocal_{air} \cdot T_{emission}/365$$

where $Clocal_{air,ann}$ = annual average concentration in air, 100 m from point source, mg/m^3
$T_{emission}$ = number of days per year that the emission takes place (**Table 3.10**)

Annual average predicted environmental concentration in air is calculated as:

$$PEClocal_{air,ann} = Clocal_{air,ann} + PECregional_{air}$$

where $PEClocal_{air,ann}$ = annual average predicted environmental conc. in air, mg/m^3
$PECregional_{air}$ = regional concentration in air, 0.00075 mg/m^3

Table 3.24 EUSES calculations, PECs in air from production, formulation and processing

	Local concentration in air during emission episode (mg/m³)	Annual average conc. in air, 100 m from point source (mg/m³)	Annual PEC_{local} in air (mg/m³) (local + regional 0.00075)
Production 1	0.335	0.275	0.276
Formulation 1	0.014	0.012	0.013
Processing 1	0.017	0.017	0.017
Processing 2	1.34	1.1	1.11
Processing 3	0.278	0.046	0.047

The indirect emission from the STP to air is given by the fraction of the emission to wastewater directed to air:

$$E_{stpair} = F_{stpair} \cdot E_{localwater}$$

where F_{stpair} = fraction of the emission to air from STP (0.43)

$E_{localwater}$ = local emission rate to water during emission episode (kg/d) (from **Table 3.10**)

E_{stpair} = local emission to air from STP during emission episode (kg/day) (from **Table 3.10**)

In calculating the deposition flux the emissions from the two sources (direct and STP) are summed:

$$DEPtotal = (Elocal_{air} + Estp_{air}) \cdot (Fass_{aer} \cdot DEP\ std_{aer} + (1\text{-}Fass_{aer}) \cdot DEPstd_{gas})$$

$$DEP_{totalann} = DEP_{total} \cdot \frac{T_{emission}}{365}$$

where $E_{localair}$ = local direct emission rate to air during emission episode, kg/day (from **Table 3.10**)

$Estp_{air}$ = local indirect emission to air from STP during episode, kg/day (from **Table 3.10**)

$Fass_{aer}$ = fraction of chemical bound to aerosol ($3.03 \cdot 10^{-9}$)

DEP_{stdaer} = standard deposition flux of aerosol-bound compounds at a source strength of 1 kg/day, mg/m²/day ($1 \cdot 10^{-2}$)

DEP_{stdgas} = deposition flux of gaseous compounds as a function of Henry's Law coefficient, at a source length of 1 kg/day ($4 \cdot 10^{-4}$)

$T_{emission}$ = number of days per year that the emission takes place days/year (from **Table 3.10**)

DEP_{total} = $_{total}$ deposition flux during emission episode (mg/m²/day)

$DEP_{totalann}$ = annual average total deposition flux (mg/m²/day)

Local emission to air from STP during emission (kg/d) episode is calculated:

$E_{stpair} = F_{stpair} \cdot E_{localwater}$

where F_{stpair} = fraction of the emission to air from STP (0.43)
$E_{localwater}$ = local emission rate to water during emission episode (kg/day)

Table 3.25 EUSES calculations, deposition fluxes from air for production, formulation and processing

Life Cycle	DEP_{total} (mg/m²/day)	$DEP_{totalann}$ (mg/m²/day)
Production 1	0.544	0.447
Formulation 1	0.023	0.012
Processing 1	0.026	0.025
Processing 2	1.93	1.59
Processing 3	0.41	0.067

3.1.6.1.2 Local PECs in the atmosphere – site-specific approach

Industry has submitted site-specific information on 23 production and production/formulation sites. All sites known to produce MTBE in the EU region are included in **Tables 3.26** and **3.27**. There are no information of real emissions of the one known processing 2 (isobutylene production) and the one known processing 3 (solvent use) site. The emissions calculated with default values are presented in **Tables 3.27** and **3.28**. For some sites, there are no specific information on possible formulation on-site. The information industry has submitted enables to calculate an emission factor to sites that cover approximately 82% of the total MTBE production volume of 3,290,000 tonnes in 1999.

Considering emissions from various sites, it is not in many cases clear if all emissions have been taken into account. In addition to emissions from the MTBE plant there are other fugitive emissions depending on the activities at the site.

With regard to the facts that no information about emission to air from STP is available and that the emission from STP to air is smaller than direct emission calculated by defaults, the E_{stpair} is not used for calculating $PEClocal_{air}$. In some cases where the emission to air is calculated with default values, the E_{stpair} is based on emission data to wastewater.

In the table showing emissions to air there are some sites with two different emission factors. This is due to differences between emissions calculated from emission to air and monitoring concentrations.

Table 3.26 Site-specific local concentrations in air and deposition fluxes from production and production/formulation sites

Site code and activity	Emission factor	Local direct emission to air $E_{localair}$ (kg/day)	Local indirect emission to air from STP $E_{localstp}$ (kg/day)	Local concentration in air $C_{localair}$ (Annual average $T_{emission}$ =350) (Φg/m³)	Annual average predicted environmental concentration in air (regional = 0.753) $PECloca l_{air,ann}$ (Φg/m³)	Total deposition flux during emission episode (Annual average $T_{emission}$ =350) Φg/m²/day
Site 1 Production Formulation	0.0002	**58.2** 1) 2) 3)	2.96 2)	16.2 (15.5)	16.3	24.5 (23.5)
Site 2 Production Formulation	def 0.005	1,644	16.9	457 (438)	439	664 (637)
Site 3 no longer producing MTBE						
Site 4 Production	0.00005	**87.7** 1) 2) 3)	-	24.4 (23.4)	24.2	35.1 (33.7)
Site 5 Production	0.002 for VOCs	**224 (VOCs)** 1) 3)	-	62.5 (59.9) (VOCs)	-	-
Site 6 Production Formulation	0.00003	**3.75** 3) 4)	-	1.04 (1.0)	1.75	1.50 (1.44)
Site 7 Production	0.00002	**39.2** 1) 3)	1.39	10.9 (10.5)	11.3	16.2 (15.5)
Site 8 Production	0.0000002	0.118 1) 3) 4)	0.025	0.033 (0.032)	0.785	0.057 (0.055)
Site 9 see Table 3.27						
Site 10 Production Formulation (running a project to change the unit to ETBE by the end of next year)	def 0.005	822	212	229 (220)	220	414 (397)
Site 11 Production Formulation	def 0.005	500	10.6	139 (133)	134	204 (196)
Site 12	0.00004	**14.8** 1) 3)	0.477	4.12 (3.95)	4.70	6.11 (5.86)
Site 13 no longer producing MTBE						
Site 14 Production Formulation	def 0.005	205	12.4	57.0 (54.7)	55.5	87.0 (83.4)
Site 15 Production Formulation	0.0008	**400**	8.29	111 (106)	107	163 (156)
Site 16 Production Formulation	0.0001	**21.9** 2)	3.06	6.09 (5.84)	6.59	9.98 (9.57)

Table 3.26 continued overleaf

Table 3.26 continued Site specific local concentrations in air and deposition fluxes

Site code and activity	Emission factor	Local direct emission to air $E_{localair}$ (kg/day)	Local indirect emission to air from STP $E_{localstp}$ (kg/day)	Local concentration in air $C_{localair}$ (Annual average $T_{emission}$ =350) (Φg/m³)	Annual average predicted environmental concentration in air (regional = 0.753) $PEClocal_{air,ann}$ (Φg/m³)	Total deposition flux during emission episode (Annual average $T_{emission}$ =350) Φg/m²/day
Site 17 Production Formulation	def 0.005	479	8.24	133 (128)	128	195 (187)
Site 18 Production Formulation	def 0.005	616	10.6	171 (164)	165	251 (241)
Site 19 Production Formulation	0.0005	173	0.11	**48.0 monitoring concentration** (46.0)	46.0	69.2 (66.4)
Site 20 Production Formulation	0.000002	**0.263**	15.3	0.073 (0.07)	0.823	6.22 (5.96)
Site 21 Production Formulation	> 0.0001	> 17.0 (2	5.89	> 4.72 (4.53)	> 5.28	>9.16 (8.78)
Site 22 Production Formulation	0.00004	**8.07**	-	2.24 (2.15) **(monitoring concentration <100)**	2.90	3.23 (3.10)
Site 23 Production Formulation	0.0004 0.0005	**122** 162	0.442	34.0 (32.6) **45 (monitoring concentration)** (43.2)	33.4 43.2	49.0 (47.0) 65.0 (62.3)
Site 24 Production Formulation	0.0002	**16.3**	11.0	4.54 (4.35) **(monitoring concentration <100)**	5.07	10.5
Site 25 Production Formulation	0.00006 0.0004	**11.0 71.9**	16.7	3.06 (2.93) **20 (monitoring concentration)** (19.2)	3.68 19.2	11.1 (10.6) 35.4 (33.9)
Site 26 Production Formulation	0.00009	**17.2**	0.836	4.77 (4.57) **(monitoring concentration <2000)**	5.32	7.21 (6.91)
Site 27 Production Formulation	0.0001	**13.0**	7.68	3.61 (3.46) **(monitoring concentration <100)**	4.21	7.93
Site 28 Production Formulation	0.0002 0.001	**14.3** 71.9	0.29	3.97 (3.81) **20 (monitoring concentration)** 19.2)	4.56 19.2	5.84 (5.60) 2.89 (2.77)
Site 29	def 0.005	822	212	228 (219)	219	414 (397)

Table 3.26 continued overleaf

Table 3.26 continued Site specific local concentrations in air and deposition fluxes

Site code and activity	Emission factor	Local direct emission to air $E_{localair}$ (kg/day)	Local indirect emission to air from STP $E_{localstp}$ (kg/day)	Local concentration in air $C_{localair}$ (Annual average $T_{emission}$ =350) (Φg/m³)	Annual average predicted environmental concentration in air (regional = 0.753) $PECloca l_{air,ann}$ (Φg/m³)	Total deposition flux during emission episode (Annual average $T_{emission}$ =350) Φg/m²/day
Site 30 Production Formulation	def 0.005	959	247	267 (256)	257	482 (462)
Site 31 Production Formulation	def 0.005	264	247	73.4 (70.4)	71.2	106 (102)
Site 32 Production Formulation	def 0.005	466	120	129 (124)	124	234 (224)

1) measured 2) calculated 3) known to be based on various measurements 4) based on permit values
Values received from industry in bold

The emission factors for the sites in **Table 3.26** range from 0.0000002 to 0.001. The default value according to the TGD is 0.005. Since there are data to calculate an emission factor from 19 sites out of 32, the highest emission factor calculated, namely 0.001, is used in EUSES calculations. The annual average concentrations in air range from 0.033 to 111 μg/m^3 and the annual average predicted environmental concentration in air ranges from 0.777 μg/l to 439 μg/l. The total deposition flux ranges from 0.057 μg/m^2 to 163 μg/m^2.

The large differences between sites may be due to the variability of emissions reported. In fact there is not a clear picture of what kind of emissions to air have been taken account in the information industry has submitted.

Table 3.27 Site-specific local concentrations in air and deposition fluxes from production and processing 2 (production of isobutylene)

Site code and activity	Emission factor	Local direct emission to air $Elocal_{air}$ (kg/day)	Local indirect emission to air from STP $Elocal_{stp}$ (kg/day)	Local concentration in air $Clocal_{air}$ (Annual average $T_{emission}$ =350) (Φg/m³)	Annual average predicted environmental concentration in air (regional 0.753) $PECloca l_{air,ann}$ (Φg/m³)	Total deposition flux suring emission episode (Annual average $T_{emission}$ =350) (Φg/m²/day)
Site 9 Production Processing 2	prod: def 0.005 proc 2: def 0.05	2075	1.17	577 (553)	554	830 (796)

There is no knowledge of emissions to air from the use of MTBE to produce isobutylene. The default value given in the TGD is used.

Table 3.28 Site-specific local concentrations in air and deposition fluxes from use as a solvent (processing 3)

Site code and activity	EMISSION FACTOR	Local direct emission to air $E_{localair}$ (kg/day)	Local indirect emission to air from STP $E_{localstp}$ (kg/day)	Local concentration in air $C_{localair}$ (Annual average $T_{emission}$ =330) (Φg/m³)	Annual average predicted environmental concentration in air (regional = 0.753) $PEClocal_{air,ann}$ (Φg/m³)	Total deposition flux suring emission episode (Annual average $T_{emission}$ =350) (Φg/m²/day)
Site 33 Solvent in the production process of pharmaceutical active agents	DEF 0.25 ?	71.5	1.03	19.9 (18.1)	19.9	29.0 (26.2)

There is no information of emissions to air from solvent use of MTBE. In **Table 3.28** a default value 0.25 from the TGD is used to calculate emissions from the only processing 3 site reported.

The emission factors to air from the sites handling with bulk storage and transfer operations of petrol and light oil range from 0.00003 – 0.04 (industry data). The monitored concentrations range from 2 to 111 µg/m^3. The calculated local concentrations in air range from 0.296 to 1.63 µg/m^3. The annual average predicted environmental concentrations range from 0.9 µg/m^3 to 188 µg/m^3. The total deposition flux ranges from 0.598 to 160 µg/m^2/day.

3.1.6.1.3 Local PEC air from service stations

Car refuelling at gas stations causes evaporative emissions of petrol components. Total evaporative losses to air during refilling of cars is on average 0.15-1.5 kg/t petrol depending on if vapour recovery system is used or not (uncontrolled or Stage 1 and 2 controls) (see Section 3.1.3.1).

Local $PEClocal_{air}$ is estimated according to the TGD (2.3.8.2) delivery of petrol from a gas station. A large size gas station delivers annually 10,000 tonnes petrol. Using emission factor of 1.54 kg/tonne petrol emission would be 15,400 kg petrol and **1,540 kg** MTBE correspondingly (petrol containing on average 10%-wt MTBE).

$\mathbf{Clocal_{air,ann}}$ = max ($Elocal_{air}$) · $Cstd_{air}$ = 1,540 kg/365 days · 2.78 · 10^{-4} mg/m^3 = **1.17 µg/m^3**

$Elocal_{air}$ max =local direct emission rate to air during episode (kg/day)
$Cstd_{air}$ = concentration in air at source strength of 1 kg/day = 2.78 · 10^{-4} mg/m^3

Annual average local concentration in air $PEClocal_{air,ann}$, 100 m from a service station, when regional concentration $regional_{air}$ has been taken into account:

$$\mathbf{PEClocal_{air,ann} = Clocal_{air,ann} + PECregional_{air} =}$$

$$\mathbf{1.17\ \mu g/m^3 + 0.75\ \mu g/m^3 = 1.92\ \mu g/m^3}$$

3.1.6.1.4 Local PEC air from petrol fuelled vehicles

There are monitoring data available from urban air concentrations of MTBE, from rush hour concentrations to long-term averages (Section 3.1.6.3). Traffic based $PEClocal_{air}$ concentration is highly dependent on local situations and local fleet composition. Traffic based local air concentration has not been estimated and it is believed that additional modelling (except EUSES regional PEC's) do not give any new valuable information over existing monitoring data.

3.1.6.2 Regional and continental predicted concentrations in air

As EUSES model output for the atmosphere, the following PEC regional and PEC continental MTBE concentrations are presented below. Results take into consideration emissions from all life cycle stages. The regional concentration in the air is considered as a calculated background value.

Regional PEC in air (total)	0.75 μg/m^3
Continental PEC in air (total)	0.22 μg/m^3

3.1.6.3 Atmospheric monitoring data

The data on atmospheric levels come mainly from localities near production sites and use sites such as petrol stations, or from general urban localities in North America (**Table 3.29**). The relevance of some of these data for the present environmental assessment is unclear. In addition, the sources and dilutions of MTBE in each instance are often not known, making it difficult to explain the variations between and within cases or to choose any one number as a representative estimate of environmental exposure levels. These data are therefore presented mainly to illustrate the general situation in ambient atmospheres (refuelling zones in pump islands and other such near-source data are excluded, cf. Section 4.1.1).

No ecotoxicological data have been found on MTBE based on inhalation exposure (or on gas intake by plants), and the availability and applicability of inhalation toxicity data on laboratory animals for assessing environmental (wildlife) effects remains to be clarified. Therefore, the atmospheric data are primarily a question of human health risks assessment, and are dealt with in more detail in Section 4.1.1 (human exposures).

Atmospheric data are in principle relevant for environmental assessment also indirectly as a means to check estimates of distribution between compartments (e.g., air-water exchange). The difficulty here lies partly in the great variation of data and in the selection of representative statistics, partly in the limited knowledge of the operative processes.

The annual mean concentration of MTBE in the atmosphere in the United States during 1987-1988 was estimated to be less than 0.7 μg/m^3 (0.2 ppb) (US EPA, 1994).

Studies in the US measuring MTBE in ambient air have reported the following levels: California average of 7 μg/m^3 (2 ppb), Los Angeles average of 14 μg/m^3 (4 ppb), and up to 550 μg/m^3 at peak rush hour (111 ppb), and San Francisco average of 3.5 μg/m^3 (1 ppb) (http://www.scvacs.org/mtbe/9807notes.shtml).

Table 3.29 Summary of MTBE concentrations (µg/N-m^3) in the atmospheric environment

Type of environment and loading	Med	Mean	Max	Information source
Background, USA (mixed)	0.7-2.7		4.1-16	Zweidinger (1993)
Semirural, USA (mixed, incl. industrial)			10	Kelly et al. (1993), ref. IPCS (1998)
Residential, USA (mixed)	1.1-62		1.5-380	Zweidinger (1993)
Community air, USA (reformul. gas)		15		Allen and Grande (1995)
Residential, CAN (mixed)	0.2-0.33		0.89	Environment Canada (1996)
Urban, CAN (mixed, incl. traffic)	0.11-0.28		0.4-1.5	Environment Canada (1996)
Urban, USA (mixed, incl. traffic)		4.7-17	12-45	IPCS (1998)
Roadside, USA (traffic)	0.7-67		9.4-240	Zweidinger (1993)
Industrial, CAN (refinery/petrol)	1.8-54		26-280	Environment Canada (1996)
Service station perimeter, FI (fueling)		12-14		Vainiontalo et al. (1996), ref. ICPS (1998)
Service station perimeter, USA (fueling)	9-75		310-340	Allen and Grande (1995) API (1993, 1995)
Petrol-contaminated sites, FI (leaks)			160,000	Reg. Env. Centre W. Finland (unpubl.)

3.1.6.4 Comparison of modelled and monitored atmospheric concentrations

In general, the regional and continental air concentrations seem to be in reasonable agreement with measured air concentrations:

EUSES estimates that PEC regional in air is 0.75 µg/m^3. The measured background in the USA is in the range of 0.7-2.7 µg/m^3 (mixed) and the measured average concentrations in highly urbanised areas in the USA are 3.5 to 17 µg/m^3. It is difficult to compare directly regional values and measured US data because of different traffic volumes, vehicle fleet and average concentration of MTBE in petrol. Therefore, large US metropolitan areas are most probable higher consumption and emission areas than the EUSES regional area and monitored and modelled results are in good agreement.

EUSES estimates PEC continental in air 0.22 µg/m^3, whereas the annual mean concentration of MTBE in the atmosphere in the United States during 1987-1988 was estimated to be less than 0.7 µg/m^3.

3.1.7 Terrestrial compartment

There are three exposure routes to be considered when estimating PEC_{local} in soil:

- Direct (point source) release of MTBE during petrol storage and refuelling tanks and vehicles,
- Dry and wet deposition from the atmosphere (infiltration of stormwater runoff and precipitation),
- STP sludge field application.

The two first issues may be considered most relevant. If entered to the topsoil the high volatility of MTBE from the topsoil layer suggests that it has a relatively short half-life on the surfaces.

However, the high persistence and mobility of MTBE enable MTBE to enter into deeper soil layers with infiltration of rainwater runoff.

The sludge field application is considered rather marginal source of MTBE into the soil because of poor adsorptivity to sludge and it is rather unlikely that MTBE will reach municipal sewage system at high concentration (higher than can be found in stormwater). However, STP sludge application from industrial point sources has been taken into consideration (EUSES calculation).

3.1.7.1 Local predicted environmental concentrations

3.1.7.1.1 PEC soil from production, formulation and processing – EUSES calculations

The exposure routes taken into account in PEC_{local} calculations are application of sewage sludge in agriculture and dry and wet deposition from the atmosphere.

Total deposition flux ($DEPtotal_{ann,}$ **Table 3.25**) is converted to concentration mg substance per kg soil per day (D_{air}) as follows:

$$D_{air} = \frac{DEPtotal_{ann}}{DEPTH_{soil} \bullet RHO_{soil}}$$

where $DEPTH_{soil}$ = mixing depth of soil (terrestrial ecosystem 0.20 m)
RHO_{soil} = bulk density of soil (1,700 kg/m^3)

Table 3.30 EUSES calculations, concentration of MTBE in deposition and sludge

	Concentration in dry sewage sludge (mg/kg) (D_{sludge})	Aerial deposition flux per kg of soil (mg/kg/day) (D_{air})
Production 1	465	0.001
Formulation 1	19.9	0.00004
Processing 1	11.4	0.00007
Processing 2	0.993	0.005
Processing 3	51.3	0.0002

Concentration in soil ($Clocal_{soil}$) can be estimated using the aerial deposition flux per kg of soil and the sludge concentrations estimated above. The predicted environmental concentration ($PEClocal_{soil}$) is estimated by adding the concentration in soil to $PECregional_{natural,soil}$ which is 0.00001 mg/kg wet weight.

Table 3.31 EUSES calculations, concentrations of MTBE in agricultural soil and grassland

	Concentration in agricultural soil >30 days (mg/kgwwt)	Concentration in agricultural soil >180 days (mg/kgwwt)	Concentration in grassland >180 days (mg/kgwwt)
Production 1	0.233	0.052	0.021
Formulation 1	0.001	0.002	0.001
Processing 1	0.006	0.002	0.0009
Processing 2	0.048	0.048	0.048
Processing 3	0.026	0.006	0.003

Table 3.32 Local predicted environmental concentrations in agricultural soil and grassland based on EUSES

	Depth of soil compartment (m)	Averaging time (days)	Rate of sludge application (kg_{dwt}/m^2/year	Endpoint	Local PEC (mg/kg wet weight)
$PEClocal_{soil}$	0.20	30	0.5	Terrestrial ecosystem	Prod.1: 0.233
					Form.1: 0.001
					Proc. 1: 0.006
					Proc. 2: 0.048
					Proc. 3: 0.026
$PEClocal_{agr,soil}$	0.20	180	0.5	Crops for human consumption	Prod. 1: 0.052
					Form. 1: 0.002
					Proc. 1: 0.002
					Proc. 2: 0.048
					Proc. 3: 0.006
$PEClocal_{grassland}$	0.10	180	0.1	Grass for cattle	Prod. 1: 0.021
					Form. 1: 0.0009
					Proc. 1: 0.001
					Proc. 2: 0.048
					Proc. 3: 0.003

Table 3.33 EUSES calculations, local predicted environmental concentrations in pore water of agricultural soil and in pore water of grassland

	$PEClocal_{agr.soil,porew}$ (mg/l)	$PEClocal_{grassland,porew}$ (mg/l)
Production 1	0.185	0.075
Formulation 1	0.008	0.003
Processing 1	0.006	0.003
Processing 2	0.17	0.17
Processing 3	0.022	0.01

3.1.7.1.2 PEC groundwater – EUSES calculations

The concentration of MTBE in groundwater is calculated for indirect exposure of humans through drinking water. As an indication for potential groundwater levels, the concentration in porewater of agricultural soil is taken. This is a worst-case assumption, neglecting transformation and dilution in deeper soil layers.

$$PEClocal_{grw} = PEClocal_{agr.soil,porew}$$

where $PEClocal_{agr.soil,porew}$ = predicted environmental concentration in porewater, mg/l
$PEClocal_{grw}$ = predicted environmental concentration in groundwater, mg/l

Table 3.34 EUSES calculations, local PECs in groundwater under agricultural soil

	$PEClocal_{agr.soil,porew}$ (mg/l)
Production 1	0.185
Formulation 1	0.008
Processing 1	0.006
Processing 2	0.17
Processing 3	0.022

Note: EUSES based calculated groundwater concentrations are not used in environmental risk characterisation.

3.1.7.1.3 PEC soil – site-specific approach

Industry has submitted some information on the MTBE concentration in sludge and on the type of the sludge treatment from 26 production and production/formulation sites, from one solvent use site and from 17 sites handling with bulk storage and transfer operations of petrol and light oil.

Table 3.35 Site-specific information on solid waste treatment (data submitted by industry)

Site	Amount of MTBE in solid waste	Type of solid waste treatment
Site 1	none, all MTBE is washed out with methanol	Ion exchange resin
Site 2	not measured	Incineration
Site 4	<1 ppm	Landfill
Site 5	total of waste production 2 tonnes/year	Incineration/landfill
Site 6		Incineration
Site 7	<1 ppm	Landfill
Site 8	none	Incineration
Site 9		dedicated landfill
Site 11		Landfill
Site 12	0.34 kg/year	Landfill
Site 14		Incineration
Site 16		via incineration to landfill
Site 17	0	solid waste does not include MTBE
Site 18	0	solid waste does not include MTBE
Site 19		Incineration
Site 21		no sludge produced containing MTBE
Site 22		if necessary, solid waste is always inertized with calcium oxide or burned
Site 23		Incineration
Site 24		if necessary, solid waste is always inertized with calcium oxide or burned
Site 25		if necessary, solid waste is always inertized with calcium oxide or burned
Site 26	below detection limit	if necessary, solid waste is always inertized with calcium oxide or burned
Site 27		if necessary, solid waste is always inertized with calcium oxide or burned
Site 28	below detection limit	if necessary, solid waste is always inertized with calcium oxide or burned
Site 29		Landfill in authorised sites
Site 30		Regeneration, deposition
Site 32		9% of the treated sludge is used as fertilizer for the plants at the refinery site
Site 33	no sludge produced containing MTBE	
Sites 34 - 50		if necessary, solid waste is always inertized with calcium oxide or burned

It is obvious from the **Table 3.35** that the MTBE concentration of the WWTP sludge is not usually known. The sludge either goes to landfill purposes or is incinerated. In some cases, the solid waste is inertized with calcium oxide before incineration. Due to missing data on the MTBE concentration in sludge and the fact that it is used for landfill purposes the default values calculated with EUSES are used when assessing the predicted concentration in the soil.

3.1.7.1.4 PEC soil from service stations

Because of the large volumes of petrol used daily in EU (>400 million litres) and large (>100,000) service stations network and storage capacity and transportation system required to provide petrol to end users, surface and subsurface releases are likely to occur.

Usually these service stations ("filling station", "refuelling station") are public and in many cases self service stations. Only large firms or firms specialised in road transport have their own filling stations.

Table 3.36 shows the number of public refuelling stations, annual petrol net consumption in EU member states and average petrol throughput per station.

Table 3.36 Petrol net consumption in 1997 and the number of refuelling stations in the EU

Country	Motor Petrol Net Consumption, 1,000 ton	Refuelling Stations	Average throughput 1,000 ton
Austria	2,094	3,254	0.644
Belgium	2,535	2,000	
Denmark	1,975	2,545	0.776
Finland	1,882	1,799	1.046
France	13,067	17,514	0.746
Germany	29,996	17,066	1.758
Greece	3,056	7,200	0.424
Ireland	1,173	2,308	0.508
Italy	17,149	20,000	
Luxembourg	542	256	2.117
Netherlands	4,145	4,150	0.999
Portugal	1,931	2,000	
Spain	9,100	6,315	1.441
Sweden	4,126	3,578	1.153
United Kingdom	22,288	14,824	1.503
Total European Union	**115,059**	**104,809**	

Note: Motor Petrol Net Consumption data is from the year 1997 (Data source: Fortum Oil & Gas Oy 1999)
The number of service stations is from the beginning of year 1999 (except Spain 1997) and estimated:Belgium, Italy, Portugal (Data source: Öljy- ja kaasualan keskusliitto, Finland 1999)

During the refuelling of motor vehicles at service stations leaking to the pavement of pump island is estimated to be 0.14 kg/t (CONCAWE, 1978). In the past at filling stations, spilled fuel could penetrate the pump island pavement whereas new and sanitised stations get closed pavement

with drainage to an oil/water separator. It is expected that the risk is low of serious local soil or groundwater pollution from normal refuelling operations of modern refuelling station.

More serious sources of soil and groundwater contamination include leakage in storage tanks, piping and joints and tank overfilling. Technical condition of underground storage tanks (UST s) is more difficult to check regularly than above ground tanks. Leaks from underground tanks are also difficult to notice at once. In the case of leaking underground storage tanks or piping released amounts can be very high compared to releases from normal operations. These accidental leaks may contaminate soil and spoil the groundwtaer in large areas.

Leaking underground storage tanks are the most numerous sources of MTBE contamination (Fogg et al., 1998). It is estimated that 10-35% of underground storage tanks in the USA are leaking or fail to pass a tightness test (Page, 1989). In one survey of 3,500 tanks, only 2% of the tanks were leaking while 10% failed to pass the tightness test. However, in about 9% of the service stations surveyed petrol was found on the top of groundwater in close proximity to station (Page, 1989).

In Finland as in many other EU countries, contamination of soil and groundwtaer by petrol has frequently taken place, and programmes have been set up to assess and manage such sites (e.g. for Denmark, see Edelgaard and Dahlstroem, 1999). In many of these cases contamination originates from petrol stations, but include also other kinds of releases e.g. from traffic accidents. In many cases contamination also by MTBE can be suspected on the basis of storage and treatment of MTBE-containing petrol brands during the time period of emission, even though specific measurements of MTBE have been made; in other cases contamination has been caused by emissions so far back in time that MTBE is not involved.

Some detailed information may be presented for petrol stations based on the joint Finnish industry-administration clean-up programme in this branch (Huttula & al, unpublished). Of the ca. 1,800 Finnish petrol stations, ca. 200 mainly old station sites are covered by the programme, ca. 140 have been already investigated, and remedial measures have been proposed for ca. 90 sites. These sites probably represent worse-than-average situations. A large part has been judged to contain mainly heavier products and not much petrol. However, the presence of more volatile substances has also been noted at several sites. Many of the ca. 25 cases where groundwtaer monitoring is carried out involve groundwtaer contamination by MTBE. The amount of MTBE released in petrol from these sites and the impact of these releases cannot be estimated on the basis of the present data.

During the years 1992-99 at Helsinki-city area the level of contamination at 50 service station areas has been studied. 48 station areas were more or less contaminated with fuel oil or petrol (>1,000 mg/kg and/or clear smell of petrol/fuel oil). Contamination is typically a result of normal refuelling spills, overfilling of UST's or insufficient tightness in petrol storage and delivery equipment. In two cases, (2/50), hydrocarbon contamination had spread clearly outside the service station area polluting soil and groundwtaer.

Analytical detection of MTBE has not been carried out routinely on the sites surveyed, but practically taken all petrol on the Finnish market contains MTBE and it can be detected in soil samples from the contaminated sites (Helsinki Env. Centre, 1999).

Refuelling Spills

A calculation is made to estimate amounts of MTBE spilled during normal refuelling of vehicles. Average leak EF, station throughput and fraction of MTBE in petrol (f_{MTBE}) are used. As a scenario, it is expected that the pump island is not sealed or the sealing does not function as

expected. The whole petrol volume spilled goes directly into the soil and no volatilisation is expected.

$$\text{Emission} = (\text{Throughput}) \cdot (\text{Efleak}) \cdot (f_{MTBE})$$

The average amount of MTBE spilled from for vehicle refuelling is 0.14 kg/tonne (BUA, 1996). Highest average annual petrol delivery capacity of a service station in EU member states is about 2,000 tonnes/a. The "average" service station would release 280 kg petrol per year (2,000 · 0.14 kg) and 5.6-28 kg MTBE (2-10 wt-% MTBE in petrol).

During a period of 10 years, 56-280 kg MTBE are released to the service station soil from each "average" station from normal refuelling operation. Neither PEC soil concentration nor any quantitative risk characterisation for local soil in service station areas has been calculated.

More detailed data on soil and groundwater pollution are in Section 3.1.7.3 "MTBE in soil and groundwtaer, monitoring data".

3.1.7.1.5 PEC soil from road traffic

Direct release

Release to the soil may occur directly from cars because of malfunctioning leaking fuel systems and of car accidents. It can be assumed that environmental concentrations would locally be highest along the roadsides. On the other hand there is not much evidence that leaking fuel systems in vehicles would cause remarkable general petrol based soil contamination on road banks, parking- and related areas. The high volatility rate of petrol and its components from the top surface of ground decreases the possibility of soil contamination contrary to less volatile leaking motor oil and diesel gasoil.

Accidental spillages during transport of petrol (tank trucks) and car accidents are undoubtedly potential sources of soil and groundwater contamination with MTBE.

However, quantitative local estimation has not been carried out from sources mentioned above, except EUSES calculation at regional/continental level (fraction of tonnage released to industrial soil 0.0001).

Wet precipitation and infiltrated runoff

The release of MTBE to the soil occurs as precipitation after release to the air from different sources. The highest measured concentrations of MTBE in urban wet precipitation in US have been 2-4 µg/l (Rykowski, 1996; Squillace et al., 1997). Highest measured concentration in urban runoff is 8.7 µg/l (0.2 to 8.7 (µg/l) with a median of 1.5 µg/l) (Delzer et al., 1996).

If the runoff is infiltrated to topsoil, the maximum concentration in porewater is 8.7 µg/l (C $local_{soilporew}$). Using equilibrium partitioning method (TGD 2.3.8.4), PEC$local_{soil}$ from wet precipitation and infiltrated runoff (worst-case assumption) would be:

$$\textbf{PEC local}_{\textbf{soil}} = (\text{PEC local}_{\text{soil,porew.}} \cdot K_{soil,water} \cdot 1{,}000)/RHO_{soil}$$

where $K_{soil,water} = Foc_{\text{comp(fraction of organic matter in soil)}} \cdot Koc = 0.02 \cdot 11.2 = 0.224\ m^3/m^3$
RHO_{soil}= density of wet soil = 2,500 kg/m^3

$$\textbf{PEC local}_{\textbf{soil}} = (0.0087\ mg/l \cdot 0.224\ m^3/m^3 \cdot 1{,}000)/2{,}500\ kg/m^3 = \textbf{0.78 µg/kg wwt}$$

3.1.7.2 Regional and continental predicted environmental concentrations in soil

The EUSES model outputs the following PEC regional and PEC continental values calculated for different soil types and porewater.

Regional

Regional PEC in agricultural soil:	0.000016 mg/kgwwt
Regional PEC in natural soil:	0.000012 mg/kgwwt
Regional PEC in industrial soil:	0.0090 mg/kgwwt
Regional PEC in pore water of agricultural soils:	0.00006 mg/l

Continental

Continental PEC in agricultural soil:	0.000004 mg/kgwwt
Continental PEC in natural soil:	0.000004 mg/kgwwt
Continental PEC in industrial soil:	0.00057 mg/kgwwt
Continental PEC in pore water of agricultural soils:	0.000014 mg/l

3.1.7.3 Monitoring data on soil and groundwater

3.1.7.3.1 General considerations

Measured data from Europe have been obtained for groundwtaer and much less for soil and unsaturated zone water or perched water. A lot of the measured data come from local petrol-contamination cases. Concentrations in groundwtaer in background areas and in exposure situations have been measured much more seldom. However, at the current time, there are a number of officially reported case studies detailing MTBE groundwater contamination which demonstrate that certain countries and areas suffer slight or more severe contamination of groundwater resources. There are currently very little routine monitoring data for MTBE in groundwtaer or drinking water as a whole. The reported pollution incidents are likely to represent only a fraction, maybe even the severest, of the total groundwater contamination cases. Since groundwater contamination by MTBE also constitutes concerns for the potability of drinking water in respect of taste and odour, these data are used also in the section on indirect human exposure (Sections 4.1.1 and 4.2).

Monitoring data from the USA show that the use of MTBE has resulted in increasing detection of MTBE in groundwater derived drinking water, with between 5 percent and 10 percent of community drinking water supplies in high oxygenate use areas, showing detectable amounts of MTBE, and approximately one percent rising to levels above 20 µg/l. Detections have raised consumer taste and odor concerns that have caused to stop using some water supplies. Private wells, which are less protected than public drinking water supplies and not monitored for chemical contamination, have also been contaminated. Cause for concern is given by the finding that up to 17% of monitored shallow groundwater wells in the USA have contained detectable levels of MTBE, the percentage of such wells being highest in urban areas. The major source of groundwater contamination appears to be releases from underground petrol storage systems (USEPA, 1999).

Due to the lack of routine monitoring programmes in Europe there are no trends in time available. However, there are survey data available from some Member States, mainly from

waterworks abstraction wells and few data from groundwater monitoring wells (mainly from areas of special importance as a potable water resource). The recent review of the situation in England and Wales is reported in Section 3.1.7.3.2.

The existing monitoring studies show that in urban areas MTBE can be detected very often in low concentrations < 1 µg/l from groundwater samples and wells. Typically, concentrations 0.1-0.2 µg/l can be detected in tap water in urban areas if MTBE is used as a petrol component.

Near refuelling stations soil and groundwater is very often more or less contaminated by fuel-based hydrocarbons (based on surveys from Finland and Denmark). Groundwater concentrations up to few hundred mg/l are often measured. Depending of the degree of contamination these sites are sources of slight or more severe contamination of groundwater in larger areas. Thus, in at least some of these cases it may be only a question of time until MTBE contamination reaches drinking water resources mostly at low but still exceeding concentration for taste and odour.

In the following sections, available results of MTBE monitoring data from some Member States are summarised. The noted regional differences in observed concentrations can be due to:

- Different relative emissions (remarkable differences in use, storage etc),
- Different transport potential (hydrogeological conditions),
- Different focus of monitoring programmes (eg. emphasising drinking water supplier wells or GW near contamination sources).

3.1.7.3.2 Occurrence of soil and groundwater contamination cases involving petrol

In the following sections, available results of MTBE monitoring data or officially reported groundwater pollution cases from some of the European Union Member States are summarised.

Austria

Within a pilot study, 101 groundwater sites were monitored (in addition 5 large river sampling sites and 3 sites for precipitation). Concentrations at about 75% of the sites were above the limit of detection 0.01 µg/l and 33% above 0.1µg/l. All samples, with the exception of a few taken downstream of known abandoned landfills, had concentrations below 20 µg/l. In 2001 MTBE will be integrated into Austria's national monitoring program (ca. 2,000 groundwater sites, 250 surface water sites (BMLF, 2000).

Denmark

There are measured data available from 6 of 16 counties. In four counties groundwater pollution cases are reported (Danish EPA, 2000a). For instance in Frederiksberg County, in 5 observation wells of a total of 16, MTBE was found in concentrations 0.11-3.5 µg/l.

In 5 of 186 abstraction wells of water works surveyed MTBE was detected in concentrations just around 30 µg/l. In addition, 14 samples contained MTBE in lower concentrations.

Monitoring soil at 479 service station areas, 427 stations were regarded as contaminated (BTEX and/or MTBE). Groundwater at 293 stations was monitored and in 126 cases, there were contamination. These monitoring data show in general, but not specifically, how common soil contamination is at refuelling sites.

The average MTBE concentration in petrol was only 0.2% in 1997 but it was higher in the beginning of 90s.

Germany

There are three officially reported groundwater pollution cases by MTBE known in Germany (UBA, 1999). All cases were caused by leaking storage tanks. In addition, a survey in Southern and Eastern Germany analysed 180 samples from wells in urban and rural areas. In the urban area, 15% of samples showed MTBE concentrations above 0.5 µg/l, but few samples from the rural areas exceeded 0.5 µg/l. The urban results were consistent with those from a local in the industrial city of Darmstadt, where MTBE was detected in 20% of samples (Klinger et al. (2000), as cited in Dottridge et al. (2000)). The average MTBE concentration in petrol was 1.2% (1997) in Germany.

Finland

Based on the present rather infrequent limited monitoring, there are about 10 considerable groundwater contamination cases in Finland, typically caused by leaking storage systems in refuelling stations. In these cases the MTBE plume has reached private and/or municipal abstraction wells and compelled to stop using them (for years). In some cases the plume is prevented from reaching the wells only by continuous protective groundwater pumping.

Contamination of soil in gas stations is common and it causes slight contamination of groundwater in urban areas.

In Finland MTBE has been used since late 1980s and the average MTBE concentration in petrol has been high compared to many other EU countries (8.5% in 1997). Finland was the first country in Europe, in the summer 1994, to use reformulated petrol with essentially the same specifications as in the USA (MTBE 12-13%).

France

In general there is no information on MTBE groundwater contamination cases in France. Instead, there are monitoring data available on MTBE in drinking water in France. These data come from the national French database of chemicals in drinking water. MTBE is measured in water at consumer level and before and after treatment in waterworks. The total number of analyses is ca. 37,000 (groundwater and surface water samples). MTBE is detected at only one site, De Lievin, Aix Noulette. Maximum concentration was 1.5 µg/l and average 0.83 µg/l. The detection limits of all the sampled sites are not available (INERIS, 2000). The average MTBE concentration in petrol in France was 1.5% (1997).

The Netherlands

According to the report (Langenhoff, 2000) there are, at present, insufficient data to make an accurate assessment of the current risk posed by MTBE to Dutch groundwater resources. The occurrence of MTBE in Dutch groundwtaer and soil is unknown. Groundwater from a few petrol stations have been analysed on MTBE. In two out of ten samples, MTBE contamination ranging between 50 and 150 µg/l was found. Thus in 1/5 of the samples, MTBE forms a serious groundwtaer contamination. Further investigation is recommended.

Sweden

There is one considerable groundwater pollution case by MTBE described from Trollhättan municipality in the county of Gothenburg, Southern Sweden (KEMI, 2000). In Trollhättan

leaking gas station pipings (1997) caused contamination of groundwater and seven private wells. Today, MTBE concentrations in groundwater still exceed 20 µg/l 600 m north from the gas station.

Information on less pronounced pollution cases or monitoring data are not available. The average MTBE concentration in petrol was 1.5% (1997).

UK

The current usage and occurrence of MTBE in groundwater in England and Wales was investigated by the UK Environment Agency (Dottridge et al., 2000). The project collected data on the occurrence of ether oxygenates in groundwater. This included known spills, leaks and the results of routine monitoring, from all possible sources including all Environment Agency Regions, water companies, oil companies and trade associations. The data included information from over 800 site investigations and almost 3,000 samples from public supply and monitoring boreholes. The data provide a representative picture of the presence and concentration of ether oxygenated in groundwater in England and Wales.

The results showed that MTBE occurred at detectable concentrations (>0.1 µg/l) at 13% of monitoring locations, but most of these concentrations were very low, typically less than 1 µg/l. In only one case was MTBE in mains water detected by the public, and only three water supply boreholes had concentrations above the taste threshold. Most boreholes with detectable MTBE are on high vulnerability aquifers. The site-investigation data show that ether oxygenates were detected in groundwater at approximately 33% of petrol retail and distribution sites. Approximately 2% of petrol retail and distribution sites investigated for MTBE are interpreted to be a potential risk to public water supply wells.

A risk assessment was undertaken, applying analytical solutions to MTBE transport from petrol stations to public water supply wells boreholes. The analysis estimates the number of PSW wells with MTBE concentrations above detection limits and taste thresholds and average travel times. The results indicate that 203 (10%) of the 1944 boreholes in England and Wales are expected to contain MTBE, with six sites above the taste threshold.

A forecast of future trends suggests that the number of boreholes with tastable concentrations of MTBE is unlikely to rise if the concentration of MTBE in fuel remains at current levels. If MTBE concentrations in fuel rise to 5% or more in the future, the incidence of taste problems may significantly increase.

The overall conclusion suggested by the project is that the ether oxygenates do not currently pose a major threat to public water supplies in England and Wales. So long as ether oxygenate concentrations in fuel do not increase, it is unlikely that there will be a future problem on the scale of that in the USA. However, continued monitoring and vigilance by the water companies is essential. Due to lack of data, the research has not considered risks to private and industrial water supplies.

In the UK most premium unleaded petrol (more than 83% of the UK market in 1999) contains less than 1% oxygenate but some contain up to 5% of oxygenates (MTBE and TAME). On average, the level of oxygenates in super unleaded petrol and Lead Replacement Petrol is higher than in premium unleaded petrol, typically around 1%, but the proportion can be as high as 5 per cent. However, these fuels accounted for less than 17% of the UK market in 1999, and this proportion is declining.

3.1.7.3.3 Summarising evaluation of measured concentration statistics in groundwater

The concentrations of MTBE in groundwater display a wide range from high levels (of up to 500,000 µg l^{-1} near the source) to background levels farther down the aquifer, with sometimes steep gradients and irregular patterns due to the heterogeneity of the source and of its surroundings (**Table 3.37** and **Table 3.38**). Coupled with uncertainty of sampling, this makes the data difficult to interpret; a generalizable typical concentration cannot be meaningfully defined.

In some Finnish cases, the spatial distribution or temporal development of concentrations in the aquifer has been monitored, also in groundwater wells designed or used for potable water extraction. However, also in most of such cases the knowledge of the local subsurface conditions, e.g. of plume geometry, and of the released amounts and release patterns are very limited. A closer modelling of local MTBE transport and fate is thus seldom possible, or has at least not been published (cf. American cases of monitoring and modelling of MTBE in groundwater).

In the USA, MTBE has been monitored extensively in groundwater. Median value (of detected concentrations only) in the almost 3,000 wells in untreated groundwater sampled by USGS in 1985-1995 was 600 ng/l in urban areas and 500 ng/l in rural areas, the maxima being above 20,000,000 ng/l (20,000 µg/l) and 150,000 ng/l, respectively (Squillace et al., 1999). Detection frequencies were 16,9% of the samples in urban and 3,4% in rural aquifers, making MTBE the second most often detected volatile organic contaminant in groundwater in the USA.

Table 3.37 Summary of measurements (µg/l) of MTBE in groundwater

(cf. Tables in Section 4.1.1)

Country	Type of groundwater and loading	Med	Mean	Max	Information source
A	101 groundwater aquifers	0.01-0.1		>20	BMLF (2000)
D	3 groundwater aquifers at petrol stations, leaking tanks		270 (one aquifer)	185-2,000	UBA (1999)
DK	Shallow groundwater aquifers at service stations, leaks			ND-30,000	Miljostyrelsen (1998)
FI	Urban aquifers, Helsinki	<DL		0.72	Municipalities (unpubl. Reports)
FI	Urban aquifers, Tampere	1.9		3.7	
FI	Shallow aquifers/potable water wells near service stations, leaks			16-330,000 [1)]	Regional authorities, firms (unpubl.)
NL	Groundwater at 4 petrol station sites			120	TNO-report (Langenhoff, 2000)
S	A groundwater aquifer, petrol station leak			>>20	KEMI (2000)
UK	Groundwater at 59 petrol station sites			832,500	UK Environment Agency (Dottridge et al., 2000)
UK	251 public water supply wells		1.1	12.7	UK Environment Agency (Dottridge et al., 2000)
UK	Extractable aquifers, mixed loading	55-480	1,100 (one aquifer)	530-2,900	Wrc (unpubl.), various surveys
USA	Urban, mixed loading	0.6		20,000	USGS surveys,
USA	Rural, mixed loading	0.5		150	Squillace et al. (1999)

[1)] range of maxima in the various local contamination cases

Table 3.38 Observed concentrations of MTBE in European samples of groundwater and perched water (including potable groundwater).
Note: many samples have been affected by emissions from storage leaks. (n=total number of samples, n_p= number of positive results)

Location	Year	n/n_p	Results (µg l^{-1})	Remarks/sampling site	Source
Denmark					
Copenhagen	1997	12/2	1-42	Groundwater aquifer	Miljostyrelsen (1998)
Fyn/DK	1997	12/8	40-6,000	Groundwater aquifer	-"-
Ribe/DK	1997	5/5	1,000-3,700	-"-	-"-
Århus/DK	1997	6/2	22,000-547,000	-"-	-"-
Fredriksborg	1997	3/0	<DL	-"-	-"-
Copenhagen	1997	?	<1-Max. 480	Groundwater near gas station	-"-
Fyn/DK	1997	?	Max. 5-1,700	-"-	-"-
Ringkøb./DK	1997	?	<DL-Max. 400	-"-	-"-
Viborg/DK	1997	?	<DL	-"-	-"-
Fredriksborg	1997	?	Max. 30,000	-"-	-"-
UK					
Northend./UK ?	?		15-160	Groundwater	Turrell et al. (1996)
Cheetham/UK ?	?		60-290	Groundwater	-"-
Sherwood	1995	8/5	<0.1-2.9 (Med=0.7)	Groundwater at abstraction	-"-
Unspec./UK	1993	25/4	<0.05-0.53	Groundwater aquifer	-"-
Unspec./UK	1994-96	57/?	<0.20-2.20	Groundwater aquifer	-"-
Finland					
Unspec./FI	1996-98	1,070/428	<5:n=642 5-10: n=87 10-100: n=175 100-1,000: n=71 1,000-10,000: n=44 10,000-100,000:n=35 >100,000: n=8	Various groundwater, perched water, leachate etc. samples mainly from contaminated sites, at variable distances from contamination source and in variable hydrogeology	VTT (unpubl.)
Unspec./FI (unpubl.)	-1999	60/53	<100: n=25 100-1,000: n=25 >10,000: n=10	Various groundwater perched water, leachate etc. samples mainly at service stations	Golder Associates Finland Ltd.
Unspec./FI	-1999	?	<1-7,000	Various, mainly gas stations	NIOH/Tampere Lab.
Unspec./FI	-1999	?	20-5,000	Various contaminated sites	PSV-SoilWater Ltd.
Lieksa/FI	1998	1	20,000	Groundwater near gas station	PSV-SoilWater Ltd.
Vierumäki/FI	1991-2001		> 50	Municipal abstraction well (closed)	FEI (unpubl.)
Ilomantsi/FI	1998	?	12,000	-"-	-"-
Juuka/FI	1998	?	1,230	Groundwater near gas station	-"-

Table 3.38 Continued overleaf

Table 3.38 continued Observed concentrations of MTBE in European samples of groundwater and perched water

Location	Year	n/n_p	Results (µg l^{-1})	Remarks/sampling site	Source
Pyhäselkä/FI	1998	5	4,200-13,000	Groundwater near gas station	Golder Assoc. Oy et al.
Pyhäselkä/FI	1996-97	10/14	Max. 23,000	Shallow wells near station	-"-
Unspec./FI	-1999	?	20-200,000	various petrol contam.	Fortum Oil & Gas Ltd.
Unspec./FI	-1999	?	0,1-10,000	various contamin. Sites	Juvegroup Ltd. (unpubl.)
Lahti/FI	2000	?	>20	Private wells & groundwater near gas station	FEI (unpubl.)
Porvoo/FI	2000	?	20	Private well near car demolish site	FEI (unpubl.)
Tuusula/FI	2000	?	>50	Private wells & groundwater near gas station	FEI (unpubl.)
Rymättylä/FI	2000	?	1,200	Private well	FEI (unpubl.)

3.1.7.3.4 Use of case-specific data for generalised assessment of groundwater contamination

Data from representative (preferably European) case studies of MTBE concentrations, releases and environmental conditions are used to derive generalised local estimates of exposure through groundwater as a result of known emissions.

3.1.7.3.5 Monitoring data on soil

Few measurements of MTBE in soil matrix or in pore gas in soil have been found from Europe (or from other areas). All these data come from sites contaminated by petrol (**Table 3.39** and **Table 3.40**). Even in these cases the measured concentrations show a relatively wide range, from below-detection levels to concentrations of 100 or, in a single case, even 1,000 µg g^{-1}D.W. (ppm) in the solid matrix or up to 130,000 µg N-m^{-3} in soil gas.

Table 3.39 Observed concentrations of MTBE in Finnish soil samples.
Note: many samples have been affected by emissions from petrol storage leaks.

Location	Year (s)	n	Results (µg g^{-1}D.W.)	Remarks/sampling site	Source
Various/FI	1999	?	-9	Petrol contamination	REC of W. Finland
Various/FI	-1999	?	100-1000	Contaminated sites	Juvegroup Ltd.
Various/FI	-1999	?	0.1-100	Contaminated gas stations	City of Helsinki Lab
Various/FI	-1999	?	<0.2-100	Gas stations/other contam.	NIOH Tampere Lab.
Lieksa, FI	1998	3/4	<0.02-80	Oil at service station	PSV-SoilWater Ltd. &al.
Ilomantsi/FI	1998	1/4	<0.02-3.1	Soil at service station	-"-

Table 3.40 Observed MTBE concentrations in Finnish soil pore gas samples.
Note: many samples have been affected by emissions from petrol storage leaks.

Location	Year(s)	n	Results (µg N-m^{-3})	Remarks/sampling site	Source
Lieksa/FI	1998	3/3	100 000-130 000	Soil at service station	PSV-SoilWater Ltd. & al.
Ilomantsi, FI	1998	0/3	<1000	Soil at service station	PSV-SoilWater Ltd. & al.

Of the site investigation reports held by the UK Environment Agency on sites potentially contaminated with ether oxygenates, from a variety of different geological and geographical settings, 96 were reviewed and summarised. Virtually all these sites were petrol stations and, in the majority of cases, the investigations were performed as part of a redevelopment plan. A limited number of sites were investigated in response to known incidents of petrol leaks. Soil was sampled for MTBE at 59 sites, 47 of which had detectable concentrations. The maximum recorded MTBE concentration in soil was 738,500 µg/kg. From the information by the Institute of Petroleum on 292 sites where oxygenates have been investigated showed that 60 sites had detectable MTBE in soil (Dottridge et al., 2000).

3.1.7.4 Comparison of modelled and monitored concentrations in terrestrial environment

Comparison of modelled and monitored concentration is not considered appropriate in this case. The existing few European monitoring data are not background values in soil or sediments but mostly from areas contaminated by leaks e.g. from underground storage tanks, and they can not be compared with scenarios used in EUSES calculations.

3.1.8 Representativeness and quality of monitoring data

3.1.8.1 Sources of monitoring data and methods of data treatment

Measurement data were sought from the open scientific literature, from other reports (including unpublished reports prepared by consultants), from chemical registers and from the Internet. Also, data collated in previous published assessments of MTBE, such as the Environmental Health Criteria document by IPCS (1998), have been reviewed and utilised.

Additionally, inquiries were made through

- co-operation with MTBE producing industry,
- administrations in some member states and in the USA,
- professional networks (e.g., CLARINET/NICOLE on contaminated land in the EU),
- mainly in Finland, by questionnaires to laboratories analysing organic contaminants in environmental samples, to regional and local administrations, and waterworks.

In the statistical treatment of data, preferably medians or, in their absence, arithmetic means have been used in addition to concentration ranges. In cases where frequency distributions have been reported, also upper e.g. 90% or 95% percentiles have been considered as distribution statistics. Detection frequencies have been expressed for some of the data; however, the significance of these frequencies depends on the detection (and reporting) limit, which has not always been stated in the information sources.

In aggregating data, attention was paid to their commensurability and quality. Very broad pooling of data was avoided. However, averaged or pooled values (for various sampling points and times or replicate samples) have been given e.g. in summary tables meant to give a general description of typical concentration levels. Measures of statistical variation between replicates has been reported in very few of the available reports (mainly for some of the occupational air data only).

3.1.8.2 Data availability and applicability

Rather limited monitoring data on MTBE in terrestrial environment and groundwater for European countries are available with the exception of few countries. Maybe one reason for that is the lack of surveys because for instance water suppliers have not been aware of or much concerned about possible MTBE contamination. Because of expected low toxicity, MTBE has not been monitored systematically within the EU countries. It can be concluded, based on the monitoring data from the USA and monitoring and modelling data from the UK, that concerns and problems with respect to MTBE may come with a time lag, in case the leakages are not prevented, in many European countries where MTBE was introduced later and in lower concentrations.

Geographical and spatial representativeness

Monitoring data on MTBE are available from various environmental samples.

The use of the more extensive monitoring data from the USA is possible for some purposes, keeping in mind the constraints on its applicability due e.g. to differences in MTBE use and emission-related factors and in environmental conditions. In the present assessment, data from outside EU have been used as a reference mainly in cases where their generalisability and quality seem reasonably good, and little or no relevant data from Europe have been identified.

The detailed location of samples (stations and points) is important for the spatial representativeness of measurements for those sample matrices with large and irregular spatial variation, and for all matrices with regard to their location relative to emission sources (especially point sources causing pronounced concentration gradients). In particular, for groundwater samples the depth dimension of sampling (the depth and height of well screens in relation to the permeable soil layers, and the placing of sampling devices) is crucial for the representativeness of the aquifer(s) to be characterised. Associated factors include the possibility of intrusion of surface water into wells and the presence there of stagnant groundwater (with insufficient sealing and flushing of wells). In the present assessment, with few exceptions such information on the representativeness of sampling has not been available. However, in some of the data crude designations have been reported or have been inferred e.g. as to whether the samples represent shallow or deep groundwater, and have been taken into account and expressed if possible. Otherwise, these factors in representativeness have been considered in a nonsystematic and nonquantitative manner on a case-by-case basis.

Temporal representativeness

Temporal representativeness of MTBE measurements may be limited by many reasons including the following:

- *seasonal* variation in concentrations and fluxes e.g. due to variable production and use patterns, and to temperature and hydrological factors or other environmental processes,
- variation e.g. in production, uses and environmental processes,

- *non-systematic* variation due e.g. to changes in production, to sporadic emissions and transient pulses such as from sudden leaks,
- duration of MTBE *use period* (in relation to the period of sampling),
- flow dynamics of *carrier phases*, e.g. in groundwater according to flow velocities,
- temporal variation in the *measurement* methodologies, e.g. in sampling focus.

In general, irregular short-term variation in monitoring data may be estimated to be less pronounced in background levels than in releases.

In the present assessment, it has not been possible to evaluate the temporal representativeness of the available measurement data comprehensively and in detail, partly because the coverage of measurements also in time has not been reported in many cases. However, this factor has been taken into consideration among others on a case-by case judgement basis in the selection, evaluation and use of the data.

Relevance of data from unintentional situations

A crucial issue in evaluating the relevance and generalisability of measurement data on MTBE is that much of it is from areas contaminated by leaks e.g. from underground storage tanks (LUST) and from other unintentional situations. It is often difficult to know if and to what extent observed concentrations result from accidental releases, from more regular substandard operating conditions such as leakage from overfilling, or from still more normal continuous emissions representing (present average) technological standards. The significance of this problem varies by area and level of assessment (e.g., it may not so significant in regional or global assessments).

A general principle in the present (1996) TGD (Part II, p. 257), is to disregard monitoring data "resulting from accidental spillage or malfunction". However, these concepts require more accurate definition, since they cover a wide variety of situations.

It is argued that, as much of the emissions of MTBE result from spills e.g. in overfills and generally from imperfect distribution, storage and handling, a total disregard of related data is not reasonable and practicable. A contributing reason is the variable technical level e.g. between member states and periods, making assumptions based on high standards unrealistic. The inclusion of data on unintentional situations, within limits, is justified also in view of the relevance of the assessment for the broader tasks of elucidating the problems posed by MTBE and for devising efficient risk management strategies.

In this assessment, data which are known to originate from distinct large-scale accidents such as in transportation are omitted, while data which are related with subtle malfunctions and misconduct of common systems are largely included. Use of data from small-scale spills and from breakdown of elementary technological standards is considered depending on the case. This is felt to be in line with the overall aim of realistic conservative assumptions in the assessment. In many cases it cannot be known to what extent the data result from normal or unintentional situations and emissions; in some of these cases this may not have been known to the authors or may even be impossible to find out, while in others it is a question of the detail and type of information given in the report. With some of the data however, such as those on large rivers or background areas of ambient air, it can be judged with more confidence that they represent more normal conditions than single emissions.

Even when unintentional conditions would not be assumed to occur in baseline exposure assessments, data from such cases can be used, within appropriate limits, to complement these assessments. For instance, results on exposure levels caused by known quantities of MTBE

released accidentally in known environmental conditions can be useful for the assessment of also steadier releases, e.g. in order to verify and refine model simulations.

3.1.8.3 Monitoring data quality

Sampling, pre-treatment and measurement methods have in many cases not been reported, not even in all original sources. This makes it difficult to evaluate the data.

Sampling and pre-treatment methods

Variation and errors may be caused in sampling and pre-treatment stages due to many factors reducing representativeness (see Section 3.1.8.2) or reliability (accuracy and precision). *Losses* of MTBE by volatilisation may occur particularly in sampling systems involving gas exchange and turbulence, while losses by sorption and breakdown are not considered significant generally. *Contamination* of samples may occur especially in subsurface soil e.g. due to drilling equipment but also in other compartments particularly at background levels. A formal and systematic discrimination of data based on these factors has not been possible.

Analytical methods

Chemical analysis of MTBE in aqueous samples by chromatography (usually gas chromatography using flame ionisation detection FID, preceded by solvent extraction or headspace or purge & trap sampling), preferably coupled with mass spectrometry (usually in Selected Ion Monitoring mode SIM), is relatively straightforward on higher concentration levels. Thus, such data have been included without discrimination if no special reasons have been obvious to exclude the data for this.

Table 3.41 Characteristics of analytical methods for MTBE in water samples (mainly based on Achten and Puettmann, in press)

	Det. lim. µg/l	Rep. lim. µg/l
Some Eur. (wastewater) methods (GC-FID)	10-1,000	
Purge & trap, GC(MS) (EPA 524.2.)	0.060-0.083	0.2
Direct injection, single-ion MS	0.050	
-"-, multiple-ion MS	0.1	
-"-, full scan MS	10	
Solid Phase MicroExtraction, GC-MS *)	0.010	

*) 8% recovery, 20% accuracy and SD 12%

3.1.9 Secondary poisoning

Exposure assessment through secondary poisoning has not been carried out for MTBE since it has low potential to accumulate to living organisms, and it is not classified as very toxic (T+), toxic (T) or harmful (Xn) according to mammalian toxicity data.

3.1.10 Humans exposed via the environment

The human intake of MTBE from indirect exposure in local and regional scenarios is presented in **Table 3.42**. In the different local assessment scenarios, all food products come from the vicinity of a point source of concern. In the regional assessment, all food products are taken from the regional model environment. The estimations are results of EUSES calculations.

Table 3.42 Estimated human intake of MTBE in mg/kg bw/d, Local and Regional

Scenario	Drinking water	Fish	Leaf crops	Root crops	Meat	Milk	Air	Total intake mg/kg/d
Production	0.24	0.022	0.0003	0.001	0.000002	0.00003	0.059	0.324
Formulation	0.010	0.0009	0.00001	0.00005	$7 \cdot 10^{-8}$	0.000001	0.003	0.014
Processing 1	0.007	0.0006	0.00002	0.00004	$5.41 \cdot 10^{-8}$	0.000001	0.004	0.012
Processing 2	0.005	0.00005	0.001	0.001	$5 \cdot 10^{-7}$	0.000009	0.237	0.244
Processing 3	0.005	0.0005	0.00005	0.0001	$5 \cdot 10^{-8}$	$1 \cdot 10^{-6}$	0.01	0.016
Regional	0.00004	0.000004	$8 \cdot 10^{-7}$	$3 \cdot 10^{-7}$	$6 \cdot 10^{10}$	$1 \cdot 10^{-8}$	0.0002	0.0002

3.2 EFFECTS ASSESSMENT: HAZARD IDENTIFICATION AND DOSE (CONCENTRATION) - RESPONSE (EFFECT) ASSESSMENT

3.2.1 Aquatic compartment

There was a reasonable amount of rather good quality data on toxicity of MTBE to aquatic organisms. Only tests that are considered valid are cited in this report.
The problem encountered in every test measuring MTBE values was that the concentration of the test substance was not maintained within 80% of the initial concentration during the test. This is most probably due to the high volatility of MTBE. All studies that did not report measured concentrations of MTBE were considered invalid for risk assessment purposes. An exception had to be made concerning the toxicity of MTBE to microorganisms since there were no measured data in any of the tests.

In a study by BenKinney et al. (1994), toxicity of MTBE to aquatic organisms was tested using the WAF-method (Water Accommodated Fraction). It was stated that MTBE although being soluble dissolves slowly. This argument has not been mentioned in any other studies. The results from the WAF studies were not significantly different from other studies.

3.2.1.1 Acute and prolonged toxicity to fish

Toxicity data of MTBE to freshwater fish are summarised in **Table 3.43** and toxicity data to marine fish in **Table 3.44**.

There are many data on the acute toxicity of MTBE to fish but only one chronic test, namely on eggs and larvae/fry of *Pimephales promelas*. The next longest period tested was 7 days which can only be considered as a prolonged test. The acute fresh water LC50s are in the range from

672 mg/l to 1,054 mg/l. The 7-day test gave a NOEC of 234 mg/l and in the long-term test, an IC20 of 279 mg/l was measured.

There are also three test results on the toxicity of MTBE to marine fish which seem to be in a same order of magnitude as the fresh water results, LC50s ranging from 574 mg/l to 1,358 mg/l.

The IC20 value of 279 mg/l for *Pimephales promelas* from the only chronic test will be taken into consideration for the derivation of PNEC for the aquatic environment.

Table 3.43 Toxicity of MTBE to freshwater fish

Species	Duration	Method	Type	Analytical monitoring	LC50, NOEC (mg/l)	Reference
Pimephales promelas	96 h	US EPA 1981	flow through	measured	672	Geiger et al. (1988)
Pimephales promelas	96 h	US EPA 1975	flow through	measured	706	Veith et al. (1983)
Pimephales promelas	96 h	WAF, US EPA, OECD	Static, renewal	measured	929	BenKinney et al. (1994)
Pimephales promelas	96 h	US EPA 1982, ASTM E729-88	flow through	measured	980	Hockett (1997a)
Oncorhynchus mykiss	96 h	ASTM E729-88, US EPA 1982	flow through	measured	887	Hockett (1997b)
Lepomis macrochirus	96 h	ASTM E729-96	flow through	measured	1054	API (1999a)
Pimephales promelas	7 days	USEPA 1000.0 (1994)	static renewal	measured	NOEC: 234 mg/l	Hockett, 1997f)
Pimephales promelas, eggs and larvae/fry	**31 days**	**ASTM E1241-92**	**flow through**	**measured**	**IC20: 279 IC25: 308**	**API, 1999g)**

Table 3.44 Acute/prolonged toxicity of MTBE to marine fish

Species	Duration	Method	Type	Analytical monitoring	LC50, NOEC (mg/l)	Reference
Menidia beryllina	96 h	WAF, USEPA, OECD (1994)	Static, renewal	measured	574	BenKinney et al. (1994)
Gasterosteus aculeatus	96 h	USEPA 850.1075, ASTM E729-88a	flow through	measured	929 (EC50: 297)	API (1999l)
Cyprinodon variegatus	96 h	USEPA 850.1075, ASTM E729-88a	flow through	measured	1358 (EC50: 663)	API (1999k)

3.2.1.2 Toxicity to aquatic invertebrates

The toxicity studies with MTBE on aquatic freshwater invertebrates are summarised in **Table 3.45** and on aquatic marine invertebrates in **Table 3.46**. There are many data on acute toxicity to aquatic invertebrates and also one long-term test with both freshwater and marine invertebrates. One test with *Ceriodaphnia dubia* which lasted 5 days is reported (Hockett, 1997e). This test can be seen as a short-term screening method for chronic toxicity for some purposes for example effluent testing. However there is not enough evidence that this test could correspond to a long-

term test with Daphnia species. This might also explain the inconsistency between the results of the *Ceriodaphnia* tests: the LC50 for 48 hours is 340 mg/l which is similar to the NOEC survival of this 5 day *Ceriodaphnia* test.

The acute LC/EC50 values for fresh water invertebrates range from 340 mg/l to 960 mg/l. The 5-day test gave a NOEC of 342 mg/l and the long-term test a NOEC of 51 mg/l. The acute LC/EC50s for marine invertebrates range from 136 mg/l to 306 mg/l and the long-term NOEC is 26 mg/l.

The tests with marine invertebrate show that MTBE is more toxic to marine invertebrates than to fresh water invertebrates. The marine NOEC value of 26 mg/l for *Mysidopsis bahia* from the 28 day test will be taken into consideration in the derivation of PNEC for the aquatic environment.

Table 3.45 Toxicity of MTBE to freshwater invertebrates

Species	Duration	Method	Type	Analytical monitoring	EC50 (mg/l)	Reference
Daphnia magna	48 h	84/449/EEC, C2	Static	measured	651.4	Huels AG (1991b)
Daphnia magna	48 h	WAF,US EPA, OECD (1994)	Static, renewal	measured	681	BenKinney et al. (1994)
Daphnia magna	48 h	US EPA 1982, ASTM 1989	Static, renewal	measured	LC50: 542 mg/l	Hockett, (1997d)
Daphnia magna	48 h	USEPA 850.1010, ASTM E729-88a	Flow through	measured	472	API (1999o)
Ceriodaphnia dubia	48 h	US EPA 1982, ASTM 1989	Static, renewal	measured	LC50: 340 mg/l	Hockett (1997c)
Brachionus calyciflorus	24 h	Other	Static	measured	960	Werner et al. (1998)
Ceriodaphnia dubia	5 days	US EPA 1002.0. ASTM E1295-89	Static, renewal	measured	202 (NOEC, reprod.) 342 (NOEC, survival) 342 (LOEC, reprod.) 580 (LOEC, survival)	Hockett (1997e)
Physa gyrina	96 h	ASTM E729-96	Flow-through	measured	559	API (1999f)
Hexagenia limbata	96 h	ASTM E729-96	Flow-through	measured	581	API (1999e)
Daphnia magna	21 days	US EPA, ASTM E1193-87	Flow-through	measured	51 (NOEC) 100 (LOEC)	API (1999h)

Table 3.46 Toxicity of MTBE to marine invertebrates

Species	Duration	Method	Type	Analytical monitoring	EC50 (mg/l)	Reference
Mysidopsis bahia	**96 h**	**WAF,US EPA, OECD (1994)**	**Static, renewal**	**measured**	**136**	**BenKinney et al. (1994)**
Mysidopsis bahia	96 h	USEPA 850.1035, ASTM E729-88a	Flow-through	measured	187 (LC50: 200)	API (1999n)
Neomysis mercedis	96 h	Other	Static, renewal	measured	LC50: 236 mg/l	Werner et al. (1998)
Callinectes sapidus	96 h	FIFRA, ASTM E729-88a	Flow-through	measured	306 (LC50: 306)	API (1999i)
Palaemonetes pugio	96 h	USEPA 850.1045	Flow-through	measured	166 (LC50: 166)	API (1999j)
Crassostrea virginica	96 h	USEPA 850.1025, ASTM E729-88a	Flow-through	measured	150	API (1999m)
Rhepoxynius abronius	96 h	ASTM E729-96, E1367-96	Static, renewal	measured	294	API (1999d)
Mysidopsis bahia	**28 days**	**USEPA 850.1350, ASTM E1191-90**	**Flow-through**	**measured**	**NOEC: 26 LOEC: 50 IC25: 32**	**API (1999n)**

3.2.1.3 Acute aquatic toxicity to sediment dwelling invertebrates

There are two acute MTBE toxicity tests done under flow through test conditions. The organisms are sediment dwelling but these tests do not include sediment. The marine amphipod *Hyalella azteca* seems to be more sensitive to MTBE than the Dipteran *Chironomus tentans.*

Since these tests with sediment dwelling invertebrates were not carried out in presence of sediment, they can only be considered as an extension to the data set for the other freshwater invertebrates. The values are consistent with those reported for the other freshwater species.

Table 3.47 Acute aquatic toxicity to sediment dwelling organisms

Species	Duration	Method	Analytical monitoring	EC50 mg/l	Reference
Chironomus tentans	48 h	ASTM E729-96	Yes	1742	API (1999b)
Hyalella azteca	96 h	ASTM E729-96	Yes	473	API (1999c)

3.2.1.4 Toxicity to algae

The toxicity of MTBE to freshwater algae is summarised in **Table 3.48**.

Table 3.48 Toxicity of MTBE to freshwater algae

Species	Duration	Method	EC/IC50 or NOEC mg/l	Reference
Selenastrum capricornutum	96 h	WAF, US EPA, OECD (1994)	ErC50: 184	BenKinney et al. (1994)
Selenastrum capricornutum	**96 h**	**ASTM E1218-90 (cell density)**	**IC50: 491 IC25: 134 IC20: 103**	**API (1999p)**
Scenedesmus subspicatus	72 h	Dir. 88/302/EEC	>800 (EbC50 and ErC50) NOEC: 470	Huels AG (1991a)

The test results on algae differ considerably from each other. No reason can be found in test reports. Unfortunately, there are only a presentation material available from the BenKinney et al. test (1994) which makes it more difficult to evaluate the test. The test is done according to US EPA regulations, the WAF-method is used according to guidelines, measured values are reported and the maintenance of the test concentration is reported every 24-hour interval and it stays within 80%. According to this information, the test seems valid. The API test is done according to ASTM guideline, the test report is available and the test seems valid. The Huels study is done according to directive 88/302/EEC, the test report is available and the test seems valid although the results have been presented as nominal concentrations. The measured test concentrations after 72 hours do not deviate by more than 20 % from the freshly prepared test solutions.

A test with *Selenastrum capricornutum* gives an ErC50 value of 184 mg/l in 96 hours. Another acute test with the same species gives an IC50 (cell density) value of 491 mg/l in 96 hours (IC25, 96 h, 134 mg/l; IC20, 96 h, 103 mg/l). A test with *Selenastrum capricornutum* gives an EbC50 and ErC50 of >800 in 72 hours (NOEC, 72 h, 470 mg/l).

As a result the IC20 value of 103 mg/l for *Selenastrum capricornutum* will be taken into consideration with the test results of other taxonomic groups for the derivation of PNEC for the aquatic environment.

3.2.1.5 QSAR calculation for aquatic organisms

Bol (1993) classified MTBE as a non-polar narcotic substance and predicted acute values of 545 (LC50), 728 (LC50) and 596 (EC50) mg/l for fish, daphnia and algae respectively. The predicted NOEC for fish was 59.9 mg/l and for *Daphnia* 185 mg/l. According to the TGD, there are reliable QSARs available for chemicals that act by a non-specific mode of action (non-polar narcosis as well as polar narcosis). Regarding non-polar narcosis, QSARs are recommended for fish (short and long term), *Daphnia* (short and long term) and algae (short term).

QSAR calculations made with equations described in the TGD give values of the same magnitude than measured values for fish and *Daphnia*. For algae, the measured values are somewhat lower. ECOSAR calculations show values similar to measured values for fish, *Daphnia* and algae.

Table 3.49 Aquatic toxicity of MTBE calculated with QSARs from the TGD [1)]

Species	Endpoint	Result in mg.l^{-1}
Fish		
Pimephales promelas	96 h LC50	451
Brachydanio rerio Pimephales promelas	28-32 d NOEC, ELS test	49.1
Daphnia		
Daphnia magna	48 h EC50, immob.	415
Daphnia magna	16 d NOEC, growth, reprod.	96.0
Algae		
Selenastrum capricornutum	72-96 h EC50, growth	452

[1)] log Kow 1.06, molecular weight 88.15

Table 3.50 Aquatic toxicity of MTBE calculated with ECOSAR [1)]

Organism	Duration	Endpoint	Predicted mg.l^{-1}
Fish, fresh water	96 h	LC50	499
Fish, salt water	96 h	LC50	72
Daphnid	48 h	LC50	501
Green algae	96 h	EC50	297

[1)] Chemical class Ethers, measured water solubility 42 000 mg/l, molecular weight 88.15, melting point –108, physical state liquid and log Kow measured 1.06

The QSAR predictions are in rather good agreement with the measured values showing in general somewhat higher toxicity to fresh water fish, *Daphnia* and algae. The predictions of the toxicity values of MTBE to salt water fish are remarkably lower than the measured concentrations ranging from 574 mg/l to 1,358 mg/l.

3.2.1.6 Toxicity to microorganisms

The toxicity of MTBE to microorganisms is summarised in **Table 3.51**. Only two studies on microorganisms have been reported. Both of them have been performed with *Pseudomonas putida* but they differ in duration and in the method used. Neither of the studies reported measured concentration of MTBE in the test culture. Since the test that lasted 4.5-5 hours is only a limit test, the EC10 value of 710 mg/l from the test lasting 18 hours and measuring cell multiplication inhibition will be used for the derivation of PNEC for the microorganisms in STP.

Table 3.51 Toxicity of MTBE to microorganisms

Species	Duration	Method	Analytical monitoring	EC10 mg/l	Reference
Pseudomonas putida	4.5 – 5 h	Inhibition of oxygen consumption	No	>1480 (nominal)	Huels AG (1991c)
Pseudomonas putida	**18 h**	**Bringmann and Kühn (1977) (cell multiplication inhibition)**	**No**	**710 (nominal)**	**Huels AG (1991d)**

3.2.1.7 Toxicity to amphibians

The effect of MTBE on the survival and development of the frog *Rana temporaria* was studied. The LC50 for tadpoles was 2,500 mg/l. Low MTBE concentration in water (100 mg/l) led to a marked increase in the numbers of tadpoles and frogs compared to controls. A sublethal MTBE concentration stimulated also the course of metamorphosis, which occurred 2 days earlier than normal in exposed animals. Unfortunately, only the abstract of the study is in English, so the validity of the test has not been evaluated (Paulov, 1987).

3.2.1.8 PNEC for the aquatic environment

There are a complete "base-set" of acute toxicity data for MTBE. Long-term studies are also available for fish, invertebrates and algae. According to the TGD, the use of an assessment factor 10 will normally only be applied when long-term toxicity NOECs are available from at least three species across three throphic levels. This is only sufficient, however if the species tested can be considered to represent one of the more sensitive groups. In this case, there is only an IC20 value of 279 mg/l, no NOEC, available for fish in the long-term test. For invertebrates, which have the lowest short-term value, there is a long-term NOEC of 26 mg/l. For algae, there is a NOEC of 470 mg/l for *Scenedesmus subspicatus*. Due to nominal values used in calculations this is not an exact NOEC value, but together with the other information on algae toxicity, e.g. an IC20 of 103 mg/l for Selenastrum capricornutum, it would be unlikely that an algae NOEC would be lower than the one for Mysidopsis bahia. Using the result from the long-term Mysidopsis bahia test, NOEC 26 mg/l, and the assessment factor 10 the **PNEC aquatic** is 2.6 mg/l.

Short-term toxicity test results indicate that MTBE has not any specific mode of toxic action in aquatic species. Variability between species and trophic levels is not high. Therefore, for intermittent release an assessment factor of 10 is used (TGD 3.3.2) giving $\mathbf{PNEC_{aquatic\_intermittent}}$ 13.6 mg/l based on a short-term EC50 for *Mysidopsis bahia*.

In the absence of any ecotoxicological data for sediment-dwelling organisms, the $PNEC_{sed}$ may provisionally be calculated using the equilibrium partitioning method with the following formula:

$$PNEC_{sed} = K_{sed\text{-}water}/RHO_{sed} \cdot PNEC_{water} \cdot 1{,}000$$

where $PNEC_{water}$ = Predicted No Effect Concentration in water ($mg.l^{-1)}$
RHO_{sed} = bulk density of wet sediment (1,300 $kgwwt.m^{-3}$)
$K_{sed\text{-}water}$ = partition coefficient sediment water (1.03 $m^3.m^{-3}$)
$PNEC_{sediment}$ = Predicted No Effect Concentration in sediment ($mg.kg^{-1}$)

The $PNEC_{sediment,organisms}$ calculated from the $PNEC_{aquatic,organisms}$ using the equilibrium partitioning method is 2.05 $mg.kgwwt^{-1}$.

Considering that fish may have the same or even higher sensitivity to the organoleptic properties of MTBE as humans, possible avoidance behaviour should also be assessed. Avoidance behaviour can be seen as an ecologically relevant endpoint leading to changed ecosystems and ecosystem functions and can also effect fish and mussel eating mammals and birds. Further consideration in relation to establishing a threshold value for possible avoidance behaviour in fish is seen necessary to address possible effects starting from surface water and having effects to the food chain.

3.2.1.9 PNEC for microorganisms in a STP

The value EC10 of 710 mg/l is used to calculate the $PNEC_{microorganisms}$. According to the TGD, the PNEC value is equal to the NOEC from a test performed with a "specific bacterial population" like for instance a *Pseudomonas putida* -population. It is also stated in the TGD that in some cases an EC10 can be regarded equal to NOEC. Since there are no measured concentrations in the test and the test design is not following the present guideline in many aspects, an assessment factor 10 is used. Accordingly, the $PNEC_{microorganisms}$ is 71 mg/l.

3.2.2 Atmospheric compartment

There are no data on the effects of MTBE through atmospheric exposure.

Because releases to air are large, it may be worth considering the low-level ozone formation potential, although the half life is not very short. From Derwent et al. (1998), the photochemical ozone creation potential (POCP) of MTBE is 15.2 relative to ethylene as 100 – compared to ethane at 12.3 which is a negligible contributor to low-level ozone, MTBE can also be considered a negligible contributor.

Terrestrial compartment

There are no toxicity data on MTBE to soil organisms and therefore the PNEC is calculated using the equilibrium partitioning method.

$$PNEC_{soil} = K_{soil\text{-}water}/RHO_{soil} \cdot PNEC_{water} \cdot 1{,}000$$

where $PNEC_{water}$ = Predicted No Effect Concentration in water (2.6 $mg.l^{-1}$)
RHO_{soil} = bulk density of wet soil (1,700 $kg.m^{-3}$)
$K_{soil\text{-}water}$ = partition coefficient soil-water (0.477 $m^3.m^{-3}$)
$PNEC_{soil}$ = Predicted No Effect Concentration in soil ($mg.kg^{-1}$)

PNEC for terrestrial organisms is 0.730 $mg.kgwwt^{-1}$.

3.2.3 Secondary poisoning

Estimated (1.6) and measured (1.4, 1.5) BCF's for fish indicate a low potential for bioconcentration as do BCF's calculated by EUSES for fish (1.59) and earthworm (1.64). Therefore, secondary poisoning is not likely.

3.3 RISK CHARACTERISATION

3.3.1 Aquatic compartment

3.3.1.1 Surface water and sediment

Predicted environmental concentrations were estimated in Section 3.1.5.1. The $PECs_{local\ water}$ are presented in **Table 3.52** along with the risk characterisation PEC/PNEC-ratios. Predicted no-effect concentrations for aquatic organisms were estimated in Section 3.2.1.8. The $PNEC_{aquatic,organisms}$ is 26 mg/l/10 = 2.6 mg/l. For intermitted release the $PNEC_{aquatic,organisms}$ is 136 mg/l/10 = 13.6 mg/l.

Table 3.52 Local PEC/PNEC ratios for surface water

Process	PEC (µg/l)	PEC/PNEC	Site code
Production	10,300	3.95	Generic
Production (sites 1-32)	See Table 3.53	See Table 3.53	Site specific
Formulation	442	0.17	Generic
Processing 1.	253	0.097	Generic
Processing 1. (tank water) *)	60,000	4.4	Measured/generic
Road traffic (runoff)	1.5	0.0008	Measured/generic
Boating (exhaust)	12	0.0065	Measured/generic
Processing 2.	23.4	0.009	Generic
Processing 3.	188	0.437	Generic

*) intermittent releases

Table 3.53 Site-specific risk characterisation ratios for surface water

Site	$PEClocal_{water}$ (mg/l)	PEC/PNEC (PNEC= 2.6 mg/l)
Site 1, production Formulation	<0.01	<0.004
Site 2 , production formulation	0.183	0.070
Site 4 , production	<0.1	<0.038
Site 5 , production	0.390	0.150
Site 6 , production Formulation	0.0015	0.0006
Site 7 , production	<0.1	<0.038
Site 8 , production	<0.00003	<0.00001
Site 9, production, use to produce isobutylene	<0.01	<0.004
Site 10 , production Formulation	2.50	0.962
Site 11 , production Formulation	0.020	0.008
Site 12	0.0015	0.0006

Table 3.53 Continued overleaf

Table 3.53 continued.. Site-specific risk characterisation ratios for surface water

Site	$PEClocal_{water}$ (mg/l)	PEC/PNEC (PNEC= 2.6 mg/l)
Site 14, production formulation	<0.0025	<0.001
Site 15, production formulation	0.018	0.007
Site 16, production formulation	0.060	0.023
Site 17, production formulation	<0.2	<0.077
Site 18, production formulation	<0.2	<0.077
Site 19, production formulation	0.0015	0.0006
Site 20, production formulation	<0.1	<0.038
Site 21, production formulation	0.55	0.212
Site 22, production formulation	<0.010	<0.004
Site 23, production formulation	0.002	0.0008
Site 24, production formulation	<0.010	<0.004
Site 25, production formulation	1.00	0.385
Site 26, production formulation	<0.010	<0.004
Site 27, production formulation	<0.010	<0.004
Site 28, production formulation	<0.010	<0.004
Site 29, production formulation	0.0015	0.0006
Site 30, production formulation	0.0015	0.0006
Site 31, production formulation	<0.03	<0.012
Site 32, production formulation	<0.02	<0.008
Site 33, use as solvent	0.0016	0.0006

The $PNEC_{sediment,organisms}$ is 2,05 mg/kg wwt. The value was calculated from the $PNEC_{aquatic,organisms}$ using the equilibrium partitioning method.

It is said in the TGD that if no measured data are available, neither for the determination of PEC_{sed} nor for the calculation of $PNEC_{sed}$, no quantitative risk characterisation for sediment can be performed. In the case of MTBE, there are no measured data available for either PEC or PNEC determination. All site-specific $PEC_{sediment}$ values are calculated from PEC_{water}. Consequently, the PEC/PNEC ratios are nearly the same as for surface water and there is no need for risk characterisation for the sediment compartment.

Local risk characterisation

The generic scenarios for formulation and processing (1, 2 and 3) lead to PEC/PNEC ratios below 1 in surface water but the scenario for production shows a ratio greater than one. Site-specific information on the other hand shows no risk to any of the known production, production/formulation or processing sites. There is no site-specific information on formulation off-site. Due to the presence of extensive and reliable site-specific data, the risk characterisation will not be based on generic scenario.

Intermittent releases to local aquatic environment from storage tank bottom waters lead to PEC/PNEC ratios greater than 1 in surface water.

Regional risk characterisation

The regional surface water PEC/PNEC ratio is 1.5 μg/l/2,600 μg/l = 0.0006. This ratio indicates that there is no risk at regional level in surface water.

Results of risk characterisation for the aquatic environment

Conclusion (i) There is a need for further information and/or testing

This conclusion is reached because there is a need for better information to adequately characterise the risks to the aquatic ecosystem regarding the emission of the substance to surface water.

The information and test requirements are: a tiered testing approach for investigation of avoidance behaviour in fish and if necessary in other wildlife animals related to water contaminated with the substance.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

This conclusion applies to production, production/formulation, formulation and processing sites; to transport, storage and delivery except for intermittent release to surface water from terminal site storage tank bottom waters; to road traffic (runoff) and to boating (exhaust).

Conclusion (iii) There is a need for limiting risks; risk reduction measures which are already being applied shall be taken into account.

This conclusion applies to intermittent release to surface water from terminal site storage tank bottom waters.

3.3.1.2 Microorganisms in wastewater treatment plants

PNEC of 71 mg/l was derived for microorganisms in WWTPs. The resulting PEC/PNEC ratios are presented in **Table 3.54** and in **Table 3.55**.

Table 3.54 Generic risk characterisation ratios (PEC/PNEC) for WWTPs

Process	PEC (μg/l)	PEC/PNEC	Site code
Production	103,000	1.45	Generic
Formulation	4,400	0.062	Generic
Processing 1.	2,510	0.035	Generic
Processing 2.	220	0.003	Generic
Processing 3.	11,400	0.16	Generic

Table 3.55 Site-specific risk characterisation ratios for microorganisms in WWTPs

Site	PEC_{stp} = $Clocal_{eff}$ (mg/l)	PEC/PNEC (PNEC=71 mg/l)
Site 1, production formulation	<0.1	<0.001
Site 2, production formulation	1.82	0.026
Site 4, production	<1	<0.014
Site 5, production	3.90	0.055
Site 6, production formulation	<0.074	0.001
Site 7, production	<1	<0.014
Site 8, production	<0.0002	<0.000003
Site 10, production formulation	<25	0.352
Site 11, production formulation	0.190	0.003
Site 12	0.0036	0.00005
Site 14, production formulation	<0.010	<0.0001
Site 15, production formulation	0.167	0.002
Site 16, production formulation	0.59	0.008
Site 17, production formulation	<2	<0.028
Site 18, production formulation	<2	<0.028
Site 19, production formulation	<0.02	0.0003
Site 20, production formulation	<1	<0.014
Site 21, production formulation	5.5	0.078
Site 22, production formulation	- [1]	-
Site 23, production formulation	0.005	0.00007
Site 24, production formulation	0.005	0.00007
Site 25, production formulation	9.98	0.141
Site 26, production formulation	0.039	0.0005
Site 27, production formulation	0.100	0.001
Site 28, production formulation	0.005	0.00007
Site 29, production formulation	0.030	0.0004
Site 30, production formulation	<0.008	<0.0001
Site 31, production formulation	<0.3	<0.004
Site 32, production formulation	<0.2	<0.003
Site 9, production, use to produce isobutylene	<0.1	<0.004
Site 33, use as solvent	<0.1	<0.001

[1] Concentration in the effluent unknown but the concentration in receiving water is <0.010 mg/l

In the generic scenario for production, the microorganisms in wastewater treatment plants are exposed to concentrations which lead to PEC/PNEC ratio greater than one. There is no generic risk from formulation and processing. Site-specific information on the other hand shows no risk to any of the known production, production/formulation or processing sites. Due to the presence of extensive and reliable site-specific data, the risk characterisation will not be based on generic scenario.

Results of risk characterisation for microorganisms in wastewater treatment plants

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

This conclusion applies to production, production/formulation, formulation and processing sites.

3.3.2 Atmosphere

Emissions of MTBE in the atmosphere are high, more than 60,000 tonnes. The highest measured peak concentrations in urban air are some hundreds of micrograms/m^3 and typical average diurnal urban concentrations are <10 µg/m^3. MTBE reacts with hydroxyl radicals in the atmosphere and the average half-life is 3-6 days. As an indirect effect, the ozone forming in troposphere is likely. The substance is not expected to contribute to the ozone peak values significantly compared to most more reactive compounds in petrol and MTBE is added as oxygenate to reduce ozone forming potential of petrol.

There are no indication or studies available that ambient air concentrations of MTBE may cause direct adverse effects for plants or animal species. Because there are no tested data for the air compartment and the calculation of $PNEC_{air}$ is not possible, no quantitative characterization of risk as a PEC/PNEC comparison is possible. Consequently, **conclusion (ii)** applies.

Results of risk characterisation for atmospheric compartment

Conclusion (ii) There is at present no need for further information or testing or risk reduction measures beyond those which are being applied already.

3.3.3 Terrestrial compartment

3.3.3.1 Soil

When released to topsoil MTBE is easily volatilised to air or dissolved to surface water runoff and infiltrated. When MTBE is released to subsurface soil adsorption to soil is poor and high mobility (dissolved in water) is the most likely transport mechanism. Leaching to groundwater is likely and high persistency is expected. Aerobic and anaerobic biodegradation rates are low in soil and groundwater.

There are no ecotoxicity test results for terrestrial organisms available. The predicted no effect concentration for terrestrial organisms was derived (0.729 mg/kg wwt) as EUSES-modelling result based on aquatic toxicity data. The resulting PEC/PNEC ratios are in **Table 3.56**.

Table 3.56 Local risk characterisation for terrestrial environment

Process	PEC mg/kgwwt	PEC/PNEC	Site code
Production	0.233	0.32	Generic
Formulation	0.01	0.014	Generic
Processing 1.	0.006	0.008	Generic
Processing 2.	0.048 0.461	0.066	Generic
Processing 3.	0.026	0.035	Generic
Runoff infiltrated	0.0007	0.0009	Specific

Local risk characterisation

The PEC/PNEC ratios in the generic scenario for production, formulation and processing are all below 1 which shows that there is no risk from these activities to terrestrial environment.

Regional risk characterisation

The highest PEC/PNEC ratio is reached in industrial soil. All the estimated PEC/PNEC ratios are below one:

- Regional PEC/PNEC (mg/kgwwt) ratio in industrial soil is 0.012,
- Regional PEC/PNEC (mg/kgwwt) ratio in agricultural soil is 0.00002.

Results of risk characterisation for soil

Conclusion (ii) There is at present no need for further information or testing or risk reduction measures beyond those which are being applied already.

This conclusion applies to production, formulation, processing and runoff infiltrated.

3.3.3.2 Groundwater

The use of MTBE in petrol has resulted in growing detection of MTBE in groundwater in some Member States. This is mainly caused by leaking underground storage tanks and spillage from overfilling the tanks. However, it is unlikely that the actual use of MTBE containing petrol as fuel had resulted in such pollution. MTBE in groundwater has not been routinely monitored in EU countries and therefore it is difficult to draw firm conclusions about the present extent of the problem at EU level. The available data from Member States demonstrate that there are numerous pollution cases and that the variability in the incidence of these cases is considerable.

In the risk characterisation related to groundwater, it is justified to consider, in addition to the ecotoxicological and toxicological aspects, the overall quality of the groundwater. Although the low odour and taste thresholds of MTBE may be seen useful as early warning indicators of groundwater pollution the water resource will in practise be polluted and unusable when the odour and taste threshold levels are exceeded. This is also supported by the provisions laid down in Council Directive 80/68/EEC on the protection of groundwater against pollution caused by certain dangerous substances.

In number of cases MTBE has been detected in drinking water in concentrations exceeding odour and taste thresholds (15-40 µ g/l) or even much higher. As the future consumption of MTBE is expected to increase in Europe, mainly as an octane booster, there is a growing risk for groundwater pollution unless appropriate actions to prevent leakages and spillages are taken.

Results of risk characterisation for groundwater

Conclusion (iii) is drawn for the overall quality of the groundwater.

Conclusion (iii) There is a need for limiting risks; risk reduction measures which are already being applied shall be taken into account

3.3.4 Secondary poisoning

As there is no indication of bioaccumulation potential of MTBE, no assessment for the secondary poisoning is carried out.

The risk characterisation following from possible avoidance behaviour of fish and consequently to the food chain are discussed in Section 3.3.1.1.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 Occupational exposure

4.1.1.1.1 General discussion

Methyl *tertiary*-butyl ether (MTBE) was recently called "the world's fastest growing petrochemical". In the 1990s, its annual world production was among the 50 top chemicals (Anonymous, 1995). The major use of MTBE is as an oxygenated additive in petrol (blended at 2-11.5 vol %). Only a minor amount is used for other purposes, such as solvent instead of diethyl ether or diisopropyl ether in both chemical and pharmaceutical industry and laboratories. **Table 4.1** presents the products which contain MTBE, and their uses.

Table 4.1 Products containing MTBE

Function of MTBE in products	MTBE content in products *)	Product	Use
Oxygenate to promote more efficient combustion of petrol	11.5-15 vol % and Average 2.8 ±1.5vol %, range 0.2-5.3 vol%, n=12	Petrol, reformulated, unleaded	Automobile fuel
Octane booster in unleaded premium/ high performance grades	Average 2.8 ±1.5vol %, range 0.2-5.3 vol%, n=12	Petrol, unleaded	Automobile fuel
Processes chemical	97.5-99.5 vol %	Neat MTBE	Solvent use for extraction and crystallisation of compounds

*) Source: Gasoline: International Energy Agency (1998); MTBE: DeWitt & Co. (some figures may include also other ethers). Specific gravity of MTBE 0.74 at 20°C

Occupational human exposure to MTBE takes place mainly in the production of MTBE, blending petrol products, during transportation and delivering these products, at petrol stations, and due to emissions of exhaust gases from various engines. Exposure is mainly of intermittent or incidental type and caused by leaks in pipes and connections, and spills during moving the product through production line to consumers. Exposure occurs mainly via inhalation. Skin exposure may also occur especially at maintenance because the use of protective gloves is often problematic.

In addition to occupational exposure, population exposure may occur through environmental contamination. Consumers pumping petrol are also exposed, but to a lesser extent than the professional attendants. Oral and dermal exposure may result from use of household water containing MTBE due to groundwater contamination.

In Finland, the production, transport and distribution of MTBE and its petrol products employed about 2,000 workers (Saarinen et al., 1998). During 1983-1993 in the USA, the jobs related to petrol employed 11,875 workers (API, 1995b).

In 1999, the number of service stations in the EU countries was 111,950 (personal information from the Finnish Oil and Gas Federation). At the end of 1998, there were 1,762 petrol stations in Finland and 529 of them were automated self-service stations. In the USA, estimations on the number of general retail automotive service stations range from 150,000 to 210,000. With the addition of government and private sector fuel dispensing facilities, the total number was estimated to be greater than 400,000 (HEI, 1996).

In Europe, the daily exposure time of attendants at service stations is probably going to decrease because super markets have increased petrol selling on a self-service basis. Actually in 1999, only one per cent of the Finnish service stations still offered refuelling services for customers (Finnish Oil and Gas Federation, 1998).

Although the number of service station attendants has decreased with the introduction of self-service, there remain employees with occupational exposure to petrol. In 1998, the number of occupationally exposed people at Finnish service stations was 8,797 (Finnish Oil and Gas Federation, 1998). However, a large part of them however, engaged in other jobs than dispensing petrol. They were cashiers, making automobile repairs, selling car accessories, keeping a coffee shop or kiosk, or doing cleaning work. Between 1983-1993 in the USA, the number of workers at service stations was 37,800 (API, 1995b).

An overview of the scenarios of occupationally exposed workers is given in **Table 4.2**. There are five basic steps in bringing MTBE to the market: 1. manufacture - producing MTBE in both chemical plants and petroleum refinery facilities; 2. formulation (blending) - introducing MTBE into motor petrol, which includes handling both neat MTBE and MTBE-blended fuels; 3. transportation - moving neat MTBE or MTBE-blended fuels with barge, tanker, railcar, truck, or pipeline to points of distribution; 4. distributing - storing MTBE-blended fuels and moving it from distribution terminals to service stations; 5. service station - storing and dispensing MTBE-blended fuels to the public.

The manufacturing of MTBE and the adjoining blending (formulation) processes (information from industry) are automated and principally closed outdoor processes. During manufacturing, incidental leakages and spills from pipeline and valve connections may cause exposure.

Sampling performed for product control analyses exposes personnel intermittently although for short periods at a time.

Filling the truck tanks for transportation in depots occurs either by top loading or bottom loading (Phillips et al., 1978). Currently, however, the top loading systems have largely been replaced by bottom loading.

Exposure during transporting and distributing occurs intermittently. Duration of one truck loading or unloading is on the average only 30 minutes each. The loading operations are repeated three to seven times per shift, and the rest of the working time is used for driving. The railcar and barge loading or unloading last a little longer but after connecting the valves the function is automated. At service stations, one automobile tank refuelling lasts about one to three minutes and is often performed on a self-service basis by customers.

During the petrol delivery operations, exposure takes mainly place while connecting or disconnecting vehicles to a storing tank. Spills or leaks and overflows may cause occasional exposure. Saturated petrol vapours escaping from the tanks when the tanks are filled with new liquid likely causes the main exposure.

Engineering control (Saarinen et al., 1996) of petrol exposure at distributing depots is carried out with vapour recovery systems. At service stations, type Stage I vapour recovery system means vapour recovery during petrol delivery and Stage II vapour recovery during refuelling automobile tanks.

The use of Stage I vapour recovery is common in the EU countries (information only from seven countries). Mean 55.3% (range 38-90%) of service stations were also equipped with Stage II recovery systems. In 1999, more than two thirds of the Finnish stations were equipped with Stage I gas recovery. Stage II vapour recovery will be installed when new stations are built and old stations renewed. In Switzerland, Stage II vapour recovery is installed in 91% and in Norway in 1% of service stations (Hakkola et al., 1998b). At service stations without Stage I system, the delivering occurs with tank vent tubes with discharge-pipes located further away from the trucks.

Mechanics performing equipment maintenance, and petrol meter calibration and repair are repeatedly exposed to petrol by inhalation of vapours and through the skin. In smaller repair shops working on older cars, about 20 percent of automotive mechanics' jobs concern repairing of the fuel system (workers' personal comments).

Other professionals, such as car drivers (chauffeurs) or traffic policemen are exposed to MTBE in exhaust gases and during self-refuelling. In Europe, the truck drivers and most taxi-drivers have vehicles that use diesel fuel without MTBE as an additive.

Concentrations of oxygenate in the atmosphere (HEI, 1996) are mainly derived from evaporative emissions and to a lesser extend from petrol combustion in engines. The major points of evaporation from automobiles are the exhaust pipe, the petrol tank when fuel is excessively hot, and leaking from the fuel lines.

Data for the report and its handling

The exposure data collected from the European companies date from the period 1988 through 2000. The companies and process circumstances could not be individually identified in the material. The EU data were partly prepared by the CONCAWE's Health Management Group and partly supplied by the European petrol producers.

In the 1990s, the MTBE content in the Finnish petrol was at the highest 11.5 vol.% and in the other Union countries on the average 2.8 vol% (± 1.5 vol.%, range 0.2-5.3, n=12) (information from the industry). Therefore, the Finnish exposure situation was examined separately. The Finnish data collected by two Finnish research groups have been published in peer-reviewed articles. For comparison, also exposure data from the USA was attached (API, 1995b).

The main part of the measurements concerned personal short-term (ST) exposure, but also personal 8h-time-weighed averages (TWA8h) were available. The scanty measurements concerning area concentrations were TWA8h measurements. In connection with the measured data, there was no information of the use of protection measures.

The measured data originated from different sources and contained company averages, either as arithmetic or geometric means. The US data were handled on a scenario basis as geometric means with geometric standard deviations. The total number of samples and the sample ranges were also given.

The MTBE content of petrol products is expressed as volume percentage (vol.%). The vapour concentrations in the air are presented as mg/m^3, if given as ppm the conversion was performed by multiplying with a factor 3.60 (3.60 x ppm = mg/m^3).

The data reported on short-term personal exposures (ST) were handled assuming an exposure period between ≤½ and 1 hour, except the data from service stations where the refuelling time of cars was shorter, being only a few minutes. The data on personal TWA8h exposure averages concerned shifts between one and eight hours. In a few cases, the working hours lasting until ten hours are included in the TWA8h column, since the exposure levels were very similar to those during the normal 8h-shift working day. In the original data, the exact duration of sampling was not always strictly stated.

The main task of the exposure estimations is to find the reasonable worst-case 8h-estimate (RWC8h) for various work scenarios. This estimation is a matter of expert judgment. The data set provided is used for evaluating the exposure, provided that it was representative enough concerning the process type, tasks and certain working situations from which it originated.

TWA8h exposure levels in the processes may differ between the process organisations and working circumstances in various companies. Therefore, the enviromental levels were reviewed on a company basis. ST-exposures are informative of concentrations occurring in various tasks performed over short periods, or exposures during incidental occasions such as repairing damages or maintenance in automated continuous processes.

The tables of the report present the highest concentrations measured (the upper range values), both maximum ST-peaks and maximum TWA8h concentrations. Additionally, one-sided 90th percentiles of both normal and lognormal distributions of the measured concentrations (Hawkins et al., 1991; Leidel et al., 1977; Mulhausen et al., 1998) are given. The 90th percentile values were only calculated if the number of measurements in the series was more than fifteen and when the means (arithmetic or geometric) and standard deviations were provided.

In occupational hygiene, the resulting data sets are often skewed due to very uneven distribution of measurement results. Thus, the best estimate for the mean of the data is the geometric mean (GM) with geometric standard deviation (GSD) (Perkins, 1997), and therefore the 90th percentile of lognormal distribution data was used as an estimator for the reasonable worst-case exposure (RWC8h).

If the number of measurements was limited and no additional information was available, such as MTBE-concentration in petrol, sampling period, sample size, calculations on which the concentrations were based, or if exposure profiles (peaks) were not described during sampling, the estimates were performed on the basis of expert judgment and by comparing with estimates from analogical scenarios. However, obvious extreme values were avoided.
Exposure concentrations were also determined by EASE-modelling (The *EASE* Model, Estimation and Assessment of Substance Exposure, EASE Windows Version 2.0, Appendix table). The used parameters of EASE gave, however, estimates which were throughout too high for inhalation exposure when compared with the available measured data. The EASE estimates for dermal exposure seemed to be quite reasonable.

In EASE-modeling, the suitable modelling parameters were non-dispersive use and direct handling with dilution ventilation for the determination of inhalation exposure in manufacturing and transport operations, except for maintenance works, for which wide-dispersive use with direct handling and dilution ventilation were used. The EASE-parameters for the estimation of dermal exposure were non-dispersive use with either incidental or intermittent direct handling, except for maintenance, which was handled with wide-dispersive use and intermittent handling.

“Non-dispersive use” was used for the scenarios because the working phases are supervised and performed by professional workers working in automated outdoors (dilution ventilation) processes without any admission of outsiders. In maintenance, however, unexpected situations

may sometimes occur. In case of accidents, the plants have their own safety programmes. Professional workers normally use personal protective equipments (PPE).

The same parameters, non-dispersive use and direct handling with dilution ventilation, were used for service station attendants' inhalation exposure. For their work, however, it is a question of relative small volume (up to 60 l) of diluted MTBE in petrol refuelled in an automobile tank at a time. Additionally, the nozzle spout needs pressing by hand for getting petrol, thus, the attendant controls himself overflows and large spills. Therefore, large incidental releases of petrol rarely occur at petrol service pumps. The work is also done in the open air. For the dermal exposure of service station attendants, non-dispersive uses with direct intermittent handling are used.

Related to MTBE exposure, the automobile repair work was considered similar to the service station work, except that skin contamination is more extensive. Drivers and other professionals are exposed like consumers.

Chemical and pharmaceutical industry and laboratories use neat MTBE for extraction and crystallisation of compounds. The work is performed in closed processes or in fume cupboards. The EASE parameters chosen are non-dispersive use with local exhaust ventilation (LEV) for inhalation exposure and non-dispersive use with direct intermittent handling for dermal exposure.

Occupational exposure scenarios

The scenarios for industrial and occupational exposures to MTBE, presented in **Table 4.2** were selected based on the information given by the industry.

New significant blending stocks for petrol each with unique properties of octane booster and clean burning of petrol are on the developing phase. Alkylate production (Miller, 1999), for which also MTBE is used as a feedstock, and the use of polyisobutylene as an alternative fuel additive (Betts, 2000) are new developing phases for the new petrol products. These alternative petrol additives are not included as scenarios in this report.

Table 4.2 Occupational exposure scenarios defined for MTBE

Scenarios	Industrial category (9) Petrochemical	Use category and source of exposure	Additional information
1 Petrol Production and use			
1.1 Production	Petrochemical plants and refineries	Production both in chemical plants and petroleum refineries	Expose of production operators
1.2 Formulation	Petrol blending with MTBE on-site or off-site	Blending MTBE into petrol. The release includes both handling of neat MTBE and blended fuels.	Exposure sources are the connection and disconnection of pipes, evaporation from spills and leaks
1.3 Transporting	Transporting to blending stations and distribution terminals	Transferring neat MTBE or blended fuels with barge, tanker, railcar, truck or pipeline to storage tanks or distribution depots	Exposure sources are connections or dis-connections of the pipes and evaporation from spills and leaks
1.4 Distributing	Distributing petrol from terminals to service stations	Moving MTBE-blended fuels from distribution terminals to service stations	Exposed workers are truck drivers
1.5 Service stations		Dispensing and storing blended fuels for the use of public	Attendants in service station, consumers when self-serving
1.6 Maintenance operations	Maintenance works in petrochemical plants, refineries, blending stations, at fuel distribution and dispensing depots, and service stations	Repairing and maintenance of manufacturing and dispensing equipment, petrol meters and local exhaust ventilators	Mechanics
1.7 Automotive repair and related		Maintenance of the fuel system.	Mechanics
1.8 Drivers and other professionals	Professional drivers and other workers	Vehicles, garages, police, customs officers, forest harvest workers	Professional workers are exposed during refuelling and from exhaust gases from petrol engines
2 Solvent use of MTBE	Chemical and pharmaceutical industry, various laboratories	Use as solvent in syntheses and analyses	Expose of production operators and laboratory personnel

Occupational exposure limits

The following table **Table 4.3** shows OELs for MTBE in the EU countries and the USA.

Table 4.3 Occupational exposure limits for MTBE

Country	Time-weighed average TWA 8h, mg/m³	Short-term exposure limit, STEL 15 min, mg/m³	Abbreviation of the list name	Reference
HSE / UK	90	270	OES	HSE (1999)
DGF / Germany	180		MAK	DGF (1998)
Sweden	110	220	NGV	ASS (2000)
The Netherlands	180	360	MAC	DECOS (1999)
Italy	180			
Denmark	180		TWA	
Ireland	180		TWA	
Finland	180		HTP	MSAH (2000)
Spain	147		TWA	
ACGIH / USA	180 (A3)		TLV	ACGIH (2001)

180 mg/m³ = 50 ppm; 360 mg/m³ = 100 ppm; 270 mg/m³ = 75 ppm; A3= Confirmed animal carcinogen with unknown relevance to humans (intended change for 2001).

Methods and strategies for measuring exposure

The evaluations of environmental and safety conditions are usually focused primarily on air monitoring, but it is often also necessary to include assessments made by experts during walk-through visits in a factory. For this report, the measured data were so extensive that there was only little need to count solely on experts.

Most of the operations involving MTBE caused exposures which were closer to the ST- (between five and 30 min) than the TWA8h exposures, although short "peaks" may have been repeated frequently during a workday. The air samples seemed to be collected during the period of time when the workload was highest. For sampling of these ST-samples, active sampling with pumps was used. Diffusive samplers were used for long-term (LT) sampling (Harper et al., 1995; Harper et al., 1996). Training the drivers themselves to do passive sampling solved sometimes the problem of air monitoring in large geographical areas with long driving distances, especially, when external exposure together with biological monitoring was under investigation (Saarinen et al., 1998).

A part of the measured results in the data provided is presented as geometric means and geometric standard deviations with range values which is correct, because the distribution of the industrial hygienic results is often skewed (Perkins, 1997). Another part of the results is given as arithmetic means with only range values. In the data sets, further details concerning work tasks and sampling circumstances were mostly lacking. The number of collected and analysed samples was in most cases too low for further statistical calculations. Therefore, expert judgment is mainly used for RWC8h exposure determinations.

Determination of airborne concentrations

Several procedures are developed to facilitate chemical analysis of MTBE. The airborne (personal and area) concentrations were mainly measured by Buchta (1993) and Palassis et al. (1993) with sample collection onto activated charcoal (or carbogen 569) and analysing by gas chromatography. For sampling, two sampling tubes were connected in series: the front tube

containing 400 mg and the back tube 200 mg of coconut shell charcoal. The charcoal tubes were connected via a tubing to battery operated personal sampling pump. Air was sampled through the tubes at a nominal flow rate of 0.2 litres per minute for either few minutes or eight hours per work shift (integrated samples). After sampling, the charcoal was removed from the tubes and desorbed with carbon disulphide. An aliquot of this solution was used for assay by capillary gas chromatography (Berger, 1996; Boneva et al., 1994; Levy et al., 1986; Johansen, 1984) and detection with flame ionisation detection in accordance with the NIOSH Method 1615 (NIOSH, 1994). With this method, the analytical detection limit (DL) for MTBE was 0.01 mg per sample. Due to potential interference commonly associated with the analyses, gas chromatography with a mass spectrometer (GC/MS) screening was also performed to confirm the identity and purity of the MTBE peaks on random samples (Hiromitsu et al., 1994). A suitable number of charcoal tubes was prepared as blanks and submitted with the sample sets for analyses. MTBE can also be removed from the adsorbent with thermal desorption (Perkin-Elmer, 1993). This method seems also to be common with small variations (Coker et al., 1989; Vainiotalo et al., 1999a).

For MTBE sample collection, 3M 3500 passive samplers were also used (Harper et al., 1995; Saarinen et al., 1998). Samples were also collected in evacuated stainless steel canisters, and concentrated by cryogenic condensation for analysis by gas chromatography (Lioy et al., 1994).

The sampling pumps were calibrated prior to and after the sampling, and for subsequent calculations of sample volumes, the means of the pre- and post-flow rates were used (Buchta, 1993).

Price and Saunders (Price et al., 1984) have also described a gas chromatographic method to determine MTBE in atmospheres. Less often, reversed-phase liquid chromatography (RPLC) was used for determination of high-octane components in petrol (Pauls, 1985). MTBE was also detected by atomic emission after separation by gas chromatography (Diehl et al., 1995). Cochrane and Hillman (Cochrane et al., 1984) used infrared for detection.

Attention was also paid to control quality of the analyses in obtaining reproducibility and verification of the instrument calibration by including known standards over a range of sample concentrations (Coker et al., 1989). Lioy et al. (1994) performed a comparison between the two methods mentioned before. The pared analyses of adsorbent and canister samples performed by two laboratories agreed upon results within a factor of 2. MTBE values in the canister samples analysed by the two laboratories were within ± 50% (Lioy et al., 1994). The detection limit by mass spectrometry was lower than 1 ng/sample (Vainiotalo et al., 1996) and there was not found any interfering substances in the analyses.

Bulk samples

In some cases, bulk samples were also analysed. The samples of various petrol grades (Buchta, 1993) were collected in separate small glass vials. The samples were diluted in carbon disulphide and analysed for vol.% of MTBE by gas chromatography according to the NIOSH Method 16158 (NIOSH, 1994). The analytical limit of detection (DL) was 0.07 vol.%.

4.1.1.1.2 Occupational exposure from production

In the manufacturing process which is a closed, automated outdoor system with a connection to central waste gas system (information from the industry), the workers' exposure to MTBE may principally occur only during incidental leaks and maintenance operations.

The personal and fixed-position (area TWA8h) samples relate mainly to 8-hour exposures during manufacture, maintenance (turnaround) and laboratory works. The short-term exposure (ST) results were scanty.

In the European MTBE production (**Table 4.4**), the personal time-weighed average air concentrations (TWA8h) ranged between <0.01 and 59 mg/m^3, and the plant means between <0.01 and 19.3 mg/m^3. The highest values were from 1988 and early 1990s. Later in the 1990s, the average TWA8h concentrations were lower. The highest single values are probably caused by incidental leaks and spills, because the mean values are generally low. The personal short-term (peak) values ranged from <0.36 to 96 mg/m^3 also indicating leaks or spills.

The highest one-sided 90th percentile of the lognormal distribution concerning the data measured during seven years in one company was 1.2 mg/m^3. Another company exhibited the same very low concentration levels, but exposure measurements were limited.

One company provided six series of measurements which were more variable and showed both low and elevated concentrations, indicating less control of exposures. These data were too limited for assessment.

The RWC8h for inhalation exposure in neat MTBE production is concluded to be 50 mg/m^3.

The US data **Table 4.5** collected from the member companies of the American Petroleum Institute (API, 1995b) confirm the same low average concentration levels as in Europe. The very high range values in comparison with the geometric means indicate, however, that incidental leaks and spills are included in the USA data. The geometric standard deviations show skewness in the material.

The EASE 8h estimate for closed processes of 97.5 vol.% MTBE production is 0-0.36 mg/m^3. It is too low in comparison with the measured results. On the other hand, the EASE 8h prediction with the pattern of non-dispersive use and direct handling with dilution ventilation (in the open air) for neat MTBE gives a value range of 1,800-3,600 mg/m^3, which is an overestimation in comparison with the measured results.

For dermal exposure in production with non-dispersive use with direct incidental handling, the EASE predicts 0-0.1 mg/cm^2/day (palms of both hands).

For sampling and laboratory work, the 8-hour exposure of the single values ranged from <0.01 to 24 mg/m^3, and the plant means from <0.01 to 16.5 mg/m^3.

In sampling and laboratory work, the RWC8h-exposure is concluded to be 25 mg/m^3. The work involves intermittent exposures with higher exposure peaks.

The predicted EASE estimate for dermal exposure at sampling and laboratory work with non-dispersive use, direct handling and intermittent contact is 0.1-1 mg/cm^2/day (palms of both hands). Protective measures are in general use.

Table 4.4 Exposure at European MTBE -production, mg/m^3

Data provided by companies										Calculated at 90th percentile		
Sampling		Personal short-term, ≤30 min		Personal TWA8h,		Area TWA8h		Measured worst exposure		Personal TWA8h		Ref.
Site, task, year, MTBE 97.5 %,		Mean	Range (n)	Mean	Range (n)	Mean	Range (n)	Peak	TWA8h	Norm. distrib	log normal distrib	Comp-any
MTBE unit 1988	Comm. operator	-	-	0.8[G]; 2.2[GSD]	0.2-1.5 (4)			-	1.5			X
1991-4	Comm. operator	-	-	-	<0.01-<4 *			-	-			X
1993-4	Process operator	-	7.8-85	-	1.4-2.2 (3)	1.3[A]	0-5.3 (3)	85	2.2 {5.3}			X
1994	Worker	-		4.7[A]	0-24 (7)	0.8[A]	0-6.2 (7)	-	24 {6.2}			X
Plant 1988	Process control	-	-	19.3[G]; 2.5[GSD]	4-39 (4)	-	-	-	39			X
1988	"	-	-	17.4[G]; 2.4[GSD]	5.9-59 (4)	-	-	-	59			X
Plant 1990	Process operator	-	-	0.06[G]; 10.5[GSD]	0.01-43 (38)	-	-	-	43	12.7	1.2	Y
1991	Operator	-	-	0.03[G]; 5.2[GSD]	0.01-1 (27)	-	-	-	1	0.5	0.25	Y
1992	Operator	-	-	0.01[G]; 1.5[GSD]	0.01-0.1 (16)	-	-	-	0.1	0.01	0.02	Y
1993	Operator	-	-	0.02[G]; 2.9[GSD]	0.01-1 (85)	-	-	-	1	0.04	0.04	Y
1995	Operator	-	-	0.01[G]; 1.54[GSD]	<0.01-0.1 (67)	-	-	-	0.1	0.02	0.02	Y
1996	Operator	-	-	0.01[G]; 1.2[GSD]	<0.01-0.02 (24)	-	-	-	0.02	0.02	0.01	Y
1992-3	Operator	5.8[A]; 6.8[M]	0.36-10 (3)	0.36[A]	<0.36-0.4 (4)	-	-	10	0.4	-	-	5(pl.1)
1993	Operator	-	-	0.24	0.01-1 (7)	-	-	-	1	-	-	7
1994-6	Operator	-	-	<0.01	<0.01 (6)	<0.2	-	-	-	-	-	2 A, B, C, D
1994-6	Operator	-	-	0.09[A]	0.06-0.1	0.3	-	-	0.1	-	-	
1997	Operator		96 (1)	0.3[A]	(3)	-	-	96	-	-	-	6
2000	Operator	-	-	0.1[G]; 2.0[GSD]	0.07-0.8 (20)	-	-	-	0.8	0.4	0.3	Z2
2000	Operator			0.09[G]; 3.1[GSD]	0.04-2 (14)	-	-		2	0.9	0.4	Z1

Table 4.4 Continued overleaf

Table 4.4 Continued Exposure at European MTBE -production, mg/m^3

Data provided by companies										**Calculated at 90th percentile**		
Sampling		**Personal short-term, ≤30 min**		**Personal TWA8h,**		**Area TWA8h**		**Measured worst exposure**		**Personal TWA8h**		**Ref.**
Site, task, year, MTBE 97.5 %,		**Mean**	**Range (n)**	**Mean**	**Range (n)**	**Mean**	**Range (n)**	**Peak**	**TWA 8h**	**normal distrib.**	**log normal distrib.**	**Comp-any**
Maintenance												
Turn around 1993	Emptying	-	-	0.9^A, 0.05^M	0.01-10 (14)	-	-	-	10	-	-	7
Turn around 1993	Startup	-	-	0.6^A, 0.2^M	0.04-2 (6)	-	-	-	2	-	-	7
1995	Tank roof	30 ^{A}, 26^M	13-57 (7)	-	-	-	-	57	-	-	-	7
Sampling and laboratory work												
1995	Sample room	-	-	1.7^A	1.2-2 (2)	-	-	-	2	-	-	7
1995	Sampl. vessel	34^A, 21^M	2.2-63 (5)	-	-	-	-	63	-	-	-	7
2995	Sampl. pipeline	3.6^A, 1.7 ^{M}	0.4-9 (3)	-	-	-	-	9	-	-	-	7
1998	Sampl. rail car	21.8	6.3-57 (5)	-	-	-	-	57	-	-	-	Lillquist et al. (1998)
1998	Laboratory tests	7.9	4.3-13 (3)	-	-	-	-	13	-	-	-	Lillquist et al. (1998)
1988	Laboratory techn.	-	-	16.5^G; 1.6^{GSD}	7.1-24 (4)	-	-	-	24			X
1988	Laboratory techn.			14.3^G; 1.5^{GSD}	18.3-23 (4)	-	-	-	23			X
1988	Laboratory techn.			1.8^G; 2.2^{GSD}	0.5-3 (4)	-	-	-	3			X
1991-4	Laboratory techn.			<0.01-<4*	-	-	-	-	-	-	-	X
2000	Lab & other works	1.9^G; 2.3^{GSD}	0.8-9 (6)	-	-	-	-	9	-			Z2

^{A} = arithmetic mean,
^{G} = geometric mean,
^{GSD} = geometric standard deviation,
^{M} = median, (n)= number of samples,
TWA8h = time-weighed average,
* depending on the detection limit, {area}sample.

Table 4.5 Exposure at MTBE production in the USA, mg/m^3.

Data provided by API report										Calculated at 90th percentile		
Sampling		Personal short term, ≤30min		Personal TWA8h		Area TWA8h		Measured worst exposure		Personal TWA8h		Ref.
Site, task, year, MTBE neat		Mean G; GSD	Range (n)	Mean G;GSD	Range (n)	Mean G; GSD	Range (n)	Peak <30 min	TWA 8h	Norm. distrib	log normal distrib.	
Manu-fact	Routine operation	3.02; 3.5	0.06-28 (33)	0.2; 6.0	0.04-896 (82)	0.47; 7.43	0.04-478 (83)	28	896 {478}	4.8	2.0	API (1995b)
Main-tenance/ turn-around	Process routine	3.6	1.8- 26 (14)	0.5; 2.3	0.1-2.5 (12)	360	(1)	26	2.5			

G = geometric mean,
GSD = geometric standard deviation
(n) = number of samples,
TWA8h = time-weighed average, {area}= samples

4.1.1.1.3 Occupational exposure from formulation

The measured data concerning formulation operations originated from three European companies. Additional data are from a report of the American Petroleum Institute concerning their member companies (API, 1995b). The processes are mainly direct sequel automated units to the manufacturing processes, albeit minor isolated units may also exist, but no data for separate fomulation processes were available.

European data (**Table 4.6**) are few in number and do not disclose MTBE content in petrol. However, the air concentrations seem to be low (often less than the detection limits). Only incidental small peaks occur.

In concordance with the exposure results in production, the RWC8h for MTBE formulation is assumed about 50 mg/m^3 for inhalation exposure. The data provided for formulation is too scanty to draw another conclusion.

In the US data (**Table 4.7**), there appear to be high peak values, which probably arise from leaks in the processes. This is obvious, because the geometric mean values of the data are low and the standard deviations indicate skewness of the results.

The EASE estimation for a closed process gives for 8-hour exposure 0- 0.36 mg/m^3 which is too low a value in comparison with the measured values. On the other hand using the parameters non-dispersive use and direct handling with dilution ventilation, give 1,800-3,600 mg/m^3 for the 8-hour exposure of neat MTBE, 360-504 mg/m^3 for the exposure to 11 vol.% MTBE fuel and 72-180 mg/m^3 to the fuel of 2.8 vol.%, respectively. All the EASE figures are too high.

The EASE model estimation for dermal exposure with non-dispersive use and direct incidental contact to neat MTBE is 0-0.1 mg/cm^2/day (palms of both hands). For sampling and laboratory work the exposure frequency is intermittent, i.e. 0.1-1 mg/cm^2/day (palms of both hands) with direct intermittent handling. The use of PPEs is common.

The predicted dermal exposure (palms of both hands) to the fuel containing MTBE with non-dispersive use and direct intermittent contact is $0.11 \cdot (0.1\text{-}1) = 0.01\text{-}0.1$ mg/cm^2/day for the 11 vol.% MTBE in fuel and $0.028 \cdot (0.1\text{-}1) = 0.003\text{-}0.03$ mg/cm^2/day for the 2.8 vol.% of MTBE in fuel.

Table 4.6 Exposure at formulation (blending and storing) of MTBE petrol in Europe, mg/m^3.

Data provided by companies										Calculated at 90th percentile		
Sampling		Personal short-term, ≤30 min exposure		Personal TWA8h exposure		Area TWA8h concentrations		Measured worst exposure		Personal TWA 8h exposure		Ref.
Job, year, MTBE content		Mean	Range (n)	Mean	Range (n)	Mean	Range (n)	Peak <30 min	TWA 8h	norm distr	log nor distr	Company
1993-4	operator			<3.6	(30)							5(Pl.1)
1993-4	operator			7.9	<3.6-36 (36)				36			5(Pl.1)
1995	operator	10.8	3.6-14 (2)	<3.6	(1)			14.4				
1996	operator	7.2	- (1)			3.6	(1)	7.2	{3.6}			
1990 drain water	bottom emiss.			<0.1								8
1990 drain water	stack emiss.	<0.1	- (3)			<0.1						8

Mean = arithmetic mean, (n) number of samples, TWA= time-weighed average

Table 4.7 Exposure at formulation (blending and storing) of MTBE petrol in the USA, mg/m^3.

Data provided by API report										Calculated at 90th percentile		
Sampling		Personal short-term, ≤15min		Personal TWA8h		Area,TWA8h		Measured worst exposure		Personal TWA8h		Refer-ences
Job, year, MTBE content,		Mean GM; GSD	Range (n)	Mean GM; GSD	Range (n)	Mean GM; GSD	Range (n)	Peak <30 min	TWA 8h	normal distrib.	log normal distrib.	
1983-93	Neat	18.4; 5.6	0.04-349 (50)	6.8; 9.2	0.14-317 (13)	10.3; 6.12	0.22-356 (33)	349	317 {356}			API (1995b)
1983-93	Fuel mix	2.1: 9.4	0.07-360 (136)	0.36; 4.1	0.07-50.4 (122)	2.1; 8.4	0.1-76 (19)	360	50.4 {76}	3.0	2.2	

GM = geometric mean, GSD = geometric standard deviation, (n) number of samples, {area}= samples

4.1.1.1.4 Occupational exposure from transportation

The transporting operations concern both neat MTBE and mixed fuel. The exposed workers are bulk terminal, railcar, truck and marine employees. Leaks from the fittings and drybreak mating surfaces contribute to the operators' exposure during the loading/unloading operations (Duffy et al., 1992; Page et al., 1989). For instance, the unloading of a railroad car involves disconnecting the bottom cap from the rail car, connecting a male unloading elbow, and connecting a female unloading drybreak to the male elbow for product transfer to a storage tank.

During loading operations, also samplings for laboratory analyses are required by removal an unloading valve cap located underneath the car, installing a sample valve, and filling a glass bottle for sampling. The operators' exposures increase especially while handling the wetted valves. After finishing the sampling, the valves become plugged and then cleaned. The bucket used to drain the overflow of the sampling increases the exposure.

The RWC8h for sampling and laboratory work associated with transportation is similar to that for production and formulation, i.e. 25 mg/m^3.

Neat MTBE transportation

The single personal TWA8h air concentrations (**Table 4.8**) during loading/unloading of neat MTBE ranged from <0.003 to 155 mg/m^3. The plant means ranged from 0.02 to 54 mg/m^3. The operations occasionally caused higher area 8-hour exposures which ranged from <3.6 to 230 mg/m^3. The area means ranged from <0.36 to 39.6 mg/m^3.

The personal ST-exposures ranged from <0.1 to 180 mg/m^3 and the means from <0.1 to 86.4 mg/m^3. There was no clear difference between exposures caused by the various loading operations (truck, rail car, ship).

All the loading data are too limited for further calculations. If the four “extreme” personal 8-hour values are rejected and only the upper 8-hour range values are considered, the RWC8h remain less than 20 mg/m^3. There are, however, also additional high area measurement values.

According to some high personal 8-hour exposures (all of them in different companies) and the high area 8-hour values, the exposure situations may vary a lot in companies.

Thus, the RWC8h for transporting operations of neat MTBE is considered 100 mg/m^3.

In the US data for neat MTBE, there are very high peak concentrations. The geometric standard deviation indicates skewness of the results.

The EASE modelling predicts as a TWA8h exposure for neat MTBE (97.5 vol.%) with parameters of non-dispersive use and direct contact with dilution ventilation 1,800-3,600 mg/m^3, which is too high in comparison with the measured results.

The predicted dermal exposure to neat MTBE with non-dispersive use and direct intermittent contact is 0.1-1 mg/cm^2/day (palms of both hands). However, PPEs are generally used.

Mixed fuel transportation

The personal TWA8h air concentrations (**Table 4.8**) during ship loading with motor fuel ranged between <0.003 and 29 mg/m^3, with plant means ranging between 0.36 and 2.74 mg/m^3.

The personal ST-measurements ranged between <0.36 and 230 mg/m^3, and the means between 3.6-97.2 mg/m^3. The personal ST-peaks indicate incidental leaks of short duration.

The data given for the exposure assessment are too limited. The exposure, however, seems to be very low for ship loading, and it may be true in reality, because after pipe connections the loading is automated and the loading period is usually long (hours). However, the phases of the connections and disconnections of valves and hoses may cause higher ST-exposure peaks.

In line with other activities with mixed fuel, the expert judgment of the RWC8h for ship loading operations of mixed fuel gives 30 mg/m^3.

The US (**Table 4.9**) measurements with a low geometric mean value and large standard deviations show strong skewness, indicating that high exposures are, however, fairly infrequent in the large number of measurements.

EASE 8-hour prediction with non-dispersive use and direct handling with dilution ventilation for neat MTBE loading is 1,800-3,600 mg/m^3, for fuel loading with 11 vol.% of MTBE 360-504 mg/m^3, and for fuel with 2.8 vol.% of MTBE 72-180 mg/m^3, respectively. All the values are overestimations in comparison with the measured results.

The predicted dermal exposure (palms of both hands) to fuel containing MTBE with non-dispersive use and direct intermittent contact is $0.11 \cdot (0.1\text{-}1) = 0.01\text{-}0.1$ mg/cm^2/day for 11 vol.% and $0.028*(0.1\text{-}1) = 0.003\text{-}0.03$ mg/cm^2/day for 2.8 vol.% of MTBE in petrol.

Table 4.8 Exposure at MTBE -transportation operations in Europe, mg/m^3

Data provided by companies										**Calculated at 90th percentile**		
Sampling		**Personal short-term, ≤ 30min**		**Personal TWA8h**		**Area, TWA8h**		**Measured worst exposure**		**Personal TWA8h**		**Ref.**
Neat MTBE, job, year		**Mean**	**Range (n)**	**Mean**	**Range (n)**	**Mean**	**Range (n)**	**Peak <30min**	**TWA8h**	**Norm distr.**	**Log nor distr.**	**Company**
1990 Harbour	Ship loading	57.6	- (1)	54	0.7-155 (3)	2.9	0.4-9 (8)	57.6	155 {9}			5(Pl.1)
Harbour	Ship loading	31.3	- (1)					31.3				5(Pl.1)
1994 Harbour	Ship loading			7.3	2-17 (3)				17			3
1995 Quay	Ship loading			2.1± 0.6 sem	0.4-11.1 (14)				11.1			4
1997 Quay, on board	Ship loading	5.4± 0.7 sem	4.3-6.4 (4)	4.1± 2.4 sem	0.4-11.7 (3)			6.4	11.7			4
1997 Quay, on-board,	Ship load pipe con	48.3	(1)	0.4	(1)			48.3	0.4			4
1996 Contractor	Shipp-ing			12.2	<0.003-94 (32)				94			1
1994-6 Superv	Ship loading			0.09	<0.01-13.6				13.6			2
1994-6 Superv.	Ship			0.02	<0.01-0.03 (3)				0.03			2

Table 4.8 continued overleaf

Table 4.8 continued Exposure at MTBE -transportation operations in Europe, mg/m^3

Data provided by companies										Calculated at 90th percentile		
Sampling		Personal short-term, ≤ 30min		Personal TWA8h		Area, TWA8h		Measured worst exposure		Personal TWA8h		Ref.
Neat MTBE, job, year		Mean	Range (n)	Mean	Range (n)	Mean	Range (n)	Peak <30min	TWA8h	Norm distr.	Log nor distr.	Company
1996 Unload,	Har-bour ship			6.5	<3.6-14.4 (5)	15.5	3.6-43 (8)		14.4 {43}			5 (Pl.1)
1996 Harbour pier	Ship unload					32		10.8-230 (15)	{230}			5 (Pl.1)
1996 Harbouring,	Ship unload					<3.6	(3)					5 (Pl.1)
1996 Harbour	Ship unload.					<3.6	(2)					5 (Pl.1)
1994-6 Operator	Termin al			2.1	<0.003-16 (44)				16.3			1
1995 Jetty	Operat or			1.9	0.13-4.6 (6)				4.6			1
Rail road car unload	Conn/ disconn	12.6	<3.4-126 (15)			4.0	3.7-6.3 (4)	126	6.3			(Lillquist et al., 1998)
1988-93 Rail car	Loadin g			3.0± 1.7 sem	0-63 (31)	<0.36	(5)		63	12.3	6.8	4
1996 Rail car loading	Operat or			0.72	0.7-1.1 (5)	14.4	0.36-158 (18)		1.1 {158}			5
2000 Rail car loading	Operat, load/ unload			30.9 G 3.2G S	3.2-116 (8)				116			Z2
1994	Tank car loading			2	- (1)				2			3
1990	Top loading	-	<0.1-21.3 (5)					21.3				8
1991	Top loading	86.4	29-162 (6)			10.8	7.2-14(2)	162	{14}			5(Pl.1)
1990	Bottom loading	<0.1	-(2)									8
1995-6	Bottom loading	54	7.2-180 (4)	3.6	<3.6-3.6 (2)	26.3	<3.6-115 (8)	180	3.6 {115}			5(Pl.2)
1995	Bottom loading			5.4	<3.6-7.2 (2)	24.1	<3.6-65.8 (3)		7.2 {65}			5(Pl.2)
1996	Bottom loading	3.6	(2)	3.6	(2)	3.6	3.6		3.6			5(Pl.2)
1996	Equipm room					39.6	3.6-76 (2)		{76}			5(Pl.1)

Table 4.8 continued overleaf

Table 4.8 continued Exposure at MTBE -transportation operations in Europe, mg/m³

Data provided by companies										Calculated at 90th percentile		
Sampling		Personal short-term, ≤ 30min		Personal TWA8h		Area, TWA8h		Measured worst exposure		Personal TWA8h		Ref.
Neat MTBE, job, year		Mean	Range (n)	Mean	Range (n)	Mean	Range (n)	Peak <30min	TWA8h	Norm distr.	Log nor distr.	Company
Mixed fuel												
1996	Ship loading			0.72	0.36-0.7 (2)				0.72			5 (Pl.1)
1996 - quay on-board	Ship loading	10.3	(1)					10.3				4
1996 Harbor	Ship loading			0.36	0.36-0.7 (8)				0.7			5 (Pl.1)
1996 Harbor	Ship loading			0.72	<0.4-2.2 (14)				2.2			5 (Pl.1)
1996 Harbor	Ship loading coupl / uncoup	3.6	<0.36-9.7 (4)			0.72 pier	<0.36-1.8 (8)	9.7	{1.8}			5 (Pl.1)
1996 Harbor	Ship loading uncoup	97.2	10.8-230 (5)	1.4	(1)			230	1.4			5 (Pl.1)
1996 Harbor contr.	Ship loading					0.72	0.36-0.7 (2)		{0.7}			5 (Pl.1)
1996 Harbor contr.	Ship loading					0.36	- 0.36 (9)		{3.6}			5 (Pl.1)
1996 static pump	Harbor ship loading					3.6	<3.6-3.6 (2)		{3.6}			5 (Pl.1)
1996 disconnect tanker	Harbor ship loading	64.1	51-73 (5)					73				7
1990	Ship unload		0.1-10.5 (3)					10.5				4
1994-1996	Tanker driver			2.74	<0.003-29 (221)				29			1, 2
Truck	loading	3.4	Nd-3.4(5)	0.5	<0.15-1.5 (2)			3.4	1.5			Lillquist et al. (1998)
	Lab testing			6.0	(1)				6			Lillquist et al. (1998)
oxyfuel	Sample collect	3.5	Nd-3.5					3.5				Lillquist et al. (1998)

Mean= arithmetic mean, sem= standard error of the mean,
(n)= number of samples, TWA= time-weighed average, {area}= samples

Table 4.9 Exposure at transportation operations in the USA, mg/m^3.

By API report										Calculated at 90th percentile		
Sampling		Personal short-term, ≤30 min		Personal TWA8h		Area, TWA8h		Measured worst exposure		Personal TWA8h		References
Year, job, MTBE content		Mean	Range (n)	Mean	Range (n)	Mean	Range (n)	Peak <30 min	TWA 8h	Norm distr.	Log norm. distr.	
1983-1993	Neat	40 GM; 7.3 GS	1.1-3780 (114)	0.9 GM 10.6GS	0.07-2563 (17)	1.7GM; 7.2GS	0.2-792 (24)	3780	2563 {792}	199	18.5	API, (1995b)
1983-1993	Fuel mix	12GM; 13GS	0.04-1829 (86)	0.5GM; 6.3GS	0.04-94 (59)	0.6GM; 10GS	0.04-1058 (155)	1829	94 {1058}	14.2	5.3	

GM= geometric mean, GS= geometric standard deviation. TWA= time-weighed average, {area}= samples

4.1.1.1.5 Occupational exposure from distributing

Petrol distribution from depot area (bulk station) to service stations is carried out with tank trucks (Phillips et al., 1978; Hakkola et al., 1996b). The drivers start their work shift (Saarinen et al., 1998) by loading the truck at the district depot, and then unload the petrol at one or several service stations. Petrol is first pumped from the storage tanks to the loading rack and then delivered to the tank trucks. The mean size of a petrol load is 20,000 litres (18,000-48,000 l). The quantity of petrol carried by a tank truck depends on tank size and local road restrictions. The load consists usually of various brands of petrol with different percentages of MTBE (range 2-11.5 vol.%). More than a half of the delivered products is often petrol and the rest is diesel oil or fuel oil (kerosene).

The major part of exposure of road tanker drivers takes place during loading and delivery operations. Exposure during driving is insignificant. The principal source for workers' exposure at depot area is created by the flow of petrol into the truck tank. The petrol flow displaces petrol vapours from the truck tank into the atmosphere or into a vapour recovery system. Leaking from the filling lines or spillage of petrol may also produce vapours through evaporation.

The drivers mainly conduct the loading and unloading operations themselves being exposed to petrol vapours for discrete intervals during workday. A driver may handle from one to seven loads per shift, but three to five loads are common. Typical loading time per load at depot rack varies from 20 to 25 minutes and unloading at service station 30 to 40 minutes depending on amount and compartments loaded/unloaded. These distributing operations take about 20 to 50% of the driver's workday (Hakkola et al., 1996b).

Because most of the distributing depots and the service stations have vapour-recovery systems, leakages and spills, and the drivers' working habits determine the exposure. The exposure levels depend also on wind direction and velocity, and ambient temperature.

The severity of drivers' exposure to petrol vapours depends on the method of loading (top loading or bottom loading), and how the vapours from the empty tanks are displaced, recovered or vented.

Two loading systems (Phillips et al., 1978) have been in use. A bottom loading operation involves connection of filling arms near the bottom side of the tank truck. Self-closing valves on the truck prevent leakage. Automatic shut-off valves on the fill lines allow several compartments to be loaded at one time. The valves allow also on each filling line the compartments to be filled without the loader being located near the loading spout. At present, the bottom loading is the generally used method.

In the depot terminals, the petrol vapour displaced from the tanks is vented through the top rear of a truck to a vapour recovery system or into the atmosphere. Especially when the loading is performed by bottom loading, the loading racks are equipped with vapour recoveries, which conduct the vapours back to the depot storage tank. The vapours generated are also capped from the annular area between the drop pipe and the loading port rim and conducted to the collection system.

Top loading operation is an older system and involves overhead filling arms with manually operated valves controlled by a handle at the top section of the drop pipe. The driver stands on the top of the truck near the loading port watching the quantity meter on the rack and closes the valve at correct volume. He loads one compartment at a time.

At service stations for product transfer to the storing tank, the unloading (Lillquist et al., 1998) involves disconnecting the bottom cap from the truck, connecting a male unloading elbow, and connecting a female unloading drybreak to the male elbow. Leaks from the fittings and drybreak mating surfaces contribute to the driver's exposure. The highest short-term exposures may occur during the connecting and disconnecting the drybreak valves. The concentrated vapours in the empty storage tank are released, and conducted either further away from the station area and released into the atmosphere or conducted back to the truck tank (Stage I recovery).

During bottom loading, the personal TWA8h exposures ranged in the European data (**Table 4.10**) from 0.01 to 180 mg/m^3. The plant mean values were from 1.3 to 8.2 mg/m^3. The range of ST- values was from 0.8 to 281 mg/m^3 and the plant means between 3.6 to 58 mg/m^3.

At top loading, values of a series of personal samples over 8 hours ranged from 3 to 4 mg/m^3 with the mean of 3 mg/m^3. The personal ST exposures (n= 3) ranged from <0.1 to 226 mg/m^3 with means ranging from 85.4 to 91 mg/m^3.

The personal 8-hour results for unloading ranged from “not detected” to 16 mg/m^3 with the mean from 1.3 to 8.8 mg/m^3. Concentrations measured in one ST-occasion during unloading ranged from 0.3 to 432 mg/m^3 with the mean of 88 mg/m^3.

In Finland (**Table 4.11**), personal TWA8h-samples were not measured. During bottom loading, the personal ST-exposure ranged from 0.1 to 42.1 mg/m^3, with the means ranging between 0.8 and 13.0 mg/m^3. Measurements during a singular top loading occasion ranged from 20 to 226 with a mean of 91 mg/m^3.

During unloading, the personal ST-exposure in the Finnish database ranged between 0.6 and 98 mg/m^3 with the means ranging from 1.8 to 71 mg/m^3. TWA8h-samples were not measured.

The provided European data (**Table 4.10**), was too limited for further calculations. If the two or three extreme upper range values are rejected, the RWC8h exposure during distributing operations remains less than 25 mg/m^3. There are, however, also three higher area values. The high values might be due to distribution of petrols containing more than 2.8 vol.% MTBE. Similar observation was made at service stations (last item in **Table 4.14**) where quite a large data set of 156 air samples gave clearly higher concentrations than those usually related to

approximately 2.8 vol.% of MTBE. In the data given, there was no information about the MTBE concentration in fuel.

From the personal 8-hour exposure data, the RWC 8h for the distribution of European petrol (principally 2.8 vol.% by bottom loading and unloading) is assessed to be 30 mg/m^3.

The Finnish data for personal TWA8h measurements were lacking and therefore, the RWC8h for the distribution of high MTBE content petrol (11 vol.%) could not be precisely determined. However, if the TWA8h is estimated, for instance, for the active exposure period of five hours (2·½h ·5 = 5h) and the 90th percentiles of lognormal distribution of the ST- exposure distributions is used for the assesment, the RWC8h would be close to 30 - 40 mg/m^3. In reality, this five hours is the maximum exposure period during a drivers's 8-hour workshift.

Thus according to expert judgment, the RWC8h for the distribution (loading and unloading) of the Finnish petrol (max 11 vol.%) is estimated to be 40 mg/m^3.

The EASE 8h predictions with non-dispersive use and direct handling with dilution ventilation for inhalation exposure are 360-504 mg/m^3 for 11 vol.% fuel and 72-180 mg/m^3 for 2.8 vol.% fuel. The predicted values are higher than the measured exposures.

The predicted dermal exposure (palms of both hands) to fuel containing MTBE with non-dispersive use and direct intermittent contact is 0.11·(0.1-1) = 0.01-0.1 mg/cm^2/day for the 11 vol.% fuel and 0.028·(0.1-1) = 0.003-0.03 mg/cm^2/day for the 2.8 vol.% fuel.

In loading operations, the connecting and disconnecting of hoses and valves are normally the occasions when the skin exposure may occur. This period is short and thick gloves possibly of nitrile rubber or leather are uncomfortable to wear. Therefore, at least in warm seasons the workers prefer to work with bare hands. Depending on the driving distances, the loading/unloading is done 2 to 7 times per shift. Thus, in the worst case the short contact with liquid fuel with bare hands may occur even four to fourteen times during a workday.

Table 4.10 Exposure to MTBE at distributing in Europe, except in Finland, mg/m^3

										Calculated at 90th percentile		
Sampling		**Personal short-term, 30 min**		**Personal TWA8h**		**Area, TWA8h**		**Measured worst exposure**		**Personal TWA8h**		**References**
Site, job, year, MTBE content (%),		**Mean**	**Range (n)**	**Mean**	**Range (n)**	**Mean**	**Range (n)**	**Peak 30 min**	**TWA 8h**	**Norm distr.**	**Log norm distr.**	**Company**
Top-loading												
Road tanker driver		91	20-226 (10)	3.0	3-4.0 (10)			226	4.0			CONCAWE (1999c)
Road tanker driver		85.6	28.8-162 (6)			3.5	1.2-6.5 (11)	162	{6.5}			CONCAWE (1997a)
Driver 1991						10.8	7-14 (2)		{14}			5 (Pl.1)
Driver 1990		-	<0.1-21 (5)					21				8

Table 4.10 continued overleaf

Table 4.10 continued Exposure to MTBE at distributing in Europe, except in Finland, mg/m^3

										Calculated at 90th percentile		
Sampling		**Personal short-term, 30 min**		**Personal TWA8h**		**Area, TWA8h**		**Measured worst exposure**		**Personal TWA8h**		**References**
Site, job, year, MTBE content (%),		**Mean**	**Range (n)**	**Mean**	**Range (n)**	**Mean**	**Range (n)**	**Peak 30 min**	**TWA 8h**	**Norm distr**	**Log norm distr.**	**Company**
Bottom-loading												
Road tanker driver	No vap rec	7.8	2.8-42 (10)	8.2	0.9-50 (42)			42	50			CONCAWE (1999c)
Road tanker driver	Vap rec	19	0.8-180 (17)	7.7	0.1-180 (42)			180	180			CONCAWE (1999c)
Road tanker driver		20.6 (2-99 min)	7-36 (14)	2.8	0.01-10 (49)	2.5	0.25-5.5 (12)	36	10 {5.5}			CONCAWE (1997a)
Driver 1991		58	7-281 (23)			13.7	3.6-50 (23)	281	{50}			5 (PI.1)
Driver 1995		54	7-180 (4)			26.3	<3.6-115 (8)	180	{115}			5(PI.2)
Driver 1996		3.6	<3.6 (6)			3.6	<3.6 (6)	3.6	{3.6}			5(PI.2)
Loading oper. 1995				3.6	<3.6 (2)	24.1	<3.6-65 (3)		3.6 {65}			5(PI.2)
Loading oper. 1996				3.6	<3.6 (2)				3.6			5(PI.2)
Truck 1994-6	Driver			1.3	0.01-21 (69)				21			2
Unloading												
Distrib-ution terminal	Rack oper			8.8	3.3-16 (6)			-	16			CONCAWE (1999c)
Distrib-ution terminal	Super-vision	88	0.3-432 (6)	1.3	0.1-9.2 (53)			432	9.2			CONCAWE (1999c)
Distrib-ution terminal	Super-vision			2.2	Nd-14 (45)				14			CONCAWE (1997a)

Table 4.10 continued overleaf

Table 4.10 continued Exposure to MTBE at distributing in Europe, except in Finland, mg/m^3

										Calculated at 90th percentile		
Sampling		**Personal short-term, 30 min**		**Personal TWA8h**		**Area, TWA8h**		**Measured worst exposure**		**Personal TWA8h**		**References**
Site, job, year, MTBE content (%),		**Mean**	**Range (n)**	**Mean**	**Range (n)**	**Mean**	**Range (n)**	**Peak 30 min**	**TWA 8h**	**Norm distr.**	**Log norm distr.**	**Company**
Equipment maintenance												
Distrib-ution terminal	Maintenance	16	- (1)	1.3	0.1-16 (37)			16	16			CONCAWE (1999c)
Distrib ution terminal	Maintenance			2.3	Nd-20 (13)				20			CONCAWE (1997a)
Float roof and dewater		<3.6	<3.6 (9)			0.2	nd-0.4 (7)	<3.6	{0.4}			CONCAWE (1997a)
Equipment room				39.6	3.6-76 (2)				76			5(Pl.2)

Mean= arithmetic mean, TWA= time-weighed average, (n) = number of samples, nd= not detected, {area}.

Table 4.11 Exposure at distributing petrol in Finland, mg/m^3

										Calculated at 90th percentile		
Sampling		**Personal short-term, 30 min**		**Personal TWA8h**		**Area, TWA8h**		**Measured worst exposure**		**Personal TWA8h**		**Ref.**
Site, job, year, MTBE content (%),		**Mean**	**Range (n)**	**Mean**	**Range (n)**	**Mean**	**Range (n)**	**Peak 30 min**	**TWA 8h**	**Norm distr.**	**Log norm distr.**	**Company**
Top-loading												
At 4-22 oC, South	4-11%,	91[A]	20-226 (4)					226				Hakkola et al. (1996b)
Bottom-loading												
At 10-15 oC	4-11% Stagel	8.1[A] ± 8.4	0.1-28 (14)					28				Saarinen et al. (1998)
At 4-22 oC, North	10-15% Stagel	13.0[A]	2.8-42 (6)					42				Hakkola et al. (1996b)
At -5 oC, Fall	11.8%	4.3[GM];2.9[GSD]	0.75-21.9 (15)					22		22	11	Vainiotalo et al. (1998a)
At 14 oC, Summer	1.3-11.5 %	6.4[GM];3.1[GSD]	0.57-33.7 (20)					34		37	27	Vainiotalo et al. (1998a)

Table 4.11 continued overleaf

Table 4.11 continued Exposure at distributing petrol in Finland, mg/m³

										Calculated at 90th percentile		
Sampling		**Personal short-term, 30 min**		**Personal TWA8h**		**Area, TWA8h**		**Measured worst exposure**		**Personal TWA8h**		**Ref.**
Site, job, year, MTBE content (%),		**Mean**	**Range (n)**	**Mean**	**Range (n)**	**Mean**	**Range (n)**	**Peak 30 min**	**TWA 8h**	**Norm distr.**	**Log norm distr.**	**Comp-any**
At -5 °C, Fall	11.8% Stagel	5.2GM; 2.9GSD	0.8-42.1 (15)					42.1		25	20	Vainiotalo et al. (1999b)
At 14°C, Summer	1.3-11.8% Stagel	7.3GM; 3.0 GSD	0.8-37.1 (20)					37.1		40	30	Vainiotalo et al. (1999b)
At 15°C, Summer	1.3-11%, n.v.r.	0.95G; 2.1GSD	0.42-2.7 (7)					2.7				Vainiotalo et al. (1999b)
Summer 1996	2.7-11%, n.v.r.	0.8GM	0.36-2.3 (5)					2.3				Finnish data base
Unloading												
At 10-15°C	4-11%, n.v.r.	23A ± 23	1.1-90 (19)					90		52	47	Saarinen et al. (1998)
At 10-15°C, North	4-22 °C, n.v.r.	16A	4.3-27 (5)					27				Hakkola et al. (1996b)
At 10-15°C, South	4-22°C, n.v.r.	71A	10-98 (6)					98				Hakkola et al. (1996b)
At 15.6°C, Summer	1.3-12%, Stage I	1.8 GM; 2.6GSD	0.6-11.5 (7)					11.5				Vainiotalo et al. (1999b)
Summer 1996	2.7-11%, n.v.r.	1.9GM	0.6-8.6 (5)					8.6				Finnish data base

A= arithmetic mean ± standard deviation , GM = geometric mean and geometric standard deviation (n) = number of samples, TWA= time-weighed average, v.r.= vapour recovery, n.v.r.= no vapour recovery

Table 4.12 Exposure to MTBE at distributing of petrol in the USA, mg/m³

By API report										**Calculated at 90th percentile**		
Sampling		**Personal short-term, ≤30min**		**Personal TWA8h,**		**Area, TWA8h**		**Measured worst exposure**		**Personal TWA8h**		**Ref.**
Job, year, MTBE content (%),		**Mean GM; GSD**	**Range (n)**	**Mean GM; GSD**	**Range (n)**	**Mean GM; GSD**	**Range (n)**	**Peak <30 min**	**TWA 8h**	**Norm distr.**	**Log norm distr.**	**API (1995b)**
1983-1993	Fuel mix	1.8; 7.2	0.04-50 (134)	0.5; 4.0	0.04-7.9 (100)	0.3: 6.36	0.07-3.6 (4)	50	7.9 {3.6}	4	3	

GM = geometric mean and geometric standard deviation. TWA= time-weighed average, ST= short-term, (n) = number of samples {area}= samples

4.1.1.1.6 Occupational exposure at service stations

In service stations, exposure to petrol vapours can be emitted through bulk delivery, during automobile refuelling, and from vapours leaking from underground storage tanks or from spills or overflows during petrol delivery or refuelling.

Overfills during filling the underground storage tanks (Page et al., 1989) are infrequent and probably do not contribute substantially to the vapour emission load at the most service stations. It was estimated that spills of 10 to 20 litres occurred once every 25 deliveries, and overfill or spill of 75-115 litre took place only once among 100 deliveries. Drips and spills occur during storage tank filling at a frequency of about once in 38,000 litres (once in every delivery) delivered. During automobile tank refuelling, spills or drips were estimated to occur once per 60 litres (once in every refuelling).

Table 4.13 Distribution of spills during automobile refuelling at service stations in the USA.

Amount released	Cincinnati (average 1.9 spills at 100 cm^2/ 4h sampling period) (%)	Phoenix (average 0.9 spills at 190 cm^2 / 4h sampling period) (%)	Los Angeles (average 0.3 spills at 40 cm^2/ 4h sampling period) (%)
None	32	27	52
Drips ≤ 1 ml	52	50	40
Drips and or spills ≥ 1 ml	14	22	7
(Percentages do not equal 100% due to rounding errors)	Conventional dispensing system	Conventional dispensing system	Vapour recovery systems, Stage II with safety latches

API (1993); Hartle (1993); Hartle et al. (1993)

Petrol releases at service station are mainly from the escape of vapours during automobile refuelling and the emissions from the underground storage tanks (Page et al., 1989). A minor contribution to the overall exposure is, however, the filling of service station underground tanks. Such exposure is primarily an exposure of the petrol truck drivers and occurs on the average at a service station only once for half an hour per day. At present, nearly all service stations have Stage I vapour recovery systems installed to capture most vapours from that source. Thus, the main sources for petrol vapours at service stations is associated with automobile refuelling, with either vapours arising from around the filler pipe or as a result of petrol spilled onto the ground (API, 1995a). The refuelling rate of an automobile averages 30 litres per minute for 0.5 to 2 minutes at a time. In Finland, the average number of customers per station was estimated 250 during a day (Vainiotalo 1999, personal information), which may be low in comparison with the European petrol stations.

Stage II recovery system on service station petrol pumps decreases attendants' and customers' exposure to petrol vapours during refuelling. It consists of metal barrel around the filler pipe connected via a tubing system to the underground storage tank (Hakkola et al., 1998b). Thus, the petrol vapours released from a car tank are pumped back to the storage tank. The recovery system may also be a rubber bonnet around the nozzle spout (McDermott et al., 1979) that presses against the rim of the fill opening of an automobile. The fill spout has a ridge that engages the rim of the fill opening to keep the nozzle and the bonnet in place. The bonnet is connected to the underground storage tank via a vapour return line. Vapour flows back to the storage tank as it is forced out by into vehicle incoming petrol or aided by additional pumping.

In the European data, the vapour recovery systems were either not in use or they were not mentioned. In Finland, the measurements were carried at stations, which were equipped with

Stage I vapour recovery systems (Saarinen et al., 2000). Only one station measured by Hakkola et al. (1998b) had additionally a Stage II-system. In this station, the air concentrations were lower and on the same level as if only petrol 95RON with MTBE content of 2.8 vol.% was refuelled. In both cases, the geometric means were on the same level 3 mg/m^3 (Hakkola et al., 1998a; Vainiotalo et al., 1999a). The USA data concerned five service stations without Stage II vapour recoveries and seven petrol stations with Stage II vapour recoveries.

The measured air concentrations in the open air are greatly influenced by meteorological conditions, temperature and especially wind, (API, 1995a). However, neither seasons nor the location of the station (urban/road-side) had any effect to the measured Finnish results (Vainiotalo et al., 1998b). The Finnish "winter" measurements for MTBE were performed in early spring and in late autumn, because electrically operated sampling pumps did not function out of doors at freezing temperatures. There were no differences between makes of automobiles or whether the vehicles were equipped with catalytic converters or not (Vainiotalo et al., 1998b). However, Hakkola et al. (1999) found somewhat lower exposures if a car was equipped with a catalytic converter. The suspected reason was that the tube between the filling opening and the car tank may have different shape in a newer car with converter.

The main difference between the exposures at service stations was expected due to the difference in the MTBE content in petrol. In most parts of Europe, petrol contains generally mean 2.8 vol.% of MTBE, and in Finland the concentration is 11 vol.% (industry information) or lower, if the product contains also higher ethers.

The range of full-shift personal exposure of service station attendants in the **Table 4.14** is from <0.003 to 101 mg/m^3 and the TWA8h means from different stations were between 0.26 and 4.9 mg/m^3. Short-term exposure was not measured, but the exposure ranges of TWA8h area samples were between<0.003 and 50.3 mg/m^3 with the TWA8h area means of 0.04 mg/m^3 to 1.5 mg/m^3.

In the Finnish data (**Table 4.15**), the concentration range of personal TWA8h samples was from 5.7 to 22.2 mg/m^3 and the only one TWA8h mean was 8.6 mg/m^3. During the actual refuelling time (mean 2 min) exposure ranged from <0.02 to 245 mg/m^3, and the ST-mean concentrations were from 3.3 to 15.3 mg/m^3. The only area measurement (TWA 8h) ranged from 0.03 to 0.24 mg/m^3 with the TWA8h mean of 0.12 mg/m^3.

In the US service station results (**Table 4.16**), where the MTBE content in petrol was high 13-15%, the personal TWA8h exposures ranged from 0.02 to 122 mg/m^3 and the TWA8h means ranged from 0.3 to 2.8 mg/m^3. The area TWA8h concentrations ranged from 0.004 to 0.9 mg/m^3 with means of from 0.02 to 1.7 mg/m^3.

Ciaccomello et al. (1996) have conducted a large study program (1,086 samples) in Italy during two annual seasons and additionally CONCAWE (1999c) has provided a database of 561 samples concerning petrol used in Europe. There is an additional European data set (156 samples) provided by the European industry with 113 personal 8-hour measurements and 43 8-hour area (cashier) measurements. The highest attendants' personal 8-hour value was 101 mg/m^3 (mean 4.9 mg/m^3) and the highest cashiers' area value was 50.3 mg/m^3 (mean 1.5 mg/m^3). This data set was compiled from various service stations representing normal conditions. There was no information about the content of MTBE in petrol. If only the data of Ciaccomello's group and that of CONCAWE are used, the highest measured range values allow to conclude 3 mg/m^3 as the RWC8h for the attendants' exposure in the European service stations for fuel containing 2.8 vol.% of MTBE.

The additional, higher exposure data (ca. 9% of all samples) in the EU region may have been collected from stations where also petrol with higher MTBE content was sold. The same matter was found also in the previous scenario for distribution.

Thus in Europe, the RWC8h for the petrol with low content of MTBE (2.8 vol.%) is 3 mg/m^3, but for stations selling various 'brands' (with higher MTBE content) of petrol the RWC8h should be compared with that for Finnish service stations which is 20 mg/m^3.

The corresponding US measurements with low content of MTBE support the low RWC8h-value (**Table 4.16**).

By assessing the Finnish MTBE exposure, the highest measured TWA8h values allow the conclusion that the RWC8h exposure is 20 mg/m^3. Thus, the RWC8h for the high MTBE content petrol (max 11 vol.%) is 20 mg/m^3.

The US data concerning petrol with a high MTBE content support the Finnish data, although the means were a little lower, because the stations had the SII vapour recovery systems in use.

For the MTBE concentration of 2.8 vol.% in petrol, the EASE estimate for 8-hour inhalation exposure to MTBE with non-dispersive use and direct handling with dilution ventilation is 72-180 mg/m^3. And when the MTBE-content is 11 vol.%, the EASE estimate for MTBE 8-hour exposure with non-dispersive use and direct handling with dilution ventilation is 360-504 mg/m^3. These EASE inhalation estimations are too high in comparison with the measured values.

The predicted dermal exposure (palms of both hands) to fuel containing MTBE with non-dispersive use and direct intermittent contact is $0.11 \cdot (0.1\text{-}1) = 0.01\text{-}0.1$ mg/cm^2/day for 11 vol.% and $0.028 \cdot (0.1\text{-}1) = 0.003\text{-}0.03$ mg/cm^2/day for 2.8 vol.% of MTBE in petrol.

Table 4.14 Exposure at European service stations, mg/m^3

Data provided by European Industry									**Calculated at 90th percentile**		
Sampling site, attendants refuelling,		**Short-term**	**Personal TWA8h**	**Area TWA8h, pump island**			**Measurd worst exposure**		**Personal TWA8h**		**Ref.**
Site, season, temp oC, MTBE content (%)			**Mean**	**Range (n)**	**Mean 8h**	**Range, (n)**	**Peak**	**TWA 8h**	**Normal distrib**	**Log normal distrib**	**Giacomello (1996**
Italy, center/ south, 1991/92.	Summer 28.6oC, 2.1%, n.v.r.		0.44^G 0.71^A	0.01-2.5 (76)	0.1	0.01-2.5 (68)		2.5 {2.5}			
Italy, center/ south, 1991/92.	Winter 10.7oC, 2.1%, n.v.r.		0.71^G 0.74^A	0.01-2.2 (128)	0.05	0.002-1.09 (79)		2.2 {1.09}			
Italy, national total, 1995	Summer 24.5oC, 2.7%, n.v.r.		0.10^G 0.26^A	0-2.4 (347)	0.04	0-1.6 (388)		2.4 {1.6}			
CONCAWE	2.1%, n.v.r.		0.3^A	0.003-1.4 (355)	0.04	0.003-0.8 (206)		1.4 {0.8}			CONCAWE (1999c)
Attendants 1994-1995			4.9$^{A*)}$	<0.003-101*) (113)	1.5$^{**)}$	<0.003-50**) (43)		101 {50}			Company 1 ***)

n= number of samples, ^{G}= geometric mean, ^{A}= arithmetic mean in parentheses, TWA= time-weighed average, {area}, n.v.r.= no vapour recovery $^{*)}$ = attentant, $^{**)}$cashier, $^{***)}$ at various service stations in Europe (standard service station environment), data sheets provided by European Industry.

Table 4.15 Exposure at Finnish service stations, mg/m^3

Published data										**Calculated at 90th percentile**		
Sampling, self-service,		**Personal short-term, refuelling**		**Personal TWA8h**		**Area, TWA8h pump island**		**Measured worst exposure**		**Personal TWA8h**		**Reference**
Site, job, season, temperature °C, MTBE content (%), vap.rec.		**Mean <5min**	**Range (n)**	**Mean**	**Range (n)**	**Mean**	**Range (n)**	**Peak <5min**	**TWA 8h**	**Norm distrib**	**Log normal distrib**	
One day-sampling, 1998	Autumn, 13°C, 7% StageI	15.3G	1.8-74 (20)					74				Hakkola et al. (1998b)
One day-sampling, 1998	Autumn, 13°C, 7%, Stage I + II	3.3G	0.2-16 (20)					16				
Urban/ road-side, 4-day-sampl.1996	Summer, 21°C, 95*2.8 % StageI	3.3G	<0.02-51 (169)	8.6G	5.7-11.6 (8)	0.12G	0.03-0.2 (16)	51	11.6 {0.2}			Vainiotalo et al. (1998b; Vainiotalo et al. (1998c); Vainiotalo et al. (1999a)
South-west, road-side and urban, 4-day sampl.1995	May-June, 22°C, 11%, Stage I	5.9G	<0.2-203 (153)		20.0-22 (8)			203	22			
South-wes, road-side and urban, 4-day-sampl. 1995	October 10°C, 11%, Stage I	6.7G	<0.4-245 (160)		17.9-18.8 (8)			245	19			

G = geometric mean, n= number of samples, TWA= time-weighed average, Stage I and II = vapour recovery (vap.rec.), *95RON containing higher ethers, about 2.8% of MTBE

Table 4.16 Exposure at the US service stations, mg/m^3

										Calculated at 90th percentile		
Refueling, full-/self-service, circumstances		**Personal short-term**		**Personal TWA 8h**		**Area, TWA 8h pump island**		**Measured worst exposure**		**Personal TWA 8h**		**Ref.**
Site, job, season, temp °C, MTBE content (%),		**Mean 15 min**	**Range (n)**	**Mean**	**Range (n)**	**Mean**	**Range (n)**	**15 min**	**TWA 8h**	**Norm distr**	**Log norm distr**	
Full-service 1994, Winter	Stage II 13.5±1.5 %	2.2[G]; 7.0[GSD]	1.2-7.6 (17)	0.7[G]; 8.4[GSD]	0.1-1.8 (21)			7.6	1.8	57.1	10.7	API, (1995c)
Full-service 1994 summer	Stage II 15±2.1%	1.1[G]; 4.1[GSD]	0.7-1.2 (22)	0.3[G]; 6.6[GSD]	0.1-1.5 (25)			1.2	1.5	10.0	3.4	
Full-service April, 1993	13.4-15.7% Stage II,	0.02		0.81[G]; 2.15[GSD]	0.30-1.9 (4)	0.02[G]; 3.5[GSD]	0.004-0.13 (16)		1.9 {0.1}	2.2	2.2	API, (1995a)
Full-service 1994	15%, Stage II			2.1[A]	0.8-4.7 (11)	0.7[A]	0.3-0.9 (3)		4.7	-	-	Cook et al. (1997)
Full-service 1993	15%, Stage II	1.4[M] 5min	1-15 (4)			0.2-1.7[M]	0.05-6 (23)	15 5min	{6}	-	-	Lioy et al. (1994)
Full-service 1992-3 winter	15%, Non-Stage II			0.4[M]	0.02-2.9 (18)				2.9	-	-	Moolenaar et al. (1994)
Full-service 1983-1993	Not mentioned (15%, Non-Stage II)	16.9[G]; 41[GSD]	4.2-490 (11)	2.8[G]; 17[GSD]	0.3-122 (13)			490	122			API (1995b)
3.4% of service 1993	12-14%.			2.1[G]; 9.3[GSD]	0.04-14.0 (30)				14.0	72	3.6	Hartle, (1993); Hartle et al. (1993)
About 3% of serve 1993	12-14%.			0.8[G]; 9[GSD]	0.4-7.6 (33)				7.6	87	13	
Self-service. 1993	13.4-15.7%, Stage II,	0.35		0.73[G]; 2.3[GSD]	0.3-2.8 (6)	0.03[G]; 3.0[GSD]	0.007-0.3 (24)		2.8 {0.3}			API, (1995a)
Self-service 1993	13.4-15.7%, Non-Stage II,			3.5[G]; 2.7[GSD]	0.6-9.4 (10)	0.05[G]; 3.6[GSD]	0.004-0.5 (40)		9.4 {0.5}			
Self-service 1993	15%, Non-Stage II	2.1[M]	-15 (4)					15				Lioy et al. (1994)
Self-service P01, 1990	12%	23.5[G]; 4.0[GSD]	0.4-140 (187/19) **					140				API (1993)

Table 4.16 continued overleaf

Table 4.16 continued Exposure at the US service stations, mg/m^3

										Calculated at 90th percentile		
Refueling, full-/self-service, circumstances		**Personal short-term**		**Personal TWA 8h**		**Area, TWA 8h pump island**		**Measured worst exposure**		**Personal TWA 8h**		**Ref.**
Site, job, season, temp °C, MTBE content (%),		**Mean 15 min**	**Range (n)**	**Mean**	**Range (n)**	**Mean**	**Range (n)**	**15 min**	**TWA 8h**	**Norm distr**	**Log norm distr**	
Self-service 02, 1990	12%	12.7G; 2.4GSD	1.5-34 (165/20)**					34				Hartle, (1993); Hartle et al. (1993)
Self-service L02, 1990	13%,	10.6G; 1.9GSD	3.9-23 (48/6)					23				API (1993)
Full-service 1993	0.0-0.18%			0.6	nd-0.6 (1/16)				0.6			
Full-service 1993	0.1-0.7%			0.13M	nd-0.5 (28)				0.5			Moolenaar et al. (1994)
2.7 % of service 1993	0.0-11% Stage II	0.7G; 2.1GSD	0.04-0.7					0.7				Hartle, (1993); Hartle et al. (1993)
Self-service C01, 1990	<0.003-0.1%	1.2G; 1.9GSD	0.27-5.3 (167/19) **					5.3				API (1993)
Self-service C02, 1990	<0.003-0.1%	1.0G; 2.4GSD	0.39-2.5 (173/20) **					2.5				
Self-service L01, 1990	0.23-0.27%	0.4G; 0.9GSD	0.1-4.9 (161/20)					4.9				
Self-service L02, 1990	0.19-0.43%	0.4G; 0.5GSD	0.2-0.6 (112/14)**					0.6				

G = geometric mean, GSD = geometric standard deviation, A = arithmetic mean, M = median, Stage I and II = vapour recovery, non-Stage II = no vapour recovery, nd= not-detected, (n) = number of samples, ** integrated samples containing 7-10 refuellings per one sample, e.g..(7/1), {area}, C02, L01, L02 = region codes.

4.1.1.1.7 Occupational exposure from maintenance operations

Maintenance and metalworking is needed through all the scenarios from petrol production to delivery, distribution and service stations. The mechanics are daily exposed during removal of pumps and repairing repellers, during replacement of railroad car drybreak couplings, and while repairing and calibrating fuel meters at transport loading racks and at service stations. They are also doing maintenance on pipelines and vapour recovery equipment. The work is done out of doors, but partly also in workshops in large open premises, although sometimes without any

active local ventilation. The latter is especially possible when servicing fuel pumps from service stations in the workshop (workers' information).

The maintenance tasks are such that the workers are exposed to MTBE vapours and their hands are in contact with petrol products. The skin exposure is a problem, because there are no adequate materials for protective gloves. Either petrol permeates the gloves or the gloves are too stiff and thick for working with small and fine parts of meters, pumps and valves.

The European measured data of exposure are very scanty (**Table 4.17**). The personal 8-hour samples ranged from 'not detected' to 10.2 mg/m^3 and the mean values of the three datasets ranged from 0.6 to 2.3 mg/m^3.

In the US production maintenance data, the personal 8-hour exposure ranged from 0.14 to 3.6 mg/m^3 and the three means ranged from 0.5 to 1.5 mg/m^3.

The exposure of maintenance mechanics in production, formulation and transportation is probably at the same level or a little higher than the process workers' exposure. Their exposure is not always caused by everyday routines but also by exceptional circumstances, where different operations are made with pipes, connections and machines.

Thus, the RWC8h for process maintenance, formulation and transportation is assessed to be 60 mg/m^3.

The measured data for 8-hour exposure in distribution maintenance range from not detected to 75.6 mg/m^3, the means of three datasets range from 1.3 to 39.6 mg/m^3.

The RWC8h for distribution and service station maintenance is assessed as 30 mg/m^3 for 2.8 vol.% fuel and as 40 mg/m^3 for 11 vol.% fuel, which values are a little higher than those estimated for other workers.

Overall, it should be pointed out that the maintenance mechanics' exposure is more incidental and variable and is composed more of higher peak concentrations than the exposure in normal distribution and service station work.

The EASE model predicts inhalation exposure to 1,800-3,600 mg/m^3 for neat MTBE, to 720-1,080 mg/m^3 for 11 vol.% MTBE in petrol, and to 504-720 mg/m^3 for 2.8% MTBE in petrol, respectively, when the EASE-parameters were wide-dispersive use and direct handling with dilution ventilation.

For dermal exposure, the EASE estimation gives with wide-dispersive use, direct intermittent handling 1-5 mg/cm^2/day (both hands) for neat MTBE, $0.11 \cdot (1\text{-}5) = 0.1\text{-}0.6$ mg/cm^2/day (both hands) for 11 vol% MTBE in petrol, and $0.028 \cdot (1\text{-}5) = 0.03\text{-}0.14$ mg/cm^2/day (both hands) for 2.8 vol% MTBE in petrol. The skin area exposed may, however, be sometimes more extensive.

Table 4.17 Exposure at maintenance operations, mg/m^3

Data from industry and the USA										Calculated 90th persentile		
Sampling site, circumstances		Personal short-term, ≤30min		Personal TWA8h		Area, TWA8h		Measured worst exposure		Personal TWA8h		
Site, job, year, MTBE content (%),		Mean	Range (n)	Mean	Range (n)	Mean	Range (n)	Peak 30 min	TWA 8h	Norm distrib	Log norm distrib	References
Production maintenance in Europe												
Refinery	Maintenance	11.5	3-35 (5)	2.3	Nd-3 (8)			35	3			CONCAWE (1999c)
1993	Turn around emptying	-	-	0.9[A], 0.05[M]	0.01-10 (14)			-	10.2			7
1993	Turn around startup	-	-	0.6[A], 0.2[M]	0.04-2.2 (6)	-	-	-	2.2			7
1995	Tank roof work	30[A], 26[M]	13-57.1 (7)					57.1	-			7
Production maintenance in the USA												
	Metal trades work	8.4[G]	<3.6-25 (5)	1.5[G]	0.6-3.6 (2)			25	3.6			Lillquist et al. (1998)
	Depressure of system.	3.2[G]	nd-3.6 (2)					3.6				
	Gauge MTBE tank	3.5	(1)					3.5				
Manufac-turing	Maintenance	3.6[G]; 2.6	1.8-26 (8)	0.5[G] 2.3[GS]	0.14-2.5 (4)	360	(1)	25	2.5			API (1995b)
Distribution terminal maintenance in Europe												
Distr terminal	Maintenance worker	15.5	- (1)	1.3	0.1-16 (37)			15.5	16			CONCAWE (1997a)
Distr terminal	Maintenance worker			2.3	Nd-20.2 (13)				20.2			
Floatroof & de-water tanks		<3.6	<3.6 (9)			0.2	nd-0.4 (7)	<3.6	{0.4}			
Equipm. room	Maintenance			39.6	3.6-75.6 (2)				75.6			5(Pl.2)

[A] = arithmetic mean, [GM] = geometric mean,. [M] = median, (n) = number of samples, TWA= time-weighed average

4.1.1.1.8 Occupational exposure from automobile repair and related tasks

Mechanics' exposure to MTBE during vehicle repair is caused by fuel when handling the fuel system. This work phase may take on an average 20% of the whole working time (workers' information) in small repair shops, which handle also old automobiles. Working with the whole fuel line is not so common in dealers' servicing facilities, although fuel filters are changed now and then.

The workers are principally aware of the health hazards of petrol, but they do not always protect the skin, because protective gloves impede the efficiency of working (worker's opinion).

No European exposure measurements were available.

In the USA, Hinton (API, 1995c) and Buchta (1993) had measured car mechanics' exposure in service halls in the areas where the MTBE content in petrol was 13.5 and 1.5 vol.%. Especially, if the engines were warm after driving, the exposure could be noticeable. The highest peak exposure was 115 mg/m^3 when changed fuel filter. However, the worst measured TWA8h exposures remained on an average low. The personal 8-hour exposure ranged from 0.07 to 9.4 and the means from 0.1 to 0.4 mg/m^3. When MTBE was used only as octane booster 1.5 vol.% in petrol, the mechanics' average exposure was 0.1 mg/m^3 ranging from <0.1 to 0.6 mg/m^3 (n=16).

The mechanic's maximum expose time to fuel per day is approximately two hours.

Because of limited exposure duration, the RWC8h for mechanics' exposure is concluded to be somewhat less than that at the service station work being from 3 mg/m^3 (2.8 vol.% fuel) to 10 mg/m^3 (11% fuel).

According to EASE, the predicted inhalation exposure to 11 vol.% MTBE with non-dispersive use and direct handling with dilution ventilation gives 360-504 mg/m^3 and 72-180 mg/m^3 for 2.8 vol.% MTBE in petrol, which values are overestimations.

Dermal exposure (both hands) with non-dispersive use and direct intermittent contact is 0.11· (0.1-1) = 0.01-0.1 mg/cm^2/d and 0.028· (0.1-1) = 0.003-0.03 mg/cm^2/d, respectively for both sorts of petrol.

Table 4.18 Exposure at automobile repair work in the USA, mg/m^3

Data from the USA								**Calculated 90th percentile**		**References**
Sampling		**Personal short-term**		**Personal TWA8h**		**Measured worst exposure**		**Personal TWA8h**		
Site, job, season, temp °C, MTBE content (%),		**Mean**	**Range (n)**	**Mean**	**Range (n)**	**Peak <15 min**	**TWA 8h**	**Normal distrib.**	**Log normal distrib**	
Automobile mechanics 1994	Winter, 13.5±1.5% (21)	3.7^G; 20^{GSD}	0.9-115 (13)	0.4^G; 16^{GSD}	0.07-9.4 (20)	115	9.4			API (1995c)
Automobile mechanics 1993	Winter 13%	0.4^G	<0.1-43 (28)			4.3				Buchta (1993)
Automobile mechanics 1994	Summer1.5± 2.1% (21)	1.5^G; 9.2^{GSD}	0.8-15 (8)	0.1^G; 6.5^{GSD}	0.07-0.6 (16)	15	0.6	1.7	1.1	API (1995c)

^{G} = geometric mean, ^{GS} = geometric standard deviation, n= number of samples, TWA= time-weighed average

4.1.1.1.9 Occupational exposure for drivers and other professionals

The types of occasions that cause professional chauffeurs to be exposed to MTBE include visits to petrol stations for refuelling, leaks from car fuel system and fuel exhaust gases. Other potential professionals are the people who use automobile as a part of employment and those who use fuel engines for other purposes. However, the engines of heavy trucks and mainly taxi cars (>95% in Finland) use normally diesel fuel, which does not contain MTBE.

There were some measurements from the USA that concerned drivers' exposure (Buchta, 1993). The measured exposure was low with a mean of 0.2 mg/m^3. The highest range value (4.6 mg/m^3)

may be affected by some short-term exposure caused by refuelling. The drivers' exposure is close to the ordinary consumer's exposure. Dermal exposure for drivers is considered to be very low.

The RWC8h for drivers and the other professionals is 0.2 mg/m^3.

4.1.1.1.10 Occupational exposure from use of MTBE as a solvent

MTBE is used almost exclusively as an additive to petrol. Only limited amounts (0.1-0.2% according to industry) of produced very pure substance (97.5%) is used for other purposes than the petrol use.

The pharmaceutical industry uses MTBE as a solvent for extraction and crystallisation of substances instead of other ethers. MTBE's benefits are that it does not generate explosive peroxides (Little et al., 1979). The industry uses the ether only in closed well-controlled circumstances (also because of fire hazard).

In laboratories, MTBE is used in some extend as a solvent for chemical analyses (Little et al. 1979; Mount et al., 1991). The amount of the ether used in a modern laboratory technique is very small (millilitres at the time) and the work is performed in fume cupboards with exhaust ventilation and by using protective clothing and gloves.

MTBE has been used for dissolution of gallstones in patients and laboratory animals (Adam et al., 1990; Allen et al., 1985; Ponchon et al., 1988; Teplick et al., 1987) for research and development purposes.

There were no exposure data available concerning other occupational uses of neat MTBE. The expert judgment is that the RWC8h in well-controlled closed processes is the same as in the laboratory work associated with MTBE production, i.e. 25 mg/m^3.

According to the EASE calculation with non-dispersive use and LEV control, the inhalation exposure is 360-720 mg/m^3. The EASE estimation is too high.

The predicted dermal exposure with parameters non-dispersive use and direct incidental contact to neat MTBE is 0.1-1 mg/cm^2/d (palms of both hands). In the pharmaceutical and chemical industry and the laboratory, the personnel uses protective clothing and gloves.

4.1.1.1.11 Summary of occupational exposure

The data available for the assessment of exposure to MTBE in Europe were mainly from the 1990s. Additionally, and for comparison there were data in the published literature from the USA and Finland. The European and the US data sets both gave closely similar average results. It was characteristic that the exposure was mainly ST-exposure with large concentration ranges. The main causes for the data variations were probably occasional leaks and spills which appeared in pipe connections, hoses and nozzles necessary for transfering the product through the production line to consumers. In the presented data, the ST-exposures were mainly specified as an exposure period during 30 minutes to one hour, except in service stations where the actual exposure time was only a few minutes during refuelling automobile tanks. The longer-term (TWA) exposures were up to 8 hours.

The manufacturing processes are automated, closed, outdoor systems with vapour recoveries. The characteristic exposure profile constitutes a background of low mean concentrations and

intervening high peak values of short duration. The statistical skewness of all the data also confirms the occurrence of high peak exposures.

The measured TWA8h exposures are less than most current OELs 180 mg/m^3. The ST-exposure peaks are sometimes slightly higher than the ST-exposure limits. The peaks vary in large ranges. One reason for the great variation of the peaks may also be that the sampling times were not standard and had varied.

The comparison of the other European mean exposure values with the Finnish values does not show very significant differences. There may be several reasons: the data material was too scanty to make certain conclusions, the sampling times and otherwise sampling strategies were different in different data groups or the samples were originally collected only as short-time samples and the results calculated further to longer-term results. Some differences on the concentration levels in these two data sets could, however, be anticipated.

All the work tasks in the plants dealing with petrol production are outdoor processes. Weather conditions, especially wind, reduce and mix effectively exposures and cause deviation in results. These physical conditions could not be handled in this report.

It may be concluded that in all scenarios related to production and delivery of petrol containing MTBE, the employees' exposure arises mainly from brief incidents, which cause elevated MTBE vapour concentrations. The exposure is highest on an average when the product is produced, formulated and transported. The leaks and spills also cause skin contact if personal protective equipment is not used.

The maintenance workers are repeatedly exposed in various tasks. They may have a special dermal exposure risk.

The other scenarios represent diverse exposures. Again, it is common that the exposure also in these groups is brief and intermittent (e.g. mechanics repairing automobile fuel lines). Drivers' exposure is caused by refuelling and of exhaust gases in the traffic and is similar as the highest consumers' exposures. The solvent use of neat MTBE occurs mainly in the pharmaceutical industry, where the exposure is controlled in the usual manner when working with toxic chemicals. In laboratories, the technicians work with small amounts of substance in fume cupboards and by using laboratory equipment and protective gloves.

Medical use of the compound has been on a research and development basis.

The exposure modelling with the EASE WINDOW Version 2.0 program gave much higher results than the measured concentrations. The differences may due to the fact that EASE modelling does not consider fluctuating exposures and variable exposure times. It neither asks the amounts (volumes) of exposing products. The peaks are obvious but, however, not very frequent if their power to the average exposures is considered, i.e. because the geometric means are low, and the geometric standard deviations and exposure ranges are large. The exposure predictions given directly by EASE are only exposures for 8-hour work and the frequency and duration of the peaks are unknown. The EASE model was judged the only reasonable way to evaluate the dermal exposure.

Table 4.19 is a summary table of the scenarios identified for the occupational exposure to methyl *tert*-butyl ether. The duration and frequency of exposure, numerical values for the proposed reasonable worst-case exposures, the results of the EASE estimation and data sources are given.

Table 4.19 Summary of occupational exposure estimates for methyl *tert*-butyl ether (MTBE)

Industrial category	Duration of exposure		Reasonable worst case, TWA(8h)	EASE-model exposure estimation (8h)		Source of data
Job	**Actual period h/d**	**Frequency d/a**	**mg/m³, by measured concentrations**	**Inhalation, mg/m³**	**Dermal exposure, mg/cm²/d**	
1.1 Production	2	200	50 (neat) 25 (sampling and laboratory work)	1,800-3,600 (0-0.36 closed process)	(neat) 0.1-1 (sampling and laboratory work)	Industry
1.2 Formulation	2	200	50 (neat and fuel) 25 (sampling and laboratory work)	1,800-3,600 (neat), 360-504 (11vol%), 72-180 (2.8 vol%)	0-0.1 (neat); 0.1-1 (neat, sampling and laboratory work)	Industry
1.3 Transporting	4	200	100 (neat: ship, rail car loading,) 30 (fuel: ship, truck loading) 25 (sampling and laboratory work)	1,800-3,600 (neat), 360-504 (11 vol%), 72-180 (2.8 vol %)	0.1-1 (neat); 0.01-0.1 (11vol%); 0.003-0.03 (2.8 vol%)	Industry
1.4 Distributing	4	200	40 (11 vol% fuel) 30 (2.8 vol% fuel)	360-504 (11 vol%), 72-180 (2.8 vol%)	0.01-0.1 (11vol%); 0.003-0.03 (2.8 vol%)	Industry; Hakkola et al. (1996b); Saarinen et al. (1998); Vainiotalo et al. 1999b)
1.5 Service stations	3	200	20 (11 vol%) 3 (2.8 vol%)	360.504 (11 vol%) 72-180 (2.8 vol%)	0.01-0.1 (11vol%); 0.003-0.03 (2.8 vol%)	Industry; Hakkola et al. (1999); Vainiotalo et al. (1999a)
1.6 Maintenance	4	150	60 (production, formulation and transportation) 40 (distributing and service stations, 11 vol%) 30 (distributing and service stations, 2.8 vol%)	1,800-3,600 (neat) 720-1080 (11 vol%) 504-720 (2.8 vol%)	1-5 (neat); 0.1-0.6 (11 vol%); 0.03-0.14 (2.8 vol%)	Industry
1.7 Automotive repair	2	200	10 (11 vol%) 3 (2.8 vol%)	360-504 (11 vol%) 72-180 (2.8 vol%)	0.01-0.1 (11vol%); 0.003-0.03 (2.8 vol%)	Buchta (1993)
1.8 Drivers and other professionals	10 min/d	200	0.2	360-504 (11 vol%) 72-180 (2.8 vol%)	Very low	Buchta (1993)
3.0 Solvent use of MTBE	2	60	25 (neat 97.5%); (expert judgment)	360-720 (neat)	0.1-1 (neat)	Industry

4.1.1.2 Consumer exposure

In the product register of Sweden, there were 24 consumer products containing MTBE. All products were petrol.

Exposure which takes place during car refuelling is included in this chapter. Exposure at pump island of service stations, in cars, in perimeter of petrol stations etc. are dealt with in Section 4.1.1.3 "Humans exposed via the environment".

In many petrol stations, petrol is unloaded at the station without collection of volatilised petrol. At the Stage I stations, during unloading from tank truck to station tank, vaporised petrol is collected, which reduces the release to the air and limits the customer and occupational exposure. At the Stage II stations, vaporised petrol is collected also during refuelling by an inlet which is attached to the petrol pistol. This decreases the exposure of consumer to MTBE vaporised during refuelling.

The proportion of the Stage II stations is 38-90% in six most advanced European countries. In Finland, the proportion of Stage II stations was only 5% in 1998 (Hakkola et al., 1998b).

MTBE was measured in the breathing zone of 40 randomly selected customers during refuelling. In Stage I stations, the average concentration was 15.3 mg/m^3 and in stage II stations it was 3.4 mg/m^3. Thus, the stage II technique reduces the MTBE concentration to about one fourth. The temperature varied between 10-17ºC and the duration of fuelling between 6-49 seconds; the average being 23 seconds. The wind speed was 2-4 meters per second (see **Table 4.1**) (Hakkola et al., 1998b).

In Finland, the customer exposure to MTBE during refuelling in two self-service petrol stations (an urban and a road-side station) was measured during May-June and October 1995 (Vainiotalo et al., 1998b). The stations were equipped with Stage I vapour recovery, i.e. vapor generated during petrol deliveries is collected and transported for recovery. The petrol at stations contained 11% of MTBE. Samples (313) were collected from the breathing zone of customers. Each sample represented a single refuelling operation. Sampling was started when the person inserted the pump pistol into the fuel tank of the car and sampling stopped when the pistol was placed into its holder. The concentration of MTBE in individual samples, was <0.2-245 mg/m^3. The geometric mean values of MTBE in two stations and two seasons were 4.4-7.4 mg/m^3 and the mean refuelling times were 58-71, with the overall range of 21-275 seconds. The overall geometric mean concentration calculated for a 1-minute refuelling time was 6 mg/m^3. The logical finding was that a higher wind speed resulted in lower average MTBE concentration at the refuelling. No statistically significant difference was observed between the two stations and between the two seasons.

Vainiotalo et al. (1999a) also measured the customer exposure (during refuelling and at pump island) to MTBE during refuelling in two self-service petrol stations during summertime. The stations were adjacent to main roads with high traffic density. The mean wind speed was 1.4 m/sec and mean air temperature was 21ºC. Samples were collected in the breathing zone of the customer. Stage I vapour recovery system, which only collects vapours during petrol unloading, but not during refuelling, was operational at the stations. The petrol pistols had rubber "splash collars". The sampling started when the pump pistol was inserted in the tank and ended when pump pistol was replaced in its holder. The 95 grade petrol which contained only 2.7% of MTBE contributed by 75% to the volume refuelled during the study; the rest of the petrol was 98/99 grade containing 12.2% of MTBE. The geometric mean concentrations at the two stations were 3.9 mg/m^3 (0.05-48.7 mg/m^3) and 2.4 mg/m^3 (<0.02-51.2 mg/m^3). The MTBE concentration of 21 out of 167 samples exceeded 20 mg/m3 during the refuelling. The average refuelling times

were 63 and 74 seconds. The overall geometric mean (n=167) for an adjusted 1-min refuelling time was 3.3 mg/m^3.

In Italy, attendants personal exposure to MTBE was measured in 1991-92 and 1995 (Giacomello, 1996). Although the customer exposure was not measured, the exposure scenario is sufficiently similar to that of an attendant. This study is also considered here, to include all relevant European studies on this subject. Number of service stations studied was 72, some of which were studied twice; urban, rural and motorway sites were all covered. Some of the stations had Stage 2 vapour recovery system operational. For the attendants, the geometric means of measurements made in different years and seasons varied between 0.1 and 0.44 mg/m^3. The range was 0-2.46 mg/m^3 and the number of samples was 551. These figures are low as compared with those reported by Vainiotalo et al. (1998b), probably due to low content of MTBE in fuel (2.1-2.7%).

Lioy et al. (1994) measured MTBE in the breathing zone during refuelling at self-service station and before and after a stop at full-service and self-service stations. The service stations were either emission control, Stage II self-service stations, non-Stage II self-service stations or non-Stage II attendant-assisted. During a 5-minute refuelling at a self-service station, the mean concentrations for personal samples (samples for the person who refuelled the car) were in excess of 1 mg/m^3 (0.3 ppm) with a peak of 14.7 mg/m^3 (4.1 ppm). The highest MTBE concentrations were recorded for individuals who used a pump without Stage II controls (Lioy et al., 1994).

Johnson (1993) has also reported relatively high levels of MTBE at the petrol stations: the peak concentrations to which the attendants are exposed to were up to 2.5 ppm (9 mg/m3).

(US EPA has established reference concentration of 3 mg/m^3 for long-term environmental exposure via ambient air.)

Table 4.20 MTBE air measurements during refuelling

Location	Year(s)	N (sampling period)	Results (µg/m^3)	Remarks/sampling sites	Reference
Helsinki, Finland	1995	313 (65s)	Range <200-245,000 Geometric means 4,400-7,400	Stage I applied, breathing zone	Vainiotalo et al. (1998b)
Helsinki, Finland	1996	167 (65s)	Range <20-51,200 Geometric means 3,900-2,400	Stage I applied, breathing zone	Vainiotalo et al. (1999a)
Helsinki, Finland	1998	40	Average 15,300 Average 3,400	Stage I applied, breathing zone Stage II applied, breathing zone	Hakkola et al. (1998b)
Milwaukee, USA	1995	8 (15 min.)	Medians 1,404, 10,500	Service station refuelling, in breathing zone	Allen et al. (1995)
New Jersey, New York, USA	1993	20 (5 min)	Range 18-619 Medians 54-148	In automobile while refuelling, breathing zone samples	Lioy et al. (1994)
New Jersey, New York, USA	1993	4 (5min)	Median 1,332	Service station refuelling, breathing zone, before, during and after refuelling, with vapour recovery (=Stage II?)	Lioy et al. (1994)
Connecticut, USA	1993	4 (5min)	Max. 14,760 Median 2,059	Service station refuelling, without vapour recovery	Lioy et al. (1994)
Phoenix and Los Angeles, USA	1990	46 (1-2min)	Range 324-136,800 Medians 12,960 and 20,880	Service station refuelling	API (1993)

Great variation observed in these studies is due to seasonal/climate factors, wind direction, refuelling time, car type, temperature, and simultaneous unloading operation at the petrol station. 10,000-20,000 l is the daily consumption of petrol at a normal service station in Finland (Vainiotalo oral information 1999). Considering the median values presented in **Table 4.20**, it is assessed that the normal concentration of MTBE during refuelling is 1,000-10,000 μg/m^3. The duration refuelling is short, i.e. about 1-5 minutes, and it takes place 2-3 times per week at the most. The reasonable worst-case (RWC) concentration is 3000-29,000 μg/m^3. The lower value represents the situation in most European countries where petrol contains 2.8 vol% of MTBE and the upper value represents the situation in Finland where petrol contains 11 vol% of MTBE. This concentration range is the same as the RWC for workers (petrol station attendants), which was calculated as the average of the upper limit of ranges representing the 8-hour exposures measured (see Section 4.1.1.1 General discussion). These two concentration ranges are used for calculation of dose in **Tables 4.7** and **4.8**.

Dermal exposure caused by refueling

Refuelling of a car or a boat motor may cause dermal contact with MTBE. No measurements are available on this scenario and route of exposure. The reasonable worst-case scenario presented below is based on modelling.

Dermal deposition/exposure was estimated using EUSES. The input data were:

- duration of contact per event: 0.5 hour,
- surface area of exposed skin (palm of one hand): 200 cm^2,
- average concentration of substance in product: 0.08 g/cm^3,
- volume of diluted product contacting the skin 0.01 cm^3,
- thickness of layer of product on skin 0.1 mm.

In this estimation, the potential dermal deposition was 11.4 μg/kg bw (0.8 mg/occasion). Obviously, most of the EUSES -input data have no effect on the estimated exposure. In a more realistic estimation, e.g. evaporation from the skin, duration of contact and skin area should be considered.

EASE modelling for dermal exposure was done as well. The use-pattern was “Wide dispersive use”, the pattern of control “Direct handling” and the contact level was “Incidental”. The resulting estimate is 0.1-1 mg/square cm/day. Taking into account that the substance contains 11 vol.% of MTBE and that the exposed skin area is 200 cm^2, the dermal exposure is 2.2-22 mg/occasion. This is relatively close to the previous estimate (0.8 mg/occasion).

Overall, these estimates for skin deposition may easily exaggerate real life absorption hazard since, 1) skin contact during refuelling is exceptional rather than normal, 2) refuelling occurs infrequently and, 3) rapid evaporation from the skin and brief contact time reduce the potential absorption through the skin. Therefore, potential dermal exposure as a source of systemic exposure in refuelling is regarded insignificant and not considered any further.

4.1.1.3 Humans exposed via the environment

In Central Europe, the average MTBE concentration of most common grades of petrol is 2.8 vol.%, whereas in Finland, the normal MTBE content in petrol is 11 vol.% (oral information from Fortum Oil, see also **Table 3.1**.). In Belgium, fuel contains 5-10% of MTBE (De Backer, 2000).

Most of the studies on MTBE concentration in the drinking water and air, cited below, have been performed in Finland, the UK or in the USA. Some analytical data from Germany, Sweden and Italy have been published. When the representative concentration levels were selected (for calculation of doses to which consumers are exposed to) weight was given to the data, which originates from Finland and also to some extent to data from the USA. Obviously, the concentration levels which are representative for Central Europe and respective dose levels would be lower than those presented below (e.g. **Tables 4.21-4.23**). This issue is again considered in the section "Total exposure via drinking water and via air".

4.1.1.3.1 Exposure via drinking water

MTBE enters surface water and groundwater because of fuel leaks and spills mostly at the service stations. In urban areas, the rainwater contains low concentration of MTBE, which causes slightly elevated MTBE concentration in groundwater. When contaminated groundwater is used as drinking water people are exposed to MTBE. Most of the analytical studies have concentrated on groundwater and thus, the data on the MTBE content of tap water are not sufficient for accurate estimates.

The physico-chemical properties of MTBE increase the possibility of serious contamination of groundwater: The water solubility of MTBE is high; 50,000mg/l at 20°C. MTBE is only weakly bound to subsurface solids and is therefore easily transported to groundwater. Furthermore, MTBE is generally resistant to biodegradation in groundwater**.** Releases can cause problems especially in areas of high water table, high bedrock surface, and dense residential areas with water supply wells and petroleum tanks (Squillace et al., 1997).

In the atmosphere, the half-life of MTBE can be as short as 3 days. The partitioning of MTBE to precipitation can result in concentration as high as 3 µg/l or more in urban precipitation and can contribute to the presence of MTBE in surface and groundwater.

Regulations on tank monitoring

In the UK, Guidelines for Petrol Filling Stations given by the Health and Safety Executive stipulate the need for consistent and accurate monitoring of petrol delivered, stored and dispensed at a filling station to detect leaks from underground tanks and the connected pipeline system. The monitoring of tank leakage should occur at least once daily and be inserted in a register. Guidelines also indicate that proper monitoring should occur showing gains or losses for each tank or compartment and connected pipeline system. The Guidelines stipulate that all relevant authorities must be informed once a leak is detected. In general, a competent person should carry out periodic examinations and servicing. With regard to tanks, a scheme for examinations including scope and frequency should be agreed between the licensee and the competent person. Nonetheless, a rule of thumb is that tanks should be re-examined every 10 years. These requirements are not legal but considered best practice. The legal requirements which are incorporated into the petrol stations building and operation permits will in most cases include the guidelines and thus, give them a binding nature in a court of law.

In July 1998, a decision was adopted by the Ministry of Trade and Industry, which describes the requirements for new underground storage tanks in Finland. The decision requires that the tanks placed in zones which are important groundwater areas need to have double coating with a leak detection system and that they resist corrosion from the content and surroundings. According to the decision, older USTs may still be used if they have been checked during the last ten years. Any unchecked underground storage tank had to be checked by July of 1999. As in the UK, the

material flows at a service station have to be recorded, which e.g. enables the detection of leaks of underground tanks and pipe joints.

MTBE in groundwater

Numerous studies have shown that MTBE released from underground tanks and spills (that take place during unloading operation at the petrol station) can contaminate the ground-water and nearby wells.

Because its relatively high solubility in water, MTBE tends to migrate faster than other fuel constituents and is likely to be present in the leading edge of the travelling plume. Spills during transfer operations are less likely to become significant sources of MTBE in potable water, because MTBE evaporates rapidly when exposed to the atmosphere (Stern et al., 1997).

The spills/releases that contaminate the groundwater are categorised as follows:

- Mild contamination caused by MTBE content of the rain water,
- Leaks/spills caused by corrosion of underground tanks, pipes and pipe joints,
- Leaks at the petrol station during normal operation at the petrol stations, especially at the stations where the run-off waters are not collected,
- Spills during the unloading at non-Stage 1 stations, and
- Spills that are due to traffic, accidents or accidental major spills at the petrol stations, which are excluded in this risk assessment.

Based on the available information, the frequency and importance of various spills cannot be fully assessed. Leaks from the underground tank and pipe joints seem more hazardous than other spills since the contamination of groundwater can be immediate and it is not mitigated by evaporation of the substance.

It is suggested that all except the category 5 release should be taken into account for this risk assessment. Continuous release from corroded tanks or releases at the petrol stations are probably not considered accidents under the current EU provisions/regulations.

Regulations on technical specifications and control of underground tanks are not harmonised in the EU, but are established on national and/or county/regional basis. Obviously, the double-jacket technology diminishes the risk of leaks, but the number/percentage of these modern tanks in not known (oral communication, representative of industry 1999). In the USA, it has been recommended that regulations should be enforced which address installation procedures, tank materials, monitoring and tank location.

The authorities and consulting companies in Finland and Denmark have provided unpublished analytical data. Some published analytical data originating from the USA are also included here. In most cases, the available data represent groundwater near to petrol stations where spills and leaks have taken place. The concentration of MTBE near service stations varies, in some studies the maximum measured has been 45 µg/l whereas in other cases concentrations up to 200,000 µg/l have been measured (see Appendix **Tables A.4 and A.5**). In the studies with the greatest number of samples, the concentrations have mostly been 5-100 µg/l. Thus, high concentration measured in some contaminated sites, are not relevant when long-term reasonable scenarios are considered.

Concentration of MTBE in potable water sources

There are some data available on the concentration of MTBE in potable water in the UK, Finland, Denmark, Germany and the USA (**Table 4.20**). Some of the sampling sites represent uncontaminated water source, whereas some observations reflect the situation caused by local contamination.

In the UK, data were collected on the occurrence of MTBE in groundwater and potable water sources (PWS) (Dottridge et al., 2000). In the UK, fuel usually contains less that 1% of MTBE and a significant proportion of fuel contains no MTBE. Super unleaded petroleum and lead replacement petrol can contain up to 5% of MTBE. In the study, data were collected from 800 site investigations and analysis of almost 3,000 samples from public water supplies and monitoring boreholes. Sources of data were Environment Agency Regions, water companies, oil companies and trade associations. Data from the years 1991-1999 were compiled. Sampling has partly been directed to sites where elevated concentrations had been observed previously. The orientation of the rest of the sampling was to cover sites not studied before.

MTBE was detected at 32 (13%) of the potable water source wells sampled during regional monitoring by authorities and by water companies (**Table 4.21**). In most cases, the detection limit was 0.1 µg/l. Ten wells (3.9%) have shown concentrations above 1 µg/l. Concentration above the taste threshold applied in the UK (5 µg/l) was measured in only one private source and three PWS wells (1.1%). Two of these high concentrations could be related to a known leakage of fuel within 200 m of the PWS. These figures are likely to be biased to some degree, since the sampling is partly targeted to the sites, where leakage or spill had been observed.

In the present risk assessment report, 15 µg/l is applied as taste and odour threshold, representing the lower threshold level identified in those few taste and odour panel studies available. Considering the biased sampling in the UK study and the low percentage (1.1%) of analytical results above 5 µg/l, it is likely that the actual percentage of drinking water wells in the UK, where the threshold of 15 µg/l is exceeded is much below 1%.

Modelling exercise of MTBE transport to wells supported the analytical results: it suggested that totally about 203 PWS wells in the UK could have detectable (>0.1 µg/l) contamination. It was estimated that six of these wells could have MTBE concentration above the threshold (15 µg/l).

Dottridge et al. (2000) predict that growing awareness of the potential problems and improved standards for underground storage tank and pipework will help to decrease the number of leakages in future.

Contrasting conditions between the UK and the USA explain why in the USA, especially in California, contamination of groundwater by MTBE is more frequent:

- Until recently, much of the fuel sold in California contained 10-15% MTBE (by volume), whereas the percentage is below 1 in the UK.
- The fuel price is far lower in the USA.
- MTBE was introduced into fuel in the USA 5-10 years earlier than in the UK.
- The level of car use per head of population is much higher in the USA.
- In California, high water consumption and low recharge have resulted in heavily depressed groundwater levels. Thus, MTBE entering groundwater in the USA is more likely to travel to a PWS borehole, whereas in the UK the contaminated groundwater more often travels to the river.

In Germany, Klinger et al. (2000) analyzed 180 samples from wells in urban and rural areas. In the urban area, 15% of the samples showed MTBE concentrations above 0.5 µg/l, but only few samples from rural areas exceeded 0.5 µg/l. The average concentration of MTBE in unleaded fuel was 1.7% in 1999, which is slightly higher than in the UK.

In Sweden, the Environmental Office of Trollhättan municipality, near Gothenburg, has measured MTBE in potable water sources. It is obvious that this serious case of groundwater contamination is exceptional and could not represent the conditions in Sweden in general. In three of 23 sites, and in 23 of 95 samples the threshold of 15 µg/l was exceeded. The maximum level measured was 310 µg/l. The likely source of contamination is a petrol station. A few years after the soil was remediated, concentrations above the Swedish tolerance (20 µg/l) have still been detected in groundwater 600 m away from the station (Environment Office of Trollhättan, 2000).

Table 4.21 MTBE concentration in potable water sources

Location	Year(s)	n	Results (µg/l)	Remarks/sampling site	Source
United Kingdom	1991-1999	1178 samples from 255 PWS wells	>0.1 in 32 PWS wells, >1.0 in 10 wells, >5.0 in 4 wells (1.1%)	Potable water sources (PWS)	Dottridge et al. (2000)
Germany		180 samples	0.5 µg/l was exceeded in 15 % of the samples from urban wells	Wells in urban and rural areas	Klinger et al. (2000)
Trollhättan, Sweden		95 samples from 23 sites	15 µg/l was exceeded 3 of 23 sites and in 23 of 95 samples	Potable water sources near to petrol stations	Environment Office of Trollhättan (2000)
Denmark	?	6 sites	42-547,000	Extractable/ potable water aquifers, mixed loading	Miljöstyrelsen (1998)
Copenhagen Denmark	1997	25/8	0.1-0.15	Potable groundwater	Miljöstyrelsen, 1998)
Helsinki, Finland	1999	4 samples	<0.1-0.72	Drinking water, source of water supply, groundwater	Piilo et al. (2000)
Lieksa, Finland	1998	8/20	<2-16	Shallow potable water and monitoring wells near station	PSV-Soil/Water Ltd, North Carelia Regional Environment Centre (unpublished)
Kitee, Finland	1988	16	Mean 370 Max. 330,000	Shallow potable water wells impacted by petrol spill	North Carelia Regional Environment Centre (unpublished)
Haraldsted, Sø, Denmark	?	2/1	<DL-0.59	Potable water source	Miljöstyrelsen (1998)
Gyrstinge, Sø, Denmark	?	2/0	<DL	Potable water source	Miljöstyrelsen (1998)
New York State, USA	1998	42 wells	In 20 % of wells, detection limit 0.1 was exceeded, the average of 8 detections was 10 µg/l, range was 1-61 µg/l.	Private wells adjacent to petrol station (<0.5 miles)	Lince et al. (1998)
Several States of the USA	1998	969	Arithmetic means by State vary from 0.41-2399 µg/l; most of the means are between 2 and 60 µg/l	Public and private wells, some monitoring data; many of the samples are taken after identified spills.	NTP (1998)

Considering all the available data, the concentration of MTBE in uncontaminated drinking water and groundwater can be estimated to 0.1-1 µg/l. The lower value is probably nearer to the prevailing concentration level and it is used for calculation of the dose (see **Table 4.22**). In that estimate, the MTBE content in rainwater has been considered. In rural areas, MTBE concentration is likely to be less than 0.1 µg/l.

For the reasonable worst-case scenario (see **Table 4.22**), 15 µg/l is regarded as maximum concentration of MTBE in the drinking water. Whereas remarkably higher concentrations have been detected in numerous groundwater and potable water samples, public/municipal potable water source is not likely to be used for any longer period of time when the organoleptic/odour threshold of 15 µg/l is exceeded.

Table 4.22 Exposure to MTBE via tap water. Concentration levels are selected to represent the situation in Europe.

Relevant area/scenario	Source of MTBE	Typical concentration µg/l	Daily dose µg/ day [1)]	Percentage of population
Urban background	Car exhausts, rain	0.1	0.2	About 50%
Soil and groundwater polluted by refineries and petrol stations	Underground tanks, leaks and spills at petrol station	15	30	?

[1)] It is assumed that ingestion of tap water is 2.0 l/day.

Not much published data are available on concentration of MTBE in groundwater and tap water in the European countries. The literature that describes the situation in the USA is briefly reviewed below, since in the future, the levels of MTBE in drinking waters of some European countries may resemble those observed in the USA. The large-scale use of MTBE began earlier in the USA than in Europe. The concentration of MTBE in petrol is higher in the USA; on the other hand the traffic density in Continental Europe is higher that in the USA. Overall, the data obtained in the USA seem sufficiently relevant to be reviewed here, although the exposure scenarios are based on European data as much as possible.

When MTBE is present in tap water, humans may be exposed to it via drinking water, inhalation of volatilised MTBE and through dermal absorption.

Based on data from the USA (Brown, 1997) and on European data, exposures through these routes are as follows:

- Through ingestion of drinking water and food, an assumption is made that the daily ingestion is 2.0 l, thus causing an intake of 0.2 µg/day (see **Table 4.22**),
- Inhalation of MTBE volatilizing from tap water during showering and bathing. According to Stern et al. (1997), the dose is estimated to be $2.7 \cdot 10^{-3}$ µg/kg/day,
- Dermal absorption of MTBE during showering and bathing (geometric mean of daily dose is assessed to be $2.6 \cdot 10^{-5}$ µg/kg/day) and
- Other water contact activities.

The geometric mean and theoretical maximum concentrations of MTBE in tap water have been examined (**Table 4.22**). The 95 percentile of the dose is a "reasonable worst-case" value, where all exposures caused by MTBE in tap water are considered (Brown, 1997).

Dose caused by these routes are added up and presented as µg/kg/day in **Table 4.23.**

Table 4.23 Concentrations of MTBE in tap water and the respective doses, estimates which represent the situation in the USA.

	Sources of MTBE in tap water			
	Atmospheric deposition		Leaks/Spills	
	Geometric mean	Theoretical maximum	Geometric mean	95 percentile
Concentration In tap water (µg/l)	0.25	2.0	3.9	64
Dose equivalent (µg/kg of bw day)	0.007	0.06	0.01	2

For drinking water, the US EPA has issued a draft lifetime health advisory of 20 to 200 µg/l, i.e. a maximum concentration in drinking water that is not expected to cause any adverse non-carcinogenic effects over lifetime exposure. In the USA as a part of National Water-Quality Assessment program, MTBE was analyzed in totally 210 samples representing shallow groundwater from urban areas (drinking water wells, springs and monitoring wells). MTBE was detected in 27% of those samples of the wells and springs sampled when the detection limit was 0.2 µg/l. 3% of the shallow wells sampled in urban areas had concentrations of MTBE that exceed 20 µg/l. Only in about 1% of samples collected from agricultural areas or representing deeper groundwater, MTBE was detected (Squillace et al., 1996). In seven of the eight urban areas studied, the sampled groundwater is the uppermost part of an aquifer used for drinking water or is possibly connected to an underlying aquifer, which is used as a municipal water supply. However, at the time of sampling, none of the urban wells sampled were being used as a source of drinking water (Squillace et al., 1995).

The average MTBE levels of the drinking water supplies in 11 US states varied between 0.41 and 2,399 µg/l. If only those states are considered where more than 50 samples were analyzed (Missouri, New Jersey, Rhode Island) the averages are 2.6-2399. However, in most states, the median concentration is below 10 µg/l, which indicates that for most consumers the concentration of MTBE in the drinking water remains low. Furthermore, many of the samples in these studies were taken after spills had been identified (NTP, 1998).

In the New York State area, private wells adjacent to the petrol station (closer than 0.5 miles from the station) were analyzed for the MTBE concentration in the water. Every fifth (20%) of the wells analyzed had MTBE concentrations at or above the detection limit 1.0 µg/l. Among the control wells (farther than 1.5 miles from the station) none had detectable concentration of MTBE. Thus, the wells near petrol stations are at risk for low-level MTBE contamination. The average of the 8 positive water samples was 10.0 µg/l and the range was 1.0-61 µg/l. Leaking underground tank was established as the cause of the highest concentration measured (Lince et al., 1998).

It has been suggested that storm-water runoff and atmospheric transport are contributors to the low environmental and water concentrations of the MTBE (Delzer et al., 1996; Squillace et al., 1997). These could explain why MTBE has been detected also in wells without no known leaks from the adjacent petrol stations.

It has been estimated that, via potable water, 5% of the population of the USA may be exposed to higher levels of MTBE than 2 µg/l (Stern et al., 1997). Some people may be exposed to very high concentrations due to local spills, but the duration of exposures is likely to be short due to dilution, rapid volatilisation and remediation measures to minimise the human exposure. After spills and leaks the concentration of MTBE in groundwater may reach levels between 100 and 100,000 ppb. According to a recent survey in the USA, 3% of the non-potable water well samples in urban areas had concentrations greater than 20 ppb and one well had a concentration of 23,000 ppb.

4.1.1.3.2 Summary of exposure estimates via drinking water

There are numerous studies on the concentration of MTBE in groundwater. However, not many studies have been published on the concentration of MTBE in representative samples of drinking water. Based on limited number of studies made in Denmark, Sweden, Finland, the UK, Germany and the USA (see **Table 4.21** and Appendix **Tables A.4 and A.5**), the following conclusions are made.

The concentration of MTBE in tap water is usually low, i.e. about 0.1 µg/l. When groundwater or shallow water has been contaminated due to leaks and spills from adjacent petrol station, the concentration of MTBE can be elevated. According to a recent evaluation by the Blue Ribbon Panel, 0.1% of drinking water supplies in the USA contain MTBE above 20 µg/l (Lince et al., 1998). Continuous use of drinking water containing more than 15 µg of MTBE/l is unlikely, since the taste and odour threshold of MTBE are 40 and 15 µg/l, respectively. Concentrations exceeding the thresholds are regarded as unacceptable based on general water quality criteria.

In extreme cases, the concentration in groundwater and in some wells potentially used for potable water is >1,000 µg/l (see Appendix **Table A.5**). This level of exposure is not likely to be continuous, since it reflects the situation caused be severe local contamination of soils, which in most cases will be remedied. Normally, in case of evident contamination of groundwater, the use of nearby wells for potable water is no longer continued. Furthermore, it is assumed that high concentration in potable water is not tolerated due to the low odour and taste threshold of MTBE.

In addition to the measured MTBE concentrations in groundwater and drinking water, results of EUSES modelling were considered. Continental PEC value in the surface water is 0.36 µg/l. This concentration is in the same order of magnitude as the representative concentrations for potable water, ie. 0.1µg/l selected for calculation of dose. The representative concentrations, based on the analytical results and supported by results of the EUSES modelling, are preferred for this assessment.

4.1.1.3.3 Exposure via air

MTBE is released to air during loading and unloading of petrol in various sites, during refuelling of cars and as a component of car exhausts. Releases from the industry and from contaminated land may cause local air pollution. The highest concentrations to which consumers are exposed have been measured to occur during refuelling of cars. That issue was dealt with in Section 4.1.1.2 “Consumer exposure”. Consumers are indirectly exposed to MTBE during their stay at the service station and when travelling in a car. Furthermore, people living near to service stations or near roads with a high traffic density are exposed to elevated concentration of MTBE in the ambient air.

In this section the following scenarios are addressed:

- Pump island of service stations,
- Perimeter of service stations,
- Commuting in car or in bus,
- Areas polluted by refineries and contaminated soil,
- Urban background.

There are not many European studies on air concentrations of MTBE. Therefore some recent studies made in the USA are also reviewed below, e.g. to show some consistencies with the results obtained in Europe.

Pump island of service stations

Vainiotalo et al. (1999a) measured MTBE concentration in ambient air at a stationary point in the middle of the pump island. Mean concentrations were 160 and 70 μg/m^3 for the two stations (see **Table 4.24**). This is in agreement with measurements of MTBE concentration inside automobile cabin during refuelling (Vayghani et al., 1999): the mean concentration of MTBE was 104 μg/m^3 (the geometric mean was 68 μg/m^3). Samples were collected during the winter when oxygenated petrol was used.

Somewhat higher concentration were measured by Vainiotalo et al. (1998c) in the pump island at service stations, one urban and one roadside in May-June and October 1995. The petrol at stations contained 11% of MTBE. The mean concentrations measured daytime in the center of the pump island were 247-1,347 μg/m^3. The levels of MTBE were dependent on e.g. volumes of petrol sold, wind speed, exhaust emission from passing traffic and deliveries of petrol to the station. The mean wind speeds were between 0.7-1.5 m/sec. and the temperatures were above 22ºC in May-June and 10 ºC in October.

In Italy, pump island measurements were made in 1991-92 and 1995 (Giacomello, 1996). The number of service stations studied was 72, some of which were studied twice; urban, rural and motorway sites were covered. Some of the stations had Stage 2 vapour recovery system operational. At the pump island the geometric mean concentrations measured varied from 38-108 μg/m^3. The range of results was 0-2,533 μg/m^3 and the number of samples was 535. Content of MTBE in the petrol was relatively low, i.e., 2.1-2.7%.

It is assessed that in the pump island of service station, 100-500μg/m^3 is the realistic range of MTBE concentrations (**Table 4.24**).

Table 4.24 MTBE in pump island and perimeter of service station.

Location	Year(s)	n (Sampling period)	Results (µg/m³)	Remarks/sampling sites	Source
Pump island/pump area at the service station					
South-western Finland	1995	15 (8h)	Range 247-1347	Pump area centre, Stage I	Vainiotalo et al. (1998c)
Helsinki, Finland	1996	167 (8h)	Mean concentrations 70-160	Stage I applied Pump island	Vainiotalo et al. (1999a)
New Jersey, USA	1994	3 (8h)	Range 288-864 Median 864	Service station pump area	Cook et al. (1995)
Perimeter of the service station					
South-western Finland	1995	35 (24h)	Mean concentrations 4.1-14.1 Range 0.5-120	Service station perimeter [1)]	Vainiotalo et al. (1998c)
Frankfurt am Main, Germany	1996	13 (24h)	Geometric mean 3.8 Maximum 9.9 [2)]	Service station perimeter Personal samplers were used	Heudorf et al. (1998)
Milwaukee, USA	1995	3 (2h)	Medians 8.6-16.2	Service station perimeter	Allen et al. (1995)
Phoenix, USA	1990	24 (12h)	Range 32-320 Median 72	Service station perimeter and upwind & downwind from the pump island [3)]	API (1993)
Connecticut and New York, USA	1995	64 (4h)	Range <3.7-504 Medians 25-50	Service station perimeter	API (1995a)

[1)] 50 m from the pump island; whether the measured level of MTBE applies to indoor air can not be assessed so far, more data are needed.
[2)] MTBE concentration in petrol in Germany is lower (1.2%) than in Finland (11%).
[3)] Most of these measurements may not represent the MTBE concentration in houses near to the service station: sampling locations are in the same quarter than the service station, the approximate distance from the pump island is about 20-30 m.

Perimeter of service stations

Vainiotalo et al. (1998c) measured MTBE concentration near service stations, one urban and one roadside in May-June and October 1995. The stations were equipped with stage I vapour recovery. The petrol at stations contained 11% of MTBE. The sampling was carried out for 24 hours per day at stationary sampling points about 50 m from the forecourt of the station. Besides the service stations, there were living houses within that distance. The concentration range of individual samples was 0.5-121 µg/m^3 (**Table 4.24**). The highest concentrations were usually observed at the downwind sampling point. The arithmetic mean concentrations of the four-day sampling periods were 4.1-14.1 µg/m^3.

The levels of MTBE were dependent on e.g. volumes of petrol sold, wind speed, exhaust emission from passing traffic and deliveries of petrol to the station. The mean wind speeds were between 0.7-1.5 m/sec. and the temperatures were above 22ºC in May-June and 10ºC in October. The MTBE concentrations were higher at the urban station, since the volume of petrol sold was higher than at the roadside station and since adjacent to the urban station there were two roads with high traffic density.

In Frankfurt am Main, Germany, the MTBE concentration in the neighbourhood of service stations was analysed using personal sampler carried by 13 persons and 7 control persons during the summer 1996 (Heudorf et al., 1998). The persons had the sampler with them all the day.

During the night, the sampler was on the bedside table. In the neighbourhood of the station, the geometric mean and the maximum concentration were 3.8 and 9.9 μg/m^3, respectively. For the controls, the respective figures were 8.4 and 20.1 μg/m^3. The person giving this maximum value (20.1 μg/m^3) had been driving a private car for 20 hours during the 2 days of the survey. Thus, these results show that there are other significant sources of MTBE in addition to the service station. Most likely, the vicinity of main roads and commuting in a car may be an important contributor to the MTBE exposure as the service station in the neighbourhood. Unfortunately, the MTBE content in the petrol and the distance between service stations and the living houses were not reported.

Other components of petrol, e.g. benzene, were measured by Heudorf (Heudorf et al., 1998) and Vainiotalo (Vainiotalo et al., 1999a). Vainiotalo observed 13-fold concentration of MTBE as compared with the concentration of benzene at the pump island, whereas concentrations of MTBE and benzene were at the same level in the study of Heudorf. This is either due to remarkable lower concentration of MTBE in petrol in Germany as compared with Finland or low consumption of MTBE-reformulated petrol in the Germany. Measurements made by API (1993) (18 sampling points) indicate that the fenceline concentrations of MTBE were about 4-fold higher as compared with the concentration of benzene (0.03 ppm vs. 0.008 ppm). More data would be useful for an assessment of representative and realistic concentrations of MTBE in houses near to petrol stations.

In Italy, the geometric mean of fence-line MTBE concentration was 5.1 μg/m3. The content of MTBE in petrol (2.1-2.7%) was lower than in Finland (Giacomello, 1996). The distance of fence-line sampling point from the pump island and the number of samples were not reported.

In the USA, the MTBE concentration in the perimeter of service stations has been measured in several studies (see **Table 4.24**). However, most of these measurements may not represent the MTBE concentration in houses near to the service station, since sampling locations are in the same quarter than the service station, the approximate distance from the pump island is only about 20-30 m.

It is assessed that in the normal scenario, there is no service station or industrial source near to the living houses. For calculation of the reasonable worst-cases scenarios it is assumed that long-term indoor concentration in the neighbourhood of service stations and main roads is 4-14 μg/m^3, based on the results obtained by Vainiotalo et al. (1998c). In the study of Heudorf et al. (1998), sampling covered 24 hours per day and a relatively low concentration was observed (3.8 μg/m^3). For a part of the sampling time, the sample reflects lower ambient concentrations than those near to a service station.

Commuting in car or in bus

Combustion of fuels containing MTBE results in tail pipe emission. Density of the traffic, type of car, season and fuel have an effect on the concentration of MTBE that the car-driver and passengers are exposed to.

Concentration of MTBE was measured in car cabin for one hour (Lioy et al., 1994). Samples were collected in New Jersey and Connecticut where MTBE concentration in petrol is 13-15%. The geometric mean concentration was 21 μg/m^3 (0.006 ppm) with a range of 4-580 μg/m^3 (0.001-0.16 ppm). The cabin concentrations were dependent on the type of vehicle. The higher interior concentrations were measured in car that also had higher rate of VOC emissions. Pre-fueling concentrations in cabin were about 36 μg/m^3 (0.01 ppm), in three cars studied, about 180 μg/m^3 during and about 54μg/m^3 after refuelling.

Rhodes et al. (1999) measured 2-hour integrated concentrations of MTBE in vehicles on roadways. Average in-vehicle concentrations ranged 3-90 μg/m^3. This concentration range is not far from that observed by Lioy et al. (1994). MTBE levels inside or just outside the vehicles were higher than at roadside stations. Percentage of MTBE in petrol was not reported.

MTBE concentration inside automobile cabins was analyzed during refuelling (Vayghani et al., 1999). Samples were collected during the winter when oxygenated petrol was used. The geometric mean concentration in the cabin was while fuelling was 432 μg/m^3. The range was <23-4,680 μg/m^3. This concentration level is somewhat higher than measured by Lioy et al. (1994) (see above). The probable reason for higher levels is content of MTBE in petrol and its high volatility during unusually warm winter days. Keeping the car windows closed during refuelling could reduce the exposure. It is obvious that the concentration of MTBE in cabin is diluted and a value representative for e.g. one hour of commuting after refuelling is lower than the concentration during refuelling. Factors, which resulted in higher MTBE concentrations, included high temperature, which increased fuel volatility, low wind speed which reduced the dispersion of the evaporated MTBE, open car windows and presence of a spill while refuelling.

In the USA, the estimated concentrations of MTBE in some non-occupational scenarios (NTP, 1998) in μg/m^3 are:

Activity	Concentration
Refuelling	36,000
Residential garage	3,600
In vehicle	360
Outdoors	36-360

Exposure to MTBE in buses, private cars and in ambient air was compared in a Korean study (Jo et al., 1998). The samples were collected in buses and cars in an urban area, in Teagy, the third-largest city of Korea, during the rush hours of winter season. In petrol, the concentration of MTBE was 6-7%. The route selected for in-auto analysis included for example a ten-lane main roadway (five lanes for each direction). In private cars, median MTBE levels of 48.5 μg/m3 were measured. This is 2-3 times higher as some measurements reported in the USA (New Jersey and Connecticut). MTBE concentrations were about 3.5 times higher in a car with carburettor engine than in the three electronic fuel-injected cars. In bus and in ambient air, the median concentrations were 15.5 and 3.5 μg/m3, respectively. The higher concentrations observed in cars as compared with buses were due to height of the vehicle, ventilation condition and the fact that the private cars used the middle lanes of the road whereas the buses travelled near the curb of the road. Furthermore, the opened door in buses improved ventilation and the diesel fuel did not contain MTBE.

In comparison, MTBE concentrations measured inside cars in the USA (16 and 23 μg/m^3) are somewhat lower as those observed in Korea (48 μg/m^3). The wintertime fuel in the USA contains 13-15% of MTBE, but on the other hand, the samples of the Korean study were collected in cars travelling on a ten-lane road. Lower wind speed in Korean study also contributes to explanation of this difference.

It is assessed that in cars and in buses, the realistic range of MTBE concentration that passengers are exposed to during commuting is 15-70 μg/m^3 (**Table 4.25**).

Areas polluted by refineries and contaminated soil

Near to refineries and factories, where MTBE is produced and/or petrol is formulated, the concentration of MTBE in ambient air can be elevated. Higher than normal air concentrations of MTBE have also been measured in areas where soil has been contaminated by MTBE. In **Appendix Table A.7**, some analytical results are presented. For estimation of dose, it is suggested that typical concentration in areas polluted by refineries or contaminated would be 5-100 μg/m^3. It is assumed that people living near these sites are exposed for 12 hours / day (**Table-4.25**).

Due to the lack of European analytical data, some measurements of benzene at the boundaries of European refineries are used to estimate the concentration of MTBE. As indicated in the section "Perimeter of petrol stations" the concentration of MTBE near to the petrol stations, is 1-13 times higher than the concentration of benzene. Benzene concentrations of more than 2000 samples from the boundaries of three refineries were measured. Most of the annual averages are at urban background level, i.e. at or below 5 μg/m^3 and remainder of averages are at levels observed at street sites (10-20 μg/m^3) (CONCAWE, 1999a; 1999b). Thus, using the factor of 5 and slightly elevated concentration of benzene 10 μg/m^3 reported by CONCAWE, it is estimated that the average MTBE concentration in some cases near to the refineries could reach 50 μg/m^3, which falls within the range given above 5-100 μg/m^3. Since the residential houses are not located at boundaries of refineries, the above figures are likely to represent a slight overestimation. The number of exposed people due to these industrial releases is likely to be limited and therefore it has not been included in the scenario of **Table 4.25**.

The number of persons living near to production sites of contaminated areas is not known. Not enough European data are available at present. Therefore, this source of exposure is not assessed for the reasonable worst-case scenario. It appears, however, that in most cases the exposure via inhalation caused by these sources is in the same order of magnitude as that caused by service station in the neighbourhood buildings.

Urban background

Based on the results published in the USA and in Canada, the median concentration of MTBE in urban areas is usually between 0.5 and 3 μg/m^3 (**Table 4.25** and Appendix **Table A.7**). This is in good agreement with the results of modelling with EUSES software, which are 1.22 μg/m^3 for regional and 0.31 μg/m^3 for continental air concentration (see Section 3.1.6.2). Median values higher than 3 μg/m^3, which are occasionally reported, are probably due to local contamination, exceptional traffic density or climate conditions.

The geometric mean concentration of MTBE in Frankfurt am Main, in the control areas as reported in Heudorf et al. (1998) was 8.4 μg/m^3. This is likely to represent the MTBE ambient air concentration of an area with high traffic density. Furthermore, the number of samples was only 6 and the conditions and time pattern of control subjects is unknown. Before more European data become available, the extensive analytical data reported from the USA and Canada are considered to be more reliable and realistic for calculating the dose.

General atmospheric concentrations of MTBE normally are below 7.2 μg/m^3 (2 ppb), and concentrations in cold wet precipitation, which will infiltrate to soil and enter the groundwater, is less than 2 μg/l (Rykowski, 1996).

Exhausts and leaks from boat engines

MTBE is released also from boat motors. In Helsinki, MTBE concentration in seawater in the boat harbour varied between 0.4-6.13 µg/l (Piilo et al., 2000). Small leaks and spills are not uncommon e.g. when petrol tube is connected and disconnected to the outboard engine. These leaks may come into contact with skin and/or run into the bilge water and evaporate causing inhaled dose of MTBE. Since outboard motors release substantial amount/percentage of unburned petrol, yachters may be exposed to MTBE in the air of marinas, as well. So far, no measurements of MTBE in the air of marinas or in boats are available.

4.1.1.3.4 Summary of exposure estimates via air

Higher than ambient concentration has been measured in pump island at the petrol station, in their immediate vicinity, and in cars. Generalised from the analytical data, scenarios related to petrol stations are presented in **Table 4.25**.

Non-occupational/consumer exposure to MTBE is also caused by car exhausts and releases from the petrol stations. Higher than background concentrations of MTBE have been measured near highways with high traffic density. People living in the houses adjacent to the petrol station, are exposed to slightly elevated air concentration of MTBE (see **Table 4.25**).

Parameters which affect the concentrations of MTBE are e.g. the concentration of MTBE in petrol, technique applied for emission control at the station (no control, Stage I or Stage II), wind direction and distance from the source of release. These factors are not always reported in articles reviewed in this report. To a large extent, these factors cause the wide range of concentrations reported, which is seen in **Table 4.20** and Appendix **Table A.7.**

Table 4.25 Exposure to MTBE via inhalation scenarios

Relevant area/scenario	Source of MTBE	Estimated duration of exposure	Typical concentration µg/m³	Percentage of population
Urban background	Car exhausts, rain	12/24 hours/day	0.5-3	about 98%
Areas polluted by refineries or contaminated area	Industry, petrol stations	12 hours/day	5-100	<1%
Perimeter of petrol stations	Petrol stations, car exhausts	12-24 hours/day	4-14 [1)]	<1%
Commuting in car or bus	Car exhausts, refuelling	1-2 hours/day	15-70	?
Pump area of gas station	Refuelling, spills, cars	1-5 min./d, 1-3 visits/week	100-500	15%

Note: The representative concentration ranges are based on published data presented in Table 4.23 and 4.24 and Appendix Table A.7.

[1)] 4 -14 ug/m3 are the mean ambient concentrations in the perimeter (50 m) of four stations studies by Vainiotalo et al. (1998c). It is assumed that the indoor concentration is the same, since the release of MTBE from the station is continuous and diffusion to the indoor air does not remarkably decrease the concentration.

[2)] Adjacent roads with high traffic density (about 15,000 cars/day) contribute to the MTBE levels observed (Vainiotalo oral information).

4.1.1.4 Combined exposure

This section summarises the total exposure that could result in a situation where a person is exposed at work under conditions that were considered as the reasonable worst case combined with the MTBE received from consumer use (petrol) and indirectly via the environment.

4.1.1.4.1 Occupational exposure

Maintenance scenarios and especially transportation subscenario were estimated to result in the highest exposure based on inhaled amounts and dermal deposition combined. The daily amount of MTBE inhaled (intake) was estimated as 600 mg, and the amount deposited on the skin as 4,200 mg. The quantitative assessment of the systemic absorbed dose is presented in the context of risk characterisation.

4.1.1.4.2 Consumer and indirect exposure via the environment combined

Exposure via drinking water and via air

Normal scenario

Inhalation of MTBE that evaporates during refuelling and unloading operations of petrol at service stations, exposure to car exhausts and ingestion of MTBE in the drinking water are main exposure scenarios. The normal scenario concerns a person, who regularly drives a car, is a customer of petrol stations and is exposed to ambient urban air concentration of MTBE. The scenario also includes some exposure via tap water caused by minor contamination of water source, which is due to precipitation of MTBE with the rainwater. The dose (intake) of the normal scenario is 26.4-251 µg/day via inhalation and 0.20 µg/day via drinking water (**Table 4.26**). It is preliminarily estimated that about 25% of the population is exposure to this daily dose of MTBE. The major part of the population exposed to a lower daily dose of MTBE.

In Central Europe, most of the petrol contains 2.8 vol% of MTBE, whereas in Finland the predominant concentration is higher (11 vol%) Most analytical data used for this report originates for Finland and the USA, where even higher MTBE contents (11-15%) are used in some states. Since there are no sufficient analytical data from Central Europe, it is preliminarily assessed that in most European countries, the dose of MTBE to which consumer is exposed to in normal scenario is about 30% of the dose range calculated in **Table 4.26**.

Table 4.26 Combined exposure to MTBE via inhalation and via tap water, normal scenario, motoring citizen.

Relevant area/scenario	Source of MTBE	Duration of exposure hours/day	Typical concentration µg/m³	Dose µg/day [1)]
Urban background	Car exhausts, rain	24 hours/day	0.5-3	10-60
Commuting in car or bus	Car exhausts	1-2 hours/day	15-70	12-116
Pump area of gas station	Refuelling, leaks, cars	1-5 min/d, 1-3 visits/week	100-500	0.4-15
Refuelling, Stage I station	Petrol pistol	1-5 min/d, 1-3 visits/week	1000-10 000	4-60
Total intake/exposure via inhalation				**26.4-251**
Drinking water, urban background	Car exhausts, rain	- [2)]	0.1 ug/l	**0.20**

For this table, the typical concentration levels are selected, based on available analytical data, to represent the situation in Finland.

[1)] Respiratory volume is about 20m³/24 hours=0.83 m³/hour=0.014m³/minute.
[2)] It is assumed that ingestion of tap water is 2.0 l/day.

The total intake in the regional scenario given by the EUSES (see **Table 3.1**) is 0.5 µg/kg bw/day, which is in good agreement with the dose estimated above. Results of EUSES model

indicate that there are other minor sources of exposure in addition of those given in **Table 4.25**, namely fish and leaf/root crops. These foods contribute to the total exposure by 0.022 µg/kg bw/day, which is negligible and is not considered further.

Average daily dose of MTBE in the USA from exposure in air and drinking water in the USA has been estimated (Brown, 1997). Doses from residential exposures, commuting and refuelling were in the range of 0.4-6 µg/kg bw/day. This estimate is in good agreement with the range of the normal exposure scenario presented above**,** which is based, as much as possible, on the European data.

It is noteworthy that most estimates for the duration of exposure presented in **Tables 4.26** and **4.27** are based on expert judgement. The duration of stay in the pump area of a service station and the duration of refuelling are based e.g. on studies made by Vainiotalo and co-workers.

The percentage of population, which is exposed to MTBE in various scenarios, is based on a preliminary assessment, probably indicating the correct order of magnitude. These figures would have to be substantiated later.

For both normal and reasonable worst-case scenarios the total (from air and drinking water) absorbed systemic dose in µg/kg bw/day is considered below in Section "Risk characterisation". Assumption that a person lives near to a petrol station or an industrial point source and that he/she is also occupationally exposed to MTBE would results in a combined exposure scenario, which is also discussed within risk characterisation.

Reasonable worst-case scenario

This scenario concerns a person who is exposed to MTBE at the petrol station during and after refuelling of the car and who lives near to (50 m) a petrol station. Commuting in a car or in a bus is also considered. In some cases, the same person might also be exposed to an elevated concentration of MTBE in the tap water. However, the long-term exposure via tap water is likely to remain at a relatively low level, since the odour and taste threshold of MTBE are low. Elevated drinking water concentrations (about 15 µg/l) have been found near the petrol stations. Thus, it is reasonable to assume that in some cases these two scenarios, ie. 1) high inhalation exposure due to near by service station and 2) elevated MTBE concentration in contaminated tap water, might coincide. The dose of the reasonable worst-case scenario is **68.6-472** µg/day via inhalation and **30** µg/day via drinking water (**Table 4.27**).

In Central Europe, most of the petrol contains 2.8 vol% of MTBE, whereas in Finland the predominant concentration is higher 11 vol%. Since there are no sufficient analytical data from Central Europe, it is preliminary assessed that the dose of MTBE to which consumer is exposed to in reasonable worst-case scenario is about 30% of the dose range calculated in **Table 4.27.** When more data become available, separate scenarios concerning the typical Central European situation can be examined, in addition to those presented in **Tables 4.26** and **4.27**.

Table 4.27 Combined exposure to MTBE via inhalation and via tap water, reasonable worst-case scenario, motoring citizen living in perimeter of a petrol station.

Relevant area/scenario	Source of MTBE	Duration of exposure Hours/day	Typical concentration µg/m³	Dose µg/day [1)]
Urban background	Car exhausts, rain	about 10-11 hours/day	0.5-3	4.2-27
Perimeter of petrol stations	Petrol stations	12 hours/day [2)]	4-14	40-140
Commuting in car or bus	Car exhausts	1-2 hours/day	15-70	12-116
Pump area of gas station	Refuelling, leaks, cars	1-5 min/d, 2-3 visits/week	100-500	0.4-15
Refuelling, Stage I station	Petrol pistol	1 min/d, 2-3 visits/week	3000-29,000	12-174
Total intake/exposure via inhalation				**68.6-472**
Oral intake in areas polluted by refineries and petrol stations	Underground tanks, leaks spills at petrol station	- [3)]	15 µg/l	**30**

For this table, the typical concentration levels are selected, based on available analytical data, to represent the situation in Finland.

[1)] Respiratory volume is about 20m³/24 hours=0.83 m³/hour=0.014m³/minute.
[2)] For some people, e.g. children, housewives and elderly exposure may be longer than 12 hours/day.
[3)] It is assumed that ingestion of tap water is 2.0 l/day.

Data from the US Bureau of Census (1995) indicate that 1 hour per day is a good estimate for time spent in vehicles per day for the driving population. While refuelling, customers may spend 5 minutes or more at the petrol service station, the average time near the pump island is lower. Reasonable estimate of an average refuelling time and refuelling events per year is 3 min and 70 events. It was estimated that, of the population in the USA:

- 83% do not live near an MTBE facility,
- 6.4% live near a petrol service station, 9.6 % live near a petrol storage facility,
- 1.1% live near a manufacturing or blending facility,
- 72% are drivers and petrol station customer and
- 41% are commuters.

The first four categories are mutually exclusive whereas the others are not.

Atmospheric concentration of MTBE (µg/m^3) and doses for non-occupationally exposed populations in various conditions/scenarios in the USA are presented in **Appendix Table A.8**.

Combined reasonable worst case scenario

When the reasonable worst case exposures are summed for all routes in the occupational scenario and the consumer + man via environment scenario, the total combined reasonable worst-case daily dose (intake) via inhalation and orally is 600.5 mg, and the daily dose (deposition) to the skin is 4,200 mg. Compared to occupational exposure, other sources play a very minor role.

4.1.2 Effects assessment: Hazard identification and Dose (concentration) - response (effect) assessment

4.1.2.1 Toxico-kinetics, metabolism and distribution

Both human and animal data are available concerning the toxicokinetics and metabolism of MTBE. Since the initial metabolic step of MTBE releases formaldehyde and t-butyl alcohol (TBA), both of which are of toxicological interest, the relevant toxicokinetic features of the two metabolites need to be addressed as well. Moreover, physiologically based pharmacokinetic models have been tentatively applied to MTBE as well as to TBA allowing some conclusions of the biochemical parameters (metabolic constants) for the rat and human.

4.1.2.1.1 Absorption and distribution

Uptake via inhalation

MTBE is efficiently absorbed via the lungs in rats and humans. Male and female F344 rats exposed nose-only to MTBE at 400 ppm or 8,000 ppm for 6 hours showed rapidly rising plasma MTBE concentrations and attainment of apparent steady-state levels within 2 hours (Miller et al., 1997). In a disposition study, the total recovery of the radioactive label in excreta and tissues over 48 hours after exposure to the same levels of [^{14}C]MTBE corresponded to the calculated dose, assuming that 50% of the inhaled MTBE had been taken up.

Human volunteer studies involving exposures up to 75 ppm MTBE for up to 4 hours also showed a rapid rise of blood MTBE levels (Nihlén et al., 1998; Pekari et al., 1996). Pulmonary retention (net respiratory uptake) of ten subjects over a 2-hour exposure, with light workload, ranged from 32 to 42% at 5, 25 or 50 ppm (Nihlén et al., 1998), while in another experiment with four subjects exposed at a sedentary state, pulmonary retention was about 40% during the last hours of 4-hour exposure to both 25 and 75 ppm (Pekari et al., 1996). In the latter study, MTBE blood levels reached 11 µmol/l (25 ppm) or 29 µmol/l (75 ppm) towards the end of exposure with indications of plateauing. Buckley et al. (1997) concluded from their observations of two individuals exposed to 5 mg/m^3 (1.4 ppm) that a portion of the inhaled MTBE (7-9%) is taken up reversibly by the mucous membranes of the upper airways. This phenomenon is plausible due to the high water solubility of MTBE, and causes a reduction of net uptake.

Uptake via oral exposure

In a study with male and female F344 rats, comparisons of the area under the plasma concentration versus time curve for MTBE after intravenous administration or oral gavage (40 mg/kg in both cases) showed that the substance was rapidly (peak concentration at 15 minutes post-dosing) and completely absorbed across the gastrointestinal tract (Miller et al., 1997). The report even cited unpublished observations that after oral administration of [14C]MTBE, the recovery of radioactivity over 7 days in the urine and faeces was virtually the same as after iv injection.

According to an abstract, human volunteers rapidly drank 6.7 µl of MTBE in 250 lemon-lime (about 5 mg). MTBE was absorbed into the blood, but not as rapidly as via inhalation, and declined with an initial half-time of about 1-3 hours. The peak blood levels of MTBE ranged from 5 to 15 ng/ml (0.06-0.17 µmol/l) (Prah et al., 2000).

Uptake via dermal exposure

Miller et al. (1997) studied dermal absorption in male and female F344 rats. Doses of 40 or 400 mg/kg MTBE (in isotonic saline solution of 10 ml/kg, i.e. MTBE concentrations of 0.4% or 4%) were injected into stainless-steel occluded dermal exposure chambers which had been cemented to shaved areas on the dorsal flanks. The skin area exposed is not given. At 6 hours post-exposure, the chambers were flushed with 20 ml of isotonic saline followed by a flush of air. Groups of four rats were killed for blood sampling after frequent intervals up to 45 hours. In a disposition study, male rats were similarly exposed to [^{14}C]MTBE and subsequently the animals were put into metabolism cages for collection of radioactivity in urine, faeces and exhaled air up to day 7 post-exposure, at which time the animals were killed and the tissue radioactivity was measured. However, the dermal chambers were flushed with saline daily. The occluded MTBE exposure resulted in low plasma levels which plateaued 2-4 hours after dosing. There was a very slow decline of the plasma MTBE concentration thereafter, and the balance calculation indicated that approximately 16% of the low dose and 34% of the high dose had been absorbed (the recovery of the radioactivity was practically complete). The dose dependence of the skin absorption efficiency might be related to the 10-fold concentration difference of the MTBE solution. Apparently, not all labelled MTBE was rinsed off at 6 hours post-exposure, as residual radioactivity was found to leach out in subsequent washings, so the occluded exposure was probably extended beyond 6 hours (Bio-Research Laboratories Ltd, 1990).

Further information concerning dermal penetration of MTBE (in petrol mixtures) in rat and human cadaver skin *in vitro* has been provided in an abstract (Yang et al., 1994). The dermal flux of MTBE through the rat skin was found to be concentration-dependent with a maximum value of 290 $\mu g/cm^2 \cdot$ min for a 15% MTBE petrol solution. The corresponding fluxes through human skin samples were 2-14 times smaller than in the rat. The authors comment that even in a five-minute human skin exposure, significant dermal penetration was observed. Rao and Ginsberg (Rao et al., 1997) used the skin permeability constant of 0.006 cm/h for MTBE in their PBPK simulation of the Miller et al. (1997) dermal exposure study with rats and found a good fit of predicted plasma MTBE concentrations. The constant was estimated from an EPA-recommended equation based on the octanol/water partition coefficient and molecular weight.

It is difficult to draw definite conclusions on the dermal absorption capability of MTBE based on the previous information. The flux of 290 $\mu g/cm^2 \cdot$ min measured *in vitro* for 15% MTBE in petrol in the rat skin model is high (by a factor of about 26) to be in line with the estimated skin permeability constant of 0.006 cm/h. In principle, the combination of non-polar and polar characteristics is expected to make the substance a fair skin penetrant. The observations of Miller et al. (1997) are in support of the notion that MTBE is at least a moderate skin penetrant under occlusive conditions. However, under most practical exposure circumstances the high volatility of MTBE would strongly limit skin absorption because of competition between penetration and an efficient loss process by evaporation.

Distribution

Based on physical-chemical properties MTBE is likely distributed extensively in the mammalian body. Some understanding of the expected tissue distribution can be gained from tissue/air partition coefficients measured *in vitro* with a vial equilibration method. Rather similar observations have been made for the F344 rat (Borghoff et al., 1996) and human (Imbriani et al., 1997; Nihlén et al., 1995) tissues. The blood/air partition coefficient was 11.5 for the rat and 17.7-20 for humans, whereas the rat fat/air coefficient was 116 and that for olive oil/air 120-140. Thus, MTBE is moderately soluble in blood, and 7-10 times more soluble in fat tissue. Solubilities

in the rat liver and muscle are rather similar to that in blood (Borghoff et al., 1990), however, in the male rat kidney it was 6 times higher than in blood due to specific binding (see later). Under *in vivo* conditions no equilibrium but steady state concentrations, determined by clearance processes, are reached in blood and tissues. The concentrations may be modified on repeated exposure by altered clearance or accumulation. However, Savolainen et al. (1985) exposed (whole body) male Wistar rats to 50, 100 or 300 ppm of MTBE for 2, 6, 10 or 15 weeks and found directly exposure-related tissue MTBE concentrations at all dose levels and throughout the whole study period; the brain/blood ratios were consistently about 1, and the perirenal fat/blood ratios about 10.

Pharmacokinetic analysis of experimental data for MTBE suggested that in F344 rats the apparent volume of distribution roughly corresponded to the body weight, with the exception of dermal exposure that showed a higher volume of distribution (Miller et al., 1997). In humans exposed via inhalation, the apparent volume of distribution was estimated as 3.7 times the body weight (Nihlén et al., 1998) ; the human body contains a higher proportion of fat than the rat.

The high *in vitro* distribution of MTBE in the male rat kidney is believed to be species- and sex-specific (Borghoff et al., 1996; Poet et al., 1997a). Special attention has been focussed on α2u-globulin (α2u) which is specific to the male rat. Binding of various chemicals to α2u inhibits its catabolism, leading to an accumulation of the protein in renal proximal tubular cells, cell injury, and renal cell proliferation. The pathology associated with the accumulation of α2u is referred to as protein droplet nephropathy or more specifically α2u nephropathy (Borghoff et al., 1990). Inhalation exposure of F344 male rats to 3,00 ppm MTBE resulted in a small increase in kidney concentrations of α2u, concurrent with a mild nephropathy (Prescott-Mathews et al., 1997). There is strong evidence that MTBE interacts with α2u (Poet et al., 1997a): the *in vitro* partition coefficient in male rat kidney homogenate was 5.5 times higher than in the female, and it was MTBE concentration-dependent (saturable). Preheating of the kidney homogenate at 60^{o}C for 1 hour reduced the partition coefficient in male (but not in female) kidney to a 3-fold higher level than in the female. The addition of purified α2u to female kidney homogenate remarkably increased the MTBE partition coefficient, whereas addition of other proteins did not. Incubation of male and female kidney homogenates with a high concentration of d-limonene oxide, which binds with a high affinity to α2u, reduced the MTBE partition coefficient in the male kidney down to the unchanged level of the female kidney. Characterisation of the MTBE binding affinity to α2u in a sealed two-compartment vial equilibration system gave a value which was three orders of magnitude lower than that for d-limonene oxide. [^{14}C]MTBE incubated with male rat kidney homogenate was found to coelute mostly with the total protein fraction while the corresponding fraction for the female kidney homogenate was less than 5%. Equilibrium dialysis and anion-exchange chromatography failed to show the association of the radioactivity with α2u or any other protein which the authors contributed to the combination of the weak binding affinity and the high vapour pressure of MTBE (Poet et al., 1997a).

A subsequent study explored the interaction of MTBE or its metabolites with male and female rat kidney proteins under *in vivo* conditions (Prescott-Mathews et al., 1999). Gavage administration of 750 mg/kg [^{14}C]MTBE for 4 consecutive days to male and female F344 rats induced a mild increase of renal α2u concentration in male rats, but the total radioactivity recovered in kidney samples was (surprisingly) similar in male and female rats. The authors attributed the latter finding to a possible loss of MTBE during tissue homogenisation. A slightly greater percentage of MTBE/metabolite-derived radioactivity coeluted with the total protein fraction from the treated male rat kidney cytosol compared to the female. As previously, gel filtration and anion exchange chromatography did not demonstrate coelution of radioactivity with the α2u fraction or any other protein fraction. In a different experiment, male and female F344 rats were gavaged with a single dose of 250, 750, or 1,500 mg/kg MTBE. After 4 or 12

hours the animals were killed, and the MTBE concentration in the headspace of a sealed vial containing minced kidney was determined. In male (but not female) kidney samples, addition of d-limonene oxide displaced MTBE and increased the headspace MTBE concentration by about 4 fold (low dose) or about 2 fold (high dose) in measurements performed 4 hours after dosing. This finding supports the interaction between MTBE and α2u in the male rat kidney following administration of MTBE.

4.1.2.1.2 Metabolism

In vivo studies

In vivo studies on the metabolism of MTBE in rats (Amberg et al., 1999; Bernauer et al., 1998; Miller et al., 1997; Savolainen et al., 1985) and in humans (Nihlén et al., 1998; Amberg et al., 1999; Nihlén et al., 1999) indicate qualitatively similar overall metabolism. MTBE is oxidatively demethylated by microsomal enzymes to formaldehyde (only indicated under *in vitro* conditions) and t-butanol (TBA). Formaldehyde has not been measured *in vivo* following MTBE exposures, but it is known to be rapidly biotransformed further to formic acid, CO_2, or becomes incorporated into one-carbon pool (McMartin et al., 1979), whereas TBA is found in the circulating blood for prolonged periods and at higher concentrations than MTBE. For instance, Pekari et al. (1996) found peak blood TBA levels of 16 μmol/l (25 ppm) or 34 μmol/l (75 ppm) at about 1 hour after the cessation of 4 hours exposure. The biotransformation of TBA (by unidentified microsomal enzymes) yields 2-metyl-1,2-propanediol and α-hydroxyisobutyric acid. In addition, low concentrations of TBA-glucuronide, free TBA and another conjugate, which was probably TBA-sulfate, were identified in urine. Variable amounts of acetone were also produced in MTBE metabolism.

In most experimental studies with rats and humans, after inhalation exposure, more than a half of the MTBE retained in the body was biotransformed to urinary metabolites and less than a half was exhaled unchanged (Amberg et al., 1999; Miller et al., 1997; Nihlén et al., 1998), however, in rats exposed to a high level via inhalation (8,000 ppm, 6 hours), the main part was exhaled indicating metabolic saturation (Miller et al., 1997). In the same study, rats given a single intravenous dose of 40 mg/kg [^{14}C]MTBE excreted 60% of the radioactivity in expired air and 35% in urine, and in dermal exposures the fractions excreted in expired air and urine were about equal. Of the radioactivity in expired air, 1-3% was identified as TBA (Miller et al., 1997). The main urinary metabolite in rats and humans was α-hydroxyisobutyric acid (accounting for about 70% of all urinary metabolites), followed by 2-methyl-1,2-propanediol and TBA conjugates (Amberg et al., 1999; Miller et al., 1997). In a study with three male and three female human volunteers exposed to 4 or 40 ppm MTBE for 4 hours, the excretion of α-hydroxyisobutyric acid showed a wide interindividual variation but no difference between the sexes. Moreover, marked pre-exposure background levels of α-hydroxyisobutyric acid were found (Amberg et al., 1999) which was apparently due to endogenous formation (Liebich et al., 1984).

The metabolic scheme for MTBE is presented in Figure 3. Further details of the metabolic fate of formaldehyde and TBA are given in Section 4.1.2.1.5.

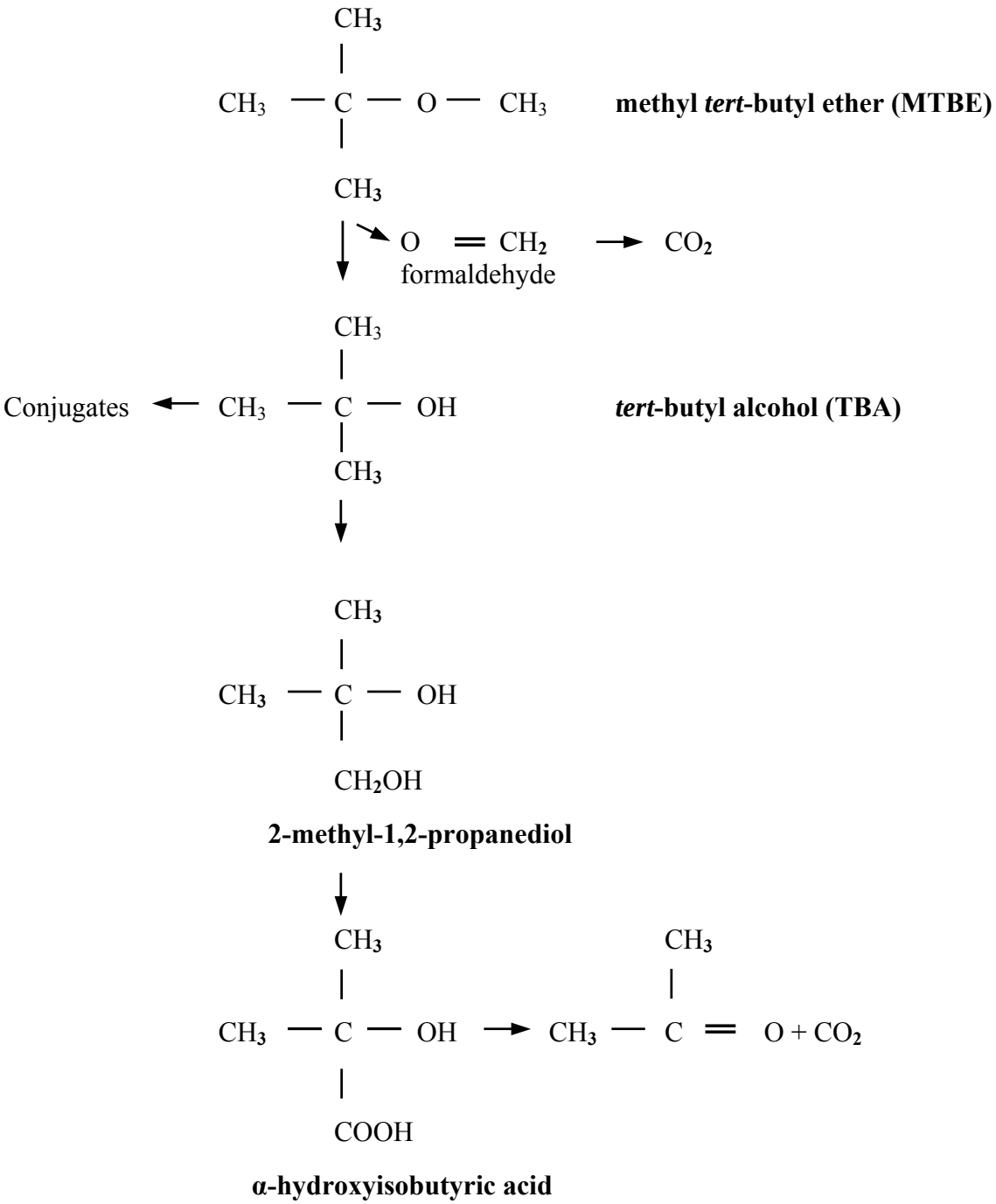


Figure 3 Scheme for MTBE metabolism

In vitro studies

The cytochrome P450 mediated biotransformation of MTBE has been explored in several *in vitro* studies with liver microsomes from the rat (Brady et al., 1990; Turini et al., 1998), mouse (Hong et al., 1999b), and humans (Hong et al., 1999a; 1997b; Poet et al., 1998), as well as with microsomes from various other organs of the rat (Hong et al., 1997a). Metabolism of MTBE by liver microsomes from male Sprague-Dawley rats produced equivalent amounts of formaldehyde and TBA with an apparent K_m of 0.67 mM (Brady et al., 1990; Turini et al., 1998). Both studies strongly suggested that when expressed, CYP2B1 was the major enzyme involved in MTBE demethylation and that CYP2E1 may have a minor role. Brady et al. (1990) showed that a single 18-hour pretreatment of rats with 1 or 5 ml/kg MTBE i.p. resulted in a dose-dependent induction of liver microsomal pentoxyresorufin dealkylase (PROD) activity (up to 50-fold), a marker of CYP2B1/2. This was also confirmed by immunoblot analysis. By contrast, TBA treatments of rats with 200 or 400 mg/kg i.p. for 4 days did not alter any of the liver monoxygenase activities studied (PROD, ethoxyresorufin-O-deethylase, benzphetamine demethylase, erythromycin demethylase, p-nitrophenol hydroxylase) (Turini et al., 1998).

A study of MTBE metabolism with microsomal preparations from different tissues of male Sprague-Dawley rats showed measurable activities in the liver, nasal mucosa and olfactory mucosa but not in the lung, kidney and the olfactory bulb (Hong et al., 1997a). Compared to the liver, nasal mucosa exhibited 9 times higher metabolising activity, and the olfactory mucosa had 46 times higher activity (0.2, 1.8, or 9.3 nmol metabolite/min/mg protein, respectively; the apparent K_m was 0.11 mM). MTBE metabolism in the olfactory mucosal microsomes was significantly (87%) inhibited at 50 μM of coumarin. The authors gave preliminary information that baculovirus-expressed rat CYP2A3, a predominant CYP form expressed in the rat olfactory mucosa and an ortholog of human CYP2A6, was found active in MTBE metabolism.

Concerning MTBE metabolism in the mouse liver microsomes, it was observed that the activities were practically the same in CYP2E1 knock-out mice (lacking 2E1 activity assayed as N-nitrosodimethylamine demethylation), C57B/6N mice and in 129/Sv mice (Hong et al., 1999b). Thus, CYP2E1 appears to play an insignificant role in metabolising MTBE in the mouse.

Microsomes from 8 human liver samples of US citizens (noncancerous neighbouring tissues of liver tumours) were found to be active in metabolising MTBE to TBA (Hong et al., 1997b). The activities ranged from 86 to 175 pmol/min per mg protein and were about a half of the corresponding activities measured in the rat and mouse. The authors even explored the activities of heterologously (baculovirus) expressed human CYP2A6 and 2E1 in MTBE metabolism and found the former much more active. A larger study involving 15 human liver samples from persons who had died of accidents gave higher MTBE metabolising activities than previously, and a wider interidividual variation (range: 204-2890 pmol TBA/min per mg protein) (Hong et al., 1999a). Michaelis-Menten kinetics was observed with three human liver samples. The apparent K_m values ranged from 28 to 89 μM, and the V_{max} values from 215 to 783 pmol/min per mg protein, respectively. In support of earlier findings, the MTBE metabolising activities were highly correlated with the CYP2A6 content in human liver microsomes. A battery of 12 human CYP enzymes expressed in human B-lymphoblastoid cells was tested for MTBE metabolising activity at 1 and 0.1 mM concentrations. CYP2A6 showed the highest activity, followed by CYP2E1. In microsomal preparations from three human liver samples, addition of 1-100 μM coumarin dose-dependently inhibited MTBE metabolism (coumarin is a CYP2A6 substrate) and, finally, addition of monoclonal antibody against human CYP2A6 caused a significant inhibition (75%) of metabolism (Hong et al., 1999a). Results from another research group, so far reported in an abstract form only, are supportive of the previous information (Poet et al., 1998). Rates of

MTBE metabolism with human liver samples were measured in a vial equilibration system, and the marker activities for CYP2A6 (coumarin 7-hydroxylation) and CYP2E1 (chlorzoxazone 6-hydroxylation) were determined. The kinetic analysis with a two-compartment mathematical model suggested both a low-affinity, high capacity pathway which correlated with CYP2A6 activity, and a high-affinity, low capacity pathway which correlated with CYP2E1 activity. The V_{max} values of the former pathway indicated a great variation among the individual samples (102-2650 pmol/min per mg protein). It remains to be seen which enzyme is the most active in the normal human situation with low tissue levels of MTBE.

Large interindividual differences have been observed in CYP2A6 apoprotein and mRNA levels in human liver samples (Pelkonen et al., 1995; Pelkonen et al., 2000). In immunoblotting experiments using purified human CYP forms as standards, CYP2A6 protein constituted 1-10% of the total liver CYP content. A fair proportion of the Japanese seems to lack the protein completely (Shimada et al., 1996). Other studies have shown a relatively high incidence of CYP2A6 gene deletion among Japanese (Nunoya et al., 1998; Oscarson et al., 1999). Coumarin 7-hydroxylation appears to be a specific marker of CYP2A6 activity (Waxman et al., 1991). This enzyme activity shows a wide (up to more than 100-fold) interindividual variation (Pelkonen et al., 2000). Recently, several human tissues were screened for the presence of CYP2A6 transcripts with the aid of gene-specific RT-PCR method. CYP2A6 mRNA was abundant in the liver, nasal mucosa contained a low amount, whereas the assay was negative in the kidney, duodenum, lung, alveolar macrophages, peripheral lymphocytes, placenta and the uterine endometrium (Koskela et al., 1999).

Metabolic clearance

In a study with F344 rats exposed to MTBE intravenously (40 mg/kg), by gavage (40 or 400 mg/kg), or dermally (40 or 400 mg/kg), the total plasma clearance, corrected for relative bioavailability, ranged from 358 to 413 ml/h (Miller et al., 1997). After inhalation exposure to 400 ppm for 6 hours, the total clearance (531 ml/h) was significantly higher than after corresponding exposure to 8,000 ppm (298 ml/h), consistent with metabolic saturation at the high level. As an indication of metabolic saturation, the plasma MTBE area under the concentration versus time curve (AUC) at 8000 ppm increased more than proportionally compared to that of 400 ppm, and there was a concomitant, less than proportional rise in plasma TBA AUC. Assuming that the metabolic fraction of the total clearance is the same as the ratio of radioactivity found in urine vs. expired air plus urine, which was 75%, the calculated metabolic clearance in the 6-hour exposure to 400 ppm MTBE is about 400 ml/h. This corresponds to about 57% of the liver blood flow, if all metabolism occurred in the liver.

In an experiment with ten human volunteers exposed to 5, 25, or 50 ppm MTBE for 2 hours during light workload, toxicokinetic analysis of data points gave mean metabolic clearance values of 0.47, 0.44, or 0.68 l/min, respectively; the 95% confidence interval was about ± 30% (Nihlén et al., 1998). A calculation of total clearance among a group of four male volunteers in the end of the 4-hour exposure at 25 or 75 ppm MTBE from the data presented in an abstract by Pekari et al. (1996) [clearance equals uptake rate divided by blood concentration] gave 0.52 l/min at the lower and 0.59 l/min at the higher exposure. The figures are slight overestimations as full steady state was not yet reached, however, they give a crude measure of the metabolic clearance, because very little unchanged substance is eliminated (to urine), and they concur with the data by Nihlén et al. (1998). The blood flow through the human liver and portal system is about 1.6 l/min, thus the hepatic extraction fraction is about 0.3-0.4, indicating limited enzymatic efficiency of biotransformation. Comparison of the tentative metabolic clearance data between rats and humans suggests that the metabolic capacity is higher in rats, as also indicated by

in vitro studies with hepatic microsomal preparations. On the other hand inhalation studies conducted so far with a limited number of human volunteers have not uncovered any remarkable interindividual differences in metabolic clearance, and no indications of metabolic saturation, up to 75 ppm MTBE in inhaled air.

In view of the limited metabolic capacity, one could anticipate MTBE to induce its own metabolism under some conditions. In the previously cited study, Brady et al. (1990) demonstrated that it might happen at least at high doses in rats. Similarly, Moser et al. (1996) exposed $B6C3F_1$ female mice to 7,800 ppm MTBE for 3 or 21 days (6 hours per day, 5 days per week) and found 5- or 14-fold increases of hepatic microsomal PROD activity. Intragastric administration of 1,800 mg/kg MTBE for three days to mice increased the PROD activity by 9-fold. Savolainen et al. (1985) reported that male Wistar rats exposed to 50, 100 or 300 ppm MTBE 6 hours daily, 5 days a week for up to 15 weeks showed an approximately 5-fold increase of the blood TBA concentration at week 6 compared to week 2 at all exposure levels, followed by lowered concentrations by weeks 10 and 15. The mechanisms underlying these findings are uncertain. Since the rising concentrations of TBA cannot be reconciled with any accumulation phenomenon ($T_{½}$ for TBA in blood is about 3 h), one is left with a hypothesis that formation of TBA was accelerated relative to its elimination. The declining concentrations later on might suggest induction of TBA metabolism.

4.1.2.1.3 Elimination

The overall picture of the chemical forms and routes involved in the elimination of MTBE in rats and humans was presented in Section 4.1.2.1.2. The following will provide supplementary information, in particular concerning rates of elimination.

In F344 rats, MTBE was rapidly eliminated from plasma in a monophasic manner with an elimination half-time of about 0.5 h after i.v., oral and inhalation routes (Miller et al., 1997). After dermal exposure, the initial $T_{½}$ for the plasma MTBE concentration ranged 1.8-2.3 hours which is explained by the expected delay (low velocity) in percutaneous absorption. In the post-dosing period of 12-45 hours, the $T_{½}$ values were much longer, which may be an artefact and due to continuing absorption from the exposing device. In the same study, the peak plasma TBA levels were reached about 2 hours post-dosing, and the monophasic elimination half-times were longer than for MTBE, ranging from one to three hours (Miller et al., 1997). After fifteen 6-hour daily exposures to 400 ppm MTBE, $T_{½}$ for TBA in plasma was significantly shorter (1.8 hours) than after a single exposure (3.3 hours), however, there was no change in the plasma MTBE or TBA levels at the end of exposure. In F344 NH rats exposed once to 4 or 40 ppm MTBE for 4 hours, blood MTBE was cleared with a $T_{½}$ of 0.5 hour (Amberg et al., 1999). Urinary excretion of MTBE metabolites (TBA, 2-methyl-1,2-propanediol, α-hydroxyisobutyric acid) exhibited half-times ranging from 2.9 hours to 5 hours.

In ddY mice, pulmonary elimination of MTBE was measured after intraperitoneal administration of 50, 100, or 500 mg/kg MTBE (Yoshikawa et al., 1994). Elimination at the two higher dose levels was characterised with two half-times, 45 min and 80 min. The proportion of MTBE exhaled was dose-dependent (23.2%, 37.6%, or 69.0% at 50, 100, or 500 mg/kg, respectively) suggesting metabolic saturation at the high dose.

Experimental human exposures to 4-75 ppm MTBE for 2 or 4 hours (Amberg et al., 1999; Nihlén et al., 1998; Pekari et al., 1996) indicate that MTBE and metabolites are eliminated rapidly. Analysis of the elimination function of MTBE in blood has been described to contain one (Amberg et al., 1999), two (Pekari et al., 1996), or four phases (Nihlén et al., 1998), and the (terminal) half-

times reported were 2.6 hours, 5 hours and 19 hours, respectively. The corresponding clearly monophasic $T_{½}$ values for TBA in blood were 5.3 hours, 11.9 hours and 10 hours, respectively. Post-exposure concentrations of MTBE and TBA in urine showed essentially the same course as the respective concentrations in blood (Pekari et al., 1996). Amberg et al. (1999) reported that the elimination half-times for the different urinary metabolites of MTBE varied between 7.8 and 17 hours.

Important additional information can be drawn from a clinical report of patients treated with percutaneous transhepatic instillation with MTBE to dissolve cholesterol stones in the gallbladder (Leuschner et al., 1991). Among 27 patients to whom MTBE was instilled in sufficient volume to fill the gallbladder three to six times per minute and then reaspirated for the total mean duration of 5.1 hours, the mean blood MTBE concentration at the end of treatment was about 450 µmol/l (0.04 mg/ml), and the concentration was approximately halved during the next 5 hours. By contrast, the mean blood TBA levels at corresponding time points were unchanged (about 540 µmol/l), and then decreased by almost a half during the following 7-13 hours. In urine the mean MTBE and TBA concentrations, 5 hours or 12-18 hours post-treatment, were approximately the same as in blood. Methanol was found in trace amounts in three patients; formaldehyde and formic acid were not detected. Among nine patients fat tissue from the abdominal wall was sampled at the end of treatment and analysed for MTBE; the concentration was about 3.4 times higher than in blood. The study included one patient who was treated for 4 hours with MTBE four weeks after caesarean section. MTBE and TBA were detected in mother's milk at concentrations which were slightly lower than in the blood (Leuschner et al., 1991). The high concentrations of MTBE and TBA measured in blood and urine indicate that this unique type of (mainly oral) exposure results in a high body burden but nevertheless elimination appears to follow the mode described for low-level inhalation exposures.

Concerning the elimination rate for MTBE in humans, if it is assumed that the slow elimination is rate-limited by mobilisation of the MTBE partitioned in slowly-perfused fat tissue, the calculation of tissue time constant for the fat compartment (the time for reaching 63% of the equilibrium concentration, or inversely, 63% desaturation) gives approximately 5.3 hours [adipose tissue volume 14.5 l, partition coefficient fat/blood 7, adipose tissue perfusion 0.32 l/min]. The consistency between the measured terminal $T_{½}$ values and the calculated tissue time constant supports the notion that the association of MTBE in tissues is partitioning by solubility. Moreover, the rapid elimination found allows to conclude that MTBE or its metabolites will not accumulate in the human body significantly.

4.1.2.1.4 Toxicokinetics and metabolism of MTBE metabolites

Formaldehyde

The potential significance of the formation of formaldehyde in MTBE metabolism was highlighted by the finding that MTBE induced *in vitro* a positive mutagenic response in the mouse lymphoma assay together with metabolic activation, which was abolished when formaldehyde dehydrogenase and NAD^+ were added (Mackerer et al., 1996). The study however involved extracellular generation of formaldehyde and may not mirror the potential mutagenicity of formaldehyde when it is produced intracellularly from the same compound. Formaldehyde is an essential intermediate in cellular metabolism that is required for the biosynthesis of purines, thymidine, and certain amino acids (the one-carbon pool). Low concentrations of formaldehyde have been found in the blood, but inhalation exposure to airborne substance among rats, monkeys and humans had no measurable effect on the blood levels (Heck d' et al., 1990). The

main metabolic pathway of formaldehyde is oxidation to formic acid which is catalyzed by formaldehyde dehydrogenase. The true substrate for the enzyme is S-hydroxymethyl-glutathione, i.e. formaldehyde reversibly conjugated with glutathione. The conjugate is oxidised to formyl-glutathione with NAD^+ as cofactor and subsequently hydrolysed to formic acid. Formic acid as well as formaldehyde itself are incorporated in the one-carbon pool via different forms of tetrahydrofolic acid (IPCS, 1989). The elimination of formaldehyde in many species including primates is extremely rapid (McMartin et al., 1979).

The reactivity of formaldehyde generated in MTBE-(O-methyl-^{14}C) metabolism in freshly isolated hepatocytes of female CD-1 mice, male $B6C3F_1$ mice and male F344 rats was investigated by analysis of DNA-protein cross-links (DPX) and RNA-formaldehyde adducts (RFA) (Casanova et al., 1997a). In female CD-1 mice, low levels of DPX and RFA were found in the hepatocytes at all [^{14}C]MTBE concentrations used (0.33-6.75 mM), and pretreatment of the mice with MTBE (1.8 g/kg by gavage on three days) had no impact on the covalent binding of [^{14}C]formaldehyde. By contrast, when CD-1 hepatocytes were incubated with [^{14}C]formaldehyde that had been added directly to the medium, both DPX and RFA increased rapidly with concentration. Similar findings were made with hepatocytes isolated from $B6C3F_1$ mice and F344 rats. In contrast to the low levels of covalent binding found in [^{14}C]MTBE metabolism, relatively large amounts of ^{14}C was incorporated into RNA, which can be expected from [^{14}C]formate, the oxidation product of [^{14}C]formaldehyde. The results support the view that the metabolism of MTBE to formaldehyde is slow relative to the rate of formaldehyde oxidation and hence the intrinsic reactivity of formaldehyde is not expressed.

t-Butyl alcohol

Tissue distribution of TBA is different from MTBE because the compound is more soluble in water and blood (distribution coefficients water/air and blood/air are 462 and 603, respectively, versus the blood/air distribution of about 20 for MTBE), and somewhat less so in fats: distribution coefficient oil/air was measured as 167 but the true value for adipose tissue is higher because it contains about 30% water (Nihlén et al., 1995). TBA is expected to be distributed rather evenly in body water and, based on solubility data, there is no suggestion of storage in any particular tissue compartment. However, the kidney/blood ratio of TBA was found to be higher in male than in female F-344 rats exposed to TBA (250, 450, or 1,750 ppm, 6 hours per day, for 1 or 8 days) via inhalation and, following exposure, TBA was retained longer in the male rat kidney compared with the female rat kidney (Borghoff et al., 1997). Moreover, inhalation exposure to 1,750 ppm TBA for 10 consecutive days increased the renal concentration of α2u in male but not in female F-344 rats (Borghoff et al., 1999) and, following oral administration of TBA to F-344 rats, TBA interacted with α2u in the male but not in female rat kidney (Williams et al., 2000b) thus providing a reasonable mechanism for specific TBA accumulation in the male rat kidney. Since little unchanged TBA is excreted in exhaled air or urine, the clearance must take place through metabolism. The metabolism apparently has a limited capacity as the elimination half-time of TBA in humans is of the order of 10 hours both after inhalation exposure to low levels of MTBE and among patients with high MTBE (and TBA) body burdens received during dissolution of gall bladder stones.

Toxicokinetic analysis, employing a PBPK model, of data from a rat study involving 6-hour exposures to 400 or 8,000 ppm MTBE suggested unknown dose-dependent changes in the kinetics of TBA (Borghoff et al., 1996). A subsequent experiment with male and female F344 rats that were given a bolus intravenous injection of 37.5, 75, 150 or 300 mg/kg TBA revealed apparent saturation of elimination at the highest dose (Poet et al., 1997b). In the male rat, clearance was about 54 ml/h (3.99 ml/min per kg) and elimination half-time 3.6 hours at the low

dose, whereas at the high dose the corresponding parameters were about 25 ml/h and 5 hours, respectively. Moreover, the steady-state volume of distribution decreased from 1.15 l/kg to 0.71 l/kg with dose, and the area under the blood TBA concentration-time curve increased disproportionally with dose. Compared to the measured total MTBE clearance which was 413 ml/h in F344 rats after intravenous administration (40 mg/kg) (Miller et al., 1997), the lower capacity to metabolise TBA (note that a higher proportion of MTBE is eliminated unchanged) becomes clear.

Although an earlier study (Cederbaum et al., 1980) identified the metabolism of TBA in rat liver microsomes via oxidative demethylation yielding formaldehyde and acetone (hydroxyl radicals were presumed to be involved), the very high K_m of 30 mM noted for the reaction seems to preclude this pathway as functionally relevant. In other rat studies, acetone appeared to be formed in TBA metabolism because somewhat increased, and highly variable, concentrations were excreted in urine (Baker et al., 1982; Bernauer et al., 1998), or found in the blood (Poet et al., 1997b). Bernauer et al. (1998) were able to identify, with NMR and GC/MS techniques, the main urinary TBA metabolites 2-methyl-1,2-propanediol and α-hydroxyisobutyric acid in rats dosed orally with [^{12}C]- or [^{13}C]TBA (250 mg/kg). They proposed that acetone is likely to be formed from further oxidation of α-hydroxyisobutyric acid.

Bernauer et al. (1998) also let one volunteer ingest 5 mg/kg [^{13}C]TBA. α-Hydroxyisobutyric acid and 2-methyl-1,2-propanediol were the major metabolites in urine detected by ^{13}C NMR analysis, and unconjugated TBA and TBA glucuronide were minor metabolites. Individually variable elevation of acetone was measured in blood and urine among four volunteers exposed to [1,2-^{13}C]MTBE at 50 ppm for two hours (Nihlén et al., 1999). Thus, the metabolic profile in terms of measurable metabolites seems to be the same in exposure to MTBE and TBA.

4.1.2.1.5 Physiologically based pharmacokinetic models

Physiologically-based pharmacokinetic models for MTBE have been designed based on experimental data from studies with F344 rats (Borghoff et al., 1996; Rao et al., 1997), and applied to human (consumer) exposure scenarios. The current understanding is that there are marked similarities between rats and humans regarding MTBE metabolism and some differences regarding tissue distribution (the specific binding in the kidney of male rats).

Recently, an exercise in developing a physiologically based pharmacokinetic model for dermal absorption of MTBE, presented in abstract form (Leavens et al., 2000), showed that the applied compartmental model overpredicted the absorption of MTBE from water solution through the arm skin to the blood of male volunteers. Another PBPK model, presented as an abstract, was devised to predict MTBE blood levels in humans following inhalation exposure (Licata et al., 2000). The model structure was flow-limited and had 6 essential compartments. Partition coefficients for kidney (similar blood/kidney ratios were found as in female F-344 rats; Borghoff, personal communication) and fat were experimentally measured in human tissue. Metabolic rate constants measured *in vitro* in human liver microsomes were extrapolated to *in vivo* whole body metabolism; all metabolism was assumed to occur in the liver following Michaelis-Menten kinetics. Model simulations were compared with data on blood concentrations of MTBE taken from 6 individuals after a 4-hour inhalation exposure to 4 or 40 ppm MTBE. The PBPK model accurately predicted MTBE pharmacokinetics at the high level for all time points, whereas it underpredicted blood MTBE concentrations at early time points at the low level.

4.1.2.1.6 Conclusions on toxicokinetics and metabolism

MTBE is efficiently absorbed orally and via inhalation. Absorption through the skin is probably moderate under occlusive conditions, whereas in open contact rapid evaporation is expected to limit the uptake strongly. Apart from specific binding to male rat kidney protein, the extensive tissue distribution of MTBE appears to be determined by solubility: concentrations in soft tissues are approximately the same as in blood with the exception of fat that may reach a ten-fold higher concentration. MTBE is metabolised to formaldehyde and TBA. Formaldehyde is believed to be metabolised extremely rapidly to formate (which is largely incorporated in the one-carbon pool) and to CO_2, and TBA is further metabolised to α-hydroxyisobutyric acid, 2-methyl-1,2-propanediol, TBA conjugates and acetone. According to current knowledge, the enzyme catalysing MTBE biotransformation to formaldyde and TBA in humans is mainly CYP2A6, which is found in significant quantities only in the liver. The rat is lacking this enzyme, so other CYP enzymes, notably 2B1 and 2E1 seem to be involved. In the rat, CYP2A3 of the olfactory and nasal epithelium exhibited even higher metabolising activities than the previously mentioned liver enzymes. In humans, CYP2E1 also appears to be active at lower MTBE concentrations, and presently it is not possible to conclude which one of the two CYP isoforms is mainly responsible for MTBE metabolism at relevant (low) tissue concentrations. The capacity for MTBE metabolism is limited, although the rat has a higher capacity than humans. Saturation of metabolism was indicated in the rat after i.p. administration of 500 mg/kg, or during 6-hour inhalation exposure to 8,000 ppm MTBE. In human inhalation exposures up to 75 ppm for four hours, no signs of saturation were found. In most experimental conditions the major part of MTBE in the body was excreted as urinary metabolites, and less than a half was exhaled unchanged, however, if the uptake rate was high the opposite was true. The elimination half-time for MTBE in blood was about 0.5 hour in the rat and about ten times longer in humans.

After exposure to MTBE, TBA is found in the blood circulation for a longer period and at higher concentrations than MTBE. TBA is highly water-soluble and distributed in total body water. Apart from lower levels found in fat, soft tissues are expected to show approximately the same concentrations as the blood. The elimination half-time for TBA in blood was about 3 hours in the rat and about 10 hours in humans. The biotransformation capacity for TBA (by unidentified microsomal enzymes) appears to be markedly lower than that for MTBE in the rat, which explains its relatively low rate of elimination. The elimination half-times for the different urinary MTBE metabolites varied between 2.9 and 5 hours in rats and between 7.8 and 17 hours in humans. These data allow concluding that MTBE or its metabolites will not accumulate in the human body significantly.

The generation of formaldehyde in MTBE metabolism is a point of major toxicological interest because the compound is reactive and mutagenic. The limited database available at the present time points to lacking, or greatly diminished, reactivity by formaldehyde, when it is produced intracellularly from MTBE at rates which are lower than those of its further metabolism.

4.1.2.2 Acute toxicity

4.1.2.2.1 Studies in animals

Oral

No deaths resulted from a limit test conducted on five male and five female rats from a dose of 2,00 mg/kg by gavage (RBM, 1996d). Animals showed hunching and piloerection during the first six days of the 14-day observation period. No other symptoms were reported. In another study, where albino rats were given doses ranging from 2,000 mg to 10,000 mg/kg, a LD50 value of 3,800 mg/kg (95% CI: 2,900-4,800 mg/kg) was obtained. The typical signs included hypoactivity, muscular weakness and hyperpnea. Prostration was also seen in the highest dose groups. These dose levels also provoked inflammation of the stomach and intestine in the pathological examination (Mastri et al., 1969). Very similar results were found in a rat study conducted by ARCO that resulted in an LD50 of 3,866 mg/kg (95% CI: 3,327-4,492 mg/kg) (ARCO, 1980). Ataxia and CNS depression, tremors and loss of righting were mostly present at doses above 1,900 mg/kg.

Inhalation

Four exposure groups with each ten male Sprague-Dawley rats / group were exposed for 4 hours to MTBE (96%) concentrations varying between 71 and 201 mg/l (nominal) (ARCO, 1980). Clinical signs included irritation in the eyes and nose, animals became uncoordinated and had an irregular and rapid breathing. In the highest concentration groups eventually this lead to a loss of strength and slowing of respiration followed by death of eight animals during the third hour of the exposure. Two rats died at the end of exposure already at 107 mg/l. The remaining eight rats of this group survived the 14-day observation period. At 71 mg/l there were no deaths. A 99% pure form of MTBE was also tested, but with concentrations varying from 68 to 230 mg/l. There were no deaths in any group below 71 mg/l but at 230 mg/l all animals died. For the 96% MTBE an LC50 value 142 mg/l/ 4h (39 ppm) was determined. With a 95% confidence level, the LC50 limits were 120 and 168 mg/l. For the 99% MTBE an LC50 value of 120 mg/l was calculated and when expressed with a 95% confidence level, the limits were 104 and 139 mg/l/ 4h.

Five female and five male per group Charles River albino rats were exposed to MTBE vapour at 44, 65, 86, 99, 167 and 395 mg/l for 4 hours. The clinical signs included ataxia, tremors, lacrimation, muscular contractions and hyperactivity. In the 86 mg/l group, six animals died and in the higher dose groups, all animals died. In the 86-dose group, the time of death varied from 110 to 225 minutes after the start of exposure. In the high dose group, the time was 25-51 minutes. The animals that survived the 14-day observation period had mild congestion of blood in the lungs. The authors of a study by Industrial Bio-Test Laboratories (Mastri et al., 1969) reported an LC50 value of 85 mg/l/ 4h. The 95% confidence level limits were 79-91 mg/l/ 4h, which is similar to that found in the ARCO study.

Dermal

Dermal toxicity of MTBE has been tested in rats and rabbits. In the rat limit (RBM, 1996b), there were no signs of toxicity noted at 2,000 mg/kg when judged by the animals' behaviour or the clinical status. However, slight erythema was noted in 40% of the animals at the site of application. The animals were observed for 14 days after the 24-hour exposure via occlusive patch. There are two rabbit tests that both have calculated an LD50 greater than 10,000 mg/kg

(ARCO, 1980; Mastri et al., 1969). No deaths were reported in either study. Both studies reported erythema and slight or moderate oedema. Skin necrosis was seen during the observation days 7-14 in the test where rabbits received either a 6,800 or a 10,200 mg/kg dose.

Other studies

An acute neurotoxicity study was conducted on 22 male and 22 female rats per group that were exposed to 0, 800, 4,000 and 8,000 ppm MTBE vapour for 6 hours. Motor activity was evaluated on 14 rats before and immediately following the exposure in a 5-hour session. The remaining eight rats/group were evaluated for their neurobehavioral function using Functional Observation Battery (FOB) prior to and 1, 6 and 24 hours after exposure. The FOB observations that were considered biologically relevant were ataxia, duck-walk gait seen in the intermediate and high exposure groups 1 hour post exposure. In addition to these symptoms, females also had increased lacrimation and piloerection at the two highest doses. Mean motor activity followed a pattern of initial decrease in activity followed by an increase, which then turned to a decline after the first three hours of the experiment. This was seen most clearly in high-dose males. In the low and intermediate groups, activity increased by about ¼. The effects were mostly reversible within 6 hours (Gill, 1989).

Table 4.28 Summary of acute toxicity studies for MTBE

Type	Species	LD50/LC50 (4h) *	Publication
Oral	Rat	3,800	Mastri et al. (1969)
Oral	Rat	3,866	ARCO (1980)
Oral	Rat	4,000	Kirwin et al. (1993)
Oral	Rat	>2,000	RBM (1996d) §
Inhalation	Rat	85	Mastri et al. (1969)
Inhalation	Rat	120-140	ARCO (1980)
Dermal	Rat	>10,200	Mastri et al. (1969)
Dermal	Rat	>10,000	ARCO (1980)
Dermal	Rat	>2,000	RBM (1996b)

§ = OECD guideline 401 or 402 study
* = Concentrations in inhalation studies are in mg/l, oral and dermal in mg/kg

4.1.2.2.2 Studies in humans

Studies of patients treated with MTBE to dissolve gallstones

In clinical trials, hundreds of patients have undergone contact dissolution of radiolucent gallbladder or bile duct stones with MTBE by instillation through a transhepatic (Allen et al., 1985; Janowitz et al., 1993; Leuschner et al., 1991; Pauletzki et al., 1995; Ponchon et al., 1988; Thistle et al., 1989; van Sonnenberg et al., 1991) or nasobiliary catheter (Murray et al., 1988; Neoptolemos et al., 1990). Dissolution of cholesterol stones in the gallbladder involves the placement of a percutaneous transhepatic catheter, and instillation and aspiration of MTBE manually four to six times a minute with a glass syringe. The volume of MTBE instilled is adjusted such that it envelops the stones but does not overflow from the gallbladder (volumes of 1-15 ml have been used). The duration of treatment has been up to seven hours per day for one to three days; dissolution of the stones has been monitored with fluoroscopy. The mean treatment time in one large study was 5.1 hours (Leuschner et al., 1991). Dissolution of stones in the bile

duct with MTBE by a nasobiliary catheter inserted following endoscopic retrograde cholagiopancreatography has proved less successful because of the variable prevalence of cholesterol stones in this condition, and difficulties in effecting optimum contact between MTBE and the gallstones (Neoptolemos et al., 1990). In most cases, after MTBE instillation, the bile was aspirated manually in 1-15 treatment cycles lasting altogether from 1.5 to 42 hours. The total volume of MTBE instilled was 30-480 ml (Neoptolemos et al., 1990). During dissolution treatment of stones in the gallbladder there is the possibility of MTBE overflow to the cystic duct and further down to the duodenum, or leakage alongside the catheter into the liver and contact with a vascular structure, whereas treatment of bile duct stones likely results in some spill-over into the intrahepatic canaliculi and duodenum; in all cases systemic absorption of MTBE is expected.

Mild complications during dissolution treatment (nausea, drowsiness, vomiting, local burning sensation) are frequent, and transient elevation of liver transaminases, fever and leukocytosis have occurred among 5-24% of the patients (Janowitz et al., 1993; Leuschner et al., 1991; Neoptolemos et al., 1990). It was proposed that since the abnormal laboratory findings have mostly peaked after the removal of the catheter they might be caused by transient leakage of bile (Thistle et al., 1989). Treatment of bile duct stones with MTBE by the nasobiliary catheter caused elevation of liver enzymes in every fourth patient but no fever or leukocytosis was reported. Therefore, it cannot be excluded that high local concentrations of MTBE in the biliary tract also had an adverse effect on hepatocytes. In rats, intrahepatic injection of MTBE (0.2 ml/kg) caused necrosis at the site of injection (Akimoto et al., 1992). MTBE may have a transient, reversible irritating and inflammatory effect on the gallbladder wall, and in the duodenum (Janowitz et al., 1993; Leuschner et al., 1991; van Sonnenberg et al., 1991).

On several occasions, the presumed overflow of MTBE during instillation to the gallbladder (i.e. not all substance was recovered during aspiration) was found to lead to reversible sedation and an odour of MTBE on the breath of the patient. Among 27 patients who were not reported to exhibit adverse symptoms (Leuschner et al., 1991), blood was sampled after the treatment (mean duration 5.1 hours). The mean blood MTBE concentration was about 450 μmol/l (0.04 mg/ml) with a two times higher maximum level, and the mean blood TBA was about 540 μmol/l, showing that marked body burdens can develop during treatment. Another group of patients was found to have losses of 4-18 ml from the balance of MTBE instilled vs. aspirated, and two patients became reversibly somnolent and had the odour of MTBE on the breath (Ponchon et al., 1988). Three hours from the start of treatment, a third patient became confused after 6 ml of MTBE could not be retrieved during 30 minutes. When the patient had recovered, the treatment continued and at 5 hours, when 15 ml of MTBE were not retrieved in 45 minutes, the patient went into coma with an odour of MTBE on the breath. Coma reversed after 4 hours but acute renal failure with anuria developed, probably due to haemolysis. Haemoglobinuria was detected before anuria set in, and reduced serum haptoglobin as well as increased serum lactate dehydrogenase and unconjugated bilirubin were found (Ponchon et al., 1988). After dialysis treatments over 18 days, the patient's renal function recovered completely.

An elderly female patient showed persistent overflow of 5 to 7 ml MTBE per hour during seven hours of treatment, and developed gradually increasing sedation, nausea and slight emesis (Thistle et al., 1989). Since the emesis contained occult blood, gastroduodenoscopy was performed, revealing superficial ulcerative duodenitis. In addition, serum haptoglobin concentration was decreased, plasma free haemoglobin level was increased, and free haemoglobin was detected in the urine, clearly indicating intravascular haemolysis. The previous data allow a crude calculation of the body burden of MTBE associated with adverse symptoms and haemolysis. Assuming an hourly overflow of 6 ml MTBE into the duodenum, the dose for a 60 kg person was about 74 mg/kg per hour. The total dose over 7 hours would have been

approximately 31 g (about 520 mg/kg). Assuming that the elimination half-time for MTBE is 5 hours, the body burden of unchanged MTBE at the end of treatment peaked at about 340 mg/kg. It is however reasonable to presume that even TBA remaining in the body after MTBE metabolism has an impact which is possibly additive to that of MTBE.

Controlled exposure studies with volunteers

Acute health effects by MTBE in volunteer subjects have been investigated at low levels corresponding to population exposures while commuting (Cain et al., 1996; Prah et al., 1994), and at moderate levels corresponding to occupational exposures (FIOH, 1997; Nihlén et al., 1998). A group of 19 male and 18 female healthy, nonsmoking subjects (mean age 25.4 and 24.7 years, respectively) were exposed in an environmental chamber for one hour to 1.39 ppm (5 mg/m^3) MTBE or to clean air (Prah et al., 1994). The exposures were separated by at least one week. The odour of MTBE was not masked. A symptom questionnaire was administered during exposure, and three examinations of the neurobehavioural evaluation system (NES) viz. Symbol

-Digit Substitution test, Switching Attention test, and the Mood Scale were assessed before and during exposure. In addition, objective measurements of ocular and nasal irritation were performed (see Section 4.1.2.3). The odour threshold of MTBE was measured, and it was found normal for all subjects. Among the two exposure situations, there was no difference in symptom reporting other than that clean air was rated as having better quality than 1.39 ppm MTBE by the female volunteers. Psychological examinations (for assessment of attention and moods) showed no difference between MTBE and clean air. The blood MTBE concentration was found to peak at 8.2 ppb (0.09 μmol/l) in one male subject and at 14.7 ppb (0.17 μmol/l) in one female subject.

Cain et al. (1996) exposed 22 male and 21 female healthy, nonsmoking subjects (age range for males 18-32 years, and for females 18-34 years) in an environmental chamber for one hour to 1.7 ppm (6 mg/m^3) MTBE, to 7.1 ppm (19 mg/m^3) of a mixture of hydrocarbons characteristic of petrol, or to clean air. The order of the exposures was balanced and unknown to both the research workers and the subjects. As in the previous study, the methods employed included the rating of environmental attributes and symptoms, attention tests (Symbol-Digit Substitution, Switching Attention) and the assessment of moods (Profile of Mood States). The part of the study concerned with objective measurements of ocular and nasal irritation is dealt with in Section 4.1.2.3. The subjects perceived differences in odour and air quality among the exposures, but showed no increase in symptoms in response to MTBE or the hydrocarbon mixture over those to air. There were no differences in the outcomes of the psychological assessments across the exposures. Concentration of MTBE in blood was monitored during and after exposure in a group of 4 subjects. The mean level of MTBE in blood rose steeply from 0.8 μg/l before exposure to 17 μg/l (0.2 μmol/l) at the end of exposure.

Ten healthy, nonsmoking male volunteers of 23 to 51 years of age were exposed (two at a time) to 5, 25, or 50 ppm MTBE in an exposure chamber during two hours while the persons were exercising at 50W on a bicycle ergometer (Nihlén et al., 1998). All subjects were first exposed to the high level, whereas the order of exposures to the intermediate and low levels was randomised; there was at least a two-week interval between the exposures. The subjects were unaware of the exposure sequence. The low level of 5 ppm was chosen such that the volunteers could smell MTBE in all exposures. The subjects rated the degree of irritative symptoms, discomfort, and central nervous system effects on a visual analog scale before, during and after exposures. Apart from positive reporting of the smell of MTBE, all questions were rated from "not at all" to "hardly at all" (0-10% of the scale), and there was no significant relation to exposure. The mean concentrations of MTBE in blood levelled off towards the end of exposure

reaching 1.4, 6.5, or 13 μmol/l at the 5, 25, or 50 ppm levels of exposure (Nihlén et al., 1998). The part of the study investigating irritancy in the eye and the nose is dealt with in Section 4.1.2.3.

Thirteen healthy nonsmoking male volunteers (mean age 23.2, SD 2.2 years) were exposed (three at a time) in a dynamic exposure chamber to 0 (room air), 25 or 75 ppm MTBE for four hours at sedentary state of activity (FIOH, 1997). The exposures were conducted at weekly intervals and in a balanced order which was, however, not complete because of some dropouts. There was no attempt to mask the odour of MTBE but the subjects were unaware of the exposure sequence. The subjects responded with a questionnaire on 15 statements concerning symptoms of irritation (three items), feelings in the head (three items), tension-nervousness (three items), and moods (two items) with a rating "not at all", "slightly", or "clearly" at 1 hour and 3 hours during exposure as well as at 1 hour post-exposure. To assess possible effects on the central nervous system (CNS), simple reaction time and standing steadiness were measured. Simple reaction time was measured with the computer-aided Swedish Performance Evaluation System. The test measures psychomotor speed and sustained attention in a monotonous situation. Tests were performed prior to exposure, at 1 hour and 3.5 hours during exposure and one hour post-exposure. Standing steadiness with and without eye control was assessed with a posturography platform which analysed movements of the centre of gravity, prior to exposure, at 1 hour, 2.5 hours and 3.5 hours during exposure and one hour post-exposure. Concerning reaction time and standing steadiness, the results showed no significant relation with exposure. Although the number of subjects was limited, the reported feeling "heavy in the head" as well as aggregated "feelings in the head", and impairment of mood (feeling less cheerful) showed a significant dose-response, and they occurred significantly more frequently at three hours of exposure to 75 ppm MTBE than at exposure to room air. For the symptom aggregate "irritation" the difference between 75 ppm MTBE and room air was of borderline significance. At exposures to 25 ppm or 75 ppm MTBE the blood MTBE levels reached 11 or 29 μmol/l, and blood TBA levels 15 or 31 μmol/l, respectively.

There are many reports of symptoms among workers exposed to MTBE (Hakkola et al., 1997; Mohr et al., 1994; Moolenaar et al., 1994; White et al., 1995), and even among commuters and public at large (Borak et al., 1998). Although one may anticipate that the symptoms are mainly of acute nature, they occurred in the setting of repeated exposures, therefore these effects are dealt with in Section4.1.2.5.

Conclusions on acute toxicity in humans

Important toxicological observations have been made in gallstone patients treated with MTBE. The treatment which typically lasts about 5 hours is associated with poorly quantifiable amounts of MTBE uptake, however, one study of 27 patients revealed the mean concentration of about 0.5 mM (maximum about 1 mM) of both MTBE and its TBA metabolite in blood at the end of treatment. This indicates a high body burden: compared to inhalation exposure over four hours to 75 ppm MTBE, the blood levels were about 17 times higher. [Note: assuming that developing blood concentrations directly correlate with inhaled levels of MTBE, body burdens of MTBE and TBA corresponding to those of MTBE treated gallstone patients could be achieved at inhalation exposure to about 1,200 ppm.] The uptake is presumed to result from MTBE overflow to the intestine although in some cases more direct absorption from vascular structures in the liver was suspected. During treatment with MTBE, mild reversible systemic complications such as drowsiness, sedation, and nausea are common. Two patients have indicated intravascular haemolysis during treatment which in one comatose patient led to acute renal failure. The other patient was reported to show persistent overflow of about 6 ml MTBE per hour during seven hours of treatment; the patient also exhibited gradually increasing sedation, nausea and slight

emesis. Assuming that this 6 ml (74 mg/kg for a 60 kg person) was absorbed from the intestine per hour, and caused both a clear depression of the central nervous system as well as haemolysis, a comparison to a more relevant occupational exposure via inhalation at a similar dose rate can be made. For a 70-kg worker with pulmonary ventilation of 21 l/min (light work) and lung retention of 40%, uptake rate of 74 mg/kg per hour is reached at about 2,860 ppm (10,300 mg/m^3) MTBE in air. Thus, regarding the high end of the dose-reponse curve, one could speculate that some central nervous system depression sets in above 1,000 ppm and haemolysis at a level which is 2-3-fold higher. It should be noted however that acute toxicity by MTBE may not be limited to CNS depression and haemolysis, although observations on other target organs (relevant for inhalation exposure) are lacking.

No data were found to address the question of whether the acute effects were caused by MTBE, its metabolites, or both together. One could predict that TBA is at least equally potent as a CNS depressant as MTBE because it has a slightly higher solubility in fats. Furthermore, because TBA reaches slightly higher levels in blood than MTBE, and stays much longer in blood circulation, it could be expected to have a higher impact on CNS functions than MTBE. Regarding other metabolites, in view of the large doses of MTBE potentially received in gallstone dissolution, even the generation of formate should be considered. Maximum concentrations of about 1 mM of both MTBE and TBA found in the blood of patients suggest that formate could be found too. However, none was found (Leuschner et al., 1991).

As regards the lower end of the dose response curve, no indications of acute toxicity was found in controlled exposures of relatively young healthy volunteers to MTBE concentrations ranging from 1.4 to 50 ppm for one or two hours, whereas 4-hour exposure at 75 ppm did increase symptom reporting of feelings in the head and feeling less cheerful. These effects were rated as slight, and there was no indication of an objective sign of CNS function impairment in terms of psychomotor performance, sustained attention, or standing steadiness. Although sensory symptoms may show greater sensitivity than objective indices, it is possible that symptoms are mediated by mechanisms other than CNS depression, especially as MTBE has a foul odour.

4.1.2.2.3 Conclusions on acute toxicity

MTBE exhibits low acute toxicity via oral, dermal and inhalation in humans and test animals. The case data from gall bladder removal patients show that the principal effects of MTBE are on central nervous system, including sedation, nausea and vomiting. At blood MTBE levels of approximately 1 mmol/l, signs of intra vascular haemolysis can be detected. In rats, for oral acute toxicity, the average LD50 is 4,000 mg/kg. Dermal LD50 is over 10,000 mg/kg and by inhalation, an LC50 of approximately 100 mg/l has been determined. In test-animals, the most typical symptom is decreased ability for muscle co-ordination and hypoactivity. According to EU classification criteria, classification is not necessary for any acute toxicity end-point.

4.1.2.3 Irritation

4.1.2.3.1 Skin

Rabbits subjected to MTBE under occlusive patch for 4 hours. After the exposure, the residual substance was washed out with water and the skin reaction was estimated and scored after 1, 24 48 and 72 hours and 6, 8, 10 and 14 days according to OECD guidelines. The results showed one hour after the end of exposure moderate to severe oedema and moderate erythema. The effects

lasted the first 8 days of the 14 days of observation. The primary irritation score (PIS) was 5 and 24+48+72-scores were 2.9 for erythema and 2.3 for oedema (Mürmann, 1985b). Another study conducted following the same test guideline (OECD 404) found no irritation in rabbits (RBM, 1992a). The study reported 0 irritation scores. However, the purity of the substance was not reported. A third study conducted by the same institute on the same rabbit species resulted to a slight erythema but not oedema (RBM, 1996a). Erythema 24+48+72-score was 0.6 and oedema score 0.

Two additional skin irritation studies are available that differ in methodology significantly from the current test guideline recommendations (ARCO, 1980). Both studies used six rabbits, which were exposed to MTBE using an occluded patch for 24 hours. The effect of skin abrasion is included in the score. In the study by ARCO, slight thickening of the spinous layer in epidermis or slight focal necrosis was present in histology. Using the Draize scoring method, a primary irritation score (PIS) of 2.2 was obtained. All animals exhibited erythema but showed no signs of oedema. The authors suggested a possibility of parasitic skin infection or trauma to explain the focalised nature of skin reactions (ARCO, 1980). In the study conducted by Cuthbert (1979), all rabbits exhibited moderate erythema and oedema. The animals were scored immediately and at 48 and 72 hours. A PIS-score of 3.4 was calculated using the scoring method recommended by US-FDA.

Table 4.29 Summary of skin irritation studies for MTBE

Reported substance Purity %	Erythema 24+48+72h Score	Oedema 24+48+72h Score	PIS	Publication
n/a	0.55	0	n/a	RBM (1996a) §
n/a	0	0	n/a	RBM (1992a) §
99.9	2.94	2.33	5.0	Mürmann (1985b) §
96.2	n/a	n/a	2.2	ARCO (1980) Hazleton (1979)
99.1	n/a	n/a	0	
n/a	n/a	n/a	3.4	Cuthbert (1979)

PIS = primary irritation score, sum of the average erythema and oedema scores for 24 hours and 48 hours observations/4)
N/A. = not available
§ = study conducted following OECD guideline 404

4.1.2.3.2 Eye

Several eye irritation studies are available with varying responses. Two studies, conducted following the protocol as suggested in OECD test guidelines, report only slight redness of the conjunctiva (redness 1.3), scores for cornea and iris were zero (RBM, 1992b, unpublished; Mürmann, 1985a, unpublished). Another study conducted later by RBM (1996c) reported redness of the conjunctiva and inflammation of the iris starting one hour after application which lasted up to 72 hours after. The report concluded MTBE to be irritating to rabbit eye.

A study, using the Draize method and nine rabbits, tested two different samples of MTBE, a 96% and 99% pure (Hazleton, 1979). For six rabbits, no washing was performed while for the remaining three rabbits the sample was rinsed off from the treated eyes after 30 seconds. The results indicated that the more impure sample produced more pronounced redness and chemosis. There was 1.2% of tert-butanol in the less pure sample while it was not an impurity in the other sample. Although tert-butanol is not at present classified as an eye irritant in the EU there are test results that show it to be moderately or severely irritating to rabbit eye (European Chemicals Bureau, 1998). On the other hand, the substance purity does not fully explain the effects, as the

Hüls study (Mürmann, 1985a) demonstrates. Also, a study based on Draize scoring method that reportedly used 100% MTBE, showed transient corneal opacity and irritating effects to the iris and conjunctiva. The effects were totally reversed after seven days. Mastri et al. (1969) reports only mild irritation after an administration of 0.1 ml of undiluted MTBE to the conjunctival sac of five albino rabbits. The eyes were scored according to Draize et al. (1944) after 1 min, 24 hours, 72 hours and 7 days. Cuthbert (1979) conducted an eye irritation test that followed mostly the same principals as those described by Draize (1944). Six rabbits were applied 0.1 ml of undiluted MTBE (purity not reported) into the outer corner of the right eye. The scoring system was that recommended by US-FDA. Moderate mild chemosis and redness of the conjunctive was reported during the first three days.

Table 4.30 Summary of the average scores for rabbit eye irritation tests

Reported Substance Purity	Cornea opacity	Iris abnormalities	Conjunctiva Redness	Conjunctiva Swelling	Publication
n/a	0	0.8	1	0.4	RBM (1996c) §
n/a	0	0	1.3	0	RBM (1992b) §
99.9%	0	0	1.3	0.4	Mürmann (1985a) §
96.2%	0.1	0	1.0	0.4	ARCO (1980)
99.1%	0	0	0.1	0	ARCO (1980)
n/a	0	0	1.6	1.2	Cuthbert (1979) *
100 %	1.2	1.2	1.7	0.2	Mastri et al. (1969) # +

§ OECD guideline 405 study; + Method used was the same as described by Draize et al. (1944);
* FDA recommended scoring which is similar to the principals presented by Draize et al. (1944)
# Averages counted only for 24 and 72 hours
N/A = not available

4.1.2.3.3 Respiratory tract

General signs of upper respiratory way irritation were seen at 70 and 230 mg/l MTBE in the acute toxicity test conducted by ARCO (1980). Tepper et al. (1994) investigated the respiratory irritation properties of MTBE in mice in ten separate experiments using half-log exposure intervals (RD_{50} = the concentration where respiratory rate is decreased to 50% of normal). Mice were exposed to 300, 1,000, 3,000, 10,000 and 30,000 mg/m3 MTBE for one hour. Two experiments, four mice per experiment, were conducted at each concentration level. Breathing frequency and respiratory waveform morphology were measured. Filtered air was used to measure the baseline control values. The lungs of the animals in the highest dose group were lavaged in order to analyse total protein and lactate dehydrogenase content. A 50% respiratory rate decrease was predicted by linear regression interpolation to occur at 16,600 mg/m^3 MTBE concentration. Slight to severe sensory irritation occurred at all concentrations. There were signs of pulmonary irritation indicative of lung injury at the highest concentration. However, the results of the lung lavage measurements did not support this observation.

4.1.2.3.4 Human studies

On request by the rapporteur, the occupational health physicians at a major MTBE producing company in Finland reviewed their health surveillance observations on workers concerning potential skin effects. No clinical findings had been made in the workforce that would point to skin irritation during handling of MTBE.

Eye and upper airway irritancy by MTBE vapours has been investigated in human volunteer studies consequent to alarming reports of eye irritation, burning of the nose or throat, cough, bronchitis and asthma among populations in some US states during introduction of MTBE in automotive petrol.

A group of 19 male and 18 female healthy, nonsmoking subjects (mean age 25.4 and 24.7 years, respectively) was exposed in an environmental chamber for one hour to 1.39 ppm (5 mg/m^3) MTBE or to clean air (Prah et al., 1994). A symptom questionnaire (including 14 items related to irritancy) was administered during exposure, and objective measures for irritancy in the eye (tear-film break-up time, ocular hyperaemia) were assessed after exposure. In addition, signs of inflammation in the eye (impression cytology) and the nose (nasal lavage) were explored with microscopic examination of inflammatory cells as well as by assays of various proinflammatory cytokines in the post-exposure phase. No significant effect by MTBE was found.

Cain et al. (1996) exposed 22 male and 21 female healthy, nonsmoking subjects (age range for males 18-32 years, and for females 18-34 years) in an environmental chamber for one hour to 1.7 ppm (6 mg/m^3) MTBE, to 7.1 ppm (19 mg/m^3) of a mixture of hydrocarbons characteristic of petrol, or to clean air. Partly the same methodology as in the previous study was employed, encompassing a symptom questionnaire, examination of eye redness, tear-film break-up time, measurement of epithelial cell turnover in the conjunctiva, and differential count of cells in the tear fluid, with emphasis on polymorphonuclear leukocytes. Cells obtained from nasal lavage were also analysed under microscope. There were no effects significantly related to MTBE exposure.

Ten healthy, nonsmoking male volunteers of 23 to 51 years of age were exposed (two at a time) to 5, 25, or 50 ppm MTBE in an exposure chamber during two hours while the persons were exercising at 50W on a bicycle ergometer (Nihlén et al., 1998). The subjects rated nasal irritation, ocular irritation, throat irritation and the smell on a visual analog scale. Ocular blinking frequency, eye redness, tear-film break-up time, self-reported tear-film break-up time and conjunctival epithelial damage were measured repeatedly at 50 ppm MTBE. Similarly, nasal lavage samples were analysed for albumin, eosinophilic cationic protein, myeloperoxidase, lysozyme and for total cells. Nasal peak flow measurements were performed at all exposure levels, and acoustic rhinometry at the two lower levels. The symptoms of irritation, all objective eye measurements, and markers of inflammation in the nose showed no relation to MTBE exposure. Nasal airway resistance increased after exposure at all levels without a dose-response, and there was a concomitant tendency of decreased nasal volume at 5 and 25 ppm.

Conclusions of eye and upper airway irritation from controlled human studies

Pure MTBE vapours up to 50 ppm in air did not cause subjective symptoms of eye or nose irritation in young, healthy nonsmoking volunteers, and the objective measures of eye and nose function as well as markers of mucous membrane inflammation were not significantly related to MTBE.

4.1.2.3.5 Conclusions on irritation

MTBE can be considered a skin irritant. Although the results on skin irritation are somewhat equivocal the results of the best-reported EU-guideline, conducted according to GLP are selected. Moreover, the MTBE industry had autonomously already recommended this that the substance be classified for this hazard. There are only slight indications of eye irritation in the well-reported studies in animals. Studies in human volunteers at low air concentrations have

shown no signs of eye irritation. Based on the scores from animal studies and the Annex 6 recommendations, MTBE is not considered an eye irritant. The results from the study in mouse or the experience in human volunteers do not give reason to classify MTBE as respiratory irritant.

4.1.2.4 Corrosivity

Based on the results seen in the skin irritation tests MTBE is not corrosive.

4.1.2.5 Sensitisation

In a Magnusson-Kligman maximisation test, twenty Guinea pigs were induced with a 1-% MTBE-water solution intracutaneously. This concentration was chosen as it was found non-irritating in preliminary tests whereas the 5% and 2% solutions were moderately irritating. Moreover, none of the adjuvant-only pre-treated animals reacted positively in the challenge phase. Parallel injections of Freund's adjuvant (FA), MTBE alone and FA + MTBE on a shaven patch in the scapular region. One week after, an occlusive topical induction was performed using a filter paper saturated with 1% MTBE/water solution, covered with an impermeable wrapping bound with occlusive tape. The topical induction phase lasted 48 hours. After a pre-test with various challenge concentrations, the animals were challenged topically with a 1% MTBE-water solution 14 days after the epicutaneous induction. No hypersensitivity reactions were reported (Cuthbert, 1979).

In another study, ten guinea pigs were induced with an initial induction of 0.5 ml MTBE in saline followed by a 0.1 ml injection into a shaved flank. The injections were given three times a week, resulting to a total of 10 induction doses (Litton Bionetics Inc., 1980b; ARCO, 1980). Fifteen days after the last injection, the guinea pigs received an *intracutaneous* challenge injection below the sensitisation site. A 1-% solution of 2,4-dinitro-1-chlorobenzene was given to a positive control group of ten guinea pigs. Skin reactions were scored 0 to 4 for erythema and oedema using the method of Draize (1959). Skin reactions in the MTBE-group varied from slight to well defined erythema with occasional oedema. Authors did not consider MTBE sensitising. The Draize scores were not given. Intracutanous challenge is not recommended procedure.

Conclusion on sensitisation

Although the studies do not formally follow the OECD guidelines, they are considered sufficient to estimate the sensitising potential of MTBE. MTBE is not sensitising in Guinea pigs and there are no observations available in humans.

4.1.2.6 Repeated dose toxicity

4.1.2.6.1 Studies in animals

28-day studies

Inhalation

Groups of 10 Fisher-344 rats and 10 CD-1 mice dose/sex were subjected to whole body MTBE vapour exposure at 0, 400, 3,000 and 8,000 ppm for 28 days, five days/week, six hours each day

(Chun et al., 1993). Additional five animals per control and high dose group were assigned to a 16-day recovery group and 10 animals to a cell proliferation study-group. Rats were weighed on weekly basis but no recording of food or water consumption was reported. The cell proliferation group was implanted with a subcutaneous micro-osmotic pump 24 hours before (mice 48 hours) sacrifice, in order to give a slow administration of 5-bromo-2-deoxyuridine. The labelled kidney distal proximal tubule cells and hepatocytes were counted. Clinical chemistry analyses were performed to control and high dose animals from samples taken before sacrifice. Only creatinine, urea nitrogen and the electrolytes were analysed. In mice, total triiodothyronine (T3), total thyroxine (T4), thyroid stimulating hormone (TSH), total bile acid and estradiol in females were determined in addition. Urine samples taken on study week 4 were analysed for proteins, pH, osmolality, alkaline phosphatase and lactate dehydrogenase. Mice brain was homogenised to determine the levels of calcium and magnesium. The necropsy protocol was in line with the recommendations in OECD guideline 412. However, only liver and kidney were studied microscopically (Chun et al., 1993). Kidney slides were stained to determine the protein accumulation to the proximal convoluted tubules using Mallory's Heidenhain staining method (Fowler and Martin, 1994).

In the rat study, there was no exposure-related mortality during the study. Clinical signs included ataxia, hypoactivity and blepharospasms. Male rats of the 8,000 ppm group had throughout the study depressed body weight gain and body weight while females were affected only slightly in body weight gain. While no treatment related changes were evident in serum chemistry, urine volume and acidity were increased. Formic acid, the acidic MTBE metabolite, may explain the change in pH. Proliferation of the kidney proximal tubular epithelial cells was increased in male rats on day 5 and at the end of the study in the mid- and high-dose groups. Kidney and adrenal weights, absolute and relative to body or brain weight, were statistically significantly increased in male rats of the high dose group (kidney: 8%, adrenal 53%) and female rats of the 3,000 and 8,000 ppm groups. The maximum percentiles of weight increases for females were 8% for kidneys and 23% for adrenals. Both sexes receiving 3,000 ppm and 8,000 ppm had increased liver weights, absolute and relative. The maximum increase in liver weight relative to final body weight was 17% in males and 10% in females. The liver weight increase was dose-related. The only microscopic lesion that could be attributed to MTBE was the accumulation of protein in the kidney tubular in male rat of the 3,000 ppm and 8,000 ppm groups. This was detected using Mallory's Heidenhain staining technique (Fowler and Martin, 1994). However, Fowler and Martin (1994) were unable to detect an increase of protein accumulation with the dose.

In mice, the clinical picture was similar to that of rats. There were no exposure-related effects on body weight or body weight gain. The only change in clinical chemistry attributable to MTBE was an increase in total T4 and TSH in high dose males. The biological significance of this alteration is, however, unknown, because no parameter in clinical pathology indicated an effect. The female high-dose mice had a dose-related decrease in their total T4 at day 5, which was also seen in the mid-dose group at day 31. However, this effect was only detected in the proliferation groups (5 mice/group) and not in the main groups (10 mice/group). There were no evident exposure-related effects seen in the urinalysis parameters. Brain calcium and magnesium were within the control values. There was a slight increase in liver cell proliferation in males and females at 8,000 ppm and in females at 3,000 ppm also. Increased Liver weight (absolute and relative) was observed in high dose males and mid- and high-dose females. Microscopically, high dose animals had hepatocellular hypertrophy in the centrilobular area, which was more severe in the males than in the females. Males and females had decreased relative spleen weights at 8,000 ppm (Chun et al., 1993).

For CD-1 mice and Fisher-344 rats, a **NOAEC of 400 ppm** was obtained.

Oral

MTBE was given by oral gavage at concentration 0, 90, 440 and 1,750 mg/kg to four groups of Sprague-Dawley rats (10/dose/sex) five days/week, i.e., 20 doses over a period of 28 days (IITRI, 1992). Clinical signs were observed daily and body weight was recorded weekly. Clinical chemistry and determinations included those suggested in the guideline 412 and additionally creatine kinase, cholesterol and triglyserides. Post-mortem examination procedure included weighing of adrenal glands, brain, gonads, heart, kidneys and spleen and the microscopic evaluation was performed on most collected tissues from the animals of the control and high dose groups. The kidneys and stomach were examined also from the low- and mid-dose groups.

Clinical signs included transient post-dosing ataxia, hypoactivity, and salivation in the low dose rats. The treatment had no effect on mean weekly body weight or body weight gain at any dose. Relative liver weights were statistically significantly increased in males (8%) and females (13%) treated with 1,750 mg/kg. The increase seemed to be dose-related, especially in females. Males had a dose-related increase in their relative kidney weights, which was statistically significant at the two highest doses. The female rats exhibited a statistically significant increase in the 90 and 1,750 mg/kg dose groups but not in the 440 mg/kg group. There were no biologically meaningful findings to correlate with these weight changes (e.g. BUN, ALAT and ASAT were not significantly changed in any group). Male relative adrenal weight was significantly greater (23%) in the high dose group than in the control animals. Pathology findings included hyaline droplet formation in proximal convoluted tubules of male rats in the mid- and high-dose groups. The authors said the hyaline droplets were attributed to α2u-globulin. Although this is a likely explanation, no further data, such as a staining using a specific antibody, was presented to substantiate this claim. In the forestomach of the high dose animals, a series of treatment related changes, such as submucosal oedema, subacute inflammation, epithelial hyperplasia and ulceration were indicative of localised irritation effects.

The NOAEL for Sprague-Dawley rat in oral exposure was 90 mg/kg due to the effects seen in the male kidney.

90-day studies

Inhalation

A 13-week, whole-body inhalation exposure with MTBE doses of 0, 250, 500 and 1,000 ppm 5 days/week, 6 hours/day, was carried out by Greenough et al. (1980) on 10/dose/sex CD-rats. Examination protocols followed the OECD 413 guideline except for haematocrit and blood phosphorus, which were not determined. Urine was analysed before treatment and after six and 12 weeks of treatment over a 4-hour food and drink deprivation. Histological examination did not include aorta, ileum part of the small intestine, caecum of the large intestine or rectum. Nares and larynx were investigated for epithelial cell hyperplasia and inflammatory changes. Lung histopathology graded vascular congestion, focal inflammatory changes, bronchus associated lymphoid tissue and accumulation of alveolar macrophages.

No treatment related deaths occurred during the course of the study. The only clinical sign reported was an increase in CNS depression with dose. There was only a marginal difference in the body weight gain of the high dose group. In the clinical chemistry and haematology values, the highest dose group males had a significantly ($p<0.001$) increased haemoglobin, increased blood urea nitrogen and lactate hydrogenase level (LDH). Female rats in this dose group had significantly reduced LDH level. These changes were evident only after 13 weeks of treatment. In necropsy, females had a slight reduction in lung weights, expressed either as absolute weight

or relative to body weight. The mean weight appeared clearly lower than in controls already in the 250 ppm group but was only significantly lower in the 1,000 ppm group. No other abnormalities found in gross or histopathological examination. Based on the change in the female lung weight, a **NOAEC of 500 ppm** is derived.

Up to eight times higher doses to those used in the Greenough study were given to Fisher-344 rats that received MTBE vapour concentrations of 0, 800, 4,000 and 8,000 ppm for 13 weeks, 5 days/week, 6 hours/day (Dodd et al., 1989; Lington et al., 1997; Daughtrey et al., 1997). Of the twenty-five animals per sex/dose assigned to the study, there were 10 animals/group in the neurotoxicity study. Neurotoxicity assay included functional observation battery (FOB), measures of motor activity 20 hours after last exposure at an examination of neuropathological signs. In the general subchronic toxicity evaluation, body weights and food consumption were recorded weekly. Haematological and serum chemistry parameters were determined before exposure, and five and 13 weeks after the exposure. The measured blood chemistry and haematological parameters, necropsy and histological examination included those listed in the OECD guideline 413. Additionally, aldosterone, corticosterone, and adrenocorticotropic hormone levels were measured at week 13. The weights of the liver, kidneys, lungs, adrenals and the brain weight were measured in all animals and testes weight from males. Nervous system was evaluated microscopically in the 10 animals that were in the neurotoxicity evaluation. Various sections of the brain, spinal cord and ganglia were included in the examination.

Kidney sections from five male rats in each treatment group and five female rats of the control and high dose animals were stained for the presence of α2u-globulin the proximal tubule using a monoclonal antibody (Swenberg et al., 1991). From these same animals, a similar set of slides was prepared as for the α2u-re-evaluation. For this, an additional set of slides for the ten remaining rats was prepared. The immunohistochemical staining was conducted in Swenberg's laboratory at the University of North Carolina. After staining, the slides were sent back to Bushy Run Research Center, where they where analysed by Fowler and Chun (1993). To identify non-specific protein accumulation in the epithelial cells of the proximal tubules, Fowler and Martin (1994) analysed the slides, which had been stained using Mallory's Heidenhain staining method.

No animals died. The only treatment related clinical finding was ataxia in the 8,000 ppm group. Body weights were significantly lower along the test period in male and female rats; differences to control at the end of the study were –6% and –3%, respectively. The mid-dose group animals had decreased body weights only during the five first weeks of the dosing. At the end of dosing, relative and absolute liver and kidney weights were significantly increased in low, mid and high dose in males (liver: 8%, 20% and 39%; kidney: 5%, 12%, 20%) and in the mid and high dose females (liver: 13% and 15%; kidney: 12%, 10%). In addition, male and female adrenal weight showed an increasing trend with the dose. Both sexes had a statistically significantly increased relative adrenal weight at the two highest doses. The weight increase was probably related to stress, since also the blood corticosterone levels were higher than in controls. Males and females had a depressed absolute brain weight and length in the 8,000 ppm group, although not statistically significantly. Haematological parameters expressed only slight, no more than 5% difference to the control values, with statistical seen significance only in the two highest doses. Namely, the changes for males were a 2-4% reduction in red blood cell count, a 2-5% increase in mean corpuscular volume (MCV), 2-3% increase in mean corpuscular haemoglobin concentration (MCHC). There was also an increase in the number of reticulocytes and leukopenia (mostly lymphopenia). These were statistically significant in either mid or high dose group. The high-dose females had increased haematocrit and segmented neutrophil count at study termination. In serum chemistry, significant effects were seen mostly in high-dose males who manifested slight increases in levels of calcium, phosphorus, albumin and total protein.

Both, the high and medium dose males, had a significant *decrease* in their liver transaminases (SGOT, SGPT). Males and females of the 8,000 ppm group had a significantly elevated blood corticosterone level, both more than 3.5 times the control level. aldosterone level in female medium and high dose rats also showed a 36% and 57% increase to control rats, although this change was not considered statistically significant. The only significant findings at necropsy were concentration-related weight (relative to body weight) increases in adrenals, liver and kidneys, males being more affected than females. Microscopically, again, only the high dose males had higher incidences of lymphoid hyperplasia in the lymph nodes, moderate haemosiderosis of the spleen and large hyaline droplets of the kidney. Peripheral and central nervous system did not have any treatment-related alterations. The 4,000 ppm males demonstrated a weak hyaline droplet response. Fowler and Martin (1994) found a greater amount of protein accumulated in the kidneys of male rats but they were not able to show an increase in droplet size or protein distribution with the dose. The immunohistochemical analysis of the kidney slides, showed the presence of α2u-globulin in the protein droplets found in tubules (Swenberg et al., 1991). However, they found neither exposure-response relationship, nor α2u-positive proteinaceous casts at the junction of the proximal tubules and the thin limb of Henle. FOB parameters showed few differences to control, such as decreased hind-limb grip in mid-concentration males and decrease in latency to rotate, which in their inconsistency were not considered indicative of nervous system dysfunction. Although some variation from control was seen in the motor activity of high dose males (-) and mid-dose females (+) on day 55, neither consistency nor dose relation could be found to give these symptoms a biological significance.

Based on the effects seen in the male kidney, a **NOAEC of 800 ppm** was derived from this study.

Oral

Male and female Sprague-Dawley rats were administered MTBE daily for 14 or 90 consecutive days (Robinson et al., 1990). The doses in the 14-day experiment were 357, 714, 1,071 and 1,428 mg/kg and for the 90-day experiment 100, 300, 900 and 1,200 mg/kg. Daily clinical observations were conducted and weights were measured twice a weekly. Food consumption was measured weekly and water consumption every third week. Clinical chemistry determinations included liver transaminases, glucose, urea nitrogen, creatinine, cholesterol, lactate dehydrogenase (LDH) and calcium and phosphorus. At necropsy, all major organs were examined grossly. Brain, liver, spleen, lungs, thymus, kidneys, adrenal glands, heart and gonads were weighed. The control and high dose animals' major organs were subjected to histopathological examination.

Although the final body weight values after the 14-day exposure of the rats in the three highest dose groups did not differ clearly from the controls, their body weight gain was significantly lower. In addition, the high dose females had a significantly reduced body weight gain. Males that received any of the three highest doses displayed an increased red blood cell compartment and haemoglobin. When compared to controls, serum glucose, creatinine and blood urea nitrogen (BUN) was significantly elevated in the high dose females. In males, BUN, SGOT (AST), LDH and cholesterol values increased in a dose-related fashion but reached a significant difference to control group at the second highest or the highest dose only. Females also showed a similar trend for increasing cholesterol but only up until the 1,071 mg/kg-dose group. Females had a reduced lung weight, which was significant with a $p<0.05$ at all doses except the highest, which had a p-value of 0.001. Males exhibited a similar trend but the change had significance only in the 714 mg/kg group. Protein droplet nephropathy was more than two times more frequent histopathological finding in the high dose group than in the control group. Males also had a significantly increased (13%) kidney weight in that dose group. Degenerative changes were

characterised by an increase of hyaline droplet formation in the proximal tubule epithelial cells. Based on the decrease in lung weight in females, the **NOAEL for 14-day exposure was <357 mg/kg.**

In the 90-day exposure, seven females and four males had died in various dose groups. As in the 14-day experiment, profound anaesthesia and diarrhoea were the only clinical findings. However, abnormalities found in the lungs in macroscopic examination at necropsy suggested gavage errors in most of these animals. There were no deaths in the control animals. Haematology failed to show a dose dependent increase or decrease in any measured parameter compared to negative control group. Male and female BUN levels were decreased in all the treated groups and both sexes. Contrary to the results seen after 14 days, the changes were statistically significant in the 90-day study in all treatment groups. As in the 14-day study, males had elevated AST and cholesterol. After 90 days, AST increase was statistically significant only in the 300 and 1,200 mg/kg group and cholesterol in the 900 mg/kg group. Kidney chronic nephropathy in the high-dose male rats was more severe and progressed to that seen in control animals when the tubular degenerative changes were observed. The 50% of the males in 1,200 mg/kg group males had also increased but small number of tubules with granular casts and increased hyaline droplets in the proximal tubular epithelial cells. Kidney relative weight increased in both sexes with dose and was significantly different from control in the two highest levels in males and in three highest doses in females. Females had an increase in the adrenal weight at 1,200 mg/kg. Both sexes had greater than control liver weights at the two highest doses (Robinson et al., 1990). Although a statistically significant weight increase can be seen in the female kidneys already at 300, the findings in clinical chemistry or microscopy do not support the setting of NOAEL at that level. Based on the statistically significant weight increase in the male liver at 900 mg/kg and the slightly inconsistently increased AST and cholesterol levels, **the NOAEL for 90-day oral exposure** in Sprague-Dawley rat is set to **300 mg/kg**.

A similar experiment to that conducted by Robinson et al., was carried out by Zhou and Ye (1999). They administered MTBE to male Sprague-Dawley rats, in gavage doses of 0, 200, 600 and 1,200 mg/kg/day, 5 days a week, for a total of 90 days. Blood collected at sacrifice and liver transaminases, lactate dehydrogenase (LDH), total protein, albumin, globulin, blood, urea nitrogen (BUN) and creatinine were determined. At necropsy liver, kidneys, testes and lungs were weighed and examined in light microscopy. Hepatic tissue slices were prepared also for electron microscopy.

Liver weights were elevated in all treatment groups. Although there were significant *decreases* in aspartate amino transferases in all dose groups when compared to controls, these changes were within normal range. All treated dose groups had significantly increased liver weight and the dose groups 600 and 1,000 mg/kg had significantly greater kidney weight than control. However, contrary to findings in other experiments, the investigators reported no changes detectable in light microscopy were reported. When examined in electron microscopy, hepatic cells of all treated groups exhibited nuclear condensation, fat droplet and lysosome appearance in cells and smooth endoplasmic reticulum disintegration. **The LOEL** in Sprague-Dawley male rat **for 90-day oral exposure was 200 mg/kg**.

Other tests

A 28-day experiment conducted with Sprague-Dawley rat, administered orally up to 1,500 mg MTBE/kg/day is described in detail in the endocrine section of this report (Williams et al., 2000a). This report mostly investigated the effects of MTBE to the endocrine hormone balance, but it also provides histological information on various organs. The effects seen in organs included increased liver and kidney weight, where kidney weight increase was statistically

significant already at 250 mg/kg. While the weight increase was dose dependent for both organs, liver weight increase was significant only in the 1,000 and 1,500 mg/kg groups. The microscopic lesions in the kidney were characteristic to protein droplet nephropathy in all dose groups. Liver was hypertrophic starting from 500 mg/kg dose level. When graded, there was an increase in hypertrophy severity with the dose. Relative testicular weight increased significantly only at 1,500 mg/kg, but as with liver and kidney weight, there seemed to be an increasing trend in the weight increase. Serum triiodothyronine was significantly increased at 1,000 and 1,500 mg/kg. There was no change in thyroxine or thyroid stimulating hormone, as there was with CD-1 mouse exposed to 8,000 ppm in the 28-day experiment (Chun et al., 1993).

Determination of α2u-globulin Accumulation in Rat Kidney

Prescott-Mathews (1997) determined the ability MTBE to cause α2u-globulin kidney nephropathy in male rat kidney. They conducted a study where 10 male and 10 female Fisher-344 rats/dose were exposed to nominal concentrations of 0, 400, 1,500, 3,000 ppm MTBE vapour, six hours/day for 10 consecutive days. To serve as a positive control, a group of four rats was given a daily gavage dose (500 mg/kg) of a known α2u-globulin inducer, 2,2,4-trimethylpentane. Three-and-a-half days before sacrifice, rats were implanted an osmotic pump that slowly released 5-bromo-2-deoxyuridine (BrdU). One half of the animals was analysed for histological endpoints and the other half for biochemical endpoints. Kidneys were homogenised and the ultracentrifugate of the cytosol fraction was quantitatively analysed for α2u-concentration by enzyme-linked immunosorbent assay (ELISA), gel electrophoresis and anion-exchange chromatography. Using standard staining methods and light microscopy, kidney sections were evaluated for adverse changes. Immunohistochemical staining for BrdU was used to evaluate labelling index and cells in S-phase (proliferation). Protein accumulation was determined using Mallory's Heidenhain technique. In addition, a semi-quantitative immunohistochemical assessment α2u-accumulation in protein droplets was conducted (Prescott-Mathews et al., 1997).

Male kidney weights were only mildly increased. Histological changes were characterised by epithelial cell necrosis, protein droplet accumulation and karyomegaly within the male rat tubules exposed to MTBE. The highest dose males had epithelial cell exfoliation into the tubular lumen. These lesions were not present in female or control rats. Kidney lesions found in histology examination were slightly more severe with increasing MTBE concentration. Protein droplet accumulation increased, statistically significantly and with the dose, in male treated rats while in females accumulation was absent. Immunohistochemical analysis of kidney slides showed some increase of α2u-globulin but it did not appear to have a linear, exposure-related nature. Cell proliferation measured as labelling index (LI) was increased in all treated male groups in the renal cortex. The two highest male dose groups also had an increase in LI in the outer stripe of outer medulla. ELISA-analysis of the kidney cytosol showed a clear positive correlation with MTBE dose and α2u-concentration. With the latter method, there was a strong positive correlation also between LI and α2u-concentration. Gel and anion-exchange chromatography failed to demonstrate accumulation of any other protein than α2u-globulin.

Table 4.31 Summary of repeated dose toxicity studies in animals

Duration / route	Animal	Doses	NOAEL/ LOAEL	Effects at LOAEL	Reference
14 days oral	Sprague-Dawley Rat	357-1,428 mg/kg*	<357/357mg/kg *	Depressed Lung weight	Robinson et al. (1990)
28 days oral	Sprague-Dawley Rat	90-1,750 mg/kg*	90/440 mg/kg*	Increased kidney weights, hyaline droplet formation in kidney pct	IITRI (1992)
28 days oral	Sprague-Dawley Rat	250-1,500 mg/kg	<250/250 mg/kg*	Kidney protein droplet nephropathy	Williams et al. (2000a)
90 days oral	Sprague-Dawley Rat	100-1,200 mg/kg*	300/900 mg/kg*	Increased liver weight, AST, increased cholesterol	Robinson et al. (1990)
90 days oral	Sprague-Dawley Rat	200-1,200 mg/kg*	<200/200 mg/kg *	+ Increased Liver weight, Signs of morphological changes to hepatocyte cell structures in electron microscopy	Zhou et al. (1999)
28 days inhalation	Fisher-344 Rat	400-8,000 ppm	400/3,000 ppm	Proliferation of the kidney proximal tubuli epithelial cells	Chun et al. (1993)
28 days inhalation	CD-1 Mouse	400-8,000 ppm	400/3,000 ppm	Liver cell proliferation	Chun et al. (1993)
13 week inhalation	CD-rat	250-1,000 ppm	500/1,000 ppm	Depressed lung weight (females), increased haemoglobin, blood urea nitrogen and ldh (males)	Greenough et al. (1980)
13 weeks inhalation	Fisher-344- Rat	800-8,000 ppm	800/4,000 ppm	Abnormalities in kidney pct morphology, changes in hormone levels, Alterations in red blood cell paramaters	Dodd et al. (1989) Lington et al. (1997)

* = Gavage administration applied
+ = LOEL
AST = aspartate amino transferase
LDH = Lactate dehydrogenase

Summary of repeated dose toxicity in animals

The principal affected organs are liver and kidneys. Mostly these changes appeared at doses of 3,000 ppm and above or at oral doses greater than 300 mg/kg. A statistically significant decrease in lung weight was noted on two separate occasions, 14-day oral and 13-week inhalation study. However, in the two-year study with rats described in the carcinogenicity section (Bird et al., 1997) or mice or in the 90-day studies with rats, there are no discernible changes in lung weight. Degenerative changes and protein droplet nephropathy of the male rat kidney proximal convoluted tubules are probably the most common findings. MTBE produced kidney lesions including protein droplet accumulation, karyomegaly, cell death and granular cast formation, in the proximal convoluted tubule (PCT) epithelial cell layer. In inhalation studies, only slight indications of kidney toxicity are seen up to 1,000 ppm. At 4,000 ppm, the male rats show clear protein droplet nephropathy. The results from the oral studies show slightly different effect levels: Williams et al. (2000a) noted protein droplet nephropathy visible in light microscopy in most male rats at 250 mg/kg. The 90-day study by Robinson et al. (1990) reported this effect only at 1,200 mg/kg. The study by Zhou et al. (1999) mentioned no signs of nephropathy up to 1,000 mg/kg in the same rat strain. Most of the available studies also report increased liver weight. The relative weight increase in the 90-day study at 4,000 ppm was 20 % males and 13 % for females. In the two-year study a relative liver weight increase of 20% was seen at 3,000 ppm. No data were available for males due to early termination; chronic progressive nephropathy was

the major cause of death in males of the 3,000 ppm and 8,000 ppm groups in that study. Zhou et al. (1999) report morphological changes of the smooth endoplasmic reticulum (SER) visible only in electron microscopy. Williams et al. (2000a) report centrilobular hypertrophy at 500 mg/kg. Hypertrophy and the subsequent weight increase and changes in SER are typically seen adaptive responses in the liver (Haschek and Rousseaux, 1998). Moreover, there does not seem to be an irreversible functional or anatomical impairment of the liver. The kidney changes are probably associated with α2u-globulin and its accumulation to proximal tubules, due to decreased hydrolysis caused by the binding of MTBE. This phenomenon is male rat specific.

Tert-butanol

The 15-week interim examination of a two-year study conducted with tert-butanol reported renal papilla mineralisation at 5 mg/ml (drinking water) in male rats (Cirvello et al. 1995). This lesion and the associated nephropathy are typical findings when α2u-globulin accumulates in hyaline droplets. The severity and frequency of nephropathy showed no differences between the treated and control at 15 weeks but it was more severe in males.

4.1.2.6.2 Human studies

Effects associated in the published literature with repeated exposures to MTBE at workplace or in the general environment in fact concern combination exposures to mixed vapours of petrol (components) and MTBE, or mixtures of benzene (and possibly other hydrocarbons) and MTBE in drinking water.

Exposure via air

After the oxygenated fuel programme (petrol containing 15% MTBE) was initiated in Fairbanks, Alaska, in November 1992, people started complaining of symptoms including headache, dizziness, and nausea to a local hotline. This soon received plenty of attention in the media. Moolenar et al. (1994) measured population exposure (blood MTBE and TBA, ambient air MTBE) during the oxygenated fuel programme and, after it had been suspended in December 1992, again in February 1993. They also made some symptom inquiries. The researchers were able to recruit "a convenience sample" of 18 workers involved with car servicing or who spent most of the workday in motor vehicles, and 7 persons who commuted to work in their own cars. Twelve of the original 18 workers and 16 additional workers from service stations and garages constituted the study group in the post-exposure phase. During the use of MTBE, the median blood MTBE concentration among workers before the workshift was 0.013 μmol/l (1.15 μg/l) and after workshift 0.02 μmol/l. The maximum concentration measured was 0.42 μmol/l. TBA concentrations were somewhat higher, the maximum value was about 1 μmol/l. Among commuters, the median blood MTBE concentrations prior to commuting and on arrival at work were 0.002 and 0.011 μmol/l, respectively. After the programme was suspended, among the core group of 12 workers, the median post-shift blood MTBE concentration was about six times lower. Using a questionnaire, the investigators inquired for 15 symptoms. Based on hotline complaints the key symptoms asked were headache, eye irritation, burning of the nose or throat, cough, nausea or vomiting, dizziness, a sensation of "spaciness" or disorientation. The other questions concerned diarrhoea, fever, sweats, skin irritation, muscle aches, fatigue, fainting, and difficulty breathing. The workers reported key symptoms frequently during the programme and only occasionally after the programme had been suspended; the workers with the highest blood MTBE concentrations appeared to report more symptoms although the relation was not significant. The study provides meaningful information about individual MTBE exposures,

which have been low. Concerning biological effects by MTBE, the study is fraught with uncertainty due to selection of subjects and potential reporting bias under conditions of intensive media coverage. On the other hand one could expect people to perceive many of the "key symptoms" as a transient acute effect while exposed to foul-smelling petrol vapours e.g. during refuelling.

In search for an explanation why the introduction of oxygenated fuels in Alaska caused a particularly strong public reaction, the odour thresholds of the Alaskan oxygenated petrol vapours were compared to those of the base petrol without MTBE (both preparations produced by Mapco) and to the oxygenated petrol used in other states (API manufactured by Sun Corporation) (Smith et al., 1995). The vapours of the Alaskan crude petrol formulated with 15% MTBE were detected at lower concentrations than those of the other blends, so the authors drew the conclusion that Mapco petrol interacted with MTBE to form a distinctive, odoriferous mixture. Lower ambient temperatures typical of Alaska had a negligible effect on odour thresholds.

A very similar survey as in Alaska was conducted in Stamford, Connecticut in early April 1993 (White et al., 1995). Publicity about the health effects of oxygenated petrol was considered minimal in the community. Among occupationally exposed groups, the highest blood MTBE levels were detected in three petrol service station attendants (median 0.17 μmol/l, max. 0.33 μmol/l), whereas the levels were highly variable among car mechanics (median 0.02 μmol/l, max. 0.42 μmol/l; n=21). Among 14 commuters, the corresponding values were 0.001 and 0.03 μmol/l. Again, the workers showing high blood MTBE concentrations were more likely to report the "key symptoms" of Moolenar et al. (Moolenaar et al., 1994) whereas none reported the other symptoms. The merits and limitations of the study are essentially the same as in Moolenar et al. (1994).

A third study was conducted on garage workers in northern New Jersey in April 1993, when the oxygenated fuel programme was still in place, and in southern New Jersey in May 1993 after the oxygenated petrol had been phased out during the preceding two months (Mohr et al., 1994). Groups of 115 garage workers in the northern part of New Jersey and 122 workers in the southern part participated (participation rate was about 80%). The subjects filled out several questionnaires including one that inquired for symptoms and their severity over the last 30 days. Limited efforts were made to estimate exposure to MTBE in northern New Jersey, whereas in southern New Jersey 1-hour air samples were collected from the garages and 20 workers also carried passive samplers. While the authors expected that workers in the north were more exposed than those in the south, some workers were found to receive a significant exposure even in the south, most likely due to servicing cars that still contained wintertime fuel. The overall symptom reporting was quite low. In the comparison among garage workers in the north and in the south there was no difference in the reporting of symptoms over the last 30 days. Both groups felt significantly worse by the end of the workday, but there was no difference between the groups across the workshift. Analysis of a subset of 13 workers in the north and 15 workers in the south who spent on average more than 5 hours / day pumping petrol indicated no difference in symptom reporting over the last 30 days, but northern workers had more pre-shift and post-shift symptoms. However, the mean age of the northern workers was 15 years higher. When the groups were matched by age, sex and education (limiting the numbers to 11 in both groups), the difference in symptom reporting disappeared.

A fourth study was conducted in Wisconsin and Illinois in February and March 1995 after significant media attention had been focussed on the use of reformulated petrol (mostly containing MTBE as an oxygenate) in metropolitan areas since November 1994, and after health complaints had been received by the State Health Departments (Anderson et al., 1995). About

500 residents in the Milwaukee metropolitan area (where reformulated petrol, RFG, was in use), in the Chicago metropolitan area (also required to use RFG), and in the remainder of Wisconsin (a control region with minimal or no use of RFG) were interviewed (altogether 1,513 interviews) by a random digit dial health survey method. The response rate was 58%. The sampled populations were found to reflect the demographic characteristics of the three areas studied. Symptom prevalence over the period from November 1, 1994 was significantly higher in Milwaukee than in Chicago and Wisconsin, whereas it was not different between the latter two. In Milwaukee, people 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. Thus it is apparent that the higher symptom prevalence in Milwaukee cannot be attributed directly to RFG, which conclusion finds further support from the fact that every symptom inquired was more prevalent in Milwaukee than in the two other areas, including symptoms not previously associated with petrol and its components. However, the researchers did not rule out subtle effects of RFG exposure, or the possibility that a relatively small number of individuals may have a greater sensitivity to RFG mixtures.

With a view to study potential hazards of exposure to petrol vapours Hakkola et al. (1996a) examined the occurrence of neuropsychological symptoms and moods among 101 petrol tanker drivers (83% of those invited) and their controls of 100 milk delivery drivers (68% of those invited) in six municipalities in different regions of Finland. The drivers were aware of the study objectives, but there was no media attention on MTBE. The comparability of the subject groups for age, duration of work history, perceived health, occurrence of chronic disease, use of alcohol, and regular medication was satisfactory. The study inquired for symptoms experienced during the last month, consisting of six symptom scales: sleeping disturbances, fatigue, memory and concentration difficulties, emotional lability, somatic complaints, and sensory and motor symptoms. The modified Profile of Mood States (POMS) used inquired for feelings and moods during the last week with scales on tension/anxiety, fatigue, forgetfulness, vigour, depression, hostility, listlessness, and uncertainty. The exposures of petrol tanker drivers to the vapours including MTBE (petrol contained 10% MTBE) were measured. In the loading and delivery phases, lasting from 10-44 minutes, the mean concentrations of C_3-C_{11} hydrocarbons ranged 44-551 mg/m^3, and the corresponding MTBE concentrations ranged 13-91 mg/m^3 (3.6-25 ppm). In the whole study population age, chronic diseases, and perceived health were related to the occurrence of symptoms and POMS scales, however, there were no significant differences among the two groups of drivers.

In order to explore possible changes during a workweek, the two groups of drivers were interviewed twice: at home before the workweek and at work at the end of the last working day of the week, employing a questionnaire concerning moods (POMS) (Hakkola et al., 1997). Moreover, after the workweek the drivers were also asked with an open question about acute symptoms. The changes of the scores in POMS over the week relative to the first interview showed significant increases in the fatigue scale among tanker drivers. A similar but less distinct effect was found for milk delivery drivers. An index of exposure to petrol vapours was constructed for each tanker driver by multiplying the working hours during the week with the proportion of loads containing petrol. When the tanker drivers were divided into two groups by the index, drivers with more exposure scored higher in fatigue and hostility, whereas the vigour score changes were greater among drivers with less exposure. Regarding the open questions, among the tanker drivers 20/101 reported symptoms during the workweek: headache (8), dizziness (1), nausea (8), dyspnoea (1), increased saliva excretion (2). One milk delivery driver had experienced irritation from exhaust gases in a tunnel. The previous results suggest that exposure to petrol vapours, including MTBE, may have a slight effect on the feelings of well-being over the workweek, but more clearly, the short-lasting exposures which sometimes may

reach significant peak levels, were not infrequently associated with acute symptoms of the kind earlier reported in the USA. To shed more light on the MTBE exposure among tanker drivers, another Finnish research group subsequently investigated two groups of drivers and found geometric mean concentrations of 4.3 mg/m^3, 1.2 ppm (n=15), and 6.4 mg/m^3, 1.8 ppm (n=20) in breathing zone samples during the loading phase (Vainiotalo et al., 1998a). The corresponding blood MTBE concentrations found 20 minutes after loading were 0.14 μmol/l and 0.21 μmol/l.

An ecological study was conducted in Anchorage and Fairbanks, Alaska, concerning outpatient visits of state employees and their dependents due to upper respiratory illnesses, bronchitis, asthma, or headaches over three winters 1990 through 1993 (Gordian et al., 1995). The size of the population involved was about 20,000. The rate of claims for the above illnesses over the three years was found to be stable. The rate of claims in the winter of 1992-93 in both Anchorage and Fairbanks peaked in December, and decreased in January and February in both Anchorage and Fairbanks even though MTBE was still being used in Anchorage.

Fiedler et al. (1994) studied with a telephone interview the occurrence of symptoms often related to MTBE among small groups of patients with multiple chemical sensitivity (n=14), chronic fatigue syndrome (n=5) and six healthy controls of comparable age, sex, education, and ethnicity. The persons were interviewed about occurrence of symptoms in environments with (e.g. driving an automobile, petrol stations) and without (e.g. shopping malls, parks) likely exposure to MTBE. The patients reported more symptoms typically associated with MTBE in all situations, particularly in shopping malls and petrol stations. The authors concluded from the limited data that the symptoms of persons known to be sensitive to chemicals were not related to situations where MTBE was most prevalent.

Blood samples from 22 car mechanics in Fairbanks were sampled in the morning and in the end of the workday during the period of use of oxygenated fuels in November-December 1992 for analysis of plasma levels of interleukin 6 (an inflammation mediator) (Duffy, 1994). The results were unremarkable.

Exposure via drinking water

A group of 60 patients (38 males and 22 females, median age 42 years, range 18-71) with various symptoms but no obvious clinical explanation other than having used contaminated tap water containing 1-76 μg/l (ppb) MTBE and 0.2-14 μg/l benzene for a period of five to eight years were examined, about one year after the last episode of exposure, for occurrence of apoptotic forms of peripheral blood lymphocytes (Vojdani et al., 1997). The control group consisted of 32 healthy individuals (17 males and 15 females) from the same geographical area without exposure to contaminated water or without other known environmental or occupational exposures to solvents or other chemicals. The patient group was characterised by the following symptoms (prevalence in excess of one third): severe headache, malaise/fatigue and exhaustion, difficulty concentrating, anxiety, dizziness/loss of balance with muscle weakness, insomnia and short-term memory loss. Among patients, 1-58% of the peripheral blood lymphocytes were undergoing apoptosis compared to 1-26% among the controls (the difference was significant). Moreover, while 89% of the cells from control persons were in the resting phase, the corresponding value for patients was 52%, and there was a shift from the resting phase to DNA synthesis (S) or to mitosis (G_2/M) phases. The study findings are interesting, and show changes in immunocompetent cells, but no conclusions can be drawn concerning the underlying causes.

Skin exposure

Although substantial evidence is lacking, due to the effective lipid extraction properties of MTBE it can be presumed that repeated skin exposure may result in skin fatigue (and consequent risk of toxic eczema), an effect common to a variety of organic solvents.

Conclusions on repeated dose toxicity in humans

There are no data on human populations repeatedly exposed to MTBE only, however, some inferences can be drawn from observations concerning exposures to the vapours of oxygenated petrol containing 10-15% MTBE. Some early studies have reported symptoms among groups of workers occupationally exposed to oxygenated petrol vapours, but the measured body burdens of MTBE were low (blood MTBE concentration invariably less than 0.5 μmol/l). The studies were not adequate to address the nature and origin of symptoms, or the dose-response. More recent studies of petrol tanker drivers tried to explore more systematically the relationships between exposures and symptoms or moods in the past and over a working week. Experiences concerning symptoms, feelings and moods related to past exposures did not indicate differences among petrol tanker drivers and milk delivery drivers, but there was a greater increase of fatigue over the workweek in the group of petrol tanker drivers with an apparent dose-response. Furthermore, 20% of the tanker drivers responded to an open question with symptoms similar to the ones reported earlier (mainly headache and nausea). Exposure measurements indicated that significant (up to 91 mg/m^3) peak levels of MTBE, on top of hydrocarbons (up to 551 mg/m^3), for about half an hour or less may arise in the loading phase. Against this background, it is not unexpected that acute, transient symptoms may arise in the context of exposure to petrol vapours. However, the presently available data do not suggest any long-term neuropsychological impairment.

4.1.2.6.3 Conclusions on repeated dose toxicity

A NOAEC of 800 ppm for inhalation exposure is selected, based on the mild liver effects seen in the 13-week rat study by Lington et al. (1997) at 4,000 ppm and in the two-year study at 3,000 ppm (Bird et al., 1997). The absence of these effects at 400 and 500 ppm in the other 13-week (Greenough et al., 1980) and the 28-day study (Chun et al., 1993) on rat supports the selection of this NOAEL value. Moreover, the effects seen at 1,000 ppm are only slight changes in red blood cell parameters and lactate (Greenough et al., 1980). In the previous study, a NOAEL of 500 ppm was chosen due to reduced lung weight seen at 1,000 ppm. However, this finding was not seen except transiently at 14 days in the 90-day oral study. Apart from slightly increased severity and incidence of chronic progressive nephropathy (CPN), there were no significant signs of toxicity in microscopical analysis at 400 ppm in the 2-year carcinogenicity study. CPN is a common pathological event in ageing rats under prolonged exposure to a xenobiotic chemical. The use of the two-year study for other toxicological end-points is somewhat limited since haematological analysis and urinalysis was performed only for the control and high dose animals. In addition, and clinical chemistry was carried out only for corticosterone.

In oral exposure, male rats exhibit hyaline droplet formation in the proximal convoluted tubules at 440 mg/kg (IITRI, 1992), an effect that is male-rat specific. In the 90-day Sprague-Dawley study by Robinson (1990), there is an absence of significant findings at 100 mg/kg. At 300 mg/kg only the female rats had a statistically significant increase in kidney weight. However, this was not accompanied by degenerative microscopical findings, which only appeared in the males of the 1,200 mg/kg group. In addition, clinical chemistry of the females showed no adverse signs that would support kidney toxicity at that level (Robinson et al. 1990). Williams et

al. (2000a) reported seemingly different results. They found increased relative kidney weight and protein droplet nephropathy with significantly increased severity and incidence in the same male rat species (Sprague-Dawley) already at 250 mg/kg. The effects seen in liver, namely weight increase, hypertrophy and slight morphological changes, are mostly seen at doses 500 mg/kg and higher. These effects may be adaptive responses, which is corroborated by the fact that there are few signs of remarkable liver toxicity even in the 2-year carcinogenicity studies (described in detail in the carcinogenicity section). In any case, less weight is put on the study by Williams et al. (2000a), since it was conducted mainly to observe changes in endocrine homeostasis with limited weight put on statistical analysis of other toxicological end-points. Based on the findings in the rat liver in the study by Robinson et al. (1990) in the sub-chronic 90-day study, a **NOAEL of 300 mg/kg** is chosen for **oral administration**.

4.1.2.7 Mutagenicity

4.1.2.7.1 Studies *in vitro*

Gene mutations in microbial systems

A number of bacterial mutagenicity tests has been conducted using *Salmonella typhimurium* as a test systems and concentrations. Convertant frequency has also been additionally determined for *Saccharomyces cerevisiae*. **Table 4.32** summarises the data on MTBE testing in prokaryotic and eukaryotic microorganism mutation tests:

Table 4.32 Genetic effects of MTBE in microbial test systems

Test system	Result Without exogenous metabolic system	Result With exogenous metabolic system	Dose µg/plate LED or HID	Reference
Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	-	-	10,000 #	Litton Bionetics Inc. (1978); ARCO (1980)
Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	-	-	5,000	Hüls (1991) §
Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	-	-	10,000	Cinelli et al. (1992)
Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	-		10,000	Life Science Research (1989b) §
Salmonella typhimurium TA98, TA100, TA102, TA1535, TA1537	-	-	5,000	RBM (1996f) §
Salmonella typhimurium TA98, TA100, TA104, TA1535	-	-	7,400	Kado et al. (1998)
Salmonella typhimurium TA102	+/-	+	500	Williams-Hill et al. (1999)
Salmonella typhimurium TA98, TA100	-	-	100	Zhou et al. (2000)
Saccharomyces cerevisiae D4	-	- *	10,000	Litton Bionetics Inc. (1978); ARCO (1980)

§ = OECD or EU guideline study
* = There was no positive control available in the activation assay for this strain
# = ml/plate (density = 0.74 at 20ºC)
LED = Lowest Effective Dose, HID = Highest Ineffective Dose

Few signs of mutagenic activity have been found in microbial tests so far. However, Williams-Hill et al. (1999) were able to demonstrate a positive result in an Ames test using TA102 strain. MTBE was described as "weakly" mutagenic when no S9 was present and "moderately" mutagenic when rat liver S9 was used. It is worth noting, however, that the response described as "weak" was very low and the significance of the difference seen in the number of revertants between the control group and the group with no metabolic activation remains unclear. When human liver S9 was added, colony formation diminished to the level where it was without S9 (Williams-Hill et al., 1999). Addition of formaldehyde dehydrogenase (FDH) to the medium inhibited mutagenicity by 25–30%. FDH oxidises formaldehyde to non-mutagenic formate and thus reduces the mutagenic impact. A shortcoming of this study is that the MTBE used was synthesised and no reference was given for the method of synthesis, giving no means to estimate the possible side products. In addition, the purity of the substance was not reported. However, this issue was later clarified through personal communication with the corresponding author, Ms. Williams-Hill. According to her (Willams-Hill, 2000), the MTBE used in the experiment was prepared by treating methanol with isobutylene under Nafion-H catalysis. The resulting MTBE was doubly distilled using all glass apparatus (boiling point: 55-56^{o}C). The purity of the material was more than 99.9% as was analysed by GC analysis. The compound was stored under nitrogen to prevent oxidation.

The authors' hypothesis was that the presence of an intact excision repair gene present in TA102 might be needed to bring out the mutagenicity, since a test conducted (Kado et al., 1998) gave a negative result with Ames strain TA104. TA102 and TA104 are both test systems, which measures oxidative damage to DNA. Nevertheless, the results indicated that the formaldehyde formed in the presence of the exogenous S9 mix is probably responsible for the positive effect seen. The weakness of mutagenic response with human S9 mix is likely to be attributable to different efficiencies of formaldehyde metabolic between rats and humans. It has been reported that the monophasic $T_{½}$ of MTBE from blood in rats is about ½ hour whereas for humans it is more than 2½ hours (Miller et al. 1997; Bernauer et al., 1998). The authors' finding of a weaker mutagenic effect with S9 and FDH is similar to the one demonstrated in the mouse lymphoma assay by Mackerer et al. (1996). The involvement of formaldehyde seems likely; the IARC formaldehyde monograph (IARC, 1995) reports positive Ames tests with TA102 when no S9 was present. However, also the strains TA100 and TA104 have been tested positive with formaldehyde but show no mutagenicity with formaldehyde metabolised from MTBE. It is possible that TA102 is more sensitive than TA100 and TA104 and therefore a positive response is seen at markedly lower concentrations of formaldehyde resulting from MTBE metabolism. Interestingly, the investigators had also tested TBA in this test system and reported it to be mutagenic with S9. This, the authors stated, probably contributed to the residual mutagenicity seen even in the presence of FDH.

Additional data are available to estimate the mutagenicity of MTBE in TA102-strain. The study conducted by RBM (1996) reports negative mutagenicity for MTBE with and without metabolic activation. The study is in accord with OECD guidelines and GLP-principles.

In general, little attention has been paid to the possible loss of the test substance due to its volatile nature, which may have an impact on the result. Kado et al. (1998) addressed this problem using a Salmonella microsuspension assay, which is a slightly modified version of the conventional Ames plate assay. This method uses a closed tube in the beginning of the experiment to minimise the escape of volatile substances.

Gene mutations and gene effects in mammalian cell systems

Mouse lymphoma cells (L5178Y TK+/-)

Mouse lymphoma cell line L5178Y TK+/- cultures were exposed to MTBE (96% and 99% pure) at concentrations ranging from 0.39 to 6.25 µl/ml for 4 hours (ARCO, 1980). After a 2-3-day recovery and expression period cells were plated on agar plates with a selection medium. After 10 days incubation, the total number of resistant colonies were counted and the ratio to cells growing in non-selective medium was determined (= mutant frequency). This assay was also run in parallel with S9 fraction from Fisher-344 rat liver homogenate to allow for metabolic activation of MTBE. Five parallel assays were conducted.

MTBE showed an increased and a dose-dependent mutation frequency in the presence of metabolic activation. However, cells cultivated without S9-mix exhibited no meaningful changes in mutation frequency when compared to controls. This suggests an involvement of MTBE metabolite in the mutagenesis. Tert-butyl alcohol (TBA) has been previously tested in a similar L5178Y TK+/- test. The results showed that TBA induced no increase in mutagenesis either with or without S9 mix (European Chemicals Bureau, 1998). Mackerer et al. (1996) investigated the possible role of formaldehyde in the mutagenic events. Formaldehyde is a metabolite of MTBE and a well-known mutagenic substance. They exposed mouse lymphoma cells to 1-4 µl/ml MTBE for 3 hours and added formaldehyde dehydrogenase (FDH) with its co-factor NAD+ to the medium. The latter two convert formaldehyde to non-mutagenic formic acid, thereby squelching the possible mutagenicity resulting from formaldehyde. The results showed that the mutation frequency did not increase when FDH and its coenzyme were present, while there was a five-fold increase in its absence.

HPRT-locus

A mammalian gene mutation test comparable to the above was conducted by Life Science (Life Science Research, 1989a) following the OECD guideline 476 and using Chinese hamster V79 cells. Hypoxanthine-guanine phosphoribosyl transferase (HPRT-gene in X-chromosome) insufficiency was used to measure mutation frequency in two independent assays. Cells were exposed to 625–10,000 µg/ml (313-2500 µg/ml with S9). S9-mix derived from Sprague-Dawley rat liver tissue was used in parallel as the metabolic activator. Mutant frequencies were counted after six and nine days of gene expression. There were no noticeable changes in mutation frequency at any concentration or observation time point with or without metabolic activation when compared to the controls. Another reverse mutation test with Chinese hamster V79 cells is available. The researchers of the study stated that when the S9-mix was present, the survival of the cells decreased steeply at concentrations 1250-10,000 µg/ml. Nevertheless, they found no change in mutation frequency (Cinelli et al., 1992).

Unscheduled DNA synthesis

The rate of unscheduled DNA synthesis in primary rat hepatocytes was used to assess MTBE's potential to damage DNA (Life Science Research, 1989c). Hepatocyte cultures were treated with concentrations ranging from 3.16 to 10,000 µg/ml for 17 h ± 30 min in the presence of tritiated thymidine. After the 7-day exposure period under autoradiographic coating, standard cell staining technique was used to visualise the resulting silver grains representative of thymidine incorporation into the nucleus and cytoplasm. At least 50 cells/slide were scored and cells of abnormal morphology or S-phase were not counted. 2-acetylaminofluorene was used as the

positive control. There was no increase in the percentage of cells in repair when compared to controls.

Cinelli et al. reported no induction of DNA synthesis in primary rat hepatocytes when cells were treated with 1,000 – 10,000 µg/ml. Mean net grain count did not increase from 5 grains per nucleus (Cinelli et al., 1992).

Hepatocytes from the livers of two male Sprague-Dawley rats were collected for an unscheduled DNA synthesis assay conducted by Zhou et al. (2000). MTBE was dissolved in DMSO, the hepatocytes were incubated with 5 µCi/ml $^{[3H]}$methylthymidine and 0, 200, 600 and 1,000 ug/ml MTBE for 3 hours at 37^{o}C. Thereafter the cells were collected onto filters, which were fixed and dried and their radioactivity was measured with liquid scintillation spectrometer. The counts increased with dose and gave the following results when expressed as counts per minute: control: 712 CPM, 200 µg/ml: 777 CPM, 600 µg/ml: 1311, 1,000 µg/ml: 1,437 CPM (statistically significant).

Chromosome mutations in Mammalian Cells

Chinese hamster ovary cells

Ability of MTBE to produce chromosome aberrations in Chinese hamster ovary (CHO) cells was investigated by exposing the cells for two hours to MTBE. The concentrations ranged from 0.01 to 5.00 µl/ml in the non-activation assay and from 0.004 to 1.000 µl/ml when metabolic activation was present. The experiment was conducted using 99% and 95% pure MTBE. Dose selection was based on an assay, where the toxicity was investigated exposing *mouse lymphoma cells* to various concentrations of MTBE. Mitotic indices were not determined. In their absence, neither a reliable estimation of cell toxicity nor the dose range relevance is possible. In addition, the difference between negative and positive controls was not big enough to draw any well-founded conclusions. No historical control data were provided. Moreover, the aberration counts had remarkably variable results from one another in the parallel experiments. An additional, second assay was performed using only the highest MTBE concentration and cyclophosphamid as positive control which gave a clearer response. As in the first assay, there was no increase in chromosomal aberration frequency. However, as stated before, the relevance of the dose remains unclear which makes the interpretation of the results difficult (Litton Bionetics Inc., 1980a).

Sister chromatid exchange

Together with the above CHO test, a sister chromatid exchange assay was conducted in parallel. The same cells, MTBE concentrations, exposure time and general study design were applied as in the CHO assay, apart from the positive controls. Twenty mitotic cells were scored. No differences were noted in the SCE frequency at any dose level with or without metabolic activation with 95% MTBE. With the 99% MTBE, equivocal positive results were obtained. There was a significant increase of SCE frequency in one of the replicates at 1µl/ml. However, because there was only a small increase of SCE induction with positive control, the test was repeated. Repeat tests failed to confirm the previously seen positive result (Litton Bionetics, 1980a).

Cell Micronucleus test

NIH/3T3 cells pre-grown for 24 hours in a flask were washed and transferred to DMEM medium containing 0, 5, 10 or 20 µl/ml MTBE (98.8% pure) (Zhou et al., 2000). After 24 hours of treatment, slides were prepared and stained with 10% Giemsa stain solution. A 20µg/ml solution

of cyclophoshamide was the positive control. The micronuclei were scored using the criteria described by Lasne et al. The frequency counts were based on 10,000 scored cells and they were expressed as the average number of micronucleated cells per 2,000 cells. Compared to control, the frequencies of micronuclei were not significantly increased.

Table 4.33 Summary of *in vitro* genotoxicity tests with MTBE

Test system	Treatment	Result	Reference
Gene mutation in Mouse lymphoma cell line L5178Y TK+/- (±S9)	0.39 to 6.25 µl/ml for 4 hours	positive	ARCO (1980)
Gene mutation in Mouse lymphoma cell line L5178Y TK+/- (±S9) (+ Formaldehyde dehydrogenase + NAD)	1-4 µl/ml 3 hours	Positive/ (negative)	Mackerer et al. (1996)
Gene mutation in HPRT-locus Chinese hamster V79 cells	625–10,000 µg/ml 313-2,500 µg/ml with S9 for 6 days	negative	Life Science Research (1989a)
Gene mutation in HPRT Chinese hamster V79 cells	1,250-10,000 µg/ml	negative	Cinelli et al. (1992)
Unscheduled DNA synthesis primary rat hepatocytes (± S9)	3.16 – 10,000 µg/ml for 17 h ± 30 min	negative	Life Science Research (1989c)
Unscheduled DNA synthesis primary rat hepatocytes (± S9)	1,000 – 10,000 µg/ml	negative	Cinelli et al. (1992)
Unscheduled DNA synthesis primary rat hepatocytes	200 – 1,000 µg/ml for 3 hours at 37° C	positive	Zhou et al. (2000)
Chinese hamster ovary cells, chromosome aberration, (±S9)	0.004 to 5.00 µl/ml 0.004 to 1.00µl/ml (s9)	Negative	Litton Bionetics Inc. (1980a)
Sister Chromatid Exchange Chinese hamster ovary 95% MTBE	0.004 to 5.00 µl/ml 0.004 to 1.00 µl/ml (s9)	negative	Litton Bionetics Inc. (1980a)
Sister Chromatid Exchange Chinese hamster ovary, 99% MTBE	0.004 to 5.00 µl/ml 0.004 to 1.00 µl/ml (s9)	equivocal	Litton Bionetics Inc. (1980a)
Mouse micronucleus (NIH/3T3), 98.8% MTBE	5, 10, 20 µl/ml	negative	Zhou et al. (2000)

4.1.2.7.2 Studies *in vivo*

Sex-linked recessive lethal test in drosophila melanogaster

Approximately 250 Oregon-R stock of wild type *Drosophila melanogaster* males were treated with 0.03-0.3% MTBE in sucrose. The dosing scheme was based on earlier toxicity and fertility tests. The survival rate at the selected doses varied between 55% and 86%. Positive control substance was ethyl methanesulfonate and 5% sucrose in water served as the negative control. Treated P1 males were mated with Basc strain of females following the Basc (Muller-5) mating scheme and 3,2,2-day sequence brooding scheme for sperm sampling. The percentage of F2-recessive lethals was counted and the significance of the results was analysed using Cochran-Armitage trend testing combined with Fisher-Irwin exact test for heterogeneity (Sernau, 1989; McKee et al., 1997).

Of the 5385 X-chromosomes tested at 0.03% MTBE, a 0.13% recessive lethal rate was found. In the mid-dose group, 0.14% recessive lethal rate was observed in 5,039 chromosomes tested. Similarly, the flies that were treated with 0.3% MTBE, had a lethal type rate of 0.11% out of the

6222 X-chromosomes tested. Negative control had an average lethal rate of 0.09% and positive control 39%.

Unscheduled DNA synthesis in mouse hepatocytes

CD-1 mice (10 of each sex/dose) received by inhalation target MTBE vapour concentrations of 400, 3,000 and 8,000 ppm to for 6 hours. Treatment was given in two consecutive days. The mice were sacrificed for hepatocyte collection 16 hours after the second exposure. The hepatocytes from the positive control, N-nitrosodimethylamine (10mg/kg), were collected 2 hours after treatment. Labelling was done by incubating the cultures with 10 μCi/ml ^{3}H-thymidine for 4 hours and then terminated by washing and a 16-hour incubation with 0.25 mM thymidine. The fixed samples were dyed and 100 nuclei per/animal were calculated (McKee et al., 1997; Vergnes et al., 1994).

The net nuclear grain counts were all less than zero for all doses and both sexes. The percentage of cells in repair was not increased; the percentages were less than 2% at all dose levels and in both sexes. It should be noted that there was no 2 hour-collection time after treatment with MTBE.

Gene mutation in HPRT-locus

Ward et al. (1995) in an *in vivo* test investigated mutagenic activity of MTBE at the HPRT-locus of spleen lymphocytes with CD-1 mice. They administered MTBE doses of 1, 10, 100 and 1,000 mg/kg by gavage, 5 days / week for three weeks. Each group consisted of 5 mice/sex/group. Lymphocytes recovered from the spleen were screened for the frequency of HPRT-mutants in a clonal assay.

Mean mutant cell frequencies (±SD) in male mice per 10^{6} evaluated cells, in respective order from negative control to the highest dose were 2.01±0.77, 2.17±0.76, 2.02±0.78, 2.93±1.56 and 2.69±0.67. Response to the positive control, ethylnitrosourea, was 10-fold. Thus, there was no increase in the mutant frequencies at any dose level when compared to the controls.

Micronucleus test in mice

Target MTBE vapour concentrations of 400, 3,000 and 8,000 ppm were administered to CD-1 mice (5M+5F/dose) for 6 hours. Treatment was given in two consecutive days. Positive control animals received an intraperitoneal injection of cyclophosphamide (15 mg/kg) to five animals/sex. Bone marrow was sampled 24-48 hours after the last exposure and the ratio of polychromatophilic and normochromatophilic cells (PCE/NCE) were counted for 1,000 erythrocytes. The proportion of micronucleated PCEs (MN-PCE) was expressed per 2,000 polychromatic erythrocytes (Vergnes et al., 1993; McKee et al., 1997).

PCE-NCE-ratio showed no meaningful changes when compared to controls. The micronucleated PC/PCE mean percentages ranged in males from 0.20% at 400 ppm to 0.23% at the two highest doses at the 24-hour sampling time. Male negative control mice had a MN-PCE/PCE percentage of 0.20% whereas the positive control group had 1.41% Female mean percentages at the 24-hour sampling time varied from 0.17% at 400 ppm to 0.27% at 8,000 ppm. Negative controls had a mean percentage of 0.20% at 24-hour sampling time and positive control mice 0.89%. Based on these results, no significant increases were evident in micronucleated polychromatophilic erythrocytes. The samples from 48-hour time point showed similar figures to 24-hour.

Swiss Webster mice (five/group) were given 250, 500, 1,000, 1,500, 1,750 mg/kg MTBE in a single intraperitoneal injection (Kado et al., 1998). Bone marrow sampling was done after 24 hours. One thousand PCEs were analysed per mouse. An intraperitoneal injection of cyclophosphamide (CP, 40 mg/kg) served as the positive control.

Percentages of micronucleated PCE varied from 0.10% (1,000 mg/kg) to 0.34% (1,750 mg/kg) in male mice. In negative control group (olive oil) the percentage was 0.30% and for cyclophosphamide (CP) 2.96%. PCE percentage varied from 63% (250 mg/kg) to 68% (1,750 mg/kg) while negative control group percentage was 65% and CP 38.1%. For female mice, a background reading of 0.16% was obtained for micronucleated PCE and for positive control group 2.82%. MTBE-dosed mice had percentages that varied from 0.20% (500 mg/kg) to 0.36% (1,500 mg/kg) which represent a small and statistically insignificant increase. The highest dose had a value that was identical to control value. Negative control mice had a PCE of 47% while the treatment groups had up to 63% PCE (500 mg/kg). Positive control had a PCE percent of 48%.

Bone marrow cytogenetic test in rat

Inhalation

Eight-week-old Fisher-344 rats received 800, 4,000 and 8,000 ppm MTBE in whole-body exposure (five of both sexes/group) for five consecutive days, 6 hours per day (Vergnes et al., 1989; McKee et al., 1997). Colchicine was given (4 mg/kg) 2-3 h after termination to produce a mitotic arrest. Sacrifice and sampling were done at six or 24 hours after the last exposure. When possible the proportion of mitotic cells was assessed from 500 cells/animal and fifty mitotic cells were evaluated for incidence and type of chromosomal damage.

When sampling was done 6 hours after treatment, the mean percentage of aberrant cells in males ranged from 5.6% (800 ppm) to 7.2% (8,000 ppm) in male rats and from 3.2% (4,000 ppm) to 4.0% (8,000 ppm) among female rats. Negative control means were 5.2% and 3.2%, respectively. At 24 hours post exposure sampling time the mean percentages of aberrant cells in males varied from 1.6% (8,000 ppm) to 2.8% (800 and 4,000 ppm) and in females from 2.4% (800 ppm) to 2.8% (4,000 and 8,000 ppm). MTBE did not produce a statistically significant increase in the incidence of chromosomal aberrations in Fisher-344 rat bone marrow cells. MTBE did not have to have clastogenic properties in this test system.

Oral

Male Sprague-Dawley rats (eight/dose) were given orally 0.04, 0.13 and 0.4 ml/kg MTBE, either as a single dose or five doses with 24 hours intervals (Litton Bionetics Inc., 1979). Colchicine was administered intraperitoneally at 4.0 mg/kg three hours before kill. The post-exposure sacrifice times were 6, 24 and 48 hours. When possible, 50 mitotic cells were scored for incidence and type of aberration. An additional assay was conducted with sacrifice time at 48 hours after the last exposure because the first experiment did not result in any mitotic cells, including the negative controls, at this time point.

At 6 hours post exposure sacrifice time, with five consecutive doses, the aberration percentages were as follows: negative control: 0.6%, low dose: 0.5%, medium dose: 1.1% and high dose: 1.3%. At 24 hours, single dose: negative control 2.8%, low dose 1.4%, medium dose 0.3%, high dose 4.0%. At 48 hours, single dose the percentages were: negative control 0.5%, low dose 0.3%, medium dose 0.3%, high dose 1.5%. Positive control was only available for 24-hour post-exposure sacrifice time: 18.2%. Although the incidence of aberrant cells was not significantly increased when compared to negative controls, there was a two or 3-fold rise in aberration

frequency depending on the sacrifice time. The increases were mainly due to greater incidence of single or parallel chromatid without centromere or cells that had an uneven multiple chromosome number.

Comet assay on rat lymphocytes

In a SOT abstract, Lee et al. (1998) measured the rate of DNA-strand breakage in Sprague-Dawley rats using the alkaline (comet) SCGE assay. They received daily gavage doses of 40, 400 or 800 mg/kg day for 28 days. Lymphocytes isolated from trunk blood were analysed in the comet assay, stained and scored for apoptosis frequency. Apoptotic type comets appeared to be increased but showed no statistical significance (n=9/group). Related parameters that are measures of DNA-strand breakage (e.g. tail length, tail moment) were significantly increased at 800 mg/kg .

Table 4.34 Summary of *in vivo* genotoxicity tests with MTBE

Test system	Treatment	Result	Reference
Sex-linked Recessive Lethal Test in Drosophila melanogaster	0.03-0.3% (in sucrose)	negative	Sernau, 1989)
Unscheduled DNA synthesis in CD-1 mouse hepatocyte	400, 3,000 or 8,000 ppm (inh.) 2 days, 6 hours / day	negative	Vergnes et al., (1994; McKee et al. (1997)
Gene Mutation in HPRT-locus, spleen lymphocytes	1, 10, 100 and 1,000 mg/kg	negative	Ward et al. (1995)
Micronucleus Test in CD-1 Mice erythrocytes	400, 3,000 or 8,000 ppm (inh.) 2 days, 6 hours / day	negative	Vergnes et al. (1993)
			McKee et al. (1997)
Micronucleus Test in Swiss Webster Mice erythrocytes	250, 500, 1,00, 1,500, 1,750 mg/kg, single i.p.	negative	Kado et al. (1998)
Bone Marrow Cytogenetic Test in Fisher-344 Rat	800, 3,000 or 8,000 ppm (inh.) 5 days, 6 hours / day	negative	Vergnes et al. (1989)
			McKee et al. (1997)
Chromosome aberration in Bone Marrow Male Sprague-Dawley rats	0.04, 0.13 or 0.4 ml/kg (i.p), single dose or 5 doses / 5 days	negative	Litton Bionetics Inc. (1979)
Comet assay on rat lymphocytes	40, 400 or 800 mg/kg, daily gavage	positive	Lee et al. (1998)

4.1.2.7.3 Genotoxicity of MTBE metabolites

Formaldehyde

As formaldehyde is a primary metabolite of MTBE, it is possible to speculate that genotoxic effects similar to those of exogenously administered formaldehyde would be found. Casanova and Heck (1997a; 1997b) investigated the ability of formaldehyde, which is endogenously generated from MTBE in the CD-1 mouse hepatocytes, to form DNA and RNA cross-links and its possible incorporation into nucleosides of DNA and RNA. The researchers used MTBE at concentrations varying from 0.33 to 6.77 mM. MTBE had a labelled ^{14}C in its methoxy carbon. The concentration range was chosen based on physiologically based pharmacokinetic models

that simulated a 6-hour inhalation exposure in mice. To study the possible induction of the liver metabolism by MTBE, eleven mice were pre-treated with 1.8 g MBTE in corn oil/kg, given once daily by gavage for three consecutive days. Control animals received only corn oil. Formaldehyde labelled with ^{14}C served as the positive control. Low levels of nucleic acid cross-linking were present at all concentrations but this change was not dose-dependent. Whereas, when formaldehyde was added directly, RNA and DNA cross-links increased steeply with increasing concentration. The carbon incorporation to nucleic acid was clearly higher into RNA, more specifically to its adenosine and guanosine nucleotides. The ^{14}C incorporated mainly to thymidine but not to purines. The incorporation increased with dose. The data support the hypothesis that MTBE is efficiently metabolised to formaldehyde at low airborne concentrations, and that the conversion from MTBE to formaldehyde is slow relative to the HCHO oxidation. No species or sex or species specificity was seen when hepatocytes from female CD-1 mice, male B6C3F mice and male F344 rats were used.

Tert-butyl alcohol

The ability of tert-butyl alcohol (TBA) to induce point mutations has been investigated in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 at doses ranging from 0 to 10 mg/plate. The results were negative with and without metabolic activation using rat and hamster S9-mixes (Zeiger et al., 1987). Williams-Hill et al. (1999) showed that the strain TA102 showed an increased number of revertants in the presence of tert-butyl alcohol. The increase showed increase of revertants with dose up to 2 mg/plate. Mutagenic responses were studied in an L5178Y tk+/tk- mouse lymphoma cell forward mutation assay. There was a small increase of mutant fraction (1.6 x control), but the result was not reproducible in three other experiments with concentrations up to 5 mg/ml (McGregor et al., 1988). NTP has reported the conduct of *in vitro* genotoxicity studies including mutation studies in bacteria, mouse lymphoma cell mutation test and chromosomal aberration studies in Chinese hamster ovary cells. Tests were conducted with and without metabolic activation and a negative result was obtained in each test. *In vivo* mutagenic capacity was estimated by counting the frequency of micronucleated erythrocytes in mouse peripheral blood of B6C3F1-mice that were exposed via drinking water to 2.5-40 mg/ml tert-butyl alcohol for 13 weeks. There was no increase in the incidence of micronucleated erythrocytes in the mice exposed to TBA when compared to controls (NTP, 1995; 1997).

4.1.2.7.4 Summary of genotoxicity

In bacterial systems, there is one positive result in an Ames test (TA102) with S9 metabolic activation. In a mouse lymphoma mutagenicity test, there was a clear positive result, but again only with metabolic activation suggesting formaldehyde involvement. However, in this case the test does not reflect realistically MTBE metabolism to formaldehyde since the formaldehyde was generated outside the cell in an artificial environment. An *in vitro* liver UDS (Sprague Dawley) showed a significantly increased UDS activity at 1,000 mg/ml. However, in an independent, well-conducted study, an *in vitro* liver UDS resulted negative. Another mammalian *in vitro* measure for mutation frequency, i.e., Chinese hamster V79 cells gave no signs of mutagenic activity. Again to contradict the positive result in the *in vitro* UDS, there is an *in vivo* liver UDS, which was conducted with CD-1 mice with a maximum dose of 8,000 ppm. The result was negative. No significant increase in chromosomal aberration has been demonstrated *in vitro* or *in vivo*. Although the study design of the two latter studies could be challenged, a more sensitive *in vivo* measure of chromosomal damage, the mouse micronucleus test, also failed to show any positive effect in two independent studies conducted via inhalation or intraperitoneally. A bone marrow cytogenetic study conducted with F-344 rat resulted negative. In an abstract-reported

comet assay conducted on rat lymphocytes, a significantly increased DNA strand breakage at an oral dose of 800 mg/kg for 28 days was displayed. However, the biological significance this result remains questionable.

For some *in vitro* tests, a residual doubt remains whether their design has properly taken into consideration the volatile nature of MTBE. Only in one publication (Kado et al., 1998), it has been stated that they had accounted for this factor in their experimental design. However, due to the high water solubility of MTBE it is likely that the vapour pressure of MTBE in medium is not so marked that significant reduction concentrations occur. Moreover, all the conventional *in vivo* tests have turned out negative.

The proliferative changes seen in rat cells of lymphoid origin have raised questions of their possible genotoxic mechanism. Nevertheless, an *in vivo* test in mouse spleen lymphocytes showed no sign of positive response. Furthermore, the aberration and cytogenetics tests *in vivo* have all come out negative. The study by Casanova et al. (1997a) gives reassuring evidence that formaldehyde endogenously generated from MTBE does not have a significant genotoxic impact. Moreover, it is known that any generated formaldehyde rapidly reacts with glutathione, forming S-hydroxymethylglutathione, a substrate for formaldehyde dehydrogenase that swiftly catalyses the oxidation of the substrate to formylglutathione, which is subsequently hydrolysed to formate. This enzymatic event is known to take place in a number of tissues in a variety of species.

Conclusions on genotoxicity and mutagenicity

Based on the available information, MTBE cannot be considered a mutagen.

4.1.2.8 Carcinogenicity

Fisher-344 rat: 104-week inhalation exposure

In a two-year carcinogenicity study, groups of 50 Fischer-344 rats of each sex are exposed to MTBE concentrations of 0, 400, 3,000, 8,000 ppm in an exposure chamber for 6hours per day, 5 days per week for 24 months (Bird et al., 1997). Bodyweight observations together with clinical signs were recorded weekly (from 13th week biweekly). Analyses for haematology parameters were performed on high dose and control animals at mid-study and at the end. Blood corticosterone levels were measured from ten randomly selected surviving males from all dose groups in the weeks 81-104 of the study. Six months before the termination of the study, urine was collected from 10 male and 10 female high dose and control rats for urinalysis. The brain, liver, kidneys, lungs, spleen, adrenals and testes were weighed at necropsy, which was performed on all animals. Histopathology examination was carried out on all observed lesions, as well as 44 organs of the high dose and control animals and on any animals that died or were sacrificed moribund. Additionally, in males, liver, kidneys and testes were examined from the two lower dose groups.

The high dose animals showed decreased body weight gain. Chronic progressive nephropathy (CPN) increased mortality in all dose groups and was dose related but it was most severe in the 3,000 and 8,000 ppm treatment groups. There was a decreased mean survival time and survival rate in males: respectively, 12% and 18% of the males the 3,000 ppm and 8,000 ppm groups, had survived in the week 82 and 97, which was the time of sacrifice for these groups. The 400 ppm and control groups had respective survival rates of 27% and 17% in the last week with respective mean survival days of 617 and 632. Female survival rates ranged between 60% and 47% during

the last study week and mean survival times were 697, 681, 697 and 676 from control to high dose group. Relative liver and kidney weights were increased in the two highest female dose groups, but the pathological changes, mainly CPN, were generally less severe in females than in males. In males, typical CPN signs, such as glomerulosclerosis, tubular proteinosis and interstitial nephritis and interstitial fibrosis, were present at all treatment levels. Male rats had an increase in parathyroid gland adenomas at the two highest doses. The 3,000 ppm group males had 3/50 and the 8,000 ppm males 1/50 parathyroid adenomas compared to zero of the 400 ppm and control groups. When compared to the controls the male rats in the 3,000 ppm group had twice as high corticosterone level. The 8,000 ppm males had 2½ times lower corticosterone level than controls. Renal tubular cell tumours were increased only in male rats of the 3,000 ppm and 8,000 ppm groups. The adenoma rates were 2% at 0 ppm, 0% at 400 ppm, 10% at 3,000 ppm and 6% at 8,000 ppm. The respective carcinoma rates were 0%, 0%, 6% and 0%. A dose dependent, statistically significant increase of testicular interstitial cell (Leydig cells) tumours was demonstrated by the following figures: 64% at 0 ppm, 70% at 400 ppm, 82% at 3,000 ppm ($p<0.05$), and 94% at 8,000 ppm ($p<0.05$). The proportion of adenomas graded as "moderate" also increased in the high-dose group.

Table 4.35 Neoplastic lesions in male Fisher-344 Rat exposed to MTBE

Proliferative lesion	Lesion incidence in percentages per dose group of animals examined			
	0 ppm	400 ppm	3,000 ppm	8,000 ppm
Parathyroid adenomas	0%	0%	8%	2%
Renal tubular cell tumours (adenomas / carcinomas.)	2%/0%	0%/0%	10%/6%	6%/0%
Testicular interstitial cell tumours (adenoma)	64%	70%	82% (*)	94% (*)

*= Statistically significantly different from control ($p<0.01$)

CD-1 Mouse: 72-week inhalation exposure

Burleigh-Flayer et al. (1992, pub. 1997) investigated MTBE's ability to cause cancer in CD-1 mice in an 18-month exposure to doses 0, 400, 3,000 and 8,000 ppm. The test protocol used was the same as in the above study with Fisher rats. In all, 47 tissues were evaluated in histopathologic analysis from those animals that were in control or high dose group. Liver, spleen and submandibular lymph nodes from males and liver, uterus and stomach from females were examined also in the low-dose groups.

The mortality rates in males were 0 ppm: 33%, 400 ppm: 22%, 3,000 ppm: 35% and 8,000 ppm: 49%. Correspondingly, for females the mortality rates were 27%, 18%, 23% and 33%, in respective order. Both sexes had an increased corticosterone level at 8,000 ppm at week 79, but only males, which had a value three times higher than that of control animals showed statistical significance. At the same time, the high-dose males and females showed a significantly decreased urine pH at weeks 51 and 79, respectively. Females in the two highest dose groups had significantly elevated liver weights (9% and 39%). Kidney weights were significantly increased in all dose groups in males. The female mice showed an increased kidney and spleen weight only at the highest dose. The male adrenal weight was increased at 8,000 ppm. Hepatocellular hypertrophy was increased in the males of 3,000 ppm and 8,000 ppm dose groups and females of the 8,000 ppm dose group. The female mice of the high dose group had a 20% incidence of hepatocellular adenomas compared with 4% incidence in controls. In this group liver carcinoma

was present in only 1/50 animals. The hepatocellular adenoma incidence in control animals was 4%, which is within the historical range of 0 - 4%. Female mice also had a concentration related and statistically significant decrease of uterine endometrium hyperplasia. Although, male adenoma frequency was similar in all male groups, the mice of the 8,000 ppm group had four times more liver carcinoma than the control mice (16% vs. control 4%). However, the difference was not statistically significant.

Table 4.36 Proliferative lesions in CD-1 mice

Proliferative lesion	Lesion frequency in percentages per dose group of animals examined			
	0 ppm	400 ppm	3,000 ppm	8,000 ppm
Hepatocellular hypertrophy (MALES)	10% (49)	12%	20%	30% (49)*
Hepatocellular hypertrophy (FEMALES)	8%	4%	6%	18%
Hepatocellular adenomas / carcinomas /combined (MALES)	22%/4%/ 25%	22%/8%/ 24%	18%/6%/ 24%	24%/16%/ 33%
Hepatocellular adenomas / carcinomas /combined (FEMALES)	4%/0%/ 4%	2%/2%/ 4%	4%/0%/ 4%	20%** / 2% /22%
Cystic hyperplasia of uterine endometrium (FEMALES)	52%	35% (48)	30%*	12%**

Numbers in parenthesis represent the total number of animals examined, otherwise 50 examined in all dose groups
* = Statistically significantly different from control ($p<0.05$)
** = Statistically significantly different from control ($p<0.01$)

Sprague-Dawley rat: 104-week oral administration

Sixty male and 60 female, eight-week-old, Sprague-Dawley rats were given, by gavage, 0, 250 mg/kg or 1,000 mg/kg of MTBE in olive oil, for 104 weeks (Belpoggi et al., 1995). The test substance dose was administered on all days except on Wednesdays and the weekends. Weak tolerance for the test substance at high dose was the justification for the unusual dosing regimen. The observation of the rats continued until their natural death; the last animal died on study week 166. Necropsy of each animal was performed at death. Histopathology was done on 35 tissues and on gross lesions. A prevalence analysis assuming non-lethal tumours was done on Leydig cell (testis interstitial cells) tumours and a log-ranked test assuming lethality of the tumours was performed on lymphoma and leukaemia.

The test animals had no treatment-related adverse clinical signs. Bodyweight of the treated groups showed no significant change when compared to controls. Water or feed consumption of the treated animals was comparable to those of the control. Gross examination at necropsy or microscopical examination did not reveal any adverse changes that were *not* tumour-related. Male survival rate maintained similar in all dose-groups up until week 88 when the rate was 50%. Between the weeks 104 and 136, the high dose group had 10-20% higher survival rate (45-15% survival rate) than the 250 mg/kg and control group (survival rate from about 30% to less than 5%). The survival of the male 250 mg/kg group remained similar to the control throughout the study. In females, survival rates were approximately 78% (control), 60% (250/mg/kg) and 40% (1,000 mg/kg) at week 88. At week 120, the respective survival rates varied between 25% and 20%.

Female rats had an increase in the incidence of lymphoimmunoblastic lymphomas and lymphoblastic leukaemia over the laboratory historical range, which the authors reported to be "in a range below 10%". In addition, in females, an increase of dysplastic proliferation of

lymphoreticular tissues (DPLT, from various body sites) was observed in both dose-groups. Dysplastic changes are occasionally associated with neoplastic transformation. There was a higher incidence of hyperplastic cells seen in the medium- than in the high-dose group, which authors suspected to have been caused by progression to lymphoma and leukaemia in the high dose group. The most frequently found neoplasm in both dose groups was lymphoimmunoblastic lymphoma localised in the lungs, with a proportion of >85% of the combined incidence. Male rats showed an increase in incidence testicular interstitial cell adenoma (**Table 4.37**). There were no signs of increase of testicular degeneration or atrophy. Females had a dose dependent decrease of fibroma and fibroadenoma of the mammary gland (66,7% in controls, 45.0% mid dose and 26.7% in high dose group). Statistical significance at level $p<0.01$ was reported in Leydig cell tumours and lymphomas and leukaemia only when the incidences were counted against the number of animals *alive* at the time of observation of the first tumour. It should also be noted that no adverse changes were reported in the kidney proximal tubules, a common pathological notation in other experiments in male rats.

The results of the study by Belpoggi et al. were published in 1995. The same authors published a re-examination of the pathology data in 1998. In the re-review, the type and number of tumours that were found are specified in more detail than previously. **Table 4.37** summarises the proliferative findings and their incidences given in the latest publication, (Belpoggi et al., 1998).

Table 4.37 Summary of proliferative lesions seen in Sprague-Dawley Rat

Proliferative lesion	Lesion frequency in percentages per dose group of animals examined		
	0 mg/kg	250 mg/kg	1,000 mg/kg
Lymphoimmunoblastic dysplasia in Females (§)	5.0%	26.7%	20.0%
Lymphoma & Leukaemia in females	3.3%	11.7%	20%
Proportion of lymphoma	100%	85%	91.7%
Testis interstitial Cell Hyperplasia (focal + diffuse/ focal)	6.7% / 25%	13.3% / 37.5%	15.0% / 2.2%
Testis interstitial Cell adenomas	3.3%	3.3%	18.3% (*)

Sixty animals examined in all cases
* = Statistically significantly different from control ($p<0.05$)
§ = Dysplasias observed in animals bearing lymphoma or leukaemia are not included

4.1.2.8.1 Discussion on carcinogenicity

Exhaustive data on MTBE genotoxicity are available *in vivo* and *in vitro*. Despite its minor shortcomings, the data show the non-genotoxic nature of MTBE. On the other hand, several theories of non-genotoxic mechanisms exist for the various tumours that are seen in rats and mice exposed to MTBE. Alternative modes of action potentially involved and the associated studies are discussed below.

Kidney Tumours in Fisher-344 Rat

Male rat kidney secretes several milligrams of α2u-globulin a day, which is normally cleared in urine via glomerular filtration. A protein similar to α2u has not been identified in human kidneys (Borghoff et al., 1993). Alpha2u-nephropathy syndrome follows from an overload of α2u-globulin that is typically induced by a xenobiotic chemical. More specifically, the accumulation

of this low molecular weight protein in the kidney tubules is caused by the binding of a chemical to it, which makes it more resistant to hydrolysis (Borghoff et al., 1990). This leads to an accumulation of hyaline droplets and injury to proximal convoluted tubule (PCT) which causes a series of lesions to PCT. There is a sequence of events that is characteristic of α2u-nephropathy syndrome. These usually include granular cast formation in outer medulla and increased severity or incidence in chronic progressive nephropathy (CPN). In longer term, linear papilla mineralisation, urothelial hyperplasia, increased cell proliferation and ultimately tubular neoplasia may be seen. Other criteria to identify α2u-globulin syndrome include affinity of the xenobiotic to α2u, non-genotoxicity and inability to produce these symptoms in females (Bird et al., 1997).

When assessing the human relevance of kidney tumours seen in rats, IARC and EPA use some of the above listed mechanistic criteria to distinguish between α2u-globulin-associated and other type of kidney tumours. Primarily, the criteria include the microscopic finding of hyaline droplets in renal proximal tubule cells and the identification of α2u-globulin as one of the proteins accumulating in the droplets. In addition, an identification of certain histopathological features, characteristic to α2u-globulin nephropathy related lesions, is needed. Secondary information can be obtained from affinity studies between the chemical and α2u-globulin. Increased proliferation of the P2 segment of the proximal tubule can also be supportive of the α2u-globulin theory. Male specificity is a prerequisite for these phenomena.

Bird et al. (1997), among others, has suggested that α2u-globulin-associated nephropathy be a possible mechanism in MTBE kidney tumour formation. Many of the typical signs listed above occur in the rat kidney in various toxicity tests with MTBE. Several subacute or subchronic toxicity tests demonstrate the formation of hyaline droplets in male rat kidney tubules (Prescott-Mathews et al., 1999; Robinson et al., 1990). Using a sensitive enzyme linked immunosorbent assay it has been shown that α2u kidney content increases with dose, although the increase was mild compared to other known inducers (Prescott-Mathews et al., 1997). The binding was demonstrated also in an *in vivo* experiment (Prescott-Mathews et al., 1999). When immunohistochemical-staining method was used, no relation could be confirmed between the increase of α2u-globulin along with increasing MTBE-dose (Swenberg et al., 1991). It has been established that there is a concentration-related increase in PCT cell necrosis. In addition, there is a strong correlation between increased cell proliferation and increased PCT α2u concentration caused by MTBE. Furthermore, this has been shown to occur in the male rat kidney only (Bird et al., 1997; Prescott-Mathews et al., 1997). Poet and Borghoff (1998) have also demonstrated an interaction between MTBE and α2u-globulin *in vitro*. Using a two-compartment vial equilibration model, they calculated a dissociation constant of $2.2 \cdot 10^{-4}$ M which is of similar magnitude to some chemicals that have been shown to cause α2u-nephropathy. However, because of technical difficulties due to low affinity for the protein and high vapour pressure, MTBE did not co-elute in anion-exchange chromatography (Poet et al., 1997a). Borghoff et al. (1998) have shown that MTBE and tert-butyl alcohol (TBA) were accumulated in the male rat kidney to a greater extent than it was in the females. This was demonstrated by an experiment where rats were exposed to 100, 400, 1,500 or 3,000 ppm MTBE, via inhalation, for up to 6 hours. The kidneys were analysed for MTBE and TBA concentration with gas chromatography and mass spectrometry. To keep MTBE from escaping, sealed vial technique was applied (Borghoff et al., 1998). A further attempt to measure MTBE-α2u-globulin binding was made by Prescott-Mathews et al. (1999) in an experiment where they administered a daily dose of 750 mg/kg (^{14}C)MTBE to four male and 4 female rats and analysed the radioactivity of the protein fraction obtained from kidney homogenate using gel and anion-exchange chromatography and scintillation counting. Again, there was no evidence of co-elution in the α2u-protein fraction. In

parallel, again using a sealed-vial equilibration technique, MTBE concentration was determined from the headspace with a gas chromatograph, with and without competitive binding of d-limonene oxide, a reversible high-affinity binder to α2u-globulin. Three single doses were used with two different sample preparation time points. The doses were 250, 750 and 1,500 mg/kg and the sample preparation time points 4 hours and 12 hours. A clear increase was seen in the concentration of free MTBE with competitive binding of d-limonene oxide. This occurred in males but not in females. At 4 hours, the binding decreased with MTBE dose while at 12 hours dose had no effect but the percentage of bound MTBE was higher at 12 hours than at 4 hours (Prescott-Mathews et al., 1999). Thus, there is evidence that shows the interaction of MTBE with α2u-globulin *in vitro*. The existing data also suggest that a male specific interaction would be present also *in vivo*.

The evidence for other α2u-nephropathy criteria is not as clear as above. For example, linear papilla mineralisation has not been demonstrated. Linear papilla mineralisation is an accumulation of calcium hydroxyapatite in the thin limbs of Henle, which is usually noted after several months of exposure. Although a more severe grading of granular casts was observed in male dose rats in a 90-day oral exposure to 1,200 mg/ml (Robinson et al., 1990) the effect is absent in the other, shorter term studies. Granular cast formation in the cortico-medullary junction is an essential histopathological piece of evidence when the relevance of α2u-globulin is established. However, granular cast formation is usually seen after a chronic exposure. The evidence of sex specificity of increased incidence and severity of CPN is also somewhat equivocal. Some signs of increase in CPN are also seen in females exposed to 3,000 and 8,000 ppm MTBE in the two-year study when compared to controls and 400 ppm. However, this is common to rats under any chemical stress. Moreover, CPN was more severe in male rats for which it was the main cause of death in the treated groups.

In summary, there are clear indications of increase of proliferation caused by MTBE interaction with α2u-globulin, which only occurs in male rats. In addition, a series of renal lesions that appear in α2u-nephropathy are found. Even if the supporting evidence is not as strong as for other known, stronger α2u-inducers it seems quite likely that this is the principal mode of action in the kidney tumorigenesis. Moreover, extremely high, 3,000 ppm doses of MTBE were required to induce these tumours in rats. Therefore, the relevance of these tumours to man is likely to be insignificant.

Liver tumours in CD-1 mice

The increase in adenoma incidence was seen only in female mice at 8,000 ppm, suggesting female specificity. Because of the results obtained from additional studies, it has been postulated that interference of MTBE in oestrogen affected tissues may play a role in the mouse liver tumour formation. Tumour promotion has been studied as a potential genotoxic mode of action due to the results seen with unleaded petrol (UG). When UG was administered to N-nitrosodiethylamine (DEN) initiated mice, an increase in incidence of liver tumours was seen (Moser et al., 1997). UG produced anti-oestrogen effects similar to those seen with MTBE. Moreover, it was demonstrated that liver tumour formation in mice was secondary to UG's interaction with oestrogen. The change in proliferation rate in mice was studied at 8,000 ppm.

In addition, Moser et al. (1997) evaluated the tumour promoting capability of MTBE by giving to B6C3F1-mice (12 female mice/group) a single intraperitoneal injection of DEN. The mice received 8,000 ppm of MTBE vapour for 16 or 32 weeks, 6 hours per day, 5 days per week. Saline acted as a control initiator. At necropsy, the liver microsomes were prepared and enzyme activities from microsomes were measured. An assay for hepatocyte proliferation activity was

performed, where the number, volume and the fraction of liver of altered hepatic foci were determined. Generally, all MTBE exposed mice, initiated and non-initiated, had increased liver weights and hypertrophy in the centrilobular and mid-zonal areas. There were no significant differences in microsomal enzyme activity or hepatocyte proliferation between saline or DEN initiated mice under MTBE exposure. After 32 weeks of MTBE exposure, the mean volume fraction and mean volume of the initiated hepatic foci decreased by a ¼ as compared to saline controls. This change correlated with the significant decrease in the mean number of macroscopic lesions. Hence, MTBE does not have promoter activity after DEN initiation.

Moser et al. (1998) investigated the possible association of changes in hormonal level and the liver tumours seen in female mice. Similar test conditions to the 2-year bioassay were used to expose 12 female B6C3F1 mice to a target concentration of 8,000 ppm MTBE for 3 or 21 days and 4 or 8 months, 6hours / day, five days a week. The changes seen in uterine, cervix and vagina are consistent with endocrine modulation. Based on the results *in vitro* MTBE does not have an affinity for oestrogen receptor. Thus, MTBE seems to have an antioestrogen-like effect but does not have specificity for oestrogen receptor. Okahara et al. (1998) evaluated in an abstract the effect of MTBE on oestrogen sensitive tissues in CD-1 mice. Mice received subcutaneously 600 or 1,500 mg/kg for five days and on days 3-5 some of the mice were also given 1 µg estradiol (n=6-11). Liver weights showed no clear, consistent increase during the study. Moser et al. (1996) reported a decrease in uterine weight and uterine endometrial hyperplasia, while a study by Belpoggi et al. (1995) showed evidence of a dose-related decrease of mammary fibroma and fibroadenoma. These conditions may have followed from disturbances of oestrogen metabolism.

Bird et al. (1997) have carried out liver cell proliferation studies in mice. When measured by the uptake of nucleotide analogue 5-bromo-2-deoxyuridine, they saw an increase in the liver proliferation in female mice only at 8,000 ppm after 5 days of exposure. However, this effect had disappeared after 28 days, possibly due to adaptive response of the liver cell.

It was stated in the previous section that male mice of the high dose group had four times more carcinoma when compared to control mice. This difference was not statistically significantly different. Moreover, when all malignant liver tumours (hepatocellular carcinoma, hemangiosarcoma, histiocytic sarcoma and adenosarcoma) are summed, there is no difference to controls. Control animals had altogether five cases of malignant liver tumours while the high dose group had eight. Furthermore, the authors reported that the combined adenoma/carcinoma incidence does not differ from that usually seen in 24-month-old CD-1 mice.

Summarised, MTBE causes changes in oestrogen sensitive tissues without affecting the serum oestrogen level. There may be a connection with these changes and the increased amount of liver adenomas seen in female mice at 8,000 ppm but there is no evidence to corroborate such a theory. MTBE increased proliferation, which may have contributed to the generation of tumours seen at high doses. When tested with N-nitrosodiethylamine, MTBE expressed no promoter activity. Again, very high doses were needed to produce the liver adenomas. The relevance of these tumours to man is questionable.

Leydig Cell tumours in Fisher-344 and Sprague-Dawley rat

Several alternatives have been listed as plausible mechanisms in the aetiology of Leydig cell tumours in rats (Cook et al., 1999). In the case of MTBE, some of the testicular paracrine factors have been under a scrutiny. Typically, there is a disturbance in hormonal homeostasis, e.g., reduced testosterone or estradiol level followed by a compensatory action which is typically seen as a high level of circulating luteinising hormone (LH). A weakening of a hormonal signal may

also cause compensation by an antagonist or agonist action of the chemical. An example of this kind of complex mechanism is agonist action on dopamine receptors, which causes a decrease in serum prolactin levels. Reduction in prolactin serum level causes LH-receptor down-regulation and a subsequent increase in LH. A number of other mechanisms have been reported. The interference that occurs in the hypothalamic-pituitary-testis axis, resulting in higher levels of luteinising hormone may be of relevance to humans due to the similarities of the regulatory pathways in humans and rats. Studies that investigate potential hormonal mode of actions of the hypothalamic-pituitary-testis axis are available.

The role of testosterone in Leydig cell tumorigenesis was investigated in an experiment, where Sprague-Dawley rats were given gavage MTBE doses ranging 40-800 mg/kg for 28 days (Day et al., 1998). The highest dose produced a significantly reduced plasma testosterone level and an increased level of corticosterone. The authors suggested that, at high dose, the evidence support MTBE involvement in alteration of male endocrine function in several organs, including testes. However, they saw no change in the LH-level. Allgaier and de Peyster (1999) conducted a similar test with equal dose but measured the plasma LH level already after 2-5 hours or 5 days. Again, there was no increase in the circulating LH level. Both of the above studies were reported as abstracts. However, a dose-related *decrease* of serum LH was found by Williams et al. (2000a) when they administered MTBE to the same rat species by gavage at 250-1,500 mg/kg for 15 or 28 days. The change was significant only at the highest dose. The high-dose rats also had a significantly decreased serum and interstitial fluid testosterone level at day 15. MTBE effect on luteinising hormone release hormone (LHRH) has been investigated in mice faeces by Billitti et al. (1999). They gave groups of five mice by gavage MTBE doses ranging from 400 to 1,500 mg/kg for five days but found no difference in faecal LHRH.

The National Toxicology Program (NTP) in the United States has collected data that give the incidence of interstitial tumours in control Fisher-344 rats since 1910. The average percentage of control animals with tumours is 89%, ranging from 64% to 98% (Haseman et al., 1990). Chun et al. (1992) have reported an intra-laboratory Leydig cell tumour historical average incidence of 88%. A Leydig cell tumour (LCT) incidence higher than that was reached only at the highest MTBE dose. Nevertheless, a clear dose-response relationship was seen in this study. The dose-response of the Leydig cell tumours was not so evident in the results obtained by Belpoggi et al. (1995) who derived a dose-response curve from only two treatment groups. Moreover, a significantly lower mortality rate in the highest dose group than in the others skews the results setting restrictions to a valid interpretation of the data. In addition, the study was a lifetime study, where one can expect to have confounded results, because LCTs are more frequent in the old rats. In other words, in this case, the longer surviving high dose rats would have been therefore more likely candidates to have a tumour. There have also been doubts that the frequency of the neoplasm might be an overestimation, due to difficulties in distinguishing them morphologically from hyperplasia. Although there is no widely accepted criteria for distinguishing between the two lesions, principally, two arbitrary size based criteria have been used. Belpoggi et al. (1995) reported in their re-review that they followed the criteria established by NTP (re-citation: Boorman, Chapin and Mitsumori, 1990).

In summary, there is evidence that MTBE causes an increase of LCT tumours in rats. However, despite that the data are still too limited to draw a conclusion on which mode of action induces the LCTs in the rats receiving MTBE. Based on the available evidence, it seems that the typical mode of action, which involves elevated LH, is not the case for MTBE. The interpretation of these results is further complicated as it is unclear how the differences in physiology and anatomy between rat and human testis contribute to susceptibility to LCT tumours. Testicular cancer is a relatively uncommon cancer in humans. Most human testicular cancers originate either from germ or from

Sertoli cells. Tumours of the testes constitute about 1% of all human neoplasm; only 2-3% of all testicular tumours are of Leydig cell origin. Moreover, one cannot overlook the fact that the tumours appear in rats only at quite high doses and that MTBE lacks genotoxic properties.

In conclusion, no definitive conclusion can be drawn about the relevance of these tumours to man due to the lack of knowledge of the possible mode of action. However, considering all the available data, the relevance to man is probably not very significant.

Haematopoietic neoplasm in Sprague-Dawley rat

In the Belpoggi study (Belpoggi et al., 1995), an increased incidence of lymphoma/leukaemia was reported to be statistically significant, $p<0.01$, at the highest dose and $p<0.1$ at the medium dose. No exact data were given on historical control incidence, but it was stated in the original report that the historical incidence of these tumours is below 10% for female rats. In this study, control tumour incidence was 3.3%. There was a 3- and 6-fold dose dependent increase to the controls in the two treated groups. Even with a historical control-value of 10%, there would be a 2-fold increase in haemolymphoreticular neoplasia of lymphatic origin.

In the earlier description of the results, it was mentioned that the total number of animals was adjusted to the number of animals seen at the time of first leukaemia observation. This method assumes that none of the animals that had died before had leukaemia, which is a fair assumption since the rats were only 1-year-old at the time. When the adjusted results are examined with Cochran-Armitage trend test, a clearly positive and very significant dose-relationship can be observed. However, as there is normally higher mortality among the high dose animals due to other toxicity, the denominators of the high dose groups may get disproportionately smaller than other group, which may lead to a false positive correlation.

The neoplasia were of lymphoid origin localised in the lungs. The differentiation of pluripotent stem cells to lymphoid progenitor cells takes place in the bone marrow. There are three *in vivo* tests available in two rat strains, which measure MTBE's ability to induce damage in chromosomes of the bone marrow cells. All of them gave a negative result. Moreover, the study in mice concluded that there was no positive response in the spleen lymphocytes, when up to 1,000 mg/kg MTBE was administered by gavage for three weeks. Spleen lymphocytes represent about ¼ of all lymphocytes. In an abstract, Lee et al. (1998) studied rat lymphocytes in an alkaline SCGE assay. This "comet assay" showed evidence of DNA strand breaking activity in male Sprague-Dawley rats at 800 mg/kg daily oral dose given for 28 d. Even so, there is little information supporting genotoxic involvement in peripheral blood cells.

In lifetime studies, lymphomas are known to occur spontaneously, which makes the interpretation of these tumours difficult. Exact figures of the historical occurrence of this tumour in this location would have been helpful. Moreover, there were no signs of neoplastic changes in the lymphoid cells in the carcinogenicity tests with CD-1 mouse and Fisher-344 rat. The publication's reporting was inadequate in many aspects, such as toxicological findings, statistical testing and methods, resulting in a low level of confidence of the results. The tumours may be of relevance but the estimation based on the information given in this study makes it difficult to interpret.

Parathyroid hyperplasia and neoplasia in Fisher-344 rat

The proliferative changes seen in the parathyroid of male Fisher rats are likely due to hyperparathyroidism, which is commonly seen in cases where parathyroid compensates in hypocalcaemia caused by, e.g., chronic renal failure. The adenoma in the two high dose group is probably associated with the resulted hyperplasia seen in parathyroid cells (Muir, 1985).

4.1.2.8.2 Carcinogenicity of MTBE metabolites

Tert-butanol

The carcinogenicity of tert-butanol (TBA) has been investigated in a two-year study using Fisher-344 rat. Male rats, 60 per group, were dosed with 0, 1.25, 2,5 and 5 mg/ml TBA in drinking water. The same number of female rats received TBA at twice this concentration. Average daily doses of TBA for males were 85, 195 or 420 mg/kg and for females 175, 330 or 650 mg/kg body weight. Additionally, groups of 60 male and female B6C3F1-mice received 0, 5, 10, 20 mg/ml TBA in their drinking water, corresponding to approximately 535, 1,035 or 2,065 mg/kg daily doses. Treatment lasted 103 weeks, except for groups of 10 male and 10 female rats that were sacrificed at 15 months for an interim evaluation. Because there were proliferative lesions in the kidneys at interim evaluation, an 8-step kidney sectioning was performed. Mortality rate in female rats at week 101 was in the control and two lowest dose groups close to 50% (Cirvello et al., 1995).

In one 5 mg/ml male rat, a renal tubule adenoma was identified at 15 weeks. At study termination, incidences of focal renal hyperplasia, together with adenoma were increased in male rats. One carcinoma was found in the kidney of a male rat receiving 5 mg/ml MTBE. Kidney lesions in females were restricted to increased proliferation at 10 mg/ml. The incidence of detected hyperplasia and tumour was augmented when the kidneys were subjected to additional step sectioning. The males of the 5 mg/ml dose group had significantly increased proliferation incidence when compared to controls. Adenoma incidence was significantly higher in the 2.5 mg/ml males. These figures were not affected by survival adjustment.

The survival rate in the mouse study was much lower than in the rats. In females, more than 50% of the animals had died before study termination, in the highest dose group survival rate was less than 1/3. There was a significantly increased incidence of thyroid gland follicular cell hyperplasia in male mice of all treatment groups. The 7 % adenoma incidence seen in the 10 mg/kg group was not statistically significantly different from control, but it exceeded the historical incidence of NTP drinking water control mice. Females had a similar trend, with the exception that they had significantly increased adenoma incidence at 20 mg/kg dose.

Formaldehyde

Formaldehyde has been categorised as “probably carcinogenic to humans” by IARC. It is also the primary metabolite of MTBE. This leads to a logical concern that MTBE might also have similar carcinogenic properties to formaldehyde and it has been speculated that formaldehyde might contribute to some of the tumours seen in test animals. One tumour type that has been associated to formaldehyde is lymphoma, which was also seen in MTBE treated Sprague-Dawley rats. Most of the cohort and case-control studies conducted with formaldehyde exposed persons, such as pathologists and embalmers, have been unable to show an association between deaths of cancers of the haematopoietic and lymphatic system caused by formaldehyde. However, studies are available that report increased risk to those persons exposed to formaldehyde. For example, one cohort study reports a significantly increased proportionate mortality ratio (PMR) and a relative risk of 1.3 (CI: 1.1-1.6) for lymphatic/haematopoietic cancers and for myeloid leukaemia with a relative risk of 1.6 (CI: 1.0-2.3). No data of formaldehyde exposure levels were provided by these studies. In test animals, a life-time study that administered to Sprague-Dawley rats up to 1,500 mg/l formaldehyde in drinking water also showed a positive, dose related correlation for lymphatic leukaemia in the treated groups (IARC, 1995).

As was already discussed in the mutagenicity section, data are available that allows one to estimate the relevance of formaldehyde in this context. Based on the studies by Casanova et al. (1997a), it appears that the formaldehyde, which is endogenously formed from MTBE in mouse liver cells, does not lead to a significant increase of DNA-crosslinks. It is also well known that the metabolism of formaldehyde to formic acid is a rapidly occurring reaction catalysed by formaldehyde dehydrogenase, an enzyme, which is found in a wide range of tissues. Ability for an efficient metabolism is expected, because formaldehyde is found in unexposed human blood due to endogenous generation from demethylation of various N-, O-, and S-compounds. Moreover, the data by Casanova et al. (1997a) and other toxicological studies allows one to deduce that the conversion to formaldehyde is the rate-limiting step and therefore accumulation of formaldehyde is not envisaged. In any event, it would be at most speculative to draw conclusions from epidemiological or animal studies where the subjects were directly exposed to relatively high concentrations of formaldehyde. Thus, it is not considered that formaldehyde is likely to be a relevant factor in the tumour formation seen with MTBE.

4.1.2.8.3 Summary of carcinogenicity

An increase in incidence of renal tubular cell carcinomas and adenomas in Fisher-344 rat at 3,000 ppm is reported. The evidence suggests that these neoplasm are a result of proliferation in response to α2u-globulin associated nephropathy. No increase of tumours was seen at 400 ppm.

CD-1 mice, in turn, had at 8,000 ppm an increased hepatocyte hypertrophy and an increased incidence of liver adenoma and carcinoma. The involvement of disturbances in oestrogen metabolism seen in mice may be a possible factor in the tumour formation. There is no decrease in blood oestrogen level but an antioestrogen-like action has been suggested to occur. MTBE did not show promoter activity when tested in female mice after N-nitrosodiethylamine (DEN) initiation. There was no increase of tumours at 400 or 3,000 ppm, thus showing little evidence of treatment relation.

The third neoplastic change, the testis interstitial cell adenoma, was found in two rat-strains, the Fisher-344 and Sprague-Dawley rat. In Fisher-344, there was a clear dose-response relationship but the tumour incidences stayed mostly below intra-laboratory historical control values. Disturbances of the hypothalamic-pituitary-testis axis has been suggested a possible mode of action. Although there are changes in the plasma corticosterone and testosterone levels of these rats, there are insufficient data to draw a definitive conclusion whether the tumour formation is relevant to man.

Equally unknown are the underlying mechanisms of the increase of lymphoma found in Sprague-Dawley rats dosed orally with 250 and 1,000 mg/kg reported by Belpoggi et al. (1995). Scarce data are available to estimate the MTBE genotoxicity in peripheral lymphocytes. Formaldehyde has been suggested as a factor but it seems unlikely based on the available information. Tert-butyl alcohol, a primary metabolite of MTBE, also caused an elevated incidence of neoplastic lesions in the kidneys of rats.

IARC (International Agency for Research on Cancer) has reviewed the MTBE related data. IARC concluded: “there is inadequate evidence in humans for the carcinogenicity of methyl *tert*-butyl ether” and that “there is limited evidence in experimental animals for the carcinogenicity of methyl *tert*-butyl ether”. According to the IARC working group evaluation, MTBE is not classifiable as to its carcinogenicity to humans (Group 3) (IARC, 1998).

Table 4.38 Summary of tumours in rodents exposed to MTBE

Animal/Sex	Dose	Tissue	Tumour	Reference
Fisher-344 rat/Male	3,000 ppm (11,000 mg/m³)	Kidney	Renal tubular adenoma and carcinoma	Bird et al. (1997)
Fisher-344 rat/Male	3,000 ppm	Testes	Interstitial cell adenoma*	Bird et al. (1997)
Sprague-Dawley/Male	1,000 mg/kg	Testes	Interstitial cell adenoma*	Belpoggi et al. (1995)
Sprague-Dawley/ Female	250 mg/kg	Haemo-lymphoreticular	Lymphoblastic lymphoma and Lymphoblastic leukaemia, lymphoimmunoblastic lymphoma	Belpoggi et al. (1995)
CD-1 Mouse/Male and Female	8,000 ppm	Liver	Hepatocellular adenoma* and hepatocellular carcinoma	Bird et al. (1997)

* = Statistically significant

4.1.2.8.4 Conclusions on carcinogenicity

MTBE produces tumours in mice and rats at doses ≥ 3,000 ppm after inhalation exposure. Tumours have been reported in rats at oral doses ≥ 250 mg/kg. There is no evidence of a direct genotoxic mode of action. Therefore, respiratory NOAEC of 400 ppm and oral LOAEL of 250 mg/kg are derived. There are indications of carcinogenicity in two species. However the treatment relation of the occurred tumours is equivocal in some studies (mouse adenoma) and the relevance of the mode of action is questionable in others (Leydig cell). Moreover, the tumours appear mostly at very high and systemically toxic doses, and MTBE is not genotoxic *in vitro* or *in vivo*. On the other hand, the human relevance of the testicular interstitial adenomas observed in rats on two separate rat strains cannot be neglected. In addition, certain uncertainty remains as to the significance of the lymphatic tumours found, in the light of the limitations of the study and inadequate reporting. The rapporteur considers MTBE as a borderline case between non-classification and Carc. Cat. 3.

4.1.2.9 Toxicity for reproduction

4.1.2.9.1 Effects on fertility

Single Generation Reproduction Study, Inhalation

During the pre-mating period, MTBE was given in a whole-body exposure to 8-weeks-old male Sprague-Dawley rats at 250, 1,000 and 2,500 ppm for 12 weeks, 5 days per week for 6 hours (Biles et al., 1987). The female rats were treated with same dosing scheme for three weeks. Two five-day mating intervals were conducted after the pre-mating exposure, during which the males and females continued to receive MTBE. Female exposure was changed to 7 days per week, 6 hours a day from first day of gestation and was paused on the 20th gestation day and again continued from the 5th day of lactation until the 20th. After the weaning of the first F1a-litter, both P-animals had a two-week rest period, after which the second mating begun. The males were sacrificed at the end of the second mating, while the females continued to receive MTBE and were sacrificed at the end of the second F1b litter weaning. Standardisation of the litters was made to 10 pups/litter on day 4 of lactation. The in-life observations of the parent-animals (P) included mortality and cross-toxicological signs. Male body weights were obtained weekly for males and for females also during gestation and lactation days weekly. At necropsy, P-animals

were evaluated grossly and testes and epididymis from males and ovaries from females were examined microscopically. Pups were weighed at birth and weekly until the day of sacrifice on day 21. Pups found dead were grossly examined for malformations internally and externally and the gonads and abnormal tissue was studied histopathologically. The protocol followed no formal guideline method but was a generally well-conducted study.

Parental toxicity

In in-life observations, neither female nor male parent-animals had any notable change in body weight development nor had they any treatment related adverse effect when compared to controls. In females of the 250 ppm and 2,500 ppm dose groups, necropsy revealed an increased incidence of dilated renal pelvis. The toxicological significance of this finding is unclear, since the 1,000 ppm group had a zero incidence. In females, relative ovary and gonad weights remained within the control value range. Males had similarly no discernible changes in their testes, epididymis, seminal vesicle or prostate weights. No treatment related effects were found in the microscopy of either sex.

Effects on fertility

Mating intervals, F1a and F1b males and females, had mating indices comparable to controls. Male fertility indices also remained comparable between control and treated groups. A slightly, although not significantly, lower pregnancy rate was seen in the mid-dose group F1a litter only. Also in the F1b litter, there were slightly but not statistically significantly lower pregnancy rates in all dose groups. The downward trend seemed to have a suggestion of dose response: control 88%, 250 ppm 79%, 1,000 ppm 79% and 2,500 ppm 76%.

Developmental effects

The mean gestation length was comparable in the treated animals when compared to controls. The number of pups at birth did not show any significant change to controls. There was a significant ($p<0.05$) decrease in pup viability indices at birth in the two highest dose groups of the F1b litter. The viability percentages were 99% in controls, 98% in low dose, 96% in the 1,000 ppm and 2,500 ppm groups. No significant difference was seen in the litter survival indices. Survival indices between the lactation days 0 and 4 were significantly (**$p<0.01$) decreased in the F1a low dose and medium dose groups (98%, **91%, **89% and 95% from control to high-dose group). Survival on lactation days 4-21 was not affected. In the F1b litter the survival indices were not different from controls. The pup body weights in the mid and high dose groups of both litters were slightly, but not significantly, lower than in controls during the days14 and 21. The most frequent post-mortem observation for pups sacrificed on day 21 was dilated renal pelvis.

Two-generation Reproduction Study, Inhalation

Groups of 25 Sprague-Dawley parent rats (P) were exposed in whole-body exposure to 0, 400, 3,000 and 8,000 ppm MTBE (Bevan et al., 1997a). The exposure started when the rats were about 6-weeks-old and lasted for 10 weeks before mating. Exposure of the females continued through the 21-day mating period, gestation and lactation starting day 5 and until the day of sacrifice, which followed the weaning of the offspring. Male exposure continued until the delivery of F1-litter. The new parents were randomly selected from the F1-litter at weaning on postnatal day 28, which was also the day they started receiving exposure. The exposure procedure was the same as it was for the P-animals. Viability was observed twice a day and body weights were recorded weekly; female body weights were recorded before mating, during

gestation and in the post-natal days until weaning. Food consumption was recorded weekly and for females at every 3-4 days on gestation. On post-natal days (PND) 0, 1, 4, 7, 14, 21 and 28, litters were counted, weighed and sexed and checked for abnormalities. On PND 4, four pups were sacrificed for an external examination that included cleft palate. All adult animals used for mating went through a post-mortem examination. Livers from F1-animals were weighed and those of the control and high dose group were studied microscopically. Pituitary, testes, epididymis, prostate and seminal vesicles and vagina, uterus, ovaries, respiratory tract and gross lesions were examined microscopically from all parent animals of the control and high dose groups. The protocol followed no formal guideline method but was a generally well-conducted study.

P animals

Hypoactivity and blepharospasms were observed in the parental rats at 3,000 and 8,000 ppm. The 8,000 ppm dose group males had a significantly reduced body weight throughout the 10-week pre-mating period. In the beginning of mating, the reduction in male bodyweight was almost 14%. There was also a significant reduction in the bodyweight gain in that group during the first 7 weeks. In the first three pre-mating weeks, male food consumption was reduced on average by 11%. Female body weights did not differ from controls in the pre-mating period but the body weight gain was significantly increased in the 8,000 ppm group in the post-natal days 21-28. The overall difference in lactation-period weight gain was more than two-fold ($p<0.05$). The reproduction data, such as pregnancy rates, gestation days and mating and fertility indices showed no meaningful differences to control.

The developmental toxicity seen in F1 litter

There was a statistically significant ($p<0.01$) increase of dead pups in the 8,000 ppm group. This followed from the death of an entire litter of 16 pups. However, there was no significant change in the survival index of the F1 generation. The high dose group male and female offspring body weights were significantly lower than the controls during the post-natal days 14-28. The female offspring of the 3,000 ppm group had significantly lower body weights also on day 14. In general, when compared to controls, no significant differences were evident in the number of pups stillborn relative to live ones, judging by the survival indices on days 4, 7, 14, 21, 28 or the lactation index.

Toxic effects seen in parent F1 animals

In the adult animals, the highest dose group of F1-males had about 15% less weight gain ($p<0.01$) during the first two weeks, accompanied by a reduced absolute body weight throughout the per-mating period. Although no decrease in weight gain was noted with the either male or female rats in the 3,000 ppm group, they still had significantly reduced body weight in the first 3-4 pre-mating weeks. Similarly to the parent animals, no differences were noted in female body weights during the gestation period. However, the high-dose group had a significantly increased (4-fold) body weight during the post-natal days 14-21 and the lactation period. Nevertheless, the food consumption was significantly ($p<0.01$) reduced by approximately 10% during the post-natal days 7-14 in these females. Gross examination at necropsy revealed statistically significantly increased relative liver weights in both sexes of the F1-animals at high dose and in males at 3,000 ppm. However, no treatment related histopathological changes were noted. Pregnancy incidence, mating and fertility and gestation indices were within the control values.

Developmental effects F2-animals

As in the F1-offspring, the F2-pups also had a significantly increased incidence of dead pups on post-natal day 4 in the high dose group. Again, in a manner similar to F1-pups, the F2-offspring had no significant difference in the survival indices when compared to controls. Male body weights of the 3,000 and 8,000 ppm dose groups were statistically significantly ($p<0.05$) reduced when compared to control group. The weight loss was seen in males of the 8,000 ppm group during the post-natal days 7-28 and in the males of the 3,000 ppm group during days 14-28.

4.1.2.9.2 Summary of effects on fertility

The reproductive function was not affected adversely and no pathological changes are seen in the gonad microscopy. In addition, there were no adverse changes observed in the gonads in any of the sub-chronic or long-term toxicity studies.

In the one-generation study, the pup viability was significantly lower in the mid- and high-dose groups of the F1b litter but there was no such change seen in the F1a litter. Furthermore, the control group of the F1b litter viability percentage was 99.0% while the F1a litter control viability was 97.6%. This may have skewed the significance seen. Moreover, no adverse effect on the survival of the pups was seen in any dose group of the second litter. There was also a significant reduction in pup survival index in pre-cull days 0-4 at 250 ppm and 1,000 ppm. Although this may be of toxicological it should be noted that there was no difference in the highest dose or in the parallel F1a-litter. In addition, there was no significant change in the survival indices during the lactation period (days 4-21).

In the two-generation study, there were general toxicity signs at 3,000 and 8,000 ppm in both generations of parental animals. No significant changes could be seen in the reproduction parameters even at the highest dose level in the Sprague-Dawley rat. There was a statistically significant increase of dead pups in both F1 and F2 generation litters with no change in survival indices. The authors did not consider the deaths in the F1 generation considered related to MTBE because the increase was due to a death of an entire litter of 16 animals

Table 4.39 Summary of effects on reproductive toxicity (fertility) of MTBE

Study definition	Dosing	Effects in P-animals	Effects in F1-animals	Effects in F2-animals
1-gen. reproduction in Sprague-Dawley rat (Biles et al., 1987)	Inhalation 250, 1,000, 2,500 ppm (900 –9,000 mg/m^3)	Renal dilated pelvis at 250 & 2,500 ppm (non-significant) + slightly lower pregnancy rate at 1,000 ppm, (non-significant)	Lowered Pup viability index at 1,000 and 2,500 ppm*, lowered survival at two lowest doses but not at high dose *	-
2-gen. reproduction in Sprague-Dawley rat (Bevan et al., 1997)	Inhalation 400, 3,000, 8,000 ppm (1,500-29,000 mg/m^3)	8,000 ppm: body weights and gain lower in males at PMP* In females body wt gain increased in PND 21-28*	8,000 ppm: increase of dead pups on PND4*, male and female body weight reduced at PND 14-28 and from week 0 to end of PMP*, abs. liver wt increased* in both sexes, relative in males*. No histological change in any tissue.	8,000 ppm: increase of dead pups on PND4*, reduced female body weight on PNDs 7-28*.
		3,000 ppm: CNS depression, increased relative liver weight*.	3,000 ppm: Reduced female body weight on PND 14 & PMP wks 0-4*, males PMP wks 0-3*, rel. Liver wt incr. in males*.	3,000 ppm: reduced male body weight on PNDs 14-28*.

PMP= Pre-mating period
PND = Post natal day
* = statistically significant
+ = toxicological significance unclear

Conclusion on reproductive toxicity

MTBE does not cause significant toxicity to reproduction in Sprague-Dawley rats.

4.1.2.9.3 Developmental toxicity

Sprague-Dawley rat, inhalation

MTBE was administered to mated Sprague-Dawley rats in an inhalation exposure chamber at concentrations 0, 250, 1,000 and 2,500 ppm (Conaway et al., 1985). The exposure was given during the gestation days 6 – 15 for 6 hours per day. Maternal body weights were recorded on days 0, 6, 12, 15, 18 and 20 and food consumption was monitored in three day intervals during the gestation days 6-18. After laparotomy, dams and foetuses were examined for gross abnormalities. Foetus weight and sex were determined and late and early resorptions were scored. If no uterine implantation sites were visible, the uterus was stained with 10% NH_4SO_4 to visualise the foci of implantation. One third of the foetuses was evaluated for soft tissue anomalies and the remaining 2/3 for skeletal defects.

No changes in body weights or body weight development could be detected in dams when compared to controls during the 6 days of pre-treatment, the 9 days of treatment period or in the five days after treatment. However, there was a significant reduction in food consumption in all treatment groups during the treatment interval on days 9-12. No treatment-related effects were noted in dam liver weights or in any other gross post-mortem observations. The pregnancy rates of treatment groups were comparable to that of control group. The mean numbers of corpora lutea, uterine implantation resorptions and live foetuses were comparable between treatment and control groups.

The foetuses of the treated dams did not show any significant difference in their weights or in the crown-rump distance, in relation to controls. There was a 58% predominance of male foetuses, which authors contributed to biological variability. When reported as "per litter" and "per foetus" no significant change in the incidence of malformations externally, in the soft tissue or the skeletal tissue.

CD-1 mice, inhalation

The test procedure and exposure regime that was used with Sprague-Dawley rat was also used to expose 30 mated CD-1 mice. The mice were exposed on the same days of gestation as the rats. Body weights and food and water consumption were not recorded on days 18-20 as the mice were sacrificed the day 18 (Conaway et al., 1985).

Maternal changes included increased lacrimation during the treatment period and a slight dose-related decrease in food consumption on days 12-15. A dose-related decrease was also observed in water consumption on days 9-12. The body weight was not affected by MTBE exposure. The number of resorption sites and their proportion to implants were slightly higher in the low and high dose groups. A likely explanation for this was that two females in these groups that had exceptionally high resorption/implant percentage. The number of live foetuses and their sex distribution was comparable to those seen in control mice. Whereas external and soft-tissue malformation rates remained comparable to control animals, there was a slight increase in skeletal tissue abnormalities in the high dose animals. Fused sternebrae was seen at frequencies per foetuses examined control: 0/191 (0.0%), 250 ppm: 1/180 (0.6%), 2/168 (1.2%) 1,000 ppm and 4/195 (2.1%) 2,500 ppm. When all separate examinations were combined, that is, external, soft tissue and skeletal examination, the cleft palate frequencies were: 2/281 (0.7%), 0/265 (0%), 1/251 (0.4%) and 2/290 (0.7%) for the control, low-, medium-, and high-concentration groups.

Considerably higher doses were used by Bevan et al. (1997b) in a developmental toxicity evaluation of 30 pregnant CD-1 mice/group that were exposed to 0, 1000, 4000, 8000 MTBE via inhalation during gestation days 6-15, 6 h/day. Maternal body weights, food consumption, and clinical signs were recorded every third gestation day. On gestation day 18 dams were sacrificed, foetuses were weighed, and their sex was determined, followed by an examination for external, visceral and skeletal alterations. Approximately one half of the foetuses from each litter was inspected for visceral abnormalities by longitudinal dissection. The remaining intact foetuses were eviscerated, fixed, stained and subjected to skeletal examination (Tyl et al., 1989; Bevan et al., 1997b).

There were no deaths or abortions and the pregnancy rate was over 93% in all groups. Treatment related clinical signs, typically seen with MTBE in other experiments, included ataxia, hypoactivity, prostration, laboured respiration and lacrimation. These symptoms were mainly noted in the animals of 8,000 and 4,000 ppm groups. The mice in the highest dose group only had a reduced body weight on gestation days 12, 15 and 18 and a reduction in body weight gain throughout the treatment and post-treatment periods. The body weight reduction remained, even when corrected for uterine weight. In the 8,000 ppm group animals, uterine weight was about 50% lower than in the controls. Total post-implantation loss was more than three-fold when compared to other groups. This resulted mostly from significantly ($p<0.01$) increased incidence of late resorption and dead foetuses. About 30% reduction in live foetuses/litter was seen in the high dose group and sex distribution was female dominant by almost 10% when compared to control. Foetal body weights were reduced significantly ($p<0.01$) by 8% and 27% in the 4,000 and 8,000 ppm dose groups, respectively. Cleft palate was the only *malformation* observed. In visceral examination of the 8,000 ppm group, out of 113 foetuses, with about 50% of each litter was examined for soft tissue craniofacial malformations, 16 were found with cleft palate, with 11

litters affected. The difference was statistically different from controls. In external examination, the control group had zero cleft palates and the 1,000 ppm group one occurrence. Only one cleft palate was found in the 4,000 ppm group. Also in the highest-dose group, there was a significantly reduced incidence of partial foetal atelectasis, a failure in the inflation of at least on region of the lung. Skeletal *variations* were increased in the high-dose group and were represented by reduced ossification in the skull, cervical, thoracic, and caudal centra, limbs and sternebrae. Similar ossification variations were also seen in the 4,000 ppm group, although not to same extent.

Fifteen male and fifteen mated female New Zealand White rabbits were tested in parallel following the above procedure. Rabbits were treated with same dose levels as the mice but on gestation days 6-18. Sacrifice was performed on the 29th gestation day. Clinical observations and food consumption recording were conducted daily and weight was recorded every third gestation day until sacrifice (Tyl, 1989; Bevan et al., 1997b).

None of the dams aborted or died during the study. The pregnancy rates remained between 80%-100% in all groups. The highest dose group suffered from a negative weight development ($p<0.01$) on gestation days 6-18, which was the treatment period. This was associated with the reduced food consumption during this time. When the maternal weight changes were corrected for gravid uterine weight they were substantially but not statistically significantly lowered when compared to controls. The only treatment related effect found on maternal rabbits was 15% increased liver weight in the 8,000 ppm group and over 70% reduced food consumption. Gestation parameters and other reproduction data were similar along all the groups. The foetuses had no significant differences in weight, in the incidence of external, visceral or skeletal malformation or variation. While all other groups had zero skeletal malformations, the highest dose group had skeletal abnormalities in 3/12 litters. These were mainly malformations of the thoracic part of the body.

4.1.2.9.4 Summary of developmental toxicity

At 2,500 ppm no significant developmental effects can be seen in either mice or rats. In mice, several gestation parameters, such as post-implantation loss and percentage of dead foetuses/litter, show an increase at 8,000 ppm. Maternal gestation body weight is significantly decreased at 8,000 ppm. Foetal body weight is adversely affected at 4,000 ppm. Skeletal variations, mainly poor ossification, are significantly increased at 4,000 ppm. CD-1 mice had a dose related increase of fused sternebrae occurrence. According to the investigators, the historical control value for this malformation is 0.16 %. The authors did not consider this treatment related since there were no increase in rib/vertebrae defects, which are commonly associated with fused sternebrae. Moreover, the CD-1 mice treated up to 8,000 ppm had no such malformation. There was a statistically significant increase in cleft palate incidence at 8,000 ppm in CD-1 mice. This dose level produced marked maternal toxicity. Although corticosterone was not measured in this particular study, Dodd and et al. (1989) have previously shown that female Fisher-344 rats and CD-1 mice treated with 8,000 ppm MTBE have markedly elevated corticosterone when compared to controls. Maternal stress may have played a role in the formation of the cleft palates seen in the mice. Rabbits show practically no signs of developmental toxicity even at 8,000 ppm.

Table 4.40 Summary of effects on reproductive toxicity (development) of MTBE

Study definition	Dosing	Maternal Effects	Embryo/foetal effects	Reference
Sprague-Dawley rat	Inhalation 250, 1,000, 2,500 ppm	Reduction in food consumption in all treatment groups during the treatment interval during days 9-12*.	A preponderance of male pups over females at 1,000 ppm*	Conaway et al. (1985)
CD-1 Mice	Inhalation 250, 1,000, 2,500 ppm	A slight, non-significant dose-related decrease in food consumption on days 12-15 in the treated groups and in water consumption during days 9-12 in the treated groups (no change in body wt)	A slight increase of sternebrae malformations (4th & 5th fused) in all treated groups, 0.6 (low), 1.2 (mid) and 2.1% (high). (Investigators stated that historically seen with low incidence in control animals with 0.16% incidence. They concluded this not treatment related since there where no increase of vertebral or rib effects usually associated with this malformation).	Conaway et al. (1985)
CD-1 Mice	Inhalation 0, 1,000, 4,000, 8,000 ppm	8000 ppm: hypoactivity, ataxia, prostration, laboured respiration, reduced body wt on GDs 12, 15, 18 and wt gain during GDs 6-15 (treatment), 15-18 (gestational), 0-18 (gestational corrected for uterine)* incr. liver wt, reduced uterine wt*, colour changes in the lungs. 4000 ppm: Ataxia, hypoactivity, reduced food cons. during GD6-10, colour changes in the lungs	8,000 ppm: incr. post impl. loss due to late resorptions and dead foetuses*, lower pct. of live and male foetuses/litter*, lower foetal body wt/litter*, Malformations: cleft palate*, Variations: reduced ossification* 4,000 ppm Reduced foetal body wt/litter* Variations: skeletal (reduced ossification in various sites*, Sternebrae no. 5&6 split)	Bevan et al. (1997)
NZW rabbit	Inhalation 1,000, 4,000, 8,000 ppm	4,000 ppm: >70% reduction in food consumption during GDs 6-10	-	Bevan et al. (1997)

GD = gestation day
* statistically significant

Conclusion on developmental toxicity

Although malformations are seen at 8,000 ppm in CD-1 mice, they are considered to occur at a dose level of marked maternal toxicity. When there is significant maternal toxicity, the probability of the occrrence of non-specific developmental effects in the offspring increases. The sternebrae malformations seen in CD-1 mice at 250-2,500 ppm are not considered treatment related. Therefore, based on the available data, MTBE is not considered toxic to foetal development.

4.1.2.9.5 Other effects on the endocrine and reproductive system

The hypothetical endocrine mechanisms of the tumour induction, especially in relation to the Leydig cell tumours in rats and the liver tumours seen in mice, have been under scrutiny. While better knowledge of these mechanisms is of interest when the human relevance of the tumours is assessed, the studies also give other information on MTBE's possible endocrine effects. It is noteworthy that most of these studies in this section are abstracts only, which did not allow a

well-organised or detailed description of them. Despite the possible lack of weight of these data, it was felt that a separate section is necessary to describe the effects.

The endocrine effects in female CD-1 mice have been investigated by Moser et al. (1998). Similar test conditions to the mouse carcinogenicity study by Bird et al. (1997) were used. Twelve female B6C3F1-mice were exposed to air or to a target concentration of 8,000 ppm MTBE for 4 or 8 months, 6 hours per day, five days a week. Results showed several effects consistent with endocrine modulation. The microscopical findings included decreased uterine, ovary and pituitary weight, fewer uterine glands, decreased number of cervical and vaginal epithelial layers. Additionally, alterations in the stages and length of the oestrous cycle and increased ACTH-immunoreactivity of the pituitary and a loss of *zona reticularis* of the adrenal cortex were seen.

Allgaier and Peyster (1999) investigated the effect of MTBE on luteinising hormone production and release in hypothalamic-pituitary unit in gonadectomised male Sprague-Dawley rats. For one group of the animals, testosterone levels were maintained artificially with testosterone propionate containing implant. Radio-immuno-assay was used to detect the plasma LH level after 2-5 hours and 5 days of 800 mg/kg daily MTBE doses by gavage. No change in LH hormone levels was found when compared to controls.

Faecal analysis was used to determine testosterone and luteinising hormone release hormone (LHRH) levels in mice (5/group) before, during and after oral MTBE dose of 400, 1,000 and 1,500 mg/kg/day for 5 days. A point sample of serum testosterone was taken and testes were investigated using light microscopy. Other than a small increase in gross disruption of tubules at 1,500 mg/kg no differences were noted in any parameter. In parallel, a similar study was conducted with the two UV/peroxidase products of MTBE, tert-butyl alcohol and tert-butyl formate. No effects were noted in testicular histology or in male hormone levels (Billitti et al., 1999).

Lington et al. (1997) have shown that Fisher-344 rats have elevated levels of corticosterone, the major glucocorticoid in female rat, in serum after 13 weeks exposure to 4,000 or 8,000 ppm MTBE. A higher plasma level of aldosterone, the mineralocorticoid derivative of corticosterone, was also detected. A similar trend of increasing serum corticosterone can be seen in the CD-1 mice and Fisher-344 rats in the two-year carcinogenicity study by Bird et al. (1997) at 3,000 ppm and 8,000 ppm. Male rats, however, show at the end of the study a more than two-fold serum corticosterone *decrease* in the 8,000 ppm treatment group when compared to controls.

Day et al. (1998) reported in an abstract that male Sprague-Dawley rats given a gavage dose (40 mg/kg) of MTBE have elevated serum corticosterone level already after 14 days. The level remained higher at 800 mg/kg after 28 days. Moreover, the study results showed that the rats had a decrease in serum testosterone level at 800 mg/kg but no change in luteinising hormone (LH). Luteinising hormone is an important regulator in the production of testosterone in its major production site, the interstitial cells of the testis.

Williams et al. (2000) conducted a study with Sprague-Dawley male rats that was divided in three parts. In one part (A), rats were treated with 0, 250, 500, 1,000 or 2,500 mg MTBE/kg/day for 28 consecutive days. To compare hormonal changes at day 15 and 28, another experiment (B) started on the same day. Rats were given MTBE 0 or 1,500 mg/kg for 15 days. Based on the findings of these two studies, an additional dose-response study (C) was conducted in which the rats received 0, 250, 500 or 1,000 mg MTBE/kg/day for 15 consecutive days. The previously used 1,500 mg dose was not used because of adverse clinical effects observed in the two other experiments. Body weights were recorded every 3-4 days throughout the study. For a positive control, 10 male rats were injected with either vehicle (1,2-propane) or 10 mg/0.25 ml flutamide,

which increases testosterone and LH secretion. After decapitation, serum was separated from the trunk blood and testicular interstitial fluid (TIF) was collected. Radioimmunoassay kits were used to determine 17β-estradiol, testosterone, dihydrotestosterone (DHT), triiodothyronine (T_3) and thyroxine (T4) from serum. Testosterone was measured also from TIF. In experiment C, serum testosterone, LH, prolactin and TIF testosterone were measured. Liver, epididymides, testes, kidneys, dorsal lateral and ventral prostate, pituitary gland adrenal glands and seminal vesicles were weighed. Right testis and kidney, adrenal glands and liver were stained with H&E and lesions seen under microscopy were graded.

During the last two weeks, the highest dose group had a statistically significantly lower (7-12%) body weight gain compared to controls. After 15 days of dosing group, relative kidney, adrenal, pituitary weight was increased in the highest dose group. Rats dosed for 28 days with 1,000 and 1,500 mg/kg showed statistically significant dose-related increase in relative liver weight. Similar increase with dose was seen in relative kidney weight at all doses. Relative testis weight was increased only at the highest dose level. Centrilobular hypertrophy of the liver was characterised by a dose-related severity, which varied from minimal to moderate. Kidneys lesions included enlarged eosinophilic bodies within epithelial cytoplasm, and individual cell necrosis, characteristic to protein droplet nephropathy. At 15 days, the high dose rats had a lower serum testosterone and rats of the same dose group that were treated for 28 days had a significant serum LH decrease. Testosterone level in the testicular interstitial fluid showed no change. The rats in the 1,500 mg/kg dose group had a decreased DHT after 28 days. T3 decreased significantly (19% of control) in rats dosed with 1000 and 15000 mg/kg for 28 days. Estradiol level was below the limit of detection in control and MTBE-treated rats.

In a previous study, Moser et al. (1996) have demonstrated that a short-term exposure to 1,800 mg/kg MTBE by gavage causes a two-fold increase in liver oestrogen metabolism rate in mouse hepatocytes. This was mainly a contribution of increased activity of liver P450 enzymes. However, no decrease in circulating oestrogen levels was noted. Furthermore, MTBE did not inhibit oestrogen binding to its receptor or alter the receptor immunoreactivity. This evidence together with normal follicular maturation and the presence of oestrous cycle, although longer, suggests that MTBE was not directly toxic to ovary or pituitary in mice (Moser et al., 1998). To study the estrogenic effects, Okahara et al. (1998) gave MTBE to CD-1 mice, by gavage at 600 or 1,500 mg/kg for five days. Dosing was given with and without a subcutaneous injection of 1 µg estradiol on days 3-5 (n=6-11). A slightly higher uterine/body weight was seen in the mice treated with both substances. All uteri treated with MTBE alone had an unusual translucent surface. One half of the mice that received 1,500 mg/kg MTBE had a delayed vaginal opening on post-natal day 26.

4.1.2.9.6 Summary of endocrine effects

At high dose, MTBE produces a number of effects on endocrine system in female mice. Although MTBE causes an increased metabolism of oestrogen in mouse liver, this does not affect the level of free hormone. Thus, MTBE seems to have a slight antioestrogen- like activity at very high doses. Consequently, a weight loss and morphologic changes are seen in uterine. Oestrous cycle length and stages were also altered. Increased interstitial testosterone level was found in rats after a 28-day exposure. (Williams et al., 2000a) reported decreased serum testosterone and LH but the results of this study did not indicate the hypothetical mode of action. Corticosterone and aldosterone levels are elevated after continued exposure to high doses of MTBE. A clear decrease in serum corticosterone level is seen in the later phase of the chronic studies. This is an expected finding, as the microscopy shows a disruption of zona reticularis in

the same time. The significance of the altered morphology of adrenal gland and adenohypophysis in the estrogenic effects is not clear. Because the data are not considered sufficient, no NOAEL is assigned.

4.1.3 Risk characterisation

4.1.3.1 General aspects

Extensive data are available for MTBE's health based evaluation. Because MTBE has been of great public interest, abundant information is available on occupational and consumer exposure, toxicokinetics and the toxicological effects' end-points. The numerous case reports of MTBE's use in cholecystolithotripsy have given valuable information in the assessment of acute effects in humans. There are also a number of reports with controlled MTBE exposure and epidemiological data. Although not all reports formally concur with EU or OECD guidelines, most of them are well-conducted studies from the '80s and '90s providing for a sound data set.

Toxicokinetics

Tests with human volunteers and F344 rats have shown that MTBE is efficiently absorbed from the lungs. Approximately 40% of the substance was retained in the lungs in subjects exposed up to 75 ppm MTBE vapour. A complete and rapid absorption occurs from the intestine; in the rat, the concentration peaked after 15 minutes and a recovery comparable to intravenous injection was reached. Tests in occluded exposure systems with rats have shown that about 16 % of the dose was absorbed from 0.4% MTBE in saline and 34% from 4% saline solution. Although moderate skin penetration can be observed in occlusive exposure, a less efficient penetration can be expected in non-occlusive conditions due to MTBE's volatile nature. Moreover, comparisons of dermal flux between rat and human cadaver skins demonstrated that human skin had 2-14 times lower flux than the rat skin when MTBE was administered in petrol. However, a very high flux (290 $\mu g/cm^2.min$) for 15% MTBE in petrol was obtained with the rat skin model. A skin permeability constant of 0.006 cm/h (obtained from a formula employing octanol/water partition coefficient and molecular weight) gave a good fit of plasma MTBE concentration.

The previous parameters related to skin absorption of MTBE are wide apart. To demonstrate the inconsistency and to allow the reader to draw some conclusion on the likely magnitude, **Table 4.36** examines predicted systemic doses of MTBE received percutaneously in maintenance work with different estimation methods. For the presentation, it was assumed that i) the worker is handling petrol pumps containing 11% MTBE in petrol, ii) human skin is half as permeable as the rat skin, iii) exposed area is 840 cm^2 (both hands), iv) skin is in contact with MTBE for 4 hours per day.

Table 4.41 Estimated percutaneous systemic daily dose of MTBE in the maintenance of petrol pumps using different measures of skin absorption

Method	Daily systemic dose (mg)
Calculation based on permeability coefficient 0.003	806
Calculation based on the deposition of 0.55 $mg/cm^2/day$ from EASE, and 17% absorption	79
Calculation based on *in vitro* flux of 145 $\mu g/cm^2.min$	29,232

The *In vitro* flux value for MTBE measured with human cadaver skin is very high. However, the credibility of the result cannot be assessed as the result has only been published in an abstract. To estimate *in vivo* flux using the MTBE permeability coefficient of 0.003 and a concentration difference of 81 mg/ml across the skin as starting points, the product yields an apparent flux of 0.24 mg/cm^2.h. This is a moderate value, similar to or higher than those obtained for aromatic hydrocarbons in hand immersion studies. Since repeated cycles of wetting and rapid drying (due to a high evaporation rate) of the hands by MTBE is likely to result in a considerably lower absorption than during immersion in the liquid (for 1,1,1-trichloroethane, a 20-fold lower rate was found; Stewart and Dodd, 1964), the calculation based on EASE model deposition and 17% uptake seems reasonable, and will be used in risk characterisation.

MTBE is moderately soluble in blood with a blood/air partition coefficient of 10, whereas the solubility to fat is ten times that. Thus, MTBE is likely to have wide distribution in the body. In humans, the volume has been estimated to be four times the body weight. In rat, a species and sex-specific accumulation occurs in the kidneys; this phenomenon is explained by MTBE's affinity for α2u-globulin, a protein normally excreted by male rat kidneys.

Studies with human liver preparations indicate that microsomal enzymes, mainly CYP2A6 and secondarily CYP2E1 of the P450-family, oxidatively metabolise MTBE to formaldehyde and tert-butyl alcohol. Formaldehyde goes through a rapid transformation to formic acid. The main urinary metabolites of TBA are α-hydroxybutyric acid and 2-methyl-1,2-propanediol and TBA-glucuronide conjugates. It may be noted that studies have shown large differences in liver CYPA6 activity between individuals. Rat experiments demonstrate that a metabolic saturation occurs at higher doses, in which case the excess MTBE is exhaled unchanged. This can be seen also in the total clearance volume, which in rat reduces to almost half when the six-hour inhalation dose changes from 400 to 8,000 ppm. Volunteer experiments, with humans exposed to a maximum of 75 ppm MTBE, have given total clearance volumes of approximately 500 l/min, with a hepatic extraction fraction of 0.4. MTBE is eliminated from the blood rapidly. In experiments, where volunteers where exposed to 4-75 ppm MTBE for 2 or 4 hours, plasma half times ranged from 2.6 to 19 hours. The patients who received MTBE directly to gallbladder in gallstone dissolution treatment, the blood MTBE concentration halved in about 5 hours (mean blood conc. was 450 μmol/l). However, the plasma half time for TBA was up to two times longer. Overall, it is worthwhile noting that qualitatively MTBE metabolism in rats and humans is similar.

Acute effects

The acute toxicity of MTBE is mild. In test animals, MTBE has low acute toxicity by all routes. LD50 values in oral administration are approximately 4,000 mg/kg. When administered dermally an LD50 of over 10,000 mg/kg has been determined. Acute inhalation toxicity in rats has an LC50 of almost 100 mg/l. The symptoms in humans are quite well documented in the case reports of gallstone dissolution patients. The most typically reported symptoms in the patients having MTBE treatment-related complications are nausea, drowsiness, vomiting and sedation. These can be accompanied by an elevation in liver transaminases and by changes in the blood picture, which indicate haemolysis. An estimated peak dose of 340 mg/kg has been reached in these treatments. In the controlled experiments, where the doses are much smaller (up to 75 ppm) only mild symptoms have been reported. The reported symptoms can be characterised as CNS depressive in nature.

Irritation

The skin irritation data for MTBE are somewhat equivocal. Some of the tests show almost no irritation response while other tests show mild to significant irritation. However, MTBE is at

least moderately irritating to skin, and based on the results of one EU-guideline study they are sufficient to classify it with R38.

MTBE is not a significant eye irritant. There are seven different tests and all of them show, at most, mild signs of ocular irritation. At least three studies with human volunteers, that conducted objective and subjective measurements of eye irritation in vapour exposure, concluded that eye irritation could not be attributed to MTBE. Similar conclusions were drawn on respiratory irritation.

Sensitisation

Two independent tests with Guinea pigs have given no indications of sensitisation. There are no human data. Sensitisation is not considered a relevant end-point in the risk characterisation.

Repeated dose toxicity

In rats, the most prominent effects are seen in the kidneys. Hyaline droplets accumulate in the proximal tubules, which leads to proliferation and in later phase to nephropathy. The available evidence suggests that this phenomenon be caused by the accumulation of α2u-globulin, which is specific to male rats. Therefore, the effects seen in the kidney are considered to have less relevance when determining the NOAEL for the risk characterisation. Liver is also affected slightly. In the oral exposure studies, slight morphological liver abnormalities were reported in males at 200 mg/kg (Zhou et al., 1999). (Williams et al., 2000a) found centrilobular hypertrophy at 500 mg/kg after 28 days and Robinson et al. (1990) reported elevated AST with weight increase at 900 mg/kg. In inhalation exposure, liver is affected mostly after 28 or 90 days at dose levels 3,000 ppm or higher. In the two-year study with rats there is a 20% weight increase in the relative liver weight in females. To some extent, the above listed liver changes can be considered adaptive. In mice, the 28-day inhalation toxicity study mainly showed changes in liver at high doses. A slight increase in liver proliferation was present in males at 8,000 ppm, and in females at both 8,000 and 3,000 ppm. Hepatocellular hypertrophy was seen at 8,000 ppm, which was exhibited more severely in males than in females. **For inhalation exposure, the NOAEL of 800 ppm** is taken forward based on the effects seen in Fisher-344 rat liver only at doses higher than 3,000 ppm, even in the two-year chronic toxicity study. This is supported by the fact that, in CD-rat, a dose of 1,000 ppm produces little signs of adverse effects in a 13-week study. Based on the mild liver effect on liver in the 90-day study with Sprague-Dawley (Robinson et al., 1990) supported by the findings from (Zhou et al., 1999), an **oral NOAEL of 300 mg/kg** is chosen for the risk characterisation.

Human studies, which have investigated, e.g., workers exposed to MTBE, give limited information on MTBE long-term-effects. Most of the studies have been unsuccessful in controlling the variables, have mixed exposure or are biased. A group of Finnish investigators found only a small but significant increase in fatigue when they compared milk delivery drivers and petrol tanker drivers. There are no data indicating adverse effects on long-term neuro-psychological function. Although substantial evidence is lacking, due to the effective lipid extraction properties of MTBE it can be presumed that repeated skin exposure may result in skin fatigue (and consequent risk of toxic eczema) for workers, an effect common to a variety of organic solvents.

Mutagenicity

The *in vitro* data are mostly negative. There is a positive result in an Ames TA102 test system and in mouse lymphoma cells. However, the subsequent data showed that the increase in mutagenicity was most likely due to the production of extracellular formaldehyde present only

when microsomal enzymes were added to the test system. Thence, the result is not considered physiologically relevant. A positive response was seen in a comet assay in rat lymphocytes, reported in an abstract. However, this result is unsupported by the six other *in vivo* tests for various mutagenicity end-points, which have demonstrated no mutagenic properties. (Zhou et al., 2000) recently found a correlation of increasing liver UDS activity *in vitro* with increasing MTBE dose. Another *in vitro* liver UDS and an *in vivo* UDS test conducted with CD-1 mice was, however, negative. Based on the available information, MTBE cannot be considered a mutagen.

Carcinogenicity

Four different types of neoplasm are reported in test animals. These include kidney adenoma and carcinoma and Leydig cell tumours in male rats, liver adenoma in female mice and lymphoma in rats. Extensive studies have been conducted to study the causal relationship of α2u-globulin and the kidney tumours. Although, the evidence is quite consistent with this mechanism, MTBE is not a strong α2u-globulin inducer. However, studies have shown that the **kidney adenomas** only appeared at inhaled doses of 3,000 ppm and higher. These tumours were not reported in the oral carcinogenicity study with Sprague-Dawley rat. Mice had an increase of liver neoplasm, or more precisely; females had a significant increase of **hepatocellular adenomas**. The possible relation of the increased adenomas to the disturbances in oestrogen homeostasis has been investigated, but these studies have shed little light on the mechanistic aspects. Nevertheless, these tumours appeared at 3,000 ppm, which is relatively high, when human potential exposure is considered.

The observations by Belpoggi et al. (1995) of increased lymphoma and leukaemia incidence in female rats are somewhat controversial. There are several complications with the results. When a lifetime study is conducted spontaneous and cryptogenic tumours, such as lymphomas and leukaemias, are known to occur (Cassarett et al., 1992). The incidence of these neoplasms may vary substantially from one study to another, even between groups. Therefore, it is important to compare the tumour incidence in treatment groups to the historical occurrence of these tumours. In this study, no exact data on the historical control incidence of this tumour type were given. If the tumours were to be considered relevant, there is a clearly increasing trend of animals bearing haemolymphoreticular neoplasia, which were mostly lymphoimmunoblastic lymphomas localised in the lungs. However, even then, the statistical power of these observations needs some discussion. The results are treated with a statistical method that assumes quick lethality to the tumour, as described by Mantel (1966). This may lead to a superficial dose-response, as the denominators in the high dose groups are smaller than in the low dose groups due to toxicity. On the other hand, the assumption that the animals that died prematurely had no tumours may also be wrong, although in this case it is unlikely since neoplasia rarely develop in rats under 1 year. There was significance only when **lymphoma** and leukaemia were summed and counted against the adjusted number of animals alive at week 56, which was the time when first observation of leukaemia was made. However, most of the proportion of lymphoma of the summed tumours was at least 85% in all dose groups. The significance level at the low-dose group (250 mg/kg) was only $p<0.1$ and the-high dose (1000 mg/kg) $p<0.01$. In addition, only two MTBE treatment groups used in the study, when typically three is the minimum. Moreover, there are no observations of this tumour type in the Fisher-344 rat or mice. In summary, there are several factors that set considerable restrictions to the proper assessment of the relevance of these tumours to man. Therefore, the level of confidence in these results is not very high.

The Belpoggi study (1995) and the study by Bird et al. (1997) both reported an increase of **testicular interstitial cell tumours**. The previous study saw a significant increase at 1,000 mg/kg oral dose. This may have been an overrepresentation due to lower mortality of high dose males during the final weeks 88-152. In the latter study (Chun et al., 1992) the incidence of

tumours seemed to have a dose relationship. However, the incidence was over the laboratory historical control only at the highest dose, 8,000 ppm. As MTBE is not a genotoxic substance, it is possible that a threshold exist for these tumours, which might lay somewhere between 400 ppm and 3,000 ppm via inhalation and <250 mg/kg orally for test animals. **A NOAEL of 400 ppm for inhalation and a LOAEL 250 mg/kg for oral administration** is derived.

Reproductive toxicity

MTBE has been tested for effects on fertility in one- and two-generation studies in Sprague-Dawley rat. The NOAEL for F1-animals in the one-generation study was 250 ppm; a lowered pup viability index was seen at LOAEL of 1,000 ppm. In the two-generation study, a NOAEL of 400 ppm was determined for both the F1- and F2-animals. The only effects seen at LOAEL were reduced body weight at 3,000 ppm and increased relative liver weight.

Developmental toxicity has been tested in rat, mouse and rabbit. There were no adverse effects noted in Sprague-Dawley rat at **2,500 ppm** or CD-1 mouse at **1,000 ppm** that were considered to have significance for development. Reduced body weight and skeletal abnormalities were seen in CD-1 mice only at 4,000 ppm, a dose causing severe toxicity to dams. Likewise, no adverse effects to the developmental of New Zealand White rabbits could be demonstrated, even at 8,000 ppm.

Changes in endocrine hormones in rat included increase in corticosterone at 4,000 ppm after 13 weeks and decrease in testosterone level at 800 mg/kg after 28 days. There was also an increased corticosterone seen in rats at **40 mg/kg** already after 14 days. However, these effects have been all but consistent and have been mostly abstract reports. The database is insufficient to conclude on the true significance rendering the derivation of a meaningful NOAEL impossible.

4.1.3.2 Exposure and reasonable worst-case scenarios

Workers

Occupational exposure to MTBE can be divided roughly into two areas: handling of pure MTBE during its manufacturing, formulation and transport, including maintenance, and exposure to MTBE from petrol during its transportation, distribution and at various maintenance tasks of petrol containing equipment. The most significant exposure route is by inhalation. The exposure measurements that are displayed here are based on both Central European petrol containing on the average 2.8% MTBE and Finnish petrol, which typically contains 11% MTBE. There are two main types of exposure situations that are considered: high-peak values with short duration and mean exposure during a longer time. Although there is little information available of the duration of the peak exposure, they are relevant in the estimation of safety margins for acute end-points. The short-term exposures were specified as an exposure period during 30 minutes to one hour, except in service stations where the actual exposure time was only a few minutes during refuelling. In the estimation of long-term end-points, the measured 8-hour exposure values obtained from industry or elsewhere were used. Calculation of the 90th percentile of measured concentrations (when possible), expert judgment and comparison of the scenarios with one another was used to derive the reasonable worst-case value. For comparison, there were published exposure data available from the USA. The European and the USA data sets gave closely similar average results. Additionally, EASE calculations were conducted. EASE gave much higher results than the measured concentrations. By contrast, EASE modelling was found appropriate for the estimation of skin exposure (deposition).

Table 4.42 presents a summary of estimated systemically absorbed daily doses of MTBE taken up via inhalation and skin for the different occupational scenarios. For source data, the reader is referred to **Table 4.19**, which indicates for each scenario the RWC 8-hour TWA air concentration of MTBE as well as the estimated skin deposition. For the calculation of inhalation uptake, it is assumed that the lung ventilation over the workday is 10 m^3 (about 21 l/min), which corresponds to light work. Retention of MTBE in the lungs is 40%. MTBE deposition on the skin is derived from EASE, the proportion assumed to be absorbed is 17%. Skin contact area for all maintenance scenarios and for automotive repair is set at 840 cm^2 (both hands). In all other scenarios the corresponding area is 420 cm^2 (palms of both hands).

Table 4.42 Estimated daily doses of MTBE taken up via inhalation and skin in occupational scenarios

Exposure scenario	Daily uptake by inhalation (mg)	Daily uptake by skin (mg)	Total daily uptake (mg)	Total uptake (mg/kg.day)
Production: Process work Sampling & laboratory	 200 100	 7 71	 207 171	 3 2.4
Formulation: Process work Sampling & laboratory	 200 100	 7 71	 207 171	 3 2.4
Transporting: Neat MTBE Fuel (11%, 2.8% MTBE) Sampling & laboratory	 400 120 100	 71 7; 2 71; 7; 2	 471 127; 122 171; 107; 102	 6.7 1.8; 1.7 2.4; 1.5; 1.5
Distributing: 11% MTBE in petrol 2.8% MTBE in petrol	 160 160	 7 2	 167 122	 2.4 1.7
Service stations: 11% MTBE in petrol 2.8% MTBE in petrol	 80 12	 7 2	 87 14	 1.2 5
Maintenance: Production, formulation & transport Distributing 11% MTBE Distributing 2.8% MTBE	 240 160 120	 714 86 20	 954 246 140	 13.6 3.5 2
Automotive repair: 11% MTBE in petrol 2.8% MTBE in petrol	 40 12	 14 4	 54 16	 0.8 0.2
Drivers and other professionals	0.8	very low	0.8	0.01
Solvent use of MTBE	100	71	171	2.4

Consumers

Direct consumer exposure to MTBE is limited to petrol, more specifically during motor vehicle refuelling. The reasonable worst-case concentration in Stage 1 station during refuelling is 3 to 29 mg/m^3. Typically, refuelling lasts typically about 1 minute and is not performed more than 1-3 times a week. The reasonable worst-case daily MTBE dose by inhalation for refuelling is 174 µg/day, which results in approximately **1 µg/kg/day** for a 70 kg person when pulmonary retention of 40% is taken into account ((174 µg/day · 0.4)/70kg). The exposure concentration was taken from Section 4.1.1.2.1 (Refuelling).

Humans exposed via the environment

There are other significant sources of exposure for the consumer which are considered indirect via the environment and are handled in the respective section. As in the working environment, pure consumer exposure is restricted mainly to inhalation but when indirect exposure is considered, a certain amount may also be ingested in drinking water. Two separate exposure scenarios have been presented previously, "normal" exposure and a worst-case scenario. In the normal case, a person is expected to be a car-driving commuter exposing himself to urban air, visit petrol stations and pump petrol. In addition, normal tap water consumption is included. The "worst-case" person does the same routines as the "normal" person but is assumed to live near an MTBE emission source (petrol station) and consume contaminated tap water. However, the margins of safety will be presented only for the reasonable worst-case exposures of different sites. The reasonable worst-case daily MTBE dose calculated for humans exposed via the environment is **2.1 µg/kg/day**, when pulmonary retention of 40% is used ([(472 µg/day -174 µg/day) · 0.4 + 30 µg/day]/70 kg). The exposure values were taken from **Table 4.27** in Section 4.1.1.4, but refuelling was omitted.

Combined consumer uptake

The proportions from different exposure routes are listed in the table below. In the final total uptake, retention percentage is based on the toxicokinetic data presented in Section 4.1.2.1.1. The summed maximal total dose/kg of bodyweight in the normal scenario is **1.4 µg/kg/day** and for the reasonable worst-case scenario **3.1 µg/kg/day**. The exposure values are presented in table **Tables 4.26** and **4.27** in Section 4.1.1.4.

Table 4.43 Summary data on systemic absorbed doses of MTBE taken up via inhalation and ingestion for two consumer scenarios

Exposure scenario	Daily uptake by inhalation (µg) [1)]	Daily uptake by ingestion (µg) [2)]	Total daily uptake (µg)	Total uptake (µg/kg.day)
Normal scenario (see Table 4.26)	10.6-100.4	0.2	10.7-100.6	0.2-1.4
Reasonable worst-case scenario (see Table 4.27)	27.4-188.8	30	57.4-218.8	0.8-3.1

[1)] 40% of the inhaled MTBE is absorbed. [2)] 100% of the ingested MTBE is absorbed. [3)] A 70kg person is assumed

4.1.3.3 Workers

This section describes the Margins of Safety (MOS) by end-point and by occupational exposure scenario. When it was not possible to calculate a MOS, a qualitative description of the risk for that particular site was given. The MOS values were not calculated for every work sub-scenario but rather for the worst-case exposure in the main scenario. For repeated dose toxicity, carcinogenicity and reproduction toxicity margins of safety are presented for inhalation and dermal exposure and both combined. Systemic doses have been calculated based on toxicokinetic data and measured exposure (**Table 4.42**). In deriving MOSs, the NOAELs were taken from studies with an appropriate exposure route.

4.1.3.3.1 Acute toxicity

Oral

In occupational use, ingestion is not anticipated.

Inhalation

Comparing the measured reasonable worst-case exposure (74 mg/m3/4h) is low compared to the levels needed to produce lethality (LC50/4h > 120,000-140,000 mg/m^3). Even with the highest peak MTBE air concentrations, concern for severe acute effects is very low. Mild acute symptoms, such as nausea, drowsiness and vomiting might appear already at much lower doses. Reversible sedation has been reported to occur during gallstone dissolution, which under exceptional conditions has resulted in estimated body burdens of about 340 mg/kg. Calculating from the uptake dynamics, it can be estimated that an air concentration of about 1,000 ppm (~3,700 mg/m3) would be required to cause the acute CNS effects. This still leaves a very high margin of safety, even with combined dermal and respiratory exposure.

Dermal

The maximum daily uptake in work scenarios is about 14 mg/kg/day (9.7 mg/kg/day by skin) from which one can assume that acute effects will not occur. LD50 is ~4,000 mg/kg and for acute sedative effects 340 mg/kg.

4.1.3.3.2 Irritation

Skin

Based on animal studies MTBE may cause irritation. In some occupational scenarios, exposure of the skin of hands to MTBE is expected to occur intermittently. On request by the rapporteur, the occupational health physicians at a major MTBE producing company in Finland reviewed their health surveillance observations concerning potential skin effects. No clinical findings had been made in the workforce that would point to skin irritation during handling of MTBE. Therefore, there are no substantial findings that would support the notion that skin irritation by MTBE is a significant risk for workers.

Due to the effective lipid extraction properties of MTBE, it can, however, be presumed that repeated skin exposure may result in skin fatigue (and consequent risk of toxic eczema), an effect common to a variety of organic solvents.

Eye

Because MTBE is not considered an eye irritant, no risk for this end-point is perceived.

4.1.3.3.3 Sensitisation

MTBE is not sensitising, therefore there is no risk for this end-point.

4.1.3.3.4 Repeated dose toxicity

The MOS values for repeated dose toxicity are listed in two separate tables: **Table 4.44** for inhalation, and **Table 4.45** for inhalation and dermal exposure combined, measured as the total body burden.

4.1.3.3.5 Mutagenicity

There are abundant data on mutagenicity, *in vitro* and *in vivo*, which have shown practically no evidence of positive response. Thus, it is concluded that mutagenicity is not a relevant end-point for MTBE risk characterisation.

4.1.3.3.6 Carcinogenicity

The MOS values for carcinogenicity are listed in separate tables for inhalation, and dermal exposure and both combined, measured as the total body burden.

4.1.3.3.7 Toxicity to reproduction

No adverse effects were seen in either the studies for reproduction efficiency or the foetal development at doses that would have been below significant maternal toxicity. Therefore, it is concluded that toxicity to reproduction is not a relevant end-point for MTBE and no MOSs are calculated.

The available information on endocrine effects is not very consistent and it is scarce, mostly abstract reports. The data do not consistently support that MTBE be an endocrine modulator. At the exposure level at which some effects are seen (LOAEL), the margins of safety are still high in all scenarios.

Table 4.44 Margins of safety listed for occupational scenarios in long-term inhalation exposure

RWC8h exposure	Repeated dose NOAEC 2,900 mg/m^3	Carcinogenicity NOAEC 1,450 mg/m^3	Reproduction Max. Conc. 29,000 mg/m^3	Development Max. Conc. 29,000 mg/m^3
Production 50 mg/m^3	58	29	n.a.	n.a.
Formulation 50 mg/m^3	58	29	n.a.	n.a.
Transporting 100 mg/m^3	29	15	n.a.	n.a.
Distributing 100 mg/m^3	29	15	n.a.	n.a.
Service stations 20 mg/m^3	145	73	n.a.	n.a.
Maintenance (Distribution) 60 mg/m^3	48	24	n.a.	n.a.
Automotive Repair 10 mg/m^3	290	145	n.a.	n.a.
Drivers etc. 0.2 mg/m^3	14,500	7,250	n.a.	n.a.
Solvent use of Neat MTBE 25 mg/m^3	118	58	n.a.	n.a.

n.a. = not applicable

Table 4.44 continued overleaf

Table 4.44 continued Margins of safety listed for occupational scenarios in long-term inhalation exposure

RWC8h exposure Dermal	Repeated dose NOAEL 300 mg/kg	Carcinogenicity LOAEL 250 mg/kg	Reproduction Max. Conc. 2,000 mg/kg *	Development Max. Conc. 2,000 mg/kg *
Production 0.1 mg/kg	3,000	2,500	n.a.	n.a.
Formulation 0.1 mg/kg	3,000	2,500	n.a.	n.a.
Transporting 1.0 mg/kg	300	250	n.a.	n.a.
Distributing 0.1 mg/kg	3,000	2,500	n.a.	n.a.
Service stations 0.1 mg/kg	3,000	2,500	n.a.	n.a.
Maintenance (Distribution) 10.2 mg/kg	29	25	n.a.	n.a.
Automotive Repair 0.2 mg/kg	1,500	1,250	n.a.	n.a.
Drivers etc. very low	n.a.	n.a.	n.a.	n.a.
Solvent use of Neat MTBE 1.0 mg/kg	300	250	n.a.	n.a.

n.a = not applicable; * Total calculated uptake was estimated using the exposures in an inhalation exposure experiment assuming 50% uptake from the lungs and alveolar ventilation rate of 7l/h, 6-hour exposure time, 300 g body weight.

RWC8h exposure	Repeated dose NOAEL 300 mg/kg	Carcinogenicity LOAEL 250 mg/kg	Reproduction Max. Conc. 2,000 mg/kg *	Development Max. Conc. 2,000 mg/kg *
Production 3 mg/kg	100	83	n.a.	n.a.
Formulation 3 mg/kg	100	83	n.a.	n.a.
Transporting 6.7 mg/kg	45	37	n.a.	n.a.
Distributing 2.4 mg/kg	125	104	n.a.	n.a.
Service stations 1.2 mg/kg	250	208	n.a.	n.a.
Maintenance (Distribution) 13.6 mg/kg	22	18	n.a.	n.a.
Automotive Repair 0.8 mg/kg	375	313	n.a.	n.a.
Drivers etc. 0.01	30,000	25,000	n.a.	n.a.
Solvent use of Neat MTBE 2.4 mg/kg	125	104	n.a.	n.a.

n.a = not applicable; * Total calculated uptake was estimated using the exposures in an inhalation exposure experiment assuming 50% uptake from the lungs and alveolar ventilation rate of 7l/h, 6-hour exposure time, 300 g body weight.

4.1.3.4 Consumers

As stated above, this section deals only with the exposure to MTBE from petrol. Petrol from the pump pistol is the only direct MTBE exposure source for the consumer. This type of exposure occurs during refuelling where MTBE evaporates and possibly spills on hands during the pumping of petrol. Inhalation exposure in this situation has been measured to range from 3 mg/m^3 to 29 mg/m^3. The duration of exposure is normally only few minutes and it it is not expected to occur more than 1-3 times a week. Dermal exposure from spillage during refuelling was estimated using modelling, which gave an estimate of dermal deposition of a mg-range. However, this was a very crude estimate, which did not take into account the fact that skin contact during refuelling is exceptional rather that normal, that the practice is infrequent and for a brief duration, and that evaporation is rapid, all factors that significantly limit the exposure. For acute end-points, only a semi-quantitative description of risk is given. A daily uptake of **1 µg/kg/day** was used in the MOS calculations.

4.1.3.4.1 Acute toxicity

Oral

Since there are no consumer products other than petrol, exposure by ingestion is not anticipated to occur in sufficient amounts to produce acute toxic symptoms. The risk of severe toxic effects for this end-point is considered insignificant for this scenario (LD50 ~4,000 mg/kg).

Dermal

Based on the modelling estimates of dermal deposition in spillage during refuelling (at most some milligrams), the risk of severe toxic effects for this end-point is considered insignificant for this scenario (LD50 ~4,000 mg/kg).

Inhalation

The maximum concentrations typically seen in petrol stations are about 29 mg/m^3, which is more than 100 times lower than the dose (3,600 mg/m^3), which was estimated to cause marked acute effects, such as dizziness, nausea, etc. The risk of severe toxic effects for this end-point is considered insignificant for this scenario.

4.1.3.4.2 Irritation

Since refuelling is not a very frequent activity and spillage to skin probably even less so, it is not anticipated that irritation occur under normal conditions.

4.1.3.4.3 Sensitisation

MTBE is not sensitising, thus the end-point is not considered relevant.

4.1.3.4.4 Repeated dose toxicity

For respiratory exposure, a NOAEC of 800 ppm or about 2,900 mg/m^3 has been derived. Based on measured data, the typical maximum concentration during refuelling at a pump island is about 29 mg/m^3 but the exposure time does not exceed more than few minutes at a time, 1-3 times a week. Because of the unevenness of the exposure, a direct calculation of MOS does not represent a realistic margin of safety. However, a MOS, in which the total uptake for this scenario is taken into the consideration, is represented in the combined exposure section as a part of the total body burden.

4.1.3.4.5 Mutagenicity

MTBE is not a mutagen, therefore this end-point is no considered relevant.

4.1.3.4.6 Carcinogenicity

A NOAEC of 1,450 mg/m3 was found. Consumer is exposed to a maximum concentration of 29 mg/m3 but only for a couple of minutes at a time, 1-3 times a week. Because of the unevenness of the exposure, a direct calculation of MOS does not represent a realistic margin of safety. However, a MOS, in which the total uptake for this scenario is taken into consideration, is represented in the combined exposure section as a part of the total body burden.

4.1.3.4.7 Toxicity to reproduction

Fertility

MTBE was not seen to cause a significant adverse effect on fertility. Therefore, this end-point is not considered relevant.

Developmental

MTBE was not assessed to be toxic to foetal development. This end-point is not considered relevant.

4.1.3.5 Humans exposed via the environment

For indirect exposure via the environment, there are two relevant routes of exposure. Oral exposure results from the consumption of contaminated drinking water ingestion. The worst-case concentration for tap water can be very high, exceeding 1,000 µg/l. However, the continuous use of water containing MTBE amounts higher than 15 µg/l is not likely since that concentration is seen as the threshold concentration where a disturbing odour and taste is experienced. The highest air MTBE concentrations are in pump areas of petrol stations, but the highest daily respiratory dose results from petrol station perimeter air. Therefore, living near a petrol station can contribute to a relatively high proportion of the daily exposure to MTBE. Furthermore, a significant source of inhalation exposure is commuting in a car or a bus, which can result to about 25% of the total daily dose. Instead of exposure concentrations, daily doses have been calculated for this scenario. This is more convenient since exposure is envisaged via different routes. In the calculation of MOSs for repeated dose and carcinogenicity end-points, NOAELs

were obtained from the tests that used oral exposure. When refuelling is subtracted a daily uptake of 2.1 µg/kg/day is obtained for the MOS calculations (see **Table 4.27**).

4.1.3.5.1 Acute toxicity

Oral

The total reasonable worst-case daily dose via, inhalation and oral route included, was calculated to be around **2.1 µg/kg/day**. This can be compared to the concentration needed to produce severe acute toxic symptoms (350,000 µg/kg). The risk of severe toxic effects for this end-point is considered insignificant for this scenario.

Dermal

Dermal exposure to MTBE from indirect exposure via environment is estimated to be very low, compared the concentration needed to produce acute toxic symptoms. The risk of severe toxic effects for this end-point is considered insignificant for this scenario.

Inhalation

The worst-case exposure via inhalation potentially occurs at petrol stations where concentrations up to 29 mg/m^3 have been measured. The concentration is over least 100 times lower than the one which was estimated to cause marked acute effects, such as dizziness, nausea, etc (3,600 mg/m^3). LC50/4h in rat is approximately 120,000 mg/m^3. The risk of severe toxic effects for this end-point is considered very low for this scenario.

4.1.3.5.2 Irritation

The frequency and amount of skin contact is likely to be very low for skin irritation to occur under normal conditions.

4.1.3.5.3 Sensitisation

MTBE is not sensitising, thus end-point is not considered relevant.

4.1.3.5.4 Repeated dose toxicity

For respiratory exposure, a NOAEL of 300 mg/kg/day has been derived. With a reasonable worst-case daily uptake of 0.0021 mg/day, it is not foreseen that toxic effects occur. A MOS of almost 150,000 can be calculated.

4.1.3.5.5 Mutagenicity

MTBE is not a mutagen, therefore this end-point is no considered relevant.

4.1.3.5.6 Carcinogenicity

A LOAEL of 250 mg/kg/day was selected. Together with the total daily uptake of 0.0021 mg/kg a **MOS of 125,000** can be obtained.

4.1.3.5.7 Toxicity to reproduction

Fertility

MTBE was not seen to cause a significant adverse effect on fertility. Therefore, this end-point is not considered relevant.

Developmental

MTBE was not assessed be toxic to foetal development. This end-point is not considered relevant.

4.1.3.6 Combined exposure

For combined exposure, the worst-case total uptake from the occupational scenarios is summed with the worst-case consumer situation (combined consumer uptake). Thus, when the daily uptake derived from the RWC consumer daily uptake (0.0031 mg/kg with refuelling and 0.0021 mg/kg without refuelling) is added to the daily uptake of 13.6 mg/kg from the maintenance and more specifically transportation. From this it is clear that total combined consumer uptake does not significantly change the MOSs calculated already at the worker section.

4.1.3.7 Conclusions

Workers

For dermal exposure, it has been estimated that the hands are the most likely areas of contact. In most tasks, protective gloves can be used to prevent irritation. However, maintenance and car repair are perceived as tasks where there is a high potential for hand contact to neat MTBE or to MTBE in petrol. Although animal studies have suggested that MTBE is a skin irritant, occupational experience does not support the notion that the potential irritancy is a significant risk for workers. However, on repeated exposure, **conclusion (iii)** is drawn for maintenance and car repair scenarios based on presumed and likely risk of defatting resulting in skin fatigue (and risk of toxic eczema). It is worth noting that because of other harmful and toxic compounds in petrol, its use is already regulated in work places.

The MOS derived from the combined exposure figures for repeated dose toxicity (systemic effects) appears rather small in the maintenance scenario (24). The conclusion of no concern for this end-point was thought rational because the effects seen at higher exposures were not considered to be either of great significance to man (kidney effects) or they were seen as adaptive responses (liver effects).

As for carcinogenicity, the MOSs appear low in the transportation (15), distribution (15) and maintenance (24) when the NOAEC from inhalation exposure data are compared to the occupational concentrations. The same is true when the combined uptake figure in the

maintenance scenario is compared to the NOAELs obtained from oral exposure studies. From the inhalation studies, the NOAEC of 1,450 mg/m3 was taken from the rat study where Leydig cell tumours were seen. However, the differences in sensitivity to these tumours between the rat and man cause considerable uncertainty when the relevance of these tumours to man is assessed. The dose level at which a statistically significant increase of the tumours was seen was 7.5 times higher (LOAEC=11,000 mg/kg) than the NOAEC. Moreover, according to the review by (Cook et al., 1999), Leydig cell tumour has only about 3% incidence of all testicular tumour types clinically identified in man. Testicular tumours contribute to 1% of all tumours diagnosed in man. The low MOS in the combined inhalation and dermal uptake is based on the LOAEL of 250 mg/kg from the study conducted by Belpoggi et al. (1995). However, although it was decided to use this study for the derivation of MOS due to lack of other oral carcinogenicity data, the reporting and overall conduct of this study is challenged, and there is not a complete confidence over the results.

Table 4.45 Conclusions for short-term end-point by work scenarios

Scenario	Acute			Irritation		Sensisitisation
	Oral	Dermal	Inhalation	Skin	Eye	
Production	ii	ii	ii	ii	ii	ii
Formulation	ii	ii	ii	ii	ii	ii
Transporting	ii	ii	ii	ii	ii	ii
Distributing	ii	ii	ii	ii	ii	ii
Service stations	ii	ii	ii	ii	ii	ii
Maintenance operations	ii	ii	ii	ii	ii	ii
Automotive Repair	ii	ii	ii	ii	ii	ii
Drivers etc.	ii	ii	ii	ii	ii	ii
Solvent use of Neat MTBE	ii	ii	ii	ii	ii	ii

Table 4.46 Conclusions for long-term (local and systemic) end-points by work scenarios and inhalation exposure

Scenario	Repeated dose				
	Mutagenicity	Local / systemic	Carcinogenicity	Fertility	Development
Production	ii	ii / ii	ii	ii	ii
Formulation	ii	ii / ii	ii	ii	ii
Transporting	ii	ii / ii	ii	ii	ii
Distributing	ii	ii / ii	ii	ii	ii
Service stations	ii	ii / ii	ii	ii	ii
Maintenance operations	ii	ii / ii	ii	ii	ii
Automotive Repair	ii	ii / ii	ii	ii	ii
Drivers etc.	ii	ii / ii	ii	ii	ii
Solvent use of Neat MTBE	ii	ii / ii	ii	ii	ii

Table 4.47 Conclusions for long-term (local and systemic) end-points by work scenarios and all exposure routes

Scenario	Repeated dose				
	Mutagenicity	Local / systemic	Carcinogenicity	Fertility	Development
Production	ii	ii / ii	ii	ii	ii
Formulation	ii	ii / ii	ii	ii	ii
Transporting	ii	ii / ii	ii	ii	ii
Distributing	ii	ii / ii	ii	ii	ii
Service stations	ii	ii / ii	ii	ii	ii
Maintenance operations	ii	**iii** / ii	ii	ii	ii
Automotive Repair	ii	**iii** / ii	ii	ii	ii
Drivers etc.	ii	ii / ii	ii	ii	ii
Solvent use of Neat MTBE	ii	ii / ii	ii	ii	ii

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Consumers

Petrol refuelling is the only known consumer use scenario where inhalation exposure is the principal route of exposure. The NOAELs obtained from inhalation experiment was compared with the highest measured air concentration met in a European petrol station. **Conclusion (ii)** is drawn for all toxicological end-points.

Humans exposed via the environment

Indirect exposure MOS calculations were only done compared to the total body burden received via inhalation and via orally. With all the indirect exposure sources combined, **conclusion (ii)** is drawn for all toxicological end-points.

Combined exposure

Using the worst-case uptake from consumer use and indirect exposure via the environment combined and the worst-case occupational exposure **conclusion (ii)** is drawn for all toxicological end-points.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

General aspects

MTBE's physical-chemical properties are characterised by high volatility, flammability and high water solubility. The odour and taste thresholds are low.

4.2.1 Exposure assessment

Exposure to MTBE is mainly due to its high vapour pressure and easy evaporation. High exposures are caused by occasional or accidental leaks and spills.

4.2.1.1 Occupational exposure

The highest occupational exposures are associated with handling neat MTBE or transporting automobile petrol (Section 4.1.1.1). The highest exposures are related to high short-term exposure peaks, which are probably caused by incidental leaks. In production, the highest short-term peak was 96 mg/m^3 (long-term 59 mg/m^3 for the operator). In formulation, the values were not higher. In transporting, the highest neat MTBE-peak was at truck loading, 180 mg/m^3, and 8-hour area concentration on a pier at ship unloading in the harbour, 230 mg/m^3. The highest short-term petrol exposure was 230 mg/m^3 at ship loading during uncoupling, but the 8-hour concentrations remained less than 30 mg/m^3. During distributing the truck loading/unloading operations caused an exposure peak of 432 mg/m^3 with an 8-hour exposure of 180 mg/m^3. The highest service station peak was 245 mg/m^3 and the highest 8-hour value was 101 mg/m^3. The maintenance workers exposure was close to the exposure concerning the process.

Occupational exposure in Europe seldom exceeded the occupational hygiene reference values. Generally, the Finnish peak concentrations from petrol with a high MTBE content did not differ greatly from the other European values.

The measured US peak exposures were higher, but they were measured in the 1980s and very early 1990s. At this time, the delivery and vapour recovery systems were probably not so advanced as today. The European results were from the 1990s.

4.2.1.2 Consumer exposure

There are no relevant exposure scenarios for high MTBE exposure in consumer use.

4.2.1.3 Humans exposed via the environment

In Section 3.1.7.3.3, the MTBE concentration analysed in groundwater is discussed. Section 4.1.1.3 addresses the occurrence of MTBE in groundwater-derived drinking water and water intended for human consumption. In the following, an overview of concentrations measured in drinking water in relation to the odour and taste threshold is given.

All the values that exceed the threshold represent conditions where leaks and spills have contaminated groundwater near a petrol station. The sampling sites have been described as being e.g. monitoring wells near a station, wells impacted by petrol spill, or wells adjacent to a petrol station.

In the light of available data, the contamination of groundwater by MTBE is not exceptional (see Section 3.1.7.3.3). Although in some cases high concentrations of MTBE have been found in drinking water, levels of MTBE exceeding the odour and taste threshold are comparatively rare (see Section 4.1.1.3). It is assessed that people using private wells near to petrol stations could be exposed to MTBE concentrations of about 15 µg/l. However, drinking water supplies managed by municipalities probably will not contain MTBE levels above the threshold, since normal quality control and customer complaints would prevent the use of such water.

4.2.2 Effects assessment: Hazard identification

4.2.2.1 Explosivity

MTBE as such is not explosive, but high concentrations of MTBE vapour can ignite explosively, e.g., by static sparks. The vapour pressure of MTBE is high, therefore, high concentrations of MTBE vapours are plausible, for instance, in case of major leaks or other accidents. The vapour pressure is at 20°C 26.8 kPa, at 25°C 33.4 kPa, at 30°C 40.8 kPa, at 38°C 48.2-55.2 kPa, and at 40°C 60.5 kPa (IUCLID, 1996).

4.2.2.2 Flammability

Neat MTBE is highly flammable. Its autoflammability temperature is 375°C. The lower flammability limit is 1.5 vol% gas in the air and the upper limit 8.4 vol% gas in the air. The flash point is –28°C.

Because of its flammability, neat MTBE is stored outdoors in a detached properly identified area, and the container materials are resistant to the product. The materials and equipment used in the area have to be spark-free.

4.2.2.3 Oxidising potential

MTBE is not considered to have oxidising properties. Although it is an ether, it is not known to form peroxides (Little et al., 1979; Mount et al., 1991).

4.2.2.4 Other relevant physico-chemical properties

MTBE has low taste and odour thresholds. Because of its relatively high water solubility (26 g/l at 10°C, 43 g/l at 20°C, 50 g/l at 25°C), MTBE separates from petrol and dissolves into water, if petrol is dispersed on water surface or is otherwise in contact with water.

4.2.3 Risk characterisation

4.2.3.1 Workers

Flammability might pose fire and explosion risk in situations where vapour of neat MTBE is generated at high concentrations. This is possible also in the open air if sparks (electric or also static) or open fire is present.

However, the flammability is a well-known feature of neat MTBE vapour and necessary precautions are normally taken to prevent ignition during storage and when transferring MTBE. Moreover, the professional workers are aware of the characteristics of neat MTBE and the entrance of outsiders to the production area is not allowed. In other scenarios concerning MTBE as an additive in petrol, the risk arises from the totality of flammable elements in automotive petrol vapours, where the part of MTBE is minor.

Flammability is not considered to cause a significant risk to workers and **conclusion (ii)** is drawn.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

4.2.3.2 Consumers

There are no relevant scenarios arising from MTBE in petrol. **Conclusion (ii)** is drawn.

4.2.3.3 Humans exposed via the environment

MTBE has a pronounced taste and odour in water at low concentrations. However, there may be significant differences in the odour and taste thresholds depending on individual sensitivity, which can be affected e.g., by smoking. When the odour and taste thresholds in water are exceeded, the contaminated drinking water is normally not used, but another supply of drinking water is then utilised. When large and important reservoirs of groundwater serving as a drinking water supply are contaminated, the consequences can be significant in terms of costs, as well as in terms of a need for temporary arrangements for drinking water. The severity of the consequences of groundwater contamination may vary greatly between countries depending on, e.g., the level of groundwater utilisation for drinking water and the condition of petrol stations' underground storage tanks in important groundwater areas.

The present risk characterisation is formulated keeping in mind that

- MTBE is not considered to cause adverse health or ecotoxic effects at taste and odour threshold level,
- Even a relatively small amount of MTBE may render large reserves of groundwater useless,
- The organoleptic properties of water are also covered by the EU directive on the "Quality of Water Intended for Human consumption" (Council Directive 98/83/EC).

Based on current monitoring data MTBE has been shown in some cases to be present in drinking water in concentrations exceeding taste and odour thresholds. As described in the environmental

part of this report this is mainly caused by leaking underground storage tanks and spillage from overfilling the tanks. While the number of pollution cases can considered relatively restricted at EU level the problem is more pronounced in some Member States. Therefore, it is justified to conclude that MTBE is causing a risk for the aesthetic quality of drinking water.

Conclusion (iii) is drawn for indirect exposure to humans via drinking water based on the risk on the aesthetic properties of drinking water.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

5 RESULTS

5.1 ENVIRONMENT

Results of risk characterisation for the aquatic environment

Conclusion (i) There is a need for further information and/or testing.

This conclusion is reached because there is a need for better information to adequately characterise the risks to the aquatic ecosystem regarding the emission of the substance to surface water.

The information and test requirements are: a tiered testing approach for investigation of avoidance behaviour in fish and if necessary in other wildlife animals related to water contaminated with the substance.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

This conclusion applies to production, production/formulation, formulation and processing sites; to transport, storage and delivery except for intermittent release to surface water from terminal site storage tank bottom waters; to road traffic (runoff) and to boating (exhaust).

Conclusion (iii) There is a need for limiting risks; risk reduction measures which are already being applied shall be taken into account.

This conclusion applies to intermittent release to surface water from terminal site storage tank bottom waters.

Results of risk characterisation for microorganisms in wastewater treatment plants

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

This conclusion applies to production, production/formulation, formulation and processing sites.

Results of risk characterisation for the atmospheric compartment

Conclusion (ii) There is at present no need for further information or testing or risk reduction measures beyond those which are being applied already.

Results of risk characterisation for soil

Conclusion (ii) There is at present no need for further information or testing or risk reduction measures beyond those which are being applied already.

This conclusion applies to production, formulation, processing and runoff infiltrated.

Results of risk characterisation for groundwater

Conclusion (iii) There is a need for limiting risks; risk reduction measures which are already being applied shall be taken into account

This conclusion applies to overall quality of groundwater. The risks are mainly related to leaking underground storage tanks and spillage from overfilling of the storage tanks.

5.2 HUMAN HEALTH

5.2.1 Human health (toxicity)

Workers

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

This conclusion applies for maintenance and automotive repair scenarios, due to the long-term local effects to skin.

Consumers

Conclusion (ii) There is at present no need for further information or testing or risk reduction measures beyond those which are being applied already.

Humans exposed via the environment

Conclusion (ii) There is at present no need for further information or testing or risk reduction measures beyond those which are being applied already.

Combined exposure

Conclusion (ii) There is at present no need for further information or testing or risk reduction measures beyond those which are being applied already.

5.2.2 Human health (risks from physico-chemical properties)

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

This conclusion is reached for humans exposed via the environment due to concerns for the potability of drinking water in respect of taste and odour as a consequence of exposure arising from leaking underground storage tanks and spillage from overfilling of the storage tanks.

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ABBREVIATIONS

ADI	Acceptable Daily Intake
AF	Assessment Factor
ASTM	American Society for Testing and Materials
ATP	Adaptation to Technical Progress
AUC	Area Under The Curve
B	Bioaccumulation
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
BCF	Bioconcentration Factor
BMC	Benchmark Concentration
BMD	Benchmark Dose
BMF	Biomagnification Factor
bw	body weight / *Bw*, *b.w.*
C	Corrosive (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
CA	Chromosome Aberration
CA	Competent Authority
CAS	Chemical Abstract Services
CEC	Commission of the European Communities
CEN	European Standards Organisation / European Committee for Normalisation
CEPE	European Committee for Paints and Inks
CMR	Carcinogenic, Mutagenic and toxic to Reproduction
CNS	Central Nervous System
COD	Chemical Oxygen Demand
CSTEE	Scientific Committee for Toxicity, Ecotoxicity and the Environment (DG SANCO)
CT_{50}	Clearance Time, elimination or depuration expressed as half-life
d.wt	dry weight / dw
dfi	daily food intake
DG	Directorate General
DIN	Deutsche Industrie Norm (German norm)
DNA	DeoxyriboNucleic Acid
DOC	Dissolved Organic Carbon
DT50	Degradation half-life or period required for 50 percent dissipation / degradation
DT90	Period required for 50 percent dissipation / degradation
E	Explosive (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
EASE	Estimation and Assessment of Substance Exposure Physico-chemical properties [Model]

EbC50	Effect Concentration measured as 50% reduction in biomass growth in algae tests
EC	European Communities
EC10	Effect Concentration measured as 10% effect
EC50	median Effect Concentration
ECB	European Chemicals Bureau
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECVAM	European Centre for the Validation of Alternative Methods
EDC	Endocrine Disrupting Chemical
EEC	European Economic Communities
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EN	European Norm
EPA	Environmental Protection Agency (USA)
ErC50	Effect Concentration measured as 50% reduction in growth rate in algae tests
ESD	Emission Scenario Document
EU	European Union
EUSES	European Union System for the Evaluation of Substances [software tool in support of the Technical Guidance Document on risk assessment]
F(+)	(Highly) flammable (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
FAO	Food and Agriculture Organisation of the United Nations
FELS	Fish Early Life Stage
foc	Organic carbon factor (compartment depending)
GLP	Good Laboratory Practice
HEDSET	EC/OECD Harmonised Electronic Data Set (for data collection of existing substances)
HELCOM	Helsinki Commission -Baltic Marine Environment Protection Commission
HPLC	High Pressure Liquid Chromatography
HPVC	High Production Volume Chemical (> 1000 t/a)
IARC	International Agency for Research on Cancer
IC	Industrial Category
IC50	median Immobilisation Concentration or median Inhibitory Concentration
ILO	International Labour Organisation
IPCS	International Programme on Chemical Safety
ISO	International Organisation for Standardisation
IUCLID	International Uniform Chemical Information Database (existing substances)
IUPAC	International Union for Pure and Applied Chemistry
JEFCA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues

Koc	organic carbon normalised distribution coefficient
Kow	octanol/water partition coefficient
Kp	solids-water partition coefficient
L(E)C50	median Lethal (Effect) Concentration
LAEL	Lowest Adverse Effect Level
LC50	median Lethal Concentration
LD50	median Lethal Dose
LEV	Local Exhaust Ventilation
LLNA	Local Lymph Node Assay
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
LOED	Lowest Observed Effect Dose
LOEL	Lowest Observed Effect Level
MAC	Maximum Allowable Concentration
MATC	Maximum Acceptable Toxic Concentration
MC	Main Category
MITI	Ministry of International Trade and Industry, Japan
MOE	Margin of Exposure
MOS	Margin of Safety
MW	Molecular Weight
N	Dangerous for the environment (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC
NAEL	No Adverse Effect Level
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NOEC	No Observed Effect Concentration
NTP	National Toxicology Program (USA)
O	Oxidizing (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
OJ	Official Journal
OSPAR	Oslo and Paris Convention for the protection of the marine environment of the Northeast Atlantic
P	Persistent
PBT	Persistent, Bioaccumulative and Toxic
PBPK	Physiologically Based PharmacoKinetic modelling
PBTK	Physiologically Based ToxicoKinetic modelling

PEC	Predicted Environmental Concentration
pH	logarithm (to the base 10) (of the hydrogen ion concentration $\{H^+\}$
pKa	logarithm (to the base 10) of the acid dissociation constant
pKb	logarithm (to the base 10) of the base dissociation constant
PNEC	Predicted No Effect Concentration
POP	Persistent Organic Pollutant
PPE	Personal Protective Equipment
QSAR	(Quantitative) Structure-Activity Relationship
R phrases	Risk phrases according to Annex III of Directive 67/548/EEC
RAR	Risk Assessment Report
RC	Risk Characterisation
RfC	Reference Concentration
RfD	Reference Dose
RNA	RiboNucleic Acid
RPE	Respiratory Protective Equipment
RWC	Reasonable Worst Case
S phrases	Safety phrases according to Annex III of Directive 67/548/EEC
SAR	Structure-Activity Relationships
SBR	Standardised birth ratio
SCE	Sister Chromatic Exchange
SDS	Safety Data Sheet
SETAC	Society of Environmental Toxicology And Chemistry
SNIF	Summary Notification Interchange Format (new substances)
SSD	Species Sensitivity Distribution
STP	Sewage Treatment Plant
T(+)	(Very) Toxic (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
TDI	Tolerable Daily Intake
TG	Test Guideline
TGD	Technical Guidance Document
TNsG	Technical Notes for Guidance (for Biocides)
TNO	The Netherlands Organisation for Applied Scientific Research
UC	Use Category
UDS	Unscheduled DNA Synthesis
UN	United Nations
UNEP	United Nations Environment Programme
US EPA	Environmental Protection Agency, USA
UV	Ultraviolet Region of Spectrum

UVCB	Unknown or Variable composition, Complex reaction products of Biological material
vB	very Bioaccumulative
VOC	Volatile Organic Compound
vP	very Persistent
vPvB	very Persistent and very Bioaccumulative
v/v	volume per volume ratio
w/w	weight per weight ratio
WHO	World Health Organization
WWTP	Waste Water Treatment Plant
Xn	Harmful (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
Xi	Irritant (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)

Appendix

Table A.1 EU producers, plant locations and plant capacities in February 2000 [ECETOC, 2000 #183]

Site	Location	Capacity tonnes/year	Feedstock	Disposa
Agip	Italy, Milazzo	60,000	FCC	C
Agip	Italy, Sannazzaro	47,000	FCC	C
Agip	Italy, Priolo	54,000	FCC/SC	C/M
Agip	Italy, Gela	55,000	SC/FCC	C
Borealis	Sweden, Stenungsund	50,000	SC	C
DEA	Germany, Heide	15,000	FCC/SC	C
DEA	Germany, Wesseling	65,000	FCC	C
DSM	Netherlands, Geleen	130,000	SC	C/M
ECOFUEL	Italy, Ravenna	160,000	SC	C/M
EXXON CHEMICAL	United Kingdom, Fawley	125,000	SC/FCC	C
FORTUM	Finland, Porvoo	120,000	SC/FCC	C
FORTUM	Portugal, Sines	45,000	SC	M
HELLENIC	Greece, Aspropyrgos	70,000	FCC	C/M
LINDSEY OIL	United Kingdom, Killingholme	100,000	FCC/SC	C/M
LYONDELL	France, Fos-Sur-Mer	610,000	TBA	M
LYONDELL	Netherlands, Botlek	590,000	TBA	M
MOTOR OIL	Greece, Corinth	34,000	FCC	C/M
NEREFCO (BP)	Netherlands, Rotterdam	65,000	FCC	C
OMW	Germany, Karlsruhe	120,000	FCC	C
OXENO	Germany, Marl	210,000	SC	M
PCK AG	Germany, Schwedt	85,000	FCC	C
PETRONOR	Spain, Somorrosteo	60,000	FCC	C
REPSOL	Spain, Puertollano	60,000	SC/FCC	C
REPSOL	Spain, La Coruna	40,000	FCC + COK	C
REPSOL				
SHELL CHEMIE	Netherlands, Pernis	160,000	SC	M
TOTAL FINA ELF	Belgium, Antwerp	180,000	SC/FCC	C
ÖMV	Austria, Schwechat	70,000	SC	C

FCC – fluid catalytic cracker
SC- steam cracker
TBA – tertiary-butyl alcohol
COK – cookery
C = captive; the MTBE produced is used for blending into petrol on site
M = merchant; the MTBE produced is sold on for blending into petrol

Table A.2 Passenger car exhaust HC and MTBE emission levels

Vehicle	Test type	Petrol	Temperature Celsius	Hydrocarbon in exhaust (HC)	MTBE in exhaust	Petrol consumption	MTBE Emission Factor	Reference
Vehicle/engine type				mg/km	mg/km	g/km		
New Car Model 2005 EURO 4	EC2000			100				
New Car Model 1999 EURO 3	EC2000			200				
New Car Model 1999 at Cold start EURO 3	EC2000		-7	500-2,500				
Pass. Cars with TWC EURO2	FTP-75test	4%wt MTBE	-7	508-617	0.4-4.2	60	0.07-0.7 wt-% of THC	VTT 1996
Pass. Cars with TWC EURO2	FTP-75test	10.3%wt MTBE	-7	533-709	6.2-15.7	69-72.4	1.1-2.3 wt-% of THC	--"--
Pass. Cars with TWC EURO2	FTP-75test	13.8%wt MTBE	-7	508-724	5.8-19.3	66.8-73.1	1.1-2.7 wt-% of THC	--"--
Pass. Cars no cat. ECE 15 04	FTP-75test	4%wt MTBE	+22	1,200-2,200	25-48	60	2.1-2.2 wt-% of THC	--"--
Pass. Cars no cat. ECE 15 04	FTP-75test	10.3%wt MTBE	+22	1,726-1,760	89.4-120.2	64.3-65.2	5.2-6.8 wt-% of THC	--"--
Pass. Cars no cat. ECE 15 04	FTP-75test	13.8%wt MTBE	+22	1,250—2,170	120-180	60	8.3-9.6 wt-% of THC	--"--
Pass. Cars no cat. ECE 15 04	FTP-75test	4% MTBE	-7	2,002-2,137	25.5-31.4	72.4-73.4	1.3-1.5 wt-% of THC	--"--
Pass. Cars no cat. ECE 15 04	FTP-75test	13,8%wt MTBE	-7	1,934-2,217	126-134	57-63.4	6.3-6.5- wt-% of THC	--"--

Source: [VTT, 1996 #103] Aakko, P., J. Kokko, M. Lappi, M. Kytö, J. Kivi, and J. Pentikäinen. 1996. Reformulation of engine gasoline to reduce emissions in Finnish conditions: Effect of reformulated gasoline's on regulated and unregulated exhaust emissions. Pages 64 + 19 app. The Technical Research Centre of Finland (VTT), Engine Technology dept., Espoo, Finland

Table A.3 VOC exhaust emission of vehicles and speed dependency source.

Processed data (Tables 5.4 and 5.7) from original publication: Ntziachristos, L., and Z. Samaras. 1999. COPERT III manual. European Environment Agency.

Control Stage and Engine capacity	Driving speed km/h	VOC Emissio g/km	Fuel consumption g/km	Kilometers/tonne petrol	Exhaust HC g/t petrol
Passenger Cars					
PRE ECE < 1.4 L	10	6.152	145.49	6,873.3	42,284
	30	2.873	79.16	12,632.4	36,296
	50	2.017	59.65	16,764.5	33,808
	80	1.456	55	18,181.8	26,474
	100	1.247	62.74	15,938.0	19,882
PRE ECE 1.4 L < CC >2.0 L	10	6.152	230.56	4,337.3	26,683
	30	2.873	115.65	8,646.7	24,844
	50	2.017	83.91	11,917.1	24,033
	80	1.456	67	14,925.4	21,732
	100	1.247	76.39	13,091.4	16,331
PRE ECE >2.0 L	10	6.152	230.56	4,337.3	26,683
	30	2.873	115.65	8,646.7	24,844
	50	2.017	83.91	11,917.1	24,033
	80	1.456	80	12,500.0	18,201
	100	1.247	88.27	11,329.3	14,132
ECE 15-00/01 <1.4 L	10	4.940	139.48	7,169.4	35,420
	30	2.280	69.81	14,324.2	32,654
	50	1.591	50.60	19,762.1	31,443
	80	1.204	44.12	22,665.5	27,285
	100	1.121	48.60	20,576.1	23,073
	130	1.032	68.22	14,658.5	15,122
ECE 15-00/01 1.4 L <CC> 2.0 L	10	4.940	202.54	4,937.3	24,392
	30	2.280	101.37	9,864.4	22,488
	50	1.591	73.48	13,609.3	21,654
	80	1.204	53.32	18,754.7	22,577
	100	1.121	60.30	16,583.7	18,596
	130	1.032	77.07	12,975.2	13,385
ECE 15-00/01> 2.0L	10	4.940	212.82	4,698.7	23,214
	30	2.280	91.94	10,876.8	24,796
	50	1.591	62.23	16,069.2	25,567
	80	1.204	59.32	16,857.7	20,294
	100	1.121	66.30	15,083.0	16,913
	130	1.032	83.07	12,038.0	12,418

Table A.3 continued overleaf.

Table A.3 continued VOC exhaust emission of vehicles and speed dependency source.

Processed data (Tables 5.4 and 5.7) from original publication: Ntziachristos, L., and Z. Samaras. 1999. COPERT III manual. European Environment Agency.

Control Stage and Engine capacity	Driving speed km/h	VOC Emissio g/km	Fuel consumption g/km	Kilometers/tonne petrol	Exhaust HC g/t petrol
ECE 15-02/03 < 1.4 L	10	4.975	127.53	7,841.5	39,010
	30	2.270	63.83	15,667.1	35,571
	50	1.577	46.26	21,614.8	34,077
	80	1.006	45.64	21,910.6	22,042
	100	0.950	51.20	19,531.3	18,555
	130	1.001	71.09	14,066.7	14,081
ECE 15-02/03 1.4 < CC > 2.0 L	10	4.975	167.49	5,970.5	29,702
	30	2.270	75.94	13,168.6	29,899
	50	1.577	52.57	19,022.6	29,990
	80	1.006	52.50	19,046.2	19,160
	100	0.950	59.68	16,756.0	15,918
	130	1.001	79.29	12,611.3	12,624
ECE 15-02/03 CC > 2.0 L	10	4.975	214.67	4,658.2	23,174
	30	2.270	93.56	10,688.6	24,268
	50	1.577	63.59	15,726.8	24,794
	80	1.006	63.88	15,654.4	15,748
	100	0.950	70.70	14,144.3	13,437
	130	1.001	94.88	10,539.6	10,550
ECE 15-04 CC < 1.4 L	10	3.869			
	30	1.807	56.80	17,605.6	31,810
	50	1.268	47.40	21,097.0	26,754
	80	0.794	43.50	22,988.5	18,244
	100	0.698	47.70	20,964.4	14,633
	130	0.823	64.20	15,576.3	12,821
ECE 15-04 1.4 < CC < 2.0 L	10	3.869	130.48	7,664.0	29,649
	30	1.807	69.32	14,425.9	26,065
	50	1.268	55.80	17,921.1	22,727
	80	0.794	48.42	20,652.6	16,390
	100	0.698	52.10	19,193.9	13,397
	130	0.823	70.52	14,180.4	11,672
ECE 15-04 CC > 2.0 L	10	3.869	177.94	5,619.7	21,741
	30	1.807	85.89	11,642.5	21,036
	50	1.268	61.22	16,335.5	20,716
	80	0.794	42.18	23,707.9	18,815
	100	0.698	45.50	21,978.0	15,341
	130	0.823	52.88	18,910.7	15,565

Table A.3 continued overleaf.

Table A.3 continued VOC exhaust emission of vehicles and speed dependency source.

Processed data (Tables 5.4 and 5.7) from original publication: Ntziachristos, L., and Z. Samaras. 1999. COPERT III manual. European Environment Agency.

Control Stage and Engine capacity	Driving speed km/h	VOC Emissio g/km	Fuel consumption g/km	Kilometers/tonne petrol	Exhaust HC g/t petrol
Improved conventional	10	1.869	67.72	14,766.7	27,600
CC < 1.4 L	30	1.350	49.92	20,032.1	27,041
	50	0.992	42.52	23,518.3	23,318
	80	0.755	50.92	19,638.6	14,835
	100	0.799	69.52	14,384.3	11,493
	130	1.166	116.92	8,552.9	9,972
1,4 L< CC< 2,0 L	10	1.680	92.39	10,823.7	18,188
	30	1.172	65.37	15,297.5	17,923
	50	0.834	51.95	19,249.3	16,054
	80	0.649	57.32	17,445.9	11,315
	100	0.739	77.90	12,837.0	9,487
	130	1.196	134.27	7,447.7	8,904
Open loop	10	1.788	72.89	13,719.3	24,525
CC < 1.4 L	30	1.146	54.59	18,318.4	21,000
	50	0.710	45.65	21,905.8	15,553
	80	0.439	49.79	20,084.4	8,825
	100	0.515	64.25	15,564.2	8,016
	130	1.012	103.49	9,662.8	9,783
1,4 L< CC < 2,0 L	30	0.417	65.32	15,309.2	6,385
	50	0.256	52.60	19,011.4	4,857
	80	0.162	58.72	17,030.0	2,752
	100	0.198	79.60	12,562.8	2,487
	130	0.401	136.12	7,346.5	2,947
EURO1	10	0.507	91.62	10,914.5	5,528
CC < 1.4 L	30	0.315	59.88	16,701.2	5,256
	50	0.191	44.84	22,303.5	4,260
	80	0.133	38.18	26,194.5	3,491
	100	0.180	44.34	22,555.0	4,060
	130	0.378	69.48	14,393.5	5,439
1,4 L< CC< 2,0 L	10	0.366	130.80	7,645.3	2,797
	30	0.230	78.98	12,661.4	2,911
	50	0.136	55.74	17,940.4	2,434
	80	0.072	42.48	23,540.5	1,705
	100	0.082	48.04	20,816.0	1,715
	130	0.175	77.98	12,823.8	2,250

Table A.3 continued overleaf.

Table A.3 continued VOC exhaust emission of vehicles and speed dependency source.

Processed data (Tables 5.4 and 5.7) from original publication: Ntziachristos, L., and Z. Samaras. 1999. COPERT III manual. European Environment Agency.

Control Stage and Engine capacity	Driving speed km/h	VOC Emissio g/km	Fuel consumption g/km	Kilometers/tonne petrol	Exhaust HC g/t petrol
CC > 2 L	10	0.440	169.17	5,911.2	2,599
	30	0.321	98.72	10,129.7	3,256
	50	0.230	64.20	15,576.3	3,576
	80	0.141	43.77	22,846.7	3,231
	100	0.116	51.05	19,588.6	2,264
	130	0.126	93.32	10,715.8	1,354
Light Duty Vehicles (Petrol)					
Conventional	5	4.905	173.711	5,756.7	28,239
	10	4.371	158.412	6,312.7	27,593
	30	2.573	108.428	9,222.7	23,727
	50	1.316	76.380	13,092.4	17,228
	80	0.446	61.938	16,145.2	7,204
	100	0.543	74.730	13,381.5	7,272
	110	0.795	87.852	11,382.8	9,050
2-stroke vehicles < 2.5 t		15.4	111.5	8,968.6	138,117
		7.2	66	15,151.5	109,091
		5.9	56.9	17,574.7	103,691
2-stroke motorcycles CC > 50					
Conventional	10	16.360	49.8	20,081.1	328,527
	50	8.400	58.8	17,009.7	142,881
	80	8.328	34.0	29,411.8	244,941
	100	8.360	37.0	27,063.6	226,252
	110	8.466	38.3	26,126.7	221,189
97/24/EC	10	4.770	19.7	50,766.6	242,157
	30	5.910	22.8	43,794.3	258,825
	50	6.250	25.1	39,856.5	249,103
	80	5.880	27.6	36,231.9	213,043
	100	5.450	28.9	34,662.0	188,908
	110	5.145	29.2	34,275.9	176,350

Table A.4 Site-specific local concentration in surface water and sediment for bulk storage and transfer operations of petrol and light oil (processing 1)

Site code & activity	Emission factor	Local emission rate to wastewater $E_{localwater}$ (kg/day)	WWTP	Effluent discharge of STP EFF_{stp} (l/day)	Emission to surface water as WWTP effluent (kg/year)	Conc. in effluent $C_{localeff}$ (mg/l)	Dilution factor	Conc. in receiving water (mg/l)	$PEC_{localwater}$ (mg/l) ($PEC_{regional}$ = 0.0015)	$PEC_{localsed}$ (mg/kg)
Site 34	0.000001		yes (1	2.6×10^5			1,000	< 0.010	0.010	<0.01
Site 35	0.0000001	0.08	yes (1 (2	6.9×10^5	1.5	0.064 (influent 0.108)	1,000	< 0.010	<0.010	<0.01
Site 36	0.0001	23.1	yes (1 (3	3.6×10^5	62.9	5.2 (influent 63.8)	1,000	< 0.010	0.010	0.01
Site 37	0.0002	9.9	yes (4	def 2.0×10^6		2.82 (influent 4.95)	def 10	0.282	0.284	0.279
Site 38	-		yes (4			4.05 (influent 7.11)	def 10	0.405	0.406	0.399
Site 39	0.000005	5.1	yes (1 (2	2.2×10^6	19.4	0.269 (influent 2.36)	1,000	0.010 – 0.100	0.100	0.01
Site 40	-		yes (4	def 2.0×10^6		551 (influent 967)	def 10	55.1	55.1	54.1
Site 41	0.000001	0.6	yes (1 (2	86 400	2.6	0.798 (influent 5.79)	1,000	< 0.010	<0.010	<0.01
Site 42	0.00006	19.2	yes (1 (2	604 800	135	6.72 (influent 31.7)	def 10	0.672 (5	0.674	0.662
Site 43	0.0002	90.7	yes (1 (3	483 840	4.3	0.267 (influent 189)	1,000	< 0.010	<0.010	<0.01
Site 44	-		yes (4	(4		124.3 (influent 131.2)	def 10	12.4	12.4	12.2
Site 45	0.00002	0.2	yes (4	(4		0.211 (influent 0.632)	def 10	0.021	0.022	0.022
Site 46	0.0006	9.8	yes (3	36 288	0.8	0.060 (influent 271.6)	1,000,000	< 0.010	<0.010	<0.01
Site 47	def 0.0005	2.25	yes (1 (2 (4	def 2.0×10^6		0.64 (influent 1.12)	def 10	0.064	0.066	0.065
Site 48	0.0003	137	yes (1 (2	259200	0.9	< 0.100 (influent 530)	1,000	< 0.010	<0.010	< 0.01
Site 49	0.000007	4.4	**yes**	3.4×10^6	28.9	0.257 (influent 1.31)	100	< 0.010	<0.010	< 0.01
Site 50	0.000001	0.8	**yes (1 (2**	259 200	9.0	1.04 (influent 3.03)	1,000	< 0.010	<0.010	<0.01

values received from industry in bold

(1 discontinuous discharge (8 h/day, 100 days/year)

(2 a stream mixing unit before WWTP inlet is installed

(3 inlet WWTP concentration and emission rate to wastewater referred to a specific stream (displacement of pipelines), not directly related to the outlet value

(4 connected to a WWTP outside the bulk terminal

(5 municipal sewer system

Table A.5 MTBE concentration in groundwater near to a petrol station

Location	Sampling years	n	Results (µg/l)	Remarks/sampling site	Source
Municipalities in Eastern, Finland	1998-99	9	<2-20 000	groundwater/perched water near to service station	PSV-Soil/Water Ltd., North Carelia REC (unpublished)
Pyhäselkä, Finland	1996-1999	75	<100-23000	various groundwater, perched water, leachate etc. samples mainly at service stations	Golder Associates Finland Ltd. (unpublished)
Unspecified, Finland	-1999	?	<1-7000	various water samples mainly from service stations	National Institute of Occupational Health,Tampere Laboratory (unpublished)
Unspecified, Finland	-1999	?	20-200000	various water samples from petrol contaminated sites	Fortum Oil & Gas Ltd(unpublished).
Unspecified,Finland	1996-98	1070/428	<5: n=642 5-10: n=87 10-100: n=175 100-1,000: n=71 1,000-10,000: n=44 10,000-100,000: n=35 >100,000: n=8	various groundwater,perched water, leachate etc. samples mainly from contaminated sites, at variable distances from contamination source and in variable hydrogeology	State Research Centre(unpublished)

Table A.6 MTBE concentration in groundwater

Location	Year(s)	n/n_p	Results (µg l^{-1})	Remarks/sampling site	Source
Several Danish cities	1997	38/17	<detection limit-547 000	Groundwater aquifers	Miljostyrelsen 1998
Several Danish cities	1997	?	<1-30 000	Groundwater near surface at service stations	-"-, ref. Oljebranchens Miljøpulje
Northenden, UK	?	?	15-160	Groundwater	Turrell & al. 1996
Cheetham, Hill, UK	?	?	60-290	Groundwater	Turrell & al. 1996
Unspecified, UK	1993	25/4	<0.05-0.53	Groundwater aquifers	Turrell & al. 1996

Table A.7 MTBE in ambient air and near to point sources (others than service station).

Location	Year(s)	N (sampling period)	Results (µg/m3)	Sampling site and remarks	Source
Ambient urban air					
Several Canadian cities	1995-1996	46	<detection limit-1.07, medians 0.13-0.33 [1)]	urban and suburban, no identified industrial releases	Environment Canada 1996, IPCS
Milwaukee, Wisconsin	1995	16 (2-24 h)	<detection limit-14.8, medians 0.47-1.87	urban monitoring stations, and roadside samples	Allen and Grande 1995, IPCS
Several U.S. cities	1992-1993	8	<detection limit-4.3, medians ND-0.7	background	Zweidinger 1993, IPCS
Several U.S. cities	1992-1993	29	<detection limit-100.9, medians 1.1-16.6	residential	Zweidinger 1993, IPCS
Several U.S. cities	1992-1993	33	<detection limit-64.5, medians 0.7-35	roadside	Zweidinger 1993, IPCS
Air polluted by refineries or contaminated sites					
Edmonton, Canada	1995-96	7	0.81-11.4 (Med=2.9)	1 km from petroleum refinery	Environment Canada 1996, IPCS
St. John, Canada	1995	4	15-281 (Med=54)	refinery boundary during odour complaints	Environment Canada 1996, IPCS
St. John, Canada	1996	3	1.02-3.73 (Med=2.4)	3 km from refinery	Environment Canada 1996, IPCS
Vancouver, Canada	1995-96	11	<detection limit-26.4 (Med=1.78)	0,5-3 km from petrol storage	Environment Canada 1996, IPCS
Vancouver, Canada	1995-96	3	0.89-1.90 (Med=1.79)	pipeline transfer point	Environment Canada 1996, IPCS
Houston, Texas, USA	1990-91	22	<0.72-10.1	semi-rural with industrial influence	Kelly et al. 1993, IPCS
Unspecified, Finland	1999	?	100-161000	ambient air from petrol contaminated site	Regional Environment Centre of Western Finland (unpubl.)
Unspecified, Finland	-1999	?	10000-100000	ambient air from contaminated sites	Juvegroup Ltd. (unpubl.)

[1)] In Canada, the content of MTBE in petrol (5.2-9%) is lower than in USA (10-15 % as an oxygenate) and Europe (IPCS 1998).

Table A.8 Atmospheric concentration of MTBE (µg/m3) and doses for non-occupationally exposed populations (Brown 1997)

Population	Geometric mean (µg/m^3)	Number of exposed persons	Geometric mean dose (µg/kg/day)
Commuters	40	30,000,000	0.25
Other drivers	20	22,800,000	0.38
Petrol station customer	150	52,800,000	0.27
Manufacturing and blending neighbors	3	815,000	1.3
Petrol station and storage neighbors	30	11,700,000	1.3
General public	1	60,500,000	0.4

European Commission

EUR 20417 EN - European Union Risk Assessment Report
Tert-butyl methyl ether, Volume 19

Editors: B.G. Hansen, S.J. Munn, S. Pakalin, C. Musset, M.Luotamo, J. de Bruijn, F. Berthault, S. Vegro, G. Pellegrini, R. Allanou, S. Scheer.

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2002 – VIII pp., 282 pp. – 17.0 x 24.0 cm

Environment and quality of life series

The report provides the comprehensive risk assessment of the substance tert-butyl methyl ether. It has been prepared by Finland in the frame of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances, following the principles for assessment of the risks to man and the environment, laid down in Commission Regulation (EC) No. 1488/94.

The evaluation considers the emissions and the resulting exposure to the environment and the human populations in all life cycle steps. Following the exposure assessment, the environmental risk characterisation for each protection goal in the aquatic, terrestrial and atmospheric compartment has been determined. For human health the scenarios for occupational exposure, consumer exposure and humans exposed via the environment have been examined and the possible risks have been identified.

The risk assessment for tert-butyl methyl ether concludes that there is concern for the environment and for human health.

The conclusions of this report will lead to risk reduction measures to be proposed by the Commissions committee on risk reduction strategies set up in support of Council Regulation (EEC) No 793/93.

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European Commission – Joint Research Centre
Institute for Health and Consumer Protection
European Chemicals Bureau (ECB)

European Union Risk Assessment Report

tert-butyl methyl ether

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