EUROPEAN COMMISSION

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TERT-BUTYL METHYL ETHER

CAS No: 1634-04-4

EINECS No: 216-653-1

Summary Risk Assessment Report

2002 **Special Publication I.02.101**

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SUMMARY RISK ASSESSMENT 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**

PREFACE

This report provides a summary, with conclusions, of the risk assessment report of the substance tert-butyl methyl ether that has been prepared by Finland in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances.

For detailed information on the risk assessment principles and procedures followed, the underlying data and the literature references the reader is referred to the original risk assessment report that can be obtained from the European Chemicals Bureau[1]. The present summary report should preferably not be used for citation purposes.

[1] European Chemicals Bureau – Existing Chemicals – http://ecb.jrc.it

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References can be found in the comprehensive Risk Assessment Report.

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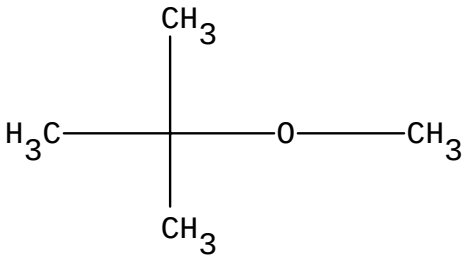
1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS No: 1634-04-4
EINECS No: 216-653-1
IUPAC Name: Propane, 2-methoxy-2-methyl-
Synonyms: tert-butyl methyl ether, methyl-1,1-dimethylethylether 1,1,1-trimethyl-dimethyl ether, methyl-tertiary-butyl ether (MTBE)
Molecular formula:: $C_5H_{12}O$
Structural formula:



Molecular weight: 88.15
Smiles notation: O(C(C)(C)C)C

1.2 PURITY/IMPURITIES, ADDITIVES

Methyl tertiary-butyl ether (MTBE) is chemically stable. It does not polymerise and does not decompose under normal conditions of temperature. Unlike most ethers, MTBE does not tend to form peroxides during storage. 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.

Table 1.1 Impurities in MTBE and their maximum percentage contents

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

Physical state:	Liquid
Melting point:	- 108 °C
Boiling temperature:	55.2-55.3 °C
Density:	0.741 g/cm^3 at 20 °C
Vapour pressure:	270 hPa at 20 °C
	330 hPa at 25 °C
Surface tension:	20 mN/m at 20 °C
Log Kow:	1.06 at 25 °C
Water solubility:	42 g/l at 20 °C
Henry's law constant:	43.8 Pa m^3/mol at 20 ^{o}C
Flash point:	-28.2 °C – closed cup method
Auto flammability	460 ^{o}C
Conversion factors:	1 ppm = 3.57 mg/m^3; at 25 ^{o}C
	1 mg/m^3 = 0.28 ppm; at 25 ^{o}C
Odour:	Terpene-like
Odour threshold in air:	Detection (average): 0.053 ppm (0.19 mg/m^3)
	Recognition (average): 0.08 ppm (0.29 mg/m^3)
Odour and taste threshold in water:	
Odour:	15 μg/l (2.5 - 190 μg/l variable sources)
Taste:	40 μg/l (2.5 - 680 μg/l variable sources)

For the present assessment 15 μg/l is used as the organoleptic threshold of MTBE in drinking water for human exposure assessment 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.

1.4 CLASSIFICATION

Currently not in Annex 1. Foreseen to be adopted at the 29th ATP of Directive 67/548/EEC[2]:

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.

[2] 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

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. It can also be prepared from methanol, *tert*-butyl alcohol (TBA) and diazomethane.

There were 25 companies producing MTBE at 35 facilities in the EU in 1997. The total production capacity of MTBE in 1997 was 3,545,000 tonnes/year and the actual volume produced was 3,030,000 tonnes. About 187,000 tonnes were imported and about 904,000 tonnes were exported outside the EU in 1997. The majority of the exported volume (> 83%) was exported to the USA and Canada. The annual consumption of MTBE within the EU was hence 2,313,000 tonnes in 1997. The consumption of MTBE has increased remarkably between the years 1995-1999 in Europe (23 %). The future consumption is expected to increase in Europe mainly as an octane booster due to the new European petrol quality requirements (EC Directive 98/70/EC).

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 (2,278,000 tonnes/1997). MTBE is the most commonly used fuel oxygenate. 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 is also used as a chemical intermediate to produce high purity isobutylene (29,000 tonnes in 1996). High purity MTBE is being used as a process reaction solvent in the pharmaceuticals industry (6,000 tonnes in 1996). Minor use patterns are use as chromatographic eluent and use as a therapeutic agent for *in vivo* dissolution of cholesterol gallstones in humans.

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. A major source of MTBE in ambient air is automobile exhaust gases.

Emissions from other use patterns 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.

MTBE is widely used as a fuel component and, consequently, there are monitoring data available from different kind of environmental samples. However, much of the data is 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.

Because of rather high vapour pressure, MTBE is one of the major VOC components in oxygenated European petrol.

3.1.2 Release scenarios

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

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

3.1.3 Environmental distribution and fate

Volatilisation may be expected from water and soil and adsorption to particulate matter is poor. 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. MTBE is expected to have high mobility in soil and leaching of the chemical into groundwater is likely. Adsorption 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.

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.

MTBE is not readily biodegradable in aquatic environment according to the standardised aerobic ready-biodegradation tests. No test results from standard inherent test systems for aquatic biodegradation are available. 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 even to use it as their sole carbon source in favourable conditions. In the EUSES model calculations, the characterisation of biodegradability in aquatic environment is "Inherently biodegradable, not fulfilling criteria".

Based on the studies available it may be concluded that rapid and reliable biodegradation of MTBE in soil cannot 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 seems 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).

According to existing data, degradation half-life of MTBE in air is 3-6 days depending on environmental conditions (predominantly OH-radical concentration). Using a degradation rate constant of $2.84 \cdot 10^{-12}$ cm^3/molecule s^{-1} and a OH –radical conc. of $5 \cdot 10^5$ radicals/cm^3, a half-life of 5.65 days is calculated. This half-life represents the 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 air.

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. Direct photolysis will not be an important removal process.

Calculated and tested bioconcentration factors as well as low octanol/water coefficient values indicate a low potential for bioconcentration. A measured BCF of 1.5 is used in the risk assessment.

3.1.4 Predicted environmental concentrations

3.1.4.1 Aquatic compartment (incl. sediment)

Industrial point sources – EUSES and site-specific

The PEC local for the aquatic compartment from industrial point sources is calculated according to the Technical Guidance Document (TGD) using EUSES calculations and site-specific assessment. Due to the presence of extensive and reliable site-specific data, the risk characterisation will be based on them.

There are 29 production and/or formulation sites, one production/processing 2 site (isobutylene production) and various processing 3 sites (use as a pharmaceutical solvent) in the EU. 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.

Table 3.1 Concentrations in waste and surface waters and sediment according to EUSES

MTBE Life cycle	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 (regional = 0.0015 mg/l) (mg/l)	PEClocals in sediment mg/kgwwt
Production 1	181	103	10.3	10.3	10.1
Formulation 1	7.75	4.4	0.44	0.442	0.433
Processing 1	4.42	2.51	0.251	0.253	0.248
Processing 2	0.387	0.22	0.022	0.023	0.023
Processing 3	20	11.4	1.14	1.14	1.11

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.

The predicted environmental concentrations for production and/or formulation 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.

In site-specific assessments, the predicted environmental concentration for isobutylene production is < 0.01 mg/l.

The predicted environmental concentration in site-specific assessments for using MTBE as a solvent in the pharmaceutical industry is 0.0016 mg/l.

Local PECs for Processing 1

Storage

MTBE may pose a significant wastewater treatment problem especially at petrol product terminals. 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.

During the storage and turnover of petrol in storage tanks, water is condensed at the bottom of these tanks. Because of the high-water solubility of MTBE, tank bottom waters may typically have a high concentration of MTBE. From time to time, tank bottom water is removed and disposed of either directly or via STP to surface water causing intermittent releases.

Because there is a 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. The PEC_{local} for surface water from depot tank bottom waters is estimated to be 60 mg/l. At terminal sites, it is believed that the major source of MTBE to surface waters is from tank bottom waters 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 consider emissions as intermittent but rather continuous and PNECs derived from long-term tests have to be used in deriving the PEC/PNEC ratio.

Road traffic

Because of the extensive and wide use of petrol as fuel in road traffic, direct releases to surface water from road traffic are likely. 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. If additional dilution in receiving surface water is not taken into account, the PEClocal $_{\text{aquatic, road runoff}}$ based on the monitoring data is 1.5 µg/l.

Petrol Fuelled Water-crafts

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 leads to concentrations of 2-3 µg/l. Concentrations may exceed 10 µg/l in the case of high traffic. Maximum measured values of 100 µg/l are considered as short-term peak values. Assuming that high traffic period average concentration represents a realistic local situation, the PEClocal $_{\text{surface water boating}}$ is 12 µg/l.

3.1.4.2 Atmosphere

Local predicted environmental concentration in the atmosphere ($PEClocal_{air}$) and deposition fluxes have been derived for the point sources production, formulation and processing. In addition, the PEC in local air has been calculated for the vicinity (100m) of a service station.

There is site-specific information on 23 production and production/formulation sites. There is no information of real emissions of the one known processing 2 site (isobutylene production) and the one known processing 3 site (solvent use). The information enables to calculate an emission factor to sites that covers approximately 82 % of the total MTBE production volume of 3,290,000 tonnes in 1999. Considering emissions from various sites, in many cases it is not 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.

Table 3.2 EUSES calculations, PECs in air from production, formulation and processing

	Local concentration in air during emission episode (mg/m^3)	Annual average conc. in air, 100 m from point source (mg/m^3)	Annual PEC_{local} in air (local + regional 0.00075) (mg/m^3)
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

Table 3.3 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

According to the site-specific data for production and production/formulation sites, 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 into account in the information submitted by industry.

Service stations

Car refuelling at service stations causes evaporative emissions of petrol components. Annual average local concentration in air, 100 m from a service station, when regional concentration has been taken into account, is 1.92 µg/m^3.

$PEClocal_{air}$ - Emission to air from petrol fuelled vehicles

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. Monitoring data are available from rush hour concentrations to long-term averages. 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 PECs) does not give any new valuable information over existing monitoring data.

3.1.4.3 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. 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 it to enter into deeper soil layers with infiltration of rainwater runoff.

The sludge field application is considered a rather marginal source of MTBE into the soil because of poor adsorption to sludge and as it is rather unlikely that MTBE will reach municipal

sewage system at a high concentration (higher than can be found in stormwater). However, STP sludge application from industrial point sources has been taken into consideration in the EUSES calculation.

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

Table 3.4 Concentration of MTBE in deposition and sludge according to EUSES

	Concentration in dry sewage sludge (D_{sludge}) (mg/kg)	Aerial deposition flux per kg of soil (D_{air}) (mg/kg/day)
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

Table 3.5 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 3.6 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

PEC soil – site-specific approach

There is some site-specific 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. The concentration of MTBE in the WWTP sludge is usually unknown. 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.

PEC soil service stations

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

Low risk of serious local soil or groundwater pollution from normal refuelling operations at modern refuelling stations is expected. 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 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 groundwater in large areas.

Monitoring data

Groundwater

Measured data from Europe have been obtained for groundwater and much less for soil and unsaturated zone water or perched water. Many measured data come from local petrol-contamination cases. Concentrations in groundwater in background areas and in exposure situations have been measured much more seldom. However, there are a number of case studies on MTBE groundwater contamination, which demonstrate that certain countries and areas suffer slight or more severe contamination of groundwater resources. There are currently very few routine monitoring data for MTBE in groundwater or drinking water as a whole. The reported pollution incidents are likely to represent only a fraction 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 when assessing indirect human exposure.

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 at least detectable amounts of MTBE, and approximately one percent rising to levels above 20 µg/l. Detections have raised consumer taste and odour 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.

Due to the lack of routine monitoring programmes on MTBE in groundwater in Europe there are no trends in time available. However, there are survey data available from seven member states, mainly from waterworks abstraction wells and few data from groundwater monitoring wells (**Table 3.7**). 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.

Table 3.7 Summary of measurements of MTBE in groundwater (µg/l)

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

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.

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.

Soil

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 cannot be compared with scenarios used in the EUSES calculations.

Rather limited monitoring data on MTBE in terrestrial environment and groundwater for European countries are available with the exception of few countries. It can be concluded, however, 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.

3.1.4.4 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 as it is not classified as very toxic (T+), toxic (T) or harmful (Xn) according to mammalian toxicity data.

3.2 EFFECTS ASSESSMENT

3.2.1 Aquatic compartment

Toxicity test results

There was a reasonable amount of rather good quality data on toxicity of MTBE to aquatic organisms.

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. 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, with LC50s ranging from 574 mg/l to 1,358 mg/l.

There are many data on acute toxicity to aquatic invertebrates and one long-term test with both freshwater and marine invertebrates. 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 invertebrates 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.

There are two acute MTBE toxicity tests with sediment dwelling invertebrates done under flow through test conditions. Though the organisms are sediment dwelling, these tests do not include sediment. The marine amphipod *Hyalella azteca* (EC50, 96 h, 473 mg/l) seems to be more sensitive to MTBE than the Dipteran *Chironomus tentans* (EC50, 48 h, 1,742 mg/l). 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.

The test results on algae differ considerably from each other. No reason can be found in test reports. 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).

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 prediction 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.

Toxicity to microorganisms

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.

PNEC for the aquatic environment

There is 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 of 10 will normally only be applied when long-term toxicity NOECs are available from at least three species across three throphic levels. However, this is only sufficient if the species tested can be considered to represent one of the more sensitive groups. Using the result from the long-term *Mysidopsis bahia* test, a NOEC of 26 mg/l, and the assessment factor of 10, the $PNEC_{aquatic}$ is 2.6 mg/l.

An assessment factor of 10 is used for intermittent releases giving a $PNEC_{aquatic\_intermittent}$ of 13.6 mg/l based on a short-term EC50 for *Mysidopsis bahia*.

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 effect also 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.

PNEC for microorganisms in a STP

The value EC10 of 710 mg/l is used to calculate the $PNEC_{microorganisms}$. 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

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

3.2.3 Terrestrial compartment

The PNEC calculated using the equilibrium partitioning method for terrestrial organisms is 0.730 $mg.kgwwt^{-1}$.

3.3 RISK CHARACTERISATION

3.3.1 Aquatic compartment

Surface water and sediment

The generic scenarios for formulation and processing (1, 2 and 3) lead to PEC/PNEC ratios below one 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 the generic scenario.

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

The regional surface water PEC/PNEC ratio is below one and there is no risk at regional level in surface water.

Results of risk characterisation for the aquatic environment

Conclusion (i) 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) (no concern) 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) (concern) applies to intermittent release to surface water from terminal site storage tank bottom waters.

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 the generic scenario.

Results of risk characterisation for micro-organisms in wastewater treatment plants

Conclusion (ii) (no concern) applies to production, production/formulation, formulation and processing sites.

3.3.2 Atmosphere

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, no quantitative characterisation of risk is possible. Therefore **conclusion (ii)** (no concern) applies.

3.3.3 Terrestrial compartment

Soil

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

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

Conclusion (ii) (no concern) applies to production, formulation, processing and runoff infiltrated.

Groundwater

The use of MTBE in petrol has resulted in growing detection of MTBE in groundwater in several 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 has resulted in such pollution. MTBE in groundwater has not been routinely monitored in

the EU countries and therefore it is difficult to draw firm conclusions about the present extent of the problem at the European 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 practice 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 many cases, MTBE has been detected in drinking water in concentrations exceeding odour and taste thresholds (15-40 µg/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.

Conclusion (iii) (concern) is drawn for the overall quality of the groundwater with respect to taste and odour.

3.3.4 Secondary poisoning

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

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 Occupational exposure

In all the 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 MTBE/petrol 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.

The other scenarios represent diverse exposures. Usually, exposure in these groups is brief and intermittent (e.g. mechanics repairing automobile fuel lines). Drivers' exposure mainly arises from refuelling and inhalation of exhaust gases in traffic and is similar to the highest consumer exposures. The use of neat MTBE as a solvent mainly occurs in the pharmaceutical industry, in which exposure is controlled in the same way as that arisen from toxic chemicals.

Table 4.1 Summary of occupational exposure estimates for MTBE

Industrial category	Duration of exposure		Reasonable worst case, TWA(8h)
Job	Actual period h/d	Frequency d/a	mg/m^3, by measured concentrations
1.1. Production	2	200	50 (neat) 25 (sampling and laboratory work)
1.2. Formulation	2	200	50 (neat and fuel) 25 (sampling and laboratory work)
1.3. Transportation	4	200	100 (neat: ship, rail car loading,) 30 (fuel: ship, truck loading) 25 (sampling and laboratory work)
1.4. Distributing	4	200	40 (11 vol% fuel) 30 (2.8 vol% fuel)
1.5. Service stations	3	200	20 (11 vol%) 3 (2.8 vol%)
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%)
1.7. Automotive repair	2	200	10 (11 vol%) 3 (2.8 vol%)
1.8. Drivers and other professionals	10 min/d	200	0.2
3.0 Solvent use of MTBE	2	60	25 (neat 97.5%); (expert judgment)

4.1.1.2 Consumer exposure

Only exposure during the refuelling situation was considered in this section. The reasonable worst-case (RWC) air concentration is 3,000-29,000 µg/m^3. The lower value represents the situation in most European countries where petrol contain 2.8 vol% of MTBE and the upper value represents the situation in Finland where petrol contains 11 vol% of MTBE. Taking in account the uptake dynamics, this amounts to a maximum daily dose of about 1.0 µg/kg/day in an adult with a refuelling of 1 min and 2-3 visits per week. Dermal exposure was estimated using EASE. 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. However, 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 reduces the absorption through the skin. Therefore, dermal exposure as a source of systemic exposure in refuelling is considered insignificant.

4.1.1.3 Humans exposed via the environment and consumer exposure (combined)

The reasonable worst-case scenario concerns a person who is exposed to MTBE at the petrol station during and after refuelling of the car and who also 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, i.e. 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. When refuelling is included, this amounts to about 3 µg/kg/day in a 70-kg adult.

4.1.2 Effects assessment

4.1.2.1 Toxicokinetics, metabolism and distribution

MTBE is a liquid with a high-vapour pressure, therefore most exposure takes place via inhalation. The substance is well absorbed and rapidly metabolised to formaldehyde and tert-butanol. Tert-Butanol is further metabolised, but at a lower rate, to 2-methyl-1,2-propanediol and α-hydroxyisobutyric acid, the latter being the main metabolite. Although the rat appears to metabolise MTBE more efficiently than humans, the profile of metabolites is the same.

4.1.2.2 Acute toxicity

Table 4.2 Summary of acute toxicity of 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) (Patty's IH&T)
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

4.1.2.3 Irritation

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 irritation scores of 0. However, the purity of the substance was not reported. A third study conducted by the same institute in the same rabbit species resulted in a slight erythema but not oedema (RBM, 1996a). Erythema 24+48+72-score was 0.6 and oedema score was 0.

Two additional skin irritation studies are available that differ in methodology significantly from the current test guideline recommendations (Cuthbert, 1979; 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, 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 4.3 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
* = substance purity was not reported

Eye

Table 4.4 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

None of the scores in the tests conducted following the OECD guideline 405 justifies the classification for eye irritation.

Respiratory tract

When tested in mice using concentrations 300 – 30,000 mg/m3 for one hour, 50% respiratory rate decrease was extrapolated to be at 16,600 mg/m3. Only the highest concentration seemed to cause irritation (Tepper et al., 1994).

Conclusions on irritation

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.

4.1.2.4 Sensitisation

There are two studies, one of which is Magnusson-Kligman test (Cuthbert, 1979). The other one used a non-standard intracutaneous challenge (Litton Bionetics Inc., 1980). Both studies gave a negative result. 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.

4.1.2.5 Repeated dose toxicity

Studies in animals

In repeated dose toxicity studies, the principal affected organs are the liver and the kidneys, mainly at inhaled concentrations of 3,000 ppm and above or at oral doses of 250 mg/kg or higher. MTBE produced protein droplet nephropathy, probably associated with the male rat specific accumulation of α2u-globulin in tubular cells. MTBE increased liver weight and induced hepatocyte hypertrophy in rats and mice. In female mice, MTBE induced a variety of microsomal P450 activities without hepatotoxicity or an increase in sustained nonfocal hepatocyte DNA synthesis.

Table 4.5 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 inhalation	Fisher-344 Rat	400-8,000 ppm	400/3,000 ppm	Proliferation of the kidney proximal tubuli epithelial cells	Chun et Kintigh (1993)
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 inhalation	CD-1 Mouse	400-8,000 ppm	400/3,000 ppm	Liver cell proliferation	Chun et Kintigh (1993)
28 days oral	Sprague-Dawley Rat	250-1,500 mg/kg	<250/250 mg/kg*	Kidney protein droplet nephropathy	Williams et al. (2000a)
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)
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 Ye (1999)

* = Gavage administration applied
+ = LOEL
AST = aspartate amino transferase
LDH = Lactate dehydrogenase

Studies in humans

There are no relevant data on repeated dose toxicity in humans.

4.1.2.6 Mutagenicity

MTBE has been extensively tested for genotoxicity in a variety of test systems both *in vit*ro and *in vivo*. Although all results have not been consistently negative, the conclusion is that the substance is not a genotoxicant.

4.1.2.7 Carcinogenicity

A slight increase in the incidence of renal tubular cell carcinomas and adenomas was found in male Fisher-344 rats at 3,000 ppm of MTBE. It is reasonable to assume that these neoplasms are associated with the cytoxicity and proliferative response of α2u-globulin nephropathy. No increase of tumours was seen at 400 ppm. In female CD-1 mice, 8,000 ppm of MTBE induced hepatocyte hypertrophy and an increased incidence of liver adenomas. At high-dose levels, MTBE clearly had an antioestrogenic effect on the mouse uterus although its mechanism could

not be identified. MTBE did not show promoter activity when tested in female mice after N-nitrosodiethylamine (DEN) initiation. Although the eventual role of MTBE in mouse liver tumour promotion is presently unclear as regards the exact mechanism, oestrogen antagonism may be involved. High levels of MTBE (≥3,000 ppm by inhalation, 1,000 mg/kg/day orally) caused testis interstitial (Leydig) cell adenomas in Fisher-344 and Sprague-Dawley rats. In Fisher-344, there was a clear dose-response relationship but the tumour incidences were within the laboratory historical control values. Whilst high MTBE doses decreased serum testosterone in Sprague-Dawley rats possibly resulting from enhanced metabolism, and there were also mild perturbations in T3 and prolactin, stimulation of the hypothalamic-pituitary-testis axis was not found. Therefore, as the mode of action is presently unclear, no definitive conclusions can be drawn regarding the relevance of this tumour for man. Equally unknown are the mechanisms for the increase of lymphoblastic lymphoma (notably in the lung) found in female Sprague-Dawley rats dosed orally with 250 and 1,000 mg/kg MTBE. Formaldehyde, a known mutagen, is not presumed to express intrinsic reactivity in MTBE metabolism because it is rapidly eliminated. By contrast, it is noteworthy that tert-butyl alcohol, the primary metabolite of MTBE, caused thyroid adenomas in female mice and kidney tumours in male rats. In summary, MTBE is suspected to function as an epigenetic promoter in animal carcinogenesis models at high dose levels. In view of the lacking or limited relevance of the findings for man, and the low potency demonstrated in animal studies, human cancer risk is presumed to be low.

Table 4.6 Summary of tumours in rodents exposed to MTBE

Animal/Sex	Dose	Tissue	Tumour	Reference
Fisher-344 rat/Male	3,000 ppm (11,000 mg/m^3)	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 Toxicity for reproduction

Effects on fertility

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 a 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 the LOAEL were reduced body weight at 3,000 ppm and increased relative liver weight.

Table 4.7 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* 3,000 ppm: CNS depression, increased relative liver weight*.	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. 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*.	8,000 ppm: increase of dead pups on PND4*, reduced female body weight on PNDs 7-28*. 3,000 ppm: reduced male body weight on PNDs 14-28*.

PMP= Pre-mating period
PND = Post natal day
* = statistically significant
+ = toxicological significance unclear

Developmental toxicity

Developmental toxicity has been tested in rats, mice and rabbits. There were no adverse effects noted in the Sprague-Dawley rat at 2,500 ppm or the CD-1 mouse at 1,000 ppm. Reduced body weight and skeletal abnormalities were seen in CD-1 only at 4,000 ppm, a dose level already toxic to dams. Likewise, no adverse effects to the developmental of New Zealand White rabbits could be demonstrated, even at 8,000 ppm.

Table 4.8 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

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. The sternebrae malformations seen in CD-1 mice at 250-2,500 ppm are not considered treatment-related.

4.1.3 Risk characterisation

4.1.3.1 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 in which there is a high potential for hand contact to neat MTBE or to MTBE in petrol. 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. On repeated exposure, **conclusion (iii)** (concern) is drawn for maintenance and car repair scenarios based on presumed and likely risk of defatting resulting in skin fatigue and a

risk of irritant contact dermatitis. It is worth noting that because of other harmful and toxic compounds, the use of petrol is already regulated in work places.

The MOS derived from the combined exposure figures for repeated dose toxicity (systemic effects) appears rather low 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 (male-rat-specific kidney effects) or they were seen as adaptive responses (liver effects).

As regards carcinogenicity, the MOSs appear low in transportation (15), distribution (15) and maintenance (24) when the NOAEC from inhalation exposure data is 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·higher (LOAEC=11,000 mg/kg) than the NOAEC. Moreover, according to the review by Cook et al. (1999), Leydig cell tumour represents only an incidence of about 3% in all the 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 the 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.

4.1.3.2 Consumers

Petrol refuelling is the only known scenario of consumer use in which 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)** (no concern) is drawn for all toxicological end-points.

4.1.3.3 Humans exposed via the environment

MOS calculations for indirect exposure were only done compared to the total body burden received via inhalation and via orally. With all the indirect exposure sources combined, **conclusion (ii)** (no concern) is drawn for all toxicological end-points.

4.1.3.4 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)** (no concern) is drawn for all toxicological end-points.

4.1.3.5 Overall conclusion

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

4.2 HUMAN HEALTH (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 applies for humans exposed via the environment due to the risk of the aesthetic properties of drinking water.

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 applies 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.