Institute for Health and
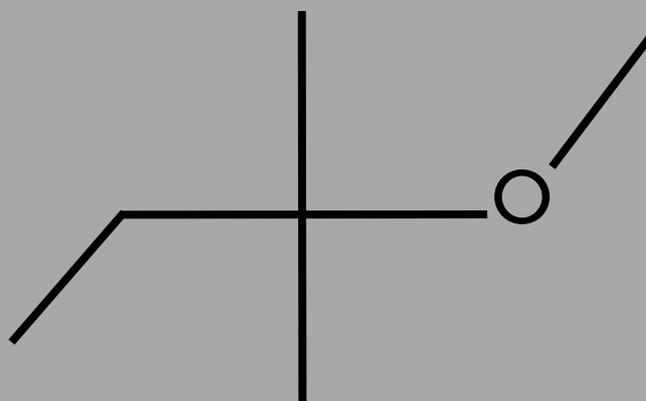Consumer Protection

European
Chemicals
Bureau

Existing Substances

European Union
Risk Assessment Report

CAS No: 994-05-8

EINECS No: 213-611-4

2-methoxy-2-methylbutane (TAME)

4th Priority List

Volume: 70

EUROPEAN COMMISSION
DIRECTORATE-GENERAL
Joint Research Centre

EUR 22236 EN

The mission of the IHCP is to provide scientific support to the development and implementation of EU polices related to health and consumer protection. The IHCP carries out research to improve the understanding of potential health risks posed by chemical, physical and biological agents from various sources to which consumers are exposed.

The Toxicology and Chemical Substances Unit (TCS), commonly known as the European Chemicals Bureau (ECB), provides scientific and technical input and know-how to the conception, development, implementation and monitoring of EU policies on dangerous chemicals including the co-ordination of EU Risk Assessments. The aim of the legislative activity of the ECB is to ensure a high level of protection for workers, consumers and the environment against dangerous chemicals and to ensure the efficient functioning of the internal market on chemicals under the current Community legislation. It plays a major role in the implementation of REACH through development of technical guidance for industry and new chemicals agency and tools for chemical dossier registration (IUCLID5). The TCS Unit ensures the development of methodologies and software tools to support a systematic and harmonised assessment of chemicals addressed in a number of European directives and regulation on chemicals. The research and support activities of the TCS are executed in close co-operation with the relevant authorities of the EU MS, Commission services (such as DG Environment and DG Enterprise), the chemical industry, the OECD and other international organisations.

European Commission
Directorate-General Joint Research Centre
Institute of Health and Consumer Protection (IHCP)
European Chemicals Bureau (ECB)

European Union Risk Assessment Report

2-METHOXY-2-METHYLBUTANE (TAME)

CAS No: 994-05-8

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RISK ASSESSMENT

A great deal of additional information on the European Union
is available on the Internet.
It can be accessed through the Europa Server
(http://europa.eu.int).

Printed in Italy

2-METHOXY-2-METHYLBUTANE (TAME)

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RISK ASSESSMENT

2006

Finland

Rapporteur for the risk assessment of 2-methoxy-2-methylbutane (TAME) is the Finnish Environment Institute.

Contact point:

<u>Environment</u>

Mrs Riitta Leinonen
Finnish Environment Institute
Riitta.Leinonen@ymparisto.fi

<u>Human health</u>

Mr. Marko Kuittinen
National Product Control Agency for Welfare and Health
Marko.Kuittinen@sttv.fi

Date of Last Literature Search :   **2004**
Review of report by MS Technical Experts finalised: **2005**
Final report: **2006**

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 Health and Environmental Risks (SCHER) 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 and confirmed in the Johannesburg Declaration on Sustainable Development at the World Summit on Sustainable Development, held in Johannesburg, South Africa in 2002.

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.

Roland Schenkel	**Mogens Peter Carl**
Director General	Director General
DG Joint Research Centre	DG Environment

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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: 994-05-8
EINECS Number: 213-611-4
IUPAC Name: 2-methoxy-2-methylbutane

Environment

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

Conclusion (iii) applies to aquatic ecosystem (including marine environment) and groundwater.

The conclusion is reached because of:

1.   exposure arising from intermittent releases to surface water from storage-tank bottom-waters at terminal sites and from releases to surface water from transportation, storage and delivery of petrol at terminal sites with direct discharge. Risk reduction measurements to the aquatic compartment should also cover possible risks to sediment.

2.   the overall quality of groundwater. The conclusion is reached because of concern of potability of groundwater with respect to taste and odour as a consequence of exposure arising from leaking underground storage tanks and tank piping, as well as spillages from overfilling the tanks. Please note that this conclusion is not based on ecotoxicological or toxicological endpoints.

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 (ii) applies to the assessed risks to the atmospheric compartment, terrestrial ecosystem, micro organisms in the sewage treatment plant and secondary poisoning.

Human health

Human health (toxicity)

Workers, Consumers and Humans exposed via the environment

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 (ii) applies to acute toxicity, repeated dose toxicity and reproductive toxicity (development). Irritation, sensitisation or mutagenicity was not included in the risk characterisation because these endpoints were assessed not to pose a hazard. Carcinogenicity was not taken forward to the risk characterisation because of the inadequacy of the available data.

Combined exposure

No assessment was conducted on combined exposure, due to negligible additional contribution to risk.

Human health (physico-chemical properties)

Humans exposed via the environment

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

Conclusion (iii) applies to drinking water contamination and 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 tank piping, as well as spillages from overfilling of the storage tanks.

CONTENTS

EUSES Calculations can be viewed as part of the report at the website of the European Chemicals Bureau: http://ecb.jrc.it

TABLES

1 GENERAL SUBSTANCE INFORMATION

CAS Number: 994-05-8
EINECS Number: 213-611-4
IUPAC Name: 2-methoxy-2-methylbutane
Molecular formula: $C_6H_{14}O$
Structural formula:
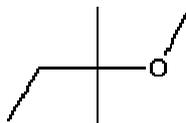
Molecular weight: 102.18 g/mol
Synonyms: *tert*-Amyl-methyl ether (TAME),
1,1-dimethylpropyl methyl ether, Butane, 2-methoxy-2-methyl-,
Ether methyl *tert*-pentyl, *tert*-Pentyl methyl ether,
Methyl 1,1-dimethylpropyl ether, Methyl 2-methyl-2-butyl ether,
SMILES: COC(C)(C)CC

1.1 PURITY/IMPURITIES, ADDITIVES

Tertiary amyl methyl ether (referred to TAME onwards) is chemically stable. Hazardous polymerisation, like formation of peroxides, will not occur under normal conditions of temperature. The degree of purity of the produced TAME within the EU is > 96% w/w (if purified). However TAME is not normally purified to high concentrations but produced and used further as 10-30% hydrocarbon mixture. TAME does not contain any additives.

Table 1.1 Overview of impurities and additives

	CAS-No	Name	Value	Comment/reference
Purities	994-05-8	Tertiary amyl methyl ether	> 96%	(refinery stream purity < 30%)
Impurities	110-82-7	Cyclohexane	$\leq 4\%$	IUCLID data
	7732-18-5	Water	< 0.5%	IUCLID data
	-	C_7-ether	< 1%	IUCLID data
	75-85-4	2-methyl 2-butanol	1.23%	Huttunen et al. (1997 b)
	-	$C_5 - C_8$ hydrocarbons	0.50%	Huttunen et al. (1997 b)
	67-56-1	Methanol	0.33%	Huttunen et al. (1997 b)
	1634-04-4	methyl tert-butyl ether	0.30%	Huttunen et al. (1997 b)
	75-65-0	tert-butanol	0.17%	Huttunen et al. (1997 b)
		butyl tert-butyl ether	0.06%	Huttunen et al. (1997 b)
	637-92-3	ethyl tert-butyl ether	0.02%	Huttunen et al. (1997 b)
	563-46-2	2 methyl-1-butene		
	513-35-9	2-methyl-2-butene		
	71-43-2	Benzene		IUCLID data
Additives	No additives	-	-	

1.2   PHYSICO-CHEMICAL PROPERTIES

Pure TAME is clear, colourless and volatile liquid at 20°C and 1,013 hPa. It has a low viscosity. It is soluble into most organic solvents and water. TAME is flammable and it reacts violently with oxidizing agents, strong acids and bases. The physico-chemical properties and validity of data are presented below.

Table 1.2   Summary of physico-chemical properties

Property	Value	Reference
Physical state	Liquid	
Melting point	-80°C	Erdölchemie 2000, Fortum 2001, Chemsafe 1994
Boiling point	86°C	Fortum 2001, Chemsafe 1994
Density	0.77 g cm^{-3} at 20°C	Erdölchemie 2000, Chemsafe 1994, CRC 1989
Vapour pressure	90 hPa at 20°C 120 hPa at 25°C	Huttunen et al. (1997), Huttunen (1996),
Water solubility	11 g/l at 20°C	Huttunen et al. (1997), Huttunen (1996), Stephenson (1992)
Partition coefficient n-octanol/water (log value)	1.55 at 20°C	Huttunen et al. (1997), Huttunen (1996),
Granulometry	not relevant	
Conversion factors	1 ppm = 4.24 mg/m^3	
Flash point	- 11°C	Erdölchemie (2000), Chemsafe (1994)
Autoflammability	415°C	Erdölchemie (2000), Chemsafe (1994)
Flammability	Highly flammable	Erdölchemie (2000), Fortum (2001)
Explosive properties	Lower limit 1.0% vol in air; 42 g m^{-3} and upper limit 7.1% vol in air; 300 g m^{-3}	Chemsafe (1994)
Oxidizing properties	Not oxidising for structural reasons	
Viscosity	0.50 mm^2 s^{-1} at 40°C	Huttunen et al. (1997), Huttunen (1996), API (1984)
Henry's constant	83 Pa m^{3}mol^{-1} at 20°C	calculated (EUSES)

Discussion on data validity

1.2.1   Melting temperature

Only one melting temperature, -80°C, is reported for TAME (Erdölchemie 2000, Fortum 2001, Chemsafe 1994).

1.2.2   Boiling temperature

Two boiling temperatures, 86 and 86.3°C, are reported for TAME (Erdölchemie 2000, Fortum 2001, (Chemsafe, 1994) (CRC, 1989). The difference is negligible and the former one has been used in environmental models.

1.2.3   Density

Density of 0.77 g cm^{-3} at 20°C (Erdölchemie 2000, Chemsafe 1994) and 0.775 g cm^{-3} at 15°C (Huttunen, 1997b) (Huttunen, 1996) are reported. These are in good agreement with the density of 0.7703 g cm^{-3} at 20°C reported in handbook (CRC 1989).

1.2.4   Vapour pressure

Various vapour pressures of TAME at different temperatures are reported in the references and they are summarised in **Table 1.3**. Krähenbühl and Gmehling (1994) have reported 29 measured vapour pressures of temperature range from 306.236 K (33.09°C) to 359.252 K (86.10°C). From that study selected vapour pressures are presented in **Figure1.1**.

Table 1.3   Vapour pressures of TAME at different temperatures with reported standard deviations (std)

Vapour pressure (std), hPa	Temperature,°C	Reference
90 (6)	20	Huttunen et al. (1997), Huttunen (1996)
210 (10)	37.8	Huttunen (1996)
100	38	Erdölchemie (2000)
220	38	Fortum (2001)
145.44	33.09	(Krähenbül and Gmehling 1994)
196.83	40.09	(Krähenbül and Gmehling 1994)
262.01	47.12	(Krähenbül and Gmehling 1994)
422.75	59.80	(Krähenbül and Gmehling 1994)
667.5	73.0	(Krähenbül and Gmehling 1994)
1,010.76	86.10	(Krähenbül and Gmehling 1994)

No data was available for the vapour pressure at 25°C. The vapour pressure at that temperature was estimated by interpolation of data from the studies done by Huttunen (1996) and Krähenbühl and Gmehling (1994) are presented in **Figure 1.1**. The vapour pressure of 120 hPa at 25°C and 90 hPa at 20°C seem to be realistic.

Figure 1.1   Vapour pressure of TAME at different temperatures. Data from Huttunen (1996) and (Krähenbül and Gmehling 1994)
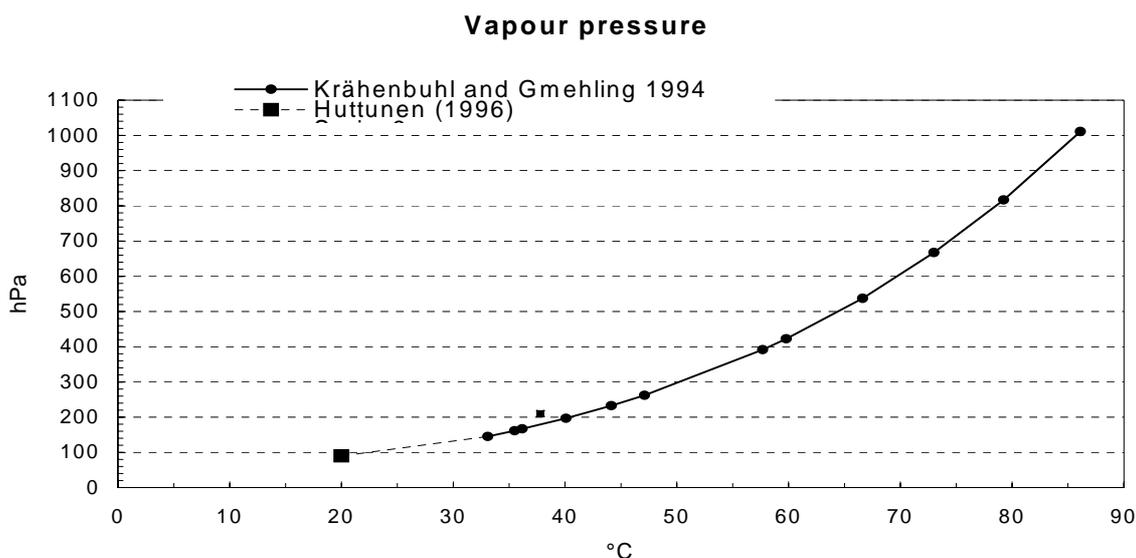
If the vapour pressure is extrapolated to 12°C, the relevant temperature for the regional model, approximately 60 hPa were the first approximate result from **Figure 1.1**. A vapour pressure of 56 hPa at 12^oC is calculated using MPBPWIN model Antoine Method (EPIWIM 2000) (Lyman et al. 1990). The value of 56 hPa is used in the characterisation of the temperature effect on environmental partitioning in Section 3.1.2.2.

1.2.5   Log K_{ow}

An octanol-water partition coefficients (log K_{ow}) of 1.55 ($\pm$ 0.021) at 20°C is reported, study based on the OECD guideline 107 according to GLP (Huttunen et al. 1997, Huttunen 1996). Identical calculated value of 1.6 at 20°C was reported also in the safety data sheet of producer (Erdölchemie 2000). A value of 1.55 has been selected for the risk assessment calculations.

1.2.6   Water solubility

The highest reported value is 12 g l^{-1} (Erdölchemie 2000) and the lowest 10.71 ($\pm$ 0.51) g l^{-1} at 20°C (Huttunen 1996; Huttunen 1997 b; Huttunen et al., 1997 a). The latter one is measured based on the OECD guideline 105 according to GLP. Stephenson (1992) has studied the solubility of TAME in water at different temperatures (standard addition method with thermal conductivity GC, **Figure 1.2**). The solubility of TAME in water decreased as the temperature increase. At 20°C the study results agreed well with the value of 11 g l^{-1} presented in the other literature and thus the rounded integer has been used in the environmental calculations.
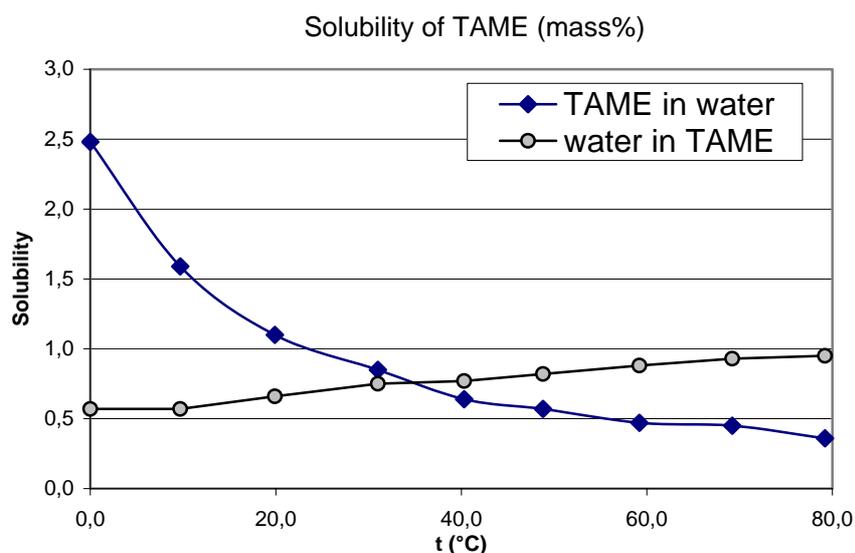
If water solubility is extrapolated to 12°C, the relevant temperature for the regional model, approximately 15 g/l is the approximate result from **Figure 1.2** above.

The solubility of TAME into water from petrol is approximately 2,400 mg/l (US EPA 1999).

1.2.7   Surface tension

Surface tension is reported to be 22.5 mNm^{-1} at 20°C and 20.5 mNm^{-1} at 40°C measured by DIN 53914 (Bayer 2001).

1.2.8   Flash Point

Value of −11°C is reported for TAME measured by the closed cup method (Erdölchemie 2000, Chemsafe 1994).

1.2.9   Autoflammability

Values of 415 and 430°C are reported based on measurements done by DIN 51794 method (Chemsafe 1994, Erdölchemie 2000, Huttunen et al. 1997, Huttunen 1996).

1.2.10   Flammability and explosive properties

TAME is highly flammable. Its vapour is heavier than air (vapour density 3.52) and explosive mixtures with air can be formed at high temperatures. The explosive limits are: lower limit 1.0%-vol in air; 42 g m^{-3} and upper limit 7.1%-vol in air; 300 g m^{-3} (Chemsafe 1994).

1.2.11   **Oxidising properties**

TAME is not an oxidising agent on the basis of structural considerations.

1.2.12   **Viscosity**

For kinematic viscosity a value of 0.50 mm^2 s^{-1} at 40°C is reported (ASTM D455 method, Huttunen et al. 1997, Huttunen 1996). For dynamic viscosity a value of 0.42 mPa at 20°C is reported (Erdölchemie 2000).

1.2.13   **Henry's law constant (H)**

The calculated value at 20°C is 83.5 Pa $m^3$$mol^{-1}$ (0.035 dimensionless) (using vapour pressure of 90 hPa and water solubility of 11 g/l) and 111 Pa $m^3$$mol^{-1}$ at 25°C (0.047 dimensionless). (EQC 1,1 model, EUSES 1.1 model) (measured, original study not allocated Miller and Stuart (2000) $1.27 \cdot 10^{-3}$ atm-m^3/g-mole (temperature not reported))

If H is calculated to the relevant temperature for the regional model of 12°C, Henry's law constant is 38.1 Pa $m^3$$mol^{-1}$ (using vapour pressure of 56 hPa and water solubility of 15 g/l). This clearly indicates lowered (slower) volatility from water to air at environmentally relevant temperatures (Generic TGD approach).

For saline water (physiological saline), a measured dimensionless air/water partition coefficient of 0.084 at room temperature is available (corresponding to 200 Pa $m^3$$mol^{-1}$). This value gives an indication that TAME is more volatile from saline water (sea water) compared to fresh water (Nihlen et al. 1997).

1.2.14   **Odour threshold in air**

Values are from a study by Vetrano et al. (Vetrano 1993)

     Detection (average)   0.027 ppm (0.12 mg/m^3)

     Recognition (average)   0.047 ppm (0.20 mg/m^3)

Results by Vetrano et al. are from a study in laboratory conditions from one set of tests (panel with 6 adult persons).

1.2.15   **Odour and taste threshold in water**

General odour and taste threshold values has not been determined here. This report refers only to one study and the results show that TAME may have very low limits for sense perception for instance in drinking water.

If any generalisation of odour and taste thresholds in water is drawn from the test results presented below, the results should be treated with care and always in comparison with other results by the same author (see MTBE results described in the last two paragraphs of this section). If larger test and data sets were available, the lowest odour and taste detection thresholds might be far below the values presented below.

Estimated values are from Vetrano (1993):

Odour detection (average)	0.194 mg/l
Odour recognition threshold (average)	0.443 mg/l
Taste detection threshold (average)	0.128 mg/l

In general, compounds with odour threshold below 1 mg/l are considered highly odorous. Results by Vetrano et al. are from distilled water in laboratory conditions from one set of tests (panel with 6 adult persons). However, these test results do not reflect the natural environmental situation, where e.g. water hardness, temperature, chlorinating or other contaminants influence to taste and odour. Thus, the concentration, at which the taste or odour makes water unacceptable for consumers, may vary greatly. Also the thresholds values differ between various persons. Values sited above are just indicative and refer only to one study. These values should not be regarded as odour and taste threshold values for TAME in general.

The situation is comparable with MTBE (CAS 1634-04-4) where a variety in the range of sensitivity of more than 100 times has been observed between tests and persons. TAME and MTBE are close structural analogs (one methyl group difference). For MTBE Vetrano et al. measured odour detection and recognition thresholds 0.095 mg/l (average) and 0.193 mg/l (average), and taste detection threshold 0.134 mg/l (average) in water (Vetrano and Cha 1993b). Methods and equipment used by Vetrano were similar (or the same) in TAME and MTBE tests. Results show that odor detection and recognition thresholds were approximately 2-3 fold higher for TAME compared to MTBE. The taste detection threshold was slightly lower for TAME, but the thresholds were very close to each others for MTBE and TAME: 0.134 mg/l and 0.129 mg/l respectively. It can be concluded from these results that inherent taste characteristics in water for humans for TAME and MTBE are similar. The measured odour thresholds are slightly different, but at the same order of magnitude.

Overall the odour detection thresholds reported for MTBE in water are 2.5 - 190 µg/l (variable sources) and taste detection thresholds in water are 2.5 - 680 µg/l (variable sources) (FEI 2001).

1.2.16   Odour

The odour of TAME has been described sweet, rubbery, fruity, ether-like and paint-like (Vetrano 1993). Camphor like.

1.2.17   Conversion factors

(101 kPa, 20 $^\circ$C):   1 ppm = 4.24 mg/m³; 1 mg/m³ = 0.24 ppm

The density of TAME is 0.775 g cm^{-3} at 15°C and the density of petrol at 15°C depending on composition may vary between 0.725-0.780 g cm^{-3} (BUA 1996). Therefore the weight % of TAME in petrol may be variable and not directly proportional on volume % (variability: 14.9-16.0%-wt conv. ratio: 0.994-1.068). If average density of petrol is taken as 0.750 then 15%-vol is proportional to 15.5%-wt and the conversion ratio is 1.033 consequently.

1.3   CLASSIFICATION

1.3.1   Current classification

The substance is not listed in Annex I of Council Directive 67/548/EEC.

1.3.2   Proposed classification

The Meeting of the Technical Committee for the Classification and Labelling of Dangerous Substances in March 2005 agreed on the following classification and labelling of TAME:

Classification

F; R11 Xn R22 R67

Labelling

F; Xn R11-22-67

S(2)-9-16-23-33

Explanation

F   Highly flammable

Xn   Harmful

R11   Highly flammable

R22   Harmful if swallowed

R67   Vapours may cause drowsiness and dizziness

S(2)   Keep out of reach of children.

S9   Keep container in a well ventilated place.

S16   Keep away from sources of ignition – no smoking

S23   Do not breath vapours

S33   Take precautionary measures against static discharges

The lack of environmental classification is based on the acute toxicity values of 10-100 mg/l and not ready biodegradability which would lead to classification R52-53. However, the long-term NOEC for the species that is most sensitive in acute tests is greater than 1 mg/l, leading to no classification for environmental effects.

2 GENERAL INFORMATION ON EXPOSURE

2.1 PRODUCTION

2.1.1 Production processes

The substance TAME belongs to the group of ethers. It is an anthropogenic chemical and there are no known natural occurring sources of the substance.

TAME is manufactured in the petroleum refineries and it is formed by the chemical combination of either of the two reactive C_5 olefins (2-ethyl-2-butene and 2-methyl-1-butene) with methanol. Fluid cat cracker (FCC) light petrol is mixed with methanol. The mixture is conducted to acidic ion exchange resin, which act as catalyst. Tertiary ether TAME is formed in an equilibrium reaction from methanol and the C_5 olefins.

After this, the reactor effluent is distilled to recover TAME. The distilled product is typically 10-30% TAME in petrol hydrocarbon mixture and not produced or isolated as a chemically pure substance. This on site product is used as a blending component of standard unleaded petrol. Some plants produce TAME and heavier ethers from tertiary olefins (C_6-C_7) in a same process.

Only a small fraction (approximately 3%) of the total amount of TAME produced in the EU is isolated as 'pure' TAME (> 96% purity), the majority (97%) is part of a 'mixed' refinery stream containing 10-30% TAME together with other mixed hydrocarbons.

2.1.2 Production capacity

TAME only began receiving serious consideration as a component for petrol blending during the early 90's. Production started in the USA in 1991 and in 1992-1994 low production was performed in UK and Germany (as an intermediate). Higher production started in Europe as the NExTAME process to produce TAME was launched in Finland in 1995 (Kivi et al. 1997).

The EU production volume exceeded 175,000 tonnes in the year 2000. The EU production sites larger than 1,000 tonnes per year were located at the following places in the year 2000 (see **Table 2.1**) A remarkable increase in capacity building and production has happened between 2000-2002, since production reached 250,000 tonnes in 2002.

Table 2.1   Production sites of TAME

Company	Location
AGIP	Gela, Italy
BP Chemicals (ERDÖLCHEMIE)	Cologne, Germany
FORTUM OIL OY	Porvoo, Finland
SARAS SpA	Sardinia, Italy
TOTALFINAELF (LIDSEY OIL)	Killingholme, United Kingdom

The produced TAME is mainly used in the EU-European market. There are no merchant plants producing TAME to refineries, but producing plants are "captive" plants located in refineries. One producer is processing TAME on site to other chemicals. There has not been remarkable

international marketing of TAME in the 90's. From the EU area, it was only once exported to Canada, 50,000 tonnes as 30%-liquid (15,000 tonnes 100% TAME) in 1999 and once imported from India (producers information). Import and export has increased slightly during the last few years (2000-2002) showing 30,000 tonnes net import to the EU –area in the current reference year 2002.

2.2 USES

2.2.1 Introduction

Table below shows the industry and use categories of TAME for the EU in 2002. The main use of TAME is as an additive/component in petrol and it is the second largest used oxygenate after MTBE. Other uses of the substance are as an intermediate in the production of pure methyl butenes.

Table 2.2 Quantities (production + import), Industry and use categories

Industry category	Use category	Quantity used tonnes	Percentage of total use
Mineral oil and fuels industry (9)	Fuel additive (28)	277,000	97
Chemical industry, chemicals used in synthesis	Intermediate (33)	10,000	3
Total		**287,000**	**100**

TAME is a petrol blending component which aids to meet current EU petrol specifications concerning octane number (RON, MON) and volatility (RVP). Research Octane Number (RON) is an indicator of petrol's anti-knock performance at lower engine speed and typical acceleration conditions, while MON (Motor Octane Number) is an indicator for fuel under higher engine speed and higher load conditions. Octane rating of TAME is 104.5 ((Research + Motor)/2). Reid Vapour Pressure (RVP) is the direct measure of volatility at ambient temperatures.

These parameters have direct influence on engine fuel economy, vehicle driveability and environmental emissions of certain regulated pollutants. The oxygen containing fuel additives improve the combustion process, resulting in a decrease in hydrocarbon and carbon monoxide emissions.

TAME is blended in petrol alone or often together with other oxygenates (MTBE, ETBE or ethanol) and other octane boosters to meet desired petrol specifications. Typically petrol may contain < 1% – > 10% TAME. In Finland premium blend (95-octane petrol) contains 4-11% TAME and super blend (98- and 99-octane) typically less, since other octane boosters are used (mainly MTBE).

A significant proportion of the EU gasoline pool contains no TAME. Since many oil refining companies have no capacity to manufacture TAME, this fraction of the total EU gasoline pool is, by definition, TAME-free. International marketing, import to EU area by these companies may somewhat blur this basic composition. Anyway, the use of TAME is at the moment more or less localised to the market areas of the European TAME producers.

Table 2.3 presents information on TAME consumption volumes in different EU member countries in the year 2002. Average concentrations in petrol are included. These averages are

calculated for petrol that contain TAME, not for total consumed petrol volume for each country. Data in **Table 2.2** has been compiled from information submitted by the producers to the rapporteur. However, the data is not complete as a remarkable proportion of consumed total volume is not included (no data available). It can not be concluded that TAME is not in use in a certain country if the name of the country is not mentioned in the table. For countries mentioned in the table, the consumption volumes can be regarded as a consumption that surely has come true, but the figures can still be high underestimates for some of the countries.

Table 2.3   Annual TAME consumption in certain EU countries in the year 2002

EU-Country	Consumption of TAME in the year 2002 (tonnes)	Average conc. %-wt of TAME in petrol
Greece	2,400	3,7%
Finland	55,000	4-11% (known range)
France	500	3,7%
Italy	70,500	0.9-3,7%
Netherlands	1,200	3,7%
Spain	7,200	3,7%
UK	45,100	3%
others (no data available)	-	-

2.2.2   Release Scenarios

TAME may be released into the environment during its life cycle steps; production, formulation, transport, storage, delivery and use. General characteristics of TAME which are relevant for the exposure assessment are listed below and discussed in more detail in Section 3.1.2.

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

1.1   Production of TAME
1.2   Formulation: petrol blending with TAME (on site and off site)
1.3   Industrial use 1 (processing 1 in EUSES): storage, transport and delivery of petrol
1.4   Private use: consumer use of petrol
1.5   Industrial use 2 (processing 2 in EUSES): TAME used as chemical intermediate
1.6   Waste disposal

The environmental exposure assessments combine the relevant exposure scenarios for TAME and apply recommended assessment methods for deriving PEC local and regional according to Technical Guidance Document (TGD 2003) and European Union System for the Evaluation of Substances (EUSES model ver. 1.0 (1997)) if applicable.

2.3   TRENDS

A remarkable increase in capacity building and production of TAME has happened between 1998-2002. In 1998 the annual consumption of TAME in Europe was approximately

100,000 tonnes and in the year 2002 consumption reached 277,000 tonnes as a petrol component. The tonnages used as an intermediate in chemicals industry have been rather stagnant.

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 of high intrinsic octane rating of aromatics, decrease in aromatics leads to loss of octane rating in base petrol. The change in aromatics concentration in petrol, approximately 7% v/v drop in five years, means a remarkable loss in octane number. This loss has to be replaced with non-aromatic, high octane blending components. That would mean substantial continuous increase in annual consumption volumes of TAME or other suitable blending components in coming years.

Demand for high octane blending compounds may increase also due to the 10 new EU-member countries where the use of lead as octane booster stops as they join the EU. This may have remarkable influence on TAME production volumes as well.

2.4 LEGISLATIVE CONTROLS

2.4.1 Petrol composition and emission control

Composition

Based on the results of the Auto/Oil programme, Directive 98/70/EC (amend 2001/71/EC) regulates the maximum content of TAME 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 (1.May-30.Sep) maximum 60.0 kPa and maximum 70kPa in Member States with arctic or otherwise severe winter conditions and winter grade gasoline with a maximum allowance level of 90kpa) 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.

According to the joint text approved by the Conciliation Committee of the European Parliament and Council the new directive amending Directive 98/70/EC will lower the allowed maximum concentration of sulphur to 10 mg/kg from 1 January 2009. Furthermore, article 6 of Directive 98/70/EC will be amended to allow the Member States by way of derogation to take more stringent measures on the quality of the petrol marketed in specific areas in order to protect the health of the population or the environment, if there is a risk of groundwater pollution.

Emission Control

Hydrocarbons (HC) from motor vehicles are regulated pollutants in the EU and historically emissions standards have been addressed to 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.

Directive (98/69/EC) introduce 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 required on petrol vehicles from 2000. The driving cycle test procedure is modified to include a cold start at -7°C.

Directive 94/63/EC (1994) "Stage I & II" 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). This vapour recovery system called Stage I will be in use at all service stations in the European Union by the end of the year 2004. Stations with annual throughput over 1,000 m^3 should have already been repaired before the beginning of 1999. There is as yet no obligation regarding vapour recovery systems during refuelling automobile tanks (Stage II). Thus the introduction of Stage II shows large regional variations in Europe. At Stage I stations, during unloading from tank truck to station tank, vaporised gasoline is collected, which reduces the release to the air and also limits the human and environmental exposure. At Stage II stations, vaporised gasoline is collected also during refuelling by an inlet which is attached to the gasoline pistol.

In general, the "VOC directive" (1999/13/EC) sets rules for hydrocarbon emissions from petrol storage and delivery in large installations (storage terminals etc.).

2.4.2 Waste water discharges to surface waters

The IPPC (Integrated Pollution Prevention and Control) Directive lays down measures designed to prevent or control emissions in order to achieve high level of protection to the environment as a whole. IPPC-installations are typically large industrial activities such as refineries. Thus the tank fields in refineries and TAME production plants are controlled through permits given and supervised by national authorities. These permits may cover the treatment of tank bottom waters. For new installations permits shall be given prior to the beginning of the operation and for existing installations by the end of 2007. However, many member states have been subject to national permit systems prior to the IPPC directive.

Storage tank fields in depots not in connection with industrial facilities are not covered by the IPPC Directive. These separate tank fields are in some Member States subject to national permit systems and thus there are site specific requirements which may cover the treatment of tank bottom waters.

There is no data available on what type of permit conditions are set for the treatment and emissions of tank bottom waters in different Member States. So far the main focus seems to have been oil compounds, which can be separated from waste waters with oil traps. Oil traps do not remove water soluble fractions, such as TAME.

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

3.1.1 General discussion

The emissions have been estimated using industry-specific and use pattern specific information wherever possible. For some lifecycle stages and environmental compartments, emissions have also been estimated using the default methods from the TGD. In these stages insufficient specific information is available to estimate the emission by other methods.

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

3.1.1.1 Release from production

TAME is produced at 5 sites within the EU. TAME is produced in closed systems in either wet or dry processes. Atmospheric emissions are expected from both types of processes but release to water occurs primarily from the wet process. Typical (but not entire) production of TAME in the EU is part of oil industry.

During the manufacturing process of TAME, 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 TAME product is extracted before the wash. Some traces of TAME can, however, be present in the MeOH-HC stream. To avoid concentration of the water stream, a small side stream is extracted from the water stream and led to the wastewater treatment unit. In the dry process, excess methanol is extracted by other means and recycled back to the process feed.

In the following emission calculations for production the default emission factors to air and waste water according to the Technical Guidance Document (TGD) are replaced by site specific data (see **Table 3.5**).

Regional and continental emissions from production

In calculating the contribution of production plants to regional and continental concentrations the following emissions will be used. There are site specific data from all of the five production sites. Total emission to air from production and formulation (formulation on site) was 43.8 tonnes/year and emissions to waste water 26.9 tonnes/year.

Table 3.1 Summary of emissions from TAME production sites (tonnes/year)

Site	Releases to Air	Releases to water	Notes
A1	15.5	0.005	site specific data
A2	10.5	1.2	site specific data
A3	11.2	2.3	site specific data

Table 3.1 continued overleaf

Table 3.1 continued Summary of emissions from TAME production sites (tonnes/year)

Site	Releases to Air	Releases to water	Notes
A4	1.1	5.7	site specific data
A5	5.5	0.25	site specific data
Total	43.8	9.45	

Instead of using default emission factors in regional/continental modelling, measured (or site specific calculated) release data is used as far as possible. The TGD default value of 10% for regional production has been substituted by production volume data of the highest production volume site.

The highest site specific emission factors (EF) reported are EF_{air} =0.015 and EF_{water}=1 · 10^{-4}. The highest EF_{air} are calculated from total HC –emissions of the production site since no TAME determinations are available. These highest values are not used in EUSES calculations, but the TGD default factor of 0.001 is used instead for emissions to air generic calculations.

3.1.1.2   Release from formulation

In the Technical Guidance Document, a formulation is defined as the stage where the chemical is combined in a process to obtain a product or preparation. Formulation of TAME covers the blending of petrol with TAME. Emissions into environment are mainly atmospheric.

There are basically two formulation techniques for blending petrol, in-line blending and batch blending. In in-line blending the petrol components (including TAME) 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 TAME is blended into 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 (Fortum 2001). It is expected that the TAME emissions in these terminals do not differ from the emissions from blending activities in the refineries since the techniques used are similar. Emissions from formulation are hence included partly in production sites and partly in "industrial/professional use 1" category (see Section 3.1.1.3), apart from EUSES calculations where the formulation stage is included separately.

Because formulation takes place in production and terminal sites, site specific emission data contain emissions from formulation but do not make a difference between specific emission sources and functions (production, formulation, storage, pump leaks, etc.). Therefore the proportions of emissions arising specifically from the formulation stage is not known, but formulation emissions are included in site specific totals (see **Table 3.1**).

3.1.1.3   Release from industrial/professional use 1 (processing 1)

The industrial use scenario (1) covers life cycle stages where transportation, storage and delivery of TAME and blended petrol takes place. Emissions are mainly atmospheric, even if emissions

to all environmental compartments are possible during storage, loading/reloading, transportation and delivery of petrol at service stations.

The default emission factor from the Technical Guidance Document for mineral oil and fuel industry (A3.8) is used (see **Table 3.3**), except emissions to air where a more detailed, vapour pressure dependent factor is used.

Release to the aquatic environment may occur during transportation of petrol/TAME through waterways and refuelling of watercrafts. Intermittent releases to the aquatic environment, to wastewater and surface water, may arise from storage tank bottom waters in terminal sites (local PEC calculation).

Release to waste water happens from petrol stations. At new and sanitised stations the car maintenance and repair halls and the service station pump island have closed pavements with rain and waste water drainage to an oil/water separator and normally further to a local municipal sewage system.

Release to soil during storage and transportation is assumed to be low, in terms of emitted volumes, compared to emissions directed to air. However these emissions are existing and soil in refuelling stations and depot areas are more or less contaminated with petrol based hydrocarbons. Such slight diffuse emissions can be considered as prevailing practice because of the widespread occurrence, even if regulations and technical standards exist to minimise such emissions. Serious soil and groundwater pollution may happen in the case of leaking of underground storage tanks or piping. More or less frequent overfilling of the tanks may lead to similar consequences. However no specific local PECs are derived here for leaking tanks.

Emissions to air are predominantly fugitive emissions directed to air during storage of petrol in tanks and during loading/emptying phases.

Reid Vapour Pressure (RVP) is the direct measure of volatility at ambient temperatures. The RVP of pure TAME is rather low, approximately 11kPa (1.6 psi), and it can be used to reduce evaporation losses from vehicles and during bulk storage and distribution of petrol.

Typically vapour pressures of ethers in hydrocarbon mixtures have good linearity over wide concentration range (European Commission 2001; Kivi et al. 1991). Therefore in estimating volatile releases of TAME from various petrol blends linear volatility behaviour can be expected over concentration range of < 1-15% TAME.

Petrol hydrocarbon releases to air during storage and refuelling

In the following section an emission factor for petrol hydrocarbons to air will be derived. This factor is further used to estimate the emission factor for TAME to air from transport, storage and delivery.

Table 3.2 summarises measured/estimated emissions to air from certain operations of petrol life cycle.

Table 3.2   Emissions factors of petrol hydrocarbons during turnover and
storage of petrol and refuelling of vehicles

Operation	Emission kg/tonne
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 (BUA 1996).
EMEP/CORINAIR Atmospheric Emission Inventory Guidebook.
European Environment Agency 1996 (CORINAIR 1995).

Taking into account filling and breathing emissions from intermediate storage tanks
($1.12 + 0.16$ kg/tonne), petrol station tanks ($1.4 + 0.08$ kg/tonne) and refuelling emissions
(1.48 kg/tonne) the data presented assume the average turnover and storage VOC emission factor
for petrol to be about 4.5 kg/tonnes maximum (without gas recovery, no Stage I or Stage II
controls).

A great deal of petrol is transported directly from the refinery depot to service stations and there
are no emissions from unloading/loading and storing phases in intermediate depots leading to
lowered total emissions. A similar lowered trend is achieved, as the gas recovery equipment is
becoming more common in refinery and intermediate depot dispatch stations and petrol stations
(Stage I controls). Refuelling gas recovery is also common in service stations in some of the EU
member states (Stage II controls) cutting emissions to air by 80-90%.

Taking into account the data in **Table 3.2**, and different emission control stage implementation
in different member states (Stage I and II controls common in some EU countries with high
petrol consumption) an average EF of 3 kg/tonne for *petrol* is used in further emission
calculation.

As a conclusion the TGD defaults values are used in the further emission estimation (industrial
use 1) for soil and wastewater and a specific emission factor of 3.0 kg/tonne is used for air.

Evaporative Emission factor for TAME

The reid vapour pressure of TAME (RVP) is lower than the reid vapour pressure of average
European grade petrol. This means that reductions in total evaporative HC emissions are reached
when low vapour pressure blending components in fuels are used.

In previous sections a total petrol emission factor of 3 kg/tonne (for industrial use 1 phase) was derived. The volatility of the blending component MTBE is very close to the average petrol volatility (European Commission, 2002). This means that pure 100% MTBE would emit the same 3 kg/tonne under the same conditions and if petrol would contain 10% MTBE, so 10% of the emitted hydrocarbon mass would be MTBE. Relational volatility between the two oxygenates TAME/MTBE is approximately 11/56 (TS 75/95 and 128/96) (Fortum 2001). This means that TAME volatility from petrol is about 20% of MTBE volatility in mass units if the wt-% concentration of these substances in petrol is equal.

RVP based volatility of TAME is herewith about 20% of the total emitted mass volume. Taking this into account and performing a comparative approach, this leads to a TAME emission factor of 0.6 kg/tonne (20% of 3kg). A good linearity of TAME evaporation over a concentration range of < 1-15% is assumed and therefore 0.6 kg/tonne TAME for the total petrol blended tonnage is used in the emission calculation for industrial use 1.

Table 3.3 Emission factors and total emissions for Industrial use 1

Compartment	EF TAME	Release (tonnes)
Air	0.0006	166.2
Wastewater	0.0005(d)	138.5
Surface water	0(d)	0
Soil	0.001(d)	277

d)   TGD Default emission factor

3.1.1.4   Release from private use

The *private use scenario* covers emissions of TAME from the use of petrol as a fuel in spark ignition engines under typical operation conditions (cars, boats, stationary engines, etc.). Emissions to all environmental compartments are possible although emissions to environment are mainly atmospheric.

Emissions to air from the use of petrol are the main source of TAME released to the environment. It covers the majority of the total emitted mass volume. Emissions are divided into two main categories: 1) evaporative emissions and 2) exhaust emissions.

The total (continental + regional) exhaust and evaporative emission of TAME is calculated using a single emission factor (0.025). The emission factor for the exhaust emission has been derived elsewhere, in the risk assessment report of MTBE (European Commission 2001). The calculation method used statistical data on annual driven mileage and fuel consumption within EU as well as measured data of pure MTBE proportion as a component in exhaust HC- emission gases per different vehicle fleet classes. Finally the emission factor and MTBE emission to air for the petrol consumption were calculated as a ratio of total emitted/consumed tonnage. Because of the similar chemical structure of MTBE and TAME the results of the previous assessment is used here. There are also studies showing absence of significant differences in the emission characteristics between MTBE and TAME petrol blends (Noorman 1993).

Releases to surface water are caused by motor boating and related activities and by urban runoff in general (roads). As far as detailed information is available these are used later in the report to calculate local PECs. Otherwise the Default emission factor from the Technical Guidance Document for mineral oil and fuel industry (private use category) is used (see **Table 3.4**)

Motor boating and comparable activities lead to direct emissions of petrol to the aquatic environment through spills and exhaust gases. There are studies showing that engine exhaust and not spills are the major emission source. Certain types of water-crafts (most outboard motors and ski jets) release their exhaust gases directly under the water surface. This technique is used for lowering the 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. Typically even > 25% of fuel may be directed unburnt to surface water from two-stroke engines.

Direct release to soil may occur for instance as a result of malfunctioning fuel systems in vehicles and engines. Accidental spillages during transport of petrol (tank trucks) and car accidents are undoubtedly potential sources of soil and groundwater contamination with TAME. However, a quantitative local estimation has not been carried out from sources mentioned above, except EUSES calculation at regional/continental level. The default emission factor from the TGD is used (mineral oil and fuel industry, private use category, fraction of tonnage released to industrial soil 0.0001).

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 gas oil.

Table 3.4   Emission factors and total release of TAME from use of petrol

Compartment	EF TAME	Release (tonnes)
Air	0,025	6,925
Water	0,0005(d)	139
Surface water	0,0001 (d)	28
Soil	0,0001(d)	28

d)   TGD Default emission factor

Regional consumption of TAME needs some consideration. On average petrol consumption within the EU is about 310 kt per million inhabitants (in 1997). The consumption has been rather stagnant over the last years. Assuming this average value for 20 million inhabitant (in 40,000 km^2) the regional consumption of petrol would be 6.2 Mt. If 6.2 Mt petrol is blended with 27,700 tonnes TAME (TGD 10% rule) the average regional concentration of TAME in petrol would be only 0.45%.

Actually the consumption of TAME is remarkably more common in some member states and sub regions than in others and therefore the actual realistic regional consumption of TAME is far higher than 10% of the total EU consumption. If the 6.2 Mt petrol is accepted as regional consumption of petrol and a total consumed volume (0.277 Mt) is used in the region the average percentage of TAME blend were 4.4% v/v at regional level. This 4.4% can be seen as a realistic value for regional assessment even if it comprises 100% of total EU consumption of TAME. Regional real 4.4% average TAME petrol blend is not uncommon (see Section 2.1.1). Thus, 277,000 tonnes are consumed regionally as a petrol blending component for private use in regional assessment.

3.1.1.5 Release from Industrial use 2 (processing 2)

Industrial use 2 covers emissions from the use of TAME as an intermediate in transformation of TAME into high purity isopentene in a continuous process. Emissions into environment are mainly atmospheric.

The processed TAME volume is used exclusively as captive on-site intermediate. The current default emission factors from the Technical Guidance Document for Chemical industry, intermediates have been replaced by specific data as it is available regarding emissions to air and waste water. The default fraction of the main source is also replaced by specific data.

3.1.1.6 Release from disposal

Soil and groundwater in petrol retails and storage sites may often be contaminated with petrol hydrocarbons. In connection to remediation activities, discharges of TAME contaminated groundwater take 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.

Site specific available data below briefly describes waste disposal protocols used in the production sites of TAME.

Site 1

Sludge from STP is pressed and landfilled, concentration of TAME in sludge and in dry sewage sludge was not detected (N/d). Washings from motor spirit tank sludges may contain up to 1% TAME. Approximately 50 tonnes/year is incinerated off-site. Solid waste: Ion exchange Resin purged and landfilled off site

Site 2

Solid waste treatment: Amount of TAME in solid waste was below the detection limit. If necessary, solid waste is always inertised with calcium oxide or burned.

Site 3

STP sludge is sent to industrial landfill. The landfill site is specially designed with several sealing layers to prevent leakage to groundwater. Any liquid that may escape is re-routed back to the WWTP for re-treatment. Spent catalyst is steam treated before it is removed from the reactors. No TAME remains after steam treatment.

Site 4

All formed STP sludge is incinerated. Concentration of TAME in sludge (mg/kg) was not detected. Solid waste treatment is incineration.

<u>Site 5</u>

No data available.

Table 3.5 Emission Summary Table

	Production 1	Formulation 1	Industrial use 1	Private use 1	Industrial use 2	Total t/yr
Relevant tonnage for application (tonnes/year)	257,000	277,000[1]			10,000	
Regional tonnage of substance (tonnes/year)	130,000	130,000	277,000	277,000	10,000	
Continental tonnage of substance (tonnes/year)	107,000	147,000	0	0	0	
Emission factors	A1.1 (1b)	A2.1 (1b)	A3.8	A4.2	A3.3	
Air	1E-03	1E-03	0.0006[4]	0.025 [4]	0.0001	
Waste water	1E-4 [2]	1E-4 [2]	0.0005	0.0005	0.0005	
Surface water	0	0	0	0.0001	0	
Industrial soil	0.0001	0.0001	0.001	0.0001	0.0001	
Fraction of the main source	B1.4	B2.6	B3.7	B4.1	B3.2	
	0.6	0.2	0.05	0.000002 [6]	1	
Emission days	350	300	350	365	350	
Regional release kg/d						
Air	356	759	455	19,000	2.7	7,490
Waste water	35.6	75.9	379	379	13.7	226
Surface water	0	0	0	75.9	0	124
Industrial soil	35.6	75.9	759	75.9	2.7	346
Local emission to air during episode kg/d	223	185	23.7		2	
Local emission to wastewater during episode kg/d	22.3	18.5	19.8		14	
Local indirect emission to air from STP during episode kg/d	13.3	11	11.8		8.5	

1)   Imported volume included
2)   See sections on emission scenarios and local PECs
3)   Use volumes submitted by industry

4)   Specific factor see 3.1.2 subsections.
5)   No release to waste water expected
6)   Fraction of emission per vehicle/engine assuming 0.5 million vehicles in use simultaneously

3.1.2 Environmental fate

3.1.2.1 Degradation in the environment

3.1.2.1.1 Atmospheric degradation

Direct photodegradation

There are spectral data available to assess the absorptivity of sunlight (UV at 190-400 nm) and hence the possible direct photodegradation potential of TAME. According to spectra UV-absorption of TAME is very poor at wavelengths higher than 280 nm (BP 2002). Therefore direct photodegradation of TAME can be regarded as very low or negligible at normal environmental conditions

Indirect photodegradation

The indirect degradation rate constants for TAME, $5.5 \cdot 10^{-12}$ cm^3 molecule/s at 298 K has been measured. The rate constant is not very temperature dependent and the corresponding half-life for a 24-hour average OH radical concentration of $5 \cdot 10^{5}$ molecule/cm^3 is 2.9 days (24-hour days) for TAME (ManTech 1993) (NSTC 1997).

The products of the gas-phase oxidation of TAME reacts to form tertiary-amyl formate, methyl acetate, acetaldehyde, acetone (minor), formaldehyde, and a number of other organics and organic nitrates in low yield (Smith et al. 1995).

Further degradation rates of primary degradation products of TAME for the same OH radical concentration are estimated as follows. The calculated lifetime of tertiary-amyl formate is 4 days. A lifetime or "residence time" 4 days is comparable to half-life 2.77 days (t½ = 0.693 $\cdot$ lifetime) (Lyman et al. 1990). Formaldehyde, acetaldehyde and acetone also undergo photolysis (Atkinson 1987), with photolysis being calculated to dominate over the OH radical reaction for formaldehyde, to be of similar importance as the OH radical reaction for acetone, and to be less important than the OH radical reaction for acetaldehyde. The lifetimes of acetone and acetaldehyde are expected to be approximately 50 days for acetone and 1.4 days for acetaldehyde.

One investigator reports the lifetime of formaldehyde in the sunlight atmosphere due to photolysis and reaction with HO radicals as 4 hours. The measured half-life for direct photolysis for formaldehyde as measured in simulated sunlight is 6.0 hours (HSDB 2000).

The kinetics of the reaction of OH with TAME was examined using a relative rate technique in which photolysis of methyl nitrate or nitrous acid was used as a source of OH. GC/FTIR/MS was used for product identification. The OH rate constant for TAME and two major products, t-amyl formate and methyl acetate, were measured. Rate constants were - $5.48 \cdot 10^{-12}$ cm^3 $molec^{-1}$ s^{-1} (TAME), $1.75 \cdot 10^{-12}$ cm^3 $molec^{-1}$ s^{-1} for t-amyl formate (t½= 4.5 days) and $3.85 \cdot 10^{-13}$ cm^3 $molec^{-1}$ s^{-1} for methyl acetate (t½= 20 days). In the presence of NOx, the yield of primary products was 0.366 t-amyl formate, 0.340 methyl acetate, 0.338 acetone, 0.549 formaldehyde, 0.026 t-amyl alcohol, 0.030 3-methoxy-3-methyl-2-butyl nitrate and 0.004 for 2-methoxy-2-methyl butyl nitrate. For TAME a tropospheric lifetime of 2.1 days was calculated (ManTech 1993).

Absolute rate constants for the reaction of OH radicals with TAME and other oxygenates in a helium atmosphere were determined over the temperature range of 230-372 K, using a pulsed laser photolysis-laser induced fluorescence technique. Based on these results ($k=6.28 \cdot 10^{-12}$ cm^3), a tropospheric lifetime of 32 hours was estimated for TAME (Teton et al. 1996).

The calculated rate for atmospheric oxidation is close to measured ones. A rate constant $5.22 \cdot {}^{-}10^{-12}$ cm^3 molecule/s at 298 K (OH conc.0.5 $\cdot \cdot$ 10^6 cm^{-3}) is the calculated value for TAME using AOPWin v.1.9 program (AOPWin 2000). The calculated rate constant is comparable to a half-life of 3.1 days/24 hour days (assuming OH conc. $0.5 \cdot 10^6$ cm^{-3} to represent a 24-hour average, covering day/night fluctuations).

Photodegradation test results for TAME are summarised in **Table 3.6**.

a) Summary of degradation results for the atmosphere

Table 3.6   Photodegradation test results (Indirect photolysis)

No.	Type of test	Rate const. and Deg	Sentisiser	Method	Test substance	Reference
1	relative rate	$5.48 \cdot 10^{-12}$ cm^3 /molecule-sec	OH	OH source, methyl nitrate and nitrous acid	TAME	(ManTech 1993)
2	absolute rate	$6.28 \cdot 10^{-12}$ cm^3 32 hr lifetime	OH	pulsed laser photolysis-laser induced fluorescence	TAME	(Teton et al. 1996)
3	relative rate	$5.5 \cdot 10^{-12} cm^3$ /molecule-sec	OH		TAME	(Smith et al. 1995)
4	calculated	$5.22 \cdot 10^{-12}$ cm^3/molecule-sec	OH (conc.0.5 $\cdot 10^6$ cm^{-3})	SAR- method developed by Atkinson et al.	TAME (SMILES)	(AOPWin 2000)

b) Discussion of degradation results for the atmosphere

There is a rather good agreement with the tested and calculated rate-constants. Hydroxyl -radical mediated photo-oxidation is the predominant photodegradation process of TAME in the atmosphere. Degradation half-lives are of the order of a few days depending on environmental conditions. Thus primary degradation of TAME is rapid in the atmosphere.

The main measured degradation products are: t-amyl formate, methyl acetate, t-amyl alcohol, acetone, formaldehyde, acetaldehyde and in the presence of nitrate: 3-methoxy-3-methyl-2-butyl nitrate and 2-methoxy-2-methyl butyl nitrate. The main degradation products are further degraded within a few days (form- and acetaldehyde) up to tens of days (acetone). Further degradation data is not available for all known degradation products of TAME.

c) Conclusion

Based on study data available, TAME is indirectly photodegraded in the atmosphere in few days. The estimated degradation half life of 2.9 days, which is based on study results, is used in further assessment.

3.1.2.1.2   Aquatic degradation

Hydrolysis

Based on physical-chemical properties of TAME and the properties of other structurally related aliphatic ethers TAME is not expected to significantly hydrolyze in natural waters under environmentally relevant pH conditions (pH 4-10) (Prager 1992).

Photolysis in water

Data on experimental determination of photolysis in water is not available. However, because of structural reasons, TAME is not expected to photolyze directly, or photooxidize significantly via reactions with photochemically produced hydroxyl radicals in water. In this assessment the calculated (EUSES) half-life value for photolysis in water DT_{50} PhotoWater is $1 \cdot 10^6$ days.

Biodegradation

Aerobic Standard Ready Biodegradation Tests

In a Closed bottle study (OECD 301D) with 1.99 ± 0.03 mg/l of test substance, 4.0% degradation of TAME was observed after 28 days (Huttunen 1996, Huttunen et al. 1997, Bealing 1995). Based on this study it can be concluded that TAME 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

Jensen and Arvin (1990) observed no biodegradation of TAME in 32 days aerobic aquatic screening studies using activated sludge inoculation material. In the same test conditions aromatic petrol components (benzene, toluene, xylenes, ethylbenzene, naphthalene) were well degraded (> 95% in 15 days) indicating that the system applied had high biodegradation potential in general (Jensen and Arvin 1990).

In an aerobic study by Steffan (1997) several propane oxidising bacteria were tested for their ability to degrade TAME. Both a laboratory strain and natural isolates were able to degrade TAME in laboratory conditions after growth on propane. High degradation rates were achieved (42%-100% mineralisation depending on the test organism in 24 hours at 25°C, 8 mgl^{-1} test substance, 70-100 mgl^{-1} inoculum). The initial oxidation of TAME resulted in the production of *tert*-amyl alcohol (TAA). Because propane oxidisers are widespread in nature, the authors suggest that these bacteria may provide a basis for the development and implementation of biologically mediated treatment processes for petrol oxygenates.

A mixed aerobic microbial culture growing on MTBE was tested for its ability to grow on other petrol components like TAME. Results showed that the culture was able to degrade TAME (benzene and toluene as well). Samples were incubated at 21-23°C. Test replicates (2) contained 30 mg/l TAME and 30 mg/l MTBE (tot. 60 mg/l oxygenates each). 100% of TAME was degraded in 7 days. TAME had little or no effect on MTBE degradation (Eweis et al. 1999).

Hernandez-Perez et al. (2001) used strains *Gordonia terrae* IFP 2001 from activated sludge and *G. terrae* IFP 2007 derived from IFP 2001. Ethyl t-butyl ether (ETBE) was use as the growing base and sole carbon and energy source. TAME was not used as carbon and energy source as this strain did not grow on TAME under the study conditions. However, cometabolic degradation of TAME was demonstrated to t-amyl alcohol (TAA) in the presence of a carbon source such as ethanol. A monooxygenase was noticed to be involved in the degradation of ethers. The ratio of alcohol produced (TAA, mol) / ether degraded (TAME, mol) was measured 0.91 ± 0.20 and for specific activity (μmol TAME g^{-1} protein min^{-1}) 45 ± 1.5 using 0.5 g cells l^{-1} and 1-1.2 mmol l^{-1} TAME incubated at 30ºC. About 50% degradation of TAME was noticed after 50 hours. Degradation was very slow until addition of 2 mmoll^{-1} ethanol after 140-hour incubation. After that rapid degradation to TAA occurred within some 30 hours (Hernadez-Perez et al. 2001) (Hernandez-Perez et al. 2001).

TAME was mineralised as a sole source of carbon and energy (at 30ºC) by a specific set of undefined mixed cultures enriched from a petroleum refinery wastewater activated sludge. The initial concentration of 77 mg/l was mineralised in 160 hours. Tert-amyl alcohol (TAA) was formed as an intermediate during biodegradation of TAME but did not accumulate in acclimated batch cultures because it was degraded much faster than it was formed through biodegradation of TAME. TAME degradation in this test system was the slowest of the five different substances tested (TAME, MTBE, ETBE, TBA and TAA). The test conditions were favourable for biodegradation and enriched cultures had a high potential to degrade tertiary ethers due to all the tested compounds were completely mineralised during the tests (Cowan and Park 1996).

Aerobic biodegradation of an oxygenates mixture TAME, ETBE and MTBE was studied in an upflow fixed-bed reactor (Kharoune et al. 2001). The upflow fixed-bed reactor (UFBR) used an external oxygenator and sintered glass rings as biomass carriers and test substances as sole source of carbon for adapted specific microbial population. The highest ETBE, MTBE and TAME removal rates achieved throughout the UFBR runs, with efficiency better than 99%, were 140 ± 5, 132 ± 2 and 135 ± 2 mg/l · day, respectively. No metabolic intermediates including tert-butyl alcohol (TBA), tert-butyl formate (TBF) and tert-amyl alcohol (TAA) were detected in the effluent during all the reactor runs. Furthermore, based on the chemical oxygen demand balance, all the removed oxygenates were completely metabolized. The results of this study suggest that the higher resistance to biodegradation exhibited by the MTBE and the TAME is probably due to the steric hindrance for the attacking enzyme(s); and the major limiting step to the oxygenate degradation maybe the accessibility and the cleavage of the ether bond, but not the assimilation of their major metabolites such as TBA, TBF and TAA. These results were concomitant with the batch tests using the reactor's immobilised biomass as inoculum.

Anaerobic biodegradation

In an anaerobic, static sediment/water microcosm study TAME was not degraded in 180 days (6 months) under all conditions tested; sulfate and/or nitrate reducing conditions and/or methanogenic conditions (Mormile et al. 1994). Sediments were collected from sites chronically contaminated with petroleum hydrocarbons. Inoculum was indigenous sedimentary micro-organisms 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 182 days of incubation TAME did not biodegrade under the test conditions in anaerobic sediment/water test system (Suflita and Mormile, 1993). Samples were collected from sites of contaminated chronically with municipal landfill leachate.

The anaerobic biotransformation of TAME in sediments was evaluated under different anoxic electron-accepting conditions over 3 years by Somsamak et. al. (2001). Enrichments were established with a polluted estuarine sediment inoculum under conditions promoting denitrification, sulfate reduction, Fe(III) reduction, or methanogenesis. Complete primary degradation of TAME was observed under sulfate-reducing conditions, concomitant with the reduction of sulfate. The primary degradation product of TAME was tert-amyl alcohol (TAA) indicating that O-demethylation was the initial step in TAME biodegradation under sulfate-reducing conditions. Further degradation of TAA did not occur. No transformation of TAME was observed under the other electron-accepting conditions over 3 years (Somsmak et al. 2001).

a) Summary of degradation results for the aquatic compartment

Abiotic

Table 3.7 Photodegradation half-life in aquatic environment

No.	t1/2 and Deg.	Method	Reference
1	$1 \cdot 10^6$ days	EUSES	TGD 2003

Biotic

Table 3.8 Summary table of biodegradation results for the aquatic compartment

No.	Type of test	Detection	Degradation	Period	Conc.	Inoculum	Reference
1	Closed bottle OECD 301D	O_2 uptake	4,0% after 28 days	28 days	2 mg/l		Huttunen (1996), Huttunen et al. (1997), Bealing (1995)
2	Non standard aerobic	GC	0% after 32 days	32 days	3 mg/l	Activated sludge non adapted	Jensen and Arvin (1990)
3	Non standard anaerobic, static sediment/water		0%	180 days		Variable, from petroleum contaminated sites	Mormile et al. (1994)
4	Non standard anaerobic, sediment/water		0%	182 days		From sites contaminated chronically with landfill leachate	Suflita and Mormile (1993)
5	Non standard sulfate reducing conds.	GC	100% primary degradation to TAA	1,160 days	1.0 mM	50 ml underwater sediment slurry from contaminated site	Somsamak et al. 2001

Table 3.8 continued overleaf

Table 3.8 continued Summary table of biodegradation results for the aquatic compartment

No.	Type of test	Detection	Degradation	Period	Conc.	Inoculum	Reference
6	Non standard aerobic		50% 100% primary degr. to t-amyl alcohol (TAA)	50 hours 80 hours	1 – 1.2 mM	0.5 g/l *Gordonia terrae* IFP 2001 from activated sludge and *G. terrae* IFP 2007 derived from IFP 2001. Ethyl t-butyl ether (ETBE) was use as the growing base and sole carbon and energy source.	Hernandez-Perez et al. (2001)
7	Non standard aerobic	GC	42-100%	24 hours	8-200 mg/l	Special propane oxidising bacteria (25 $^{\circ}$C)	Steffan et al. (1997)
8	Non standard aerobic		100%	7 days	30 mg/l	Special bacteria growing on MTBE (21-23 $^{\circ}$C)	Eweis et al. (1999)
9	Non standard aerobic	O$_2$ uptake + GC	> 99%	160 hours	77 mg/l	Undefined mixed cultures enriched from a petroleum refinery wastewater activated sludge	Cowan and Park (1996)
10	Non standard aerobic	GC	> 99%	continuous reactor	130-140 mg/l	Adapted, specific microbial population	Kharoune et al. (2001)

GC   Substance specific Gas Chromatographic analysis

b) Discussion of degradation results for the aquatic compartment

Biodegradation in aquatic compartment:

TAME 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 and conclusions are made according to the non-standard tests. Degradation has been observed in non standard aerobic tests using special types of inoculum, pure cultures and mixed cultures. Anaerobically, primary degradation (transformation) to t-amyl alcohol has been demonstrated as well in specific sulphate reducing conditions. These studies show that at least some microbial species are capable to degrade TAME and to use it even as their sole carbon source. Thus, it can be concluded that TAME is biodegradable under certain conditions in aquatic aerobic environment. However, these natural potential microbial TAME degraders in the aquatic environment are extremely rare.

c) Conclusion

The characterisation of biodegradability of TAME in aquatic environment and STPs are "not biodegradable" which is used in the EUSES model calculations.

For those STPs having continuous TAME exposure, adapted microbial population capable to degrade TAME may exist. Existing monitoring data from production sites seems to confirm this. However, adaptation is not regarded here as a default condition for all STPs and scenarios and therefore a more conservative approach regarding the biodegradability classification in STPs has been chosen.

3.1.2.1.3   Degradation in soil

The susceptibility of TAME to anaerobic (sulphate and/or nitrate reducing conditions and/or methanogenic conditions) biodegradation has been evaluated. No degradation was observed in 180 days when the microcosms were incubated with various inocula, regardless of the electron acceptor status (Mormile et al. 1994). Sediments, soil and groundwater used in the test system were from sites chronically contaminated with petroleum hydrocarbons.

TAME (3 mg/L) was not degraded in 60 days when incubated with aquifer material, soil, or activated sludge (Moller and Arvin 1990).

Soil with previous exposure to MTBE was tested in laboratory microcosms to measure its capacity to biodegrade TAME. Microcosms were constructed using contaminated soil, sterile groundwater and were incubated at ambient groundwater temperature (16°C) under aerobic conditions.

Zenker et al. observed no biodegradation of TAME after one year (neither MTBE, ETBE or DIPE). In the same test conditions tert-butyl alcohol (TBA) was completely biodegraded after approximately 200 days (Zenker et al. 1999).

a) Summary of degradation results for the terrestrial compartment

The stability in soil test results for TAME are summarised in **Table 3.9**.

Table 3.9   Stability in soil test results

No.	Type of test	Dissipation	Method	Reference
1	anaerobic	no biodegradation after 180 days	sediment/water microcosm from contaminated sites	Mormile et al.1994
2	aerobic	no biodegradation after 60 days	soil (+ sludge and aquifer material)	Moller and Arvin 1990
3	aerobic	no biodegradation after 1 year	soil/groundwater microcosm. from contaminated area	Zenker et al. 1999

b) Discussion of degradation results for the terrestrial compartment

Based on the few studies available it may be concluded that rapid and reliable biodegradation of TAME in soil can not be assumed in any normal environmental conditions indicating very slow degradation in soil. The biodegradability of TAME in soil in aerobic and anaerobic conditions seem to be very slow and favourable conditions for degradation are difficult to attain.

c) Conclusion

In the further EUSES model calculations the characterisation of biodegradability in soil is "not biodegradable" (half-life $1 \cdot 10^6$ day).

3.1.2.1.4   Summary of environmental degradation

Table 3.10 summarises the half-life/rate constants which have been used in environmental transformation and distribution assessment for TAME. It should be noticed that a great deal of the

rate constants and half lives in **Table 3.10** are just EUSES default values for non degradable substances, but not actual measured values for TAME.

Table 3.10 Environmental degradation rates used in modelling

Parameter	Value	Description
K_{OH}	$5.5 \cdot 10^{-12}$ cm³/molec s (measured)	Specific degradation rate constant with OH-radicals
K_{DegAir}	0.24 /day (measured)	Rate constant for degradation in air
$DT_{50HydrWater}$	$1 \cdot 10^6$ day	Half-life for hydrolysis in water
$DT_{50PhotoWater}$	$1 \cdot 10^6$ day	Half-life for photolysis in water
$K_{BioWater}$	0 day	Rate constant for biodegradation in surface water
$DT50_{DegWater}$	$5 \cdot 10^5$ day	Total half-life for degradation in bulk surface water
$DT50_{BioSoil}$	$1 \cdot 10^6$ day	Half-life for biodegradation in bulk soil
$K_{DegSoil}$	$2.31 \cdot 10^{-3}$ day	Total rate constant for degradation in bulk soil
$DT_{50BioAerSed}$	$1 \cdot 10^6$ day	Half-life for biodegradation in aerated sediment
$K_{DegSediment}$	$1 \cdot 10^7$ day	Total half-life for degradation in bulk sediment
K_{BioStp}	0 /day	Rate constant for biodegradation in STP
K_{DegStp}	0 /day	Total rate constant for degradation in STP

3.1.2.2   Distribution

The theoretical distribution of TAME between four environmental compartments at equilibrium is calculated at two temperatures using the fugacity model EQC v.1.1 (Mackay level I). The results in **Table 3.11** clearly indicate that volatilisation may be expected from water and soil and adsorption to particulate matter is poor. The change in temperature has clear effect on the distribution between compartments.

Table 3.11 Static equilibrium partitioning

Compartment	Partitioning % at 20ºC	Partitioning % at 12ºC
Air	95.7	90.2
Water	4.264	9.68
Sediment	0.0008	0.0019
Soil	0.038	0.086

At lower temperatures as the water solubility of TAME increases and vapour pressure decreases the equilibrium partitioning is less in the air compartment side and higher proportion of the substance is in the water phase. In EUSES modelling vapour pressure and water solubility values for 20°C are used (water solubility 11 g/l at 20°C, 15 g/l at 12°C and vapour pressure 90 hPa at 20°C, 56 hPa at 12°C).

3.1.2.2.1   Adsorption

The partition coefficients for TAME have been calculated using EUSES (see **Table 3.12**).

Table 3.12 Partition coefficients used in modelling

Parameter	Value	Description
K_{oc}	22.7 l/kg	Partition coefficient organic carbon-water
Kp_{susp}	2.27 l/kg	Partition coefficient solids-water in suspended matter
Kp_{sed}	1.13 l/kg	Partition coefficient solids-water in sediment
Kp_{soil}	0.454 l/kg	Partition coefficient solids-water in soil
$K_{soil-water}$	0.88 m³/m³	Partition coefficient soil-water
$K_{susp-water}$	1.47 m³/m³	Partition coefficient suspended matter-water
$K_{sed-water}$	1.37 m³/m⁻³	Partition coefficient sediment-water
Kp_{rs}	6.81 m³/m³	Partition coefficient solids-water in raw sewage sludge
Kp_{ps}	6.81 m³/m³	Partition coefficient solids-water in settled sewage sludge
Kp_a	8.4 m³/m³	Partition coefficient solids-water in activated sewage sludge
Kp_{sls}	8.4 m³/m³	Partition coefficient solids-water in effluent sewage sludge
$K_{air-water}$	0.016 m³/m³	Partition coefficient air-water

Because of structural reasons (low molecular weight aliphatic ether) it can be concluded that physisorption is the predominant adsorption mechanism of TAME. No chemisorption processes like covalent bond formation or ion exchange is expected. TAME is expected to have moderate to high mobility in soil based on an estimated Koc of 22.7

3.1.2.2.2 Precipitation

There are no measured data available on atmospheric dry or wet precipitation of TAME.

3.1.2.2.3 Distribution in wastewater treatment plants

The fraction of TAME in the STP directed to air, water and sludge is 0.40, 0.60 and $2.5 \cdot 10^{-3}$, respectively (EUSES data). A removal percentage of 40% in STP is used in local PEC calculations.

3.1.2.3 Accumulation and metabolism

a) Summary of results for accumulation and metabolism

There are no bioconcentration test results available for TAME. Neither there exists information on possible metabolic pathways in species in the environment, except what has been observed in mammalian tests and reported in sections dealing with human health.

The measured octanol/water partition coefficient value of TAME is 1.55 (log value) This value gives first estimate of low bioconcentration potential of the substance. Calculated BCF values are summarised in **Table 3.13**.

b) Discussion of accumulation and metabolism

There are no bioconcentration studies available. However, it is unlikely that TAME would bioconcentrate in high extent or would accumulate in biota for long time periods.

c) Conclusion

The following BCFs and BAFs for TAME have been calculated using EUSES.

Table 3.13 Bioconcentration factors used in modelling

Parameter	Value	Description
BCF_{Fish}	4.14 L/KG	Bioconcentration factor for fish
BCF_{Biota}	4.14 l/kg	Bioconcentration factor for aquatic biota
BCF_{Worm}	2.73 kg/kg	Bioconcentration factor for earthworms
BAF_{Meat}	8.91E-07 d/kg	Bioaccumulation factor for meat
BAF_{Milk}	7.94E-06 d/kg	Bioaccumulation factor for milk

Calculated results indicate low bioconcentration potential of TAME from abiotic environmental compartments to biological material and bioconcentration via the food chain is unlikely.

3.1.3 Aquatic compartment (incl. sediment)

3.1.3.1 Calculation of predicted environmental concentrations (PEC_{local})

Local aquatic PECs are derived for the emission sources mentioned below. The surface water assessment is expected to be protective for sediment too.

- production and formulation (site specific and generic)
- industrial use (generic)
- intermittent release from storage tank bottom waters (generic calculation)
- boating

The local PEC calculations and results are presented in the sub-sections of Section 3.1.4.1. In addition, stormwater runoff is a source of TAME to surface water. However, there is not enough monitoring data available to make quantitative PEC calculations for runoff. Known concentrations in runoff are only few micrograms/litre maximum and remain clearly below the current PNEC values, indicating no risk for runoff waters.

3.1.3.1.1 Calculation of PEC_{local} for production

Site specific $PEC_{local(water)}$ from production and formulation sites

All sites known to produce TAME in EU region in February 2002 are listed in alphabetical order in **Table 2.1**. There are 5 production and/or formulation sites and one production/industrial use 2 site in the EU region. If there are not specific information on possible formulation on-site, it is assumed that all TAME is formulated on site. When actual emission or concentration data is

available it is assumed that emissions from formulation are included in the site specific emission data submitted by the producer.

There are emission data or measured concentrations reported from all production and/or formulation sites.

Table 3.14 Site specific local aquatic concentrations from production and production/formulation sites (values received from industry in bold)

Company-site specific data	Site 1	Site 2	Site 3	Site 4	Site 5
Release waste water (kg/d)	58	4.6 (280μg /l)	6.6	12 (C)	0.8 (ind)
Removal rate in WWTP (%)	40	40	40	40	40
WWTP effluent flow (m³/day)	$7.8 \cdot 10^3$	$1.6 \cdot 10^4$	$6.2 \cdot 10^4$	$1.2 \cdot 10^4$	$7 \cdot 10^3$
Flow receiving water (m³ /day)		sea		sea	sea
Dilution	10 D	100 (D) D	1000 (D) 3600 (M)	70 (M)	100 (D)
Conc. in effluent (mg/l)	0.00026 (M)	0.185 (C) < det. level	0.11 (C) Not detectable (not given)	0.1 (M) [1] < det. Level (0.1 mg/l)	0.0001 < det. level (0.5 μg/l)
PEC surface water (mg/l) (PECregional = 0.0005)	0.0005	0.0015	0.0001	0.0015	0.0005

1) 　 Known to be based on various measurements
D) 　 Default;
IND) 　 Industry;
C) 　 Calculated by rapporteur
M) 　 Measured

Site 1

Continuous process. Water: Concentrations in influent and effluent of WWTP [mg/l] Inlet ex Dissolved Air Flotation (DAF) units =7.7mg/l Ex Biological WWTP Plant = <1mg/l, :HC effluents: Outlet: 3,595 (kg/year) WWTP effluent flow [m³/s] 0.091m³/s. Emission rate to waste water kg/day Ex DAF units 58kg/day Emission to surface water with WWTP effluent < 5kg/year TAME. There is also a limited set of TAME measurements, showing at the time of measurements a maximal WWTP inlet concentration 6,614 μg/m³ and outlet concentration of 263 μg/m³. With an annual WWTP flow of 2,8 $\cdot$ 10⁶ m³ (=0.091 m³/sec), this corresponds to around 0.75 kg TAME/year.

Site 2

Continuous process. All waste waters are treated in WWTP. Emission rate to waste water (inlet WWTP) 4.6 kg/day WWTP effluent continuous flow 0.19 m³/s Concentrations in influent of WWTP 280 μg/l Concentrations in effluent of WWTP < 200 μg/l (analytical LOD) Emission to surface water as WWTP effluent < 1,200 kg/year (worst possible case: upper limit corresponding to continuous effluent flow at a concentration equal to the analytical detection limit) Sampling protocols not given. Analysis protocols GC/MS. Emission to surface water: Sea – estimated concentration < 1 μg/L (derived from the dilution factor) Dilution factor in receiving water > 1,000,000

Site 3

Continuous process. All waste water and storm waters are routed via phase separator to the biological WWTP. Concentrations in influent and effluent of WWTP [mg/l]

During the period January 1999 to August 2000, 3 samples per day (each representing an 8-hour average) were taken at the inlet and outlet of the WWTP. Influent 0.275 kg/hour (minimum 0.143, maximum 5.923, SD 0.178) (1,667 values available, of which 1,606 were below a 100 μg/l limit of detection). Note that a value of 100 μg/l has been used in calculating the mean when no TAME could be measured, leading to an overestimate of concentration in influent).

Effluent 0.048 kg/hr (minimum 0.003, maximum 1.441, SD 0.093, 95% of all values below 0.223 kg/hour) (1,570 values available, of which 396 were below a 2 μg/l limit of detection. Note that a value of 2 μg/l has been used in calculating the mean when no TAME could be measured, leading to an overestimate of concentration in effluent.)

Average throughput of WWTP: 2,584 m^3/hour (minimum 1,429, maximum 3,615, SD 264, accuracy of flow meter +/- 3%) Receiving water = river, flow rate 2,500 m^3/s at point of discharge.

Site 4

Continuous process All waste waters treated in biological WWTP. Frequent monitoring of TAME in waste water. Sampling and analysis protocol is well described. Concentrations in influent 0.1-2.3 mg/l (N= >13,000) and effluent 0,1 mg/l results 98, 5% (N=390) of WWTP

Note: the mean influent concentration overestimates the amount of TAME entering the WWTP. This is because of the number of results < 0.1 mg/l which have been entered as 0.1 mg/l when calculating the average. WWTP effluent flow 12,000 m^3/day Dilution factor in receiving sea water; 70 – 100.

Site 5

Continuous process. 0.8 kg TAME is released daily to waste water. No frequent analytical monitoring. According to site specific data 1.5 kg/year is released via WWTP effluent (0.09 m^3/s flow) to sea water. TAME is not detectable in effluent. Analytical GS/MS detection limit is 0.5 μg of TAME/ l.

3.1.3.1.2 Calculation of PEC$_{local}$ for formulation

Formulation takes place in refineries. Site specific data is available and release from formulation stage of TAME life stage is included. See previous section.

3.1.3.1.3 Calculation of PEC$_{local}$ for industrial/professional use

TAME may pose a significant wastewater treatment problem especially at petrol product terminals. Few wastewater characterisation works have been done concerning oxygenates concentration in waste streams. Because of high water solubility of ether oxygenates, petrol tank bottom water may contain these substances at concentrations of several grams per liter (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 TAME tank bottom waters may have high concentration. From time to time tank bottom water is removed and disposed either directly or via STP to surface water causing intermittent releases. The volume and frequency of tank bottom water releases are highly site specific. Bottom water problems are difficult in cavern storage since these caverns always have an oil-water interface, through which oxygenate migration occur (Dewitt and Company Inc. 1998). Tanks having floating roofs without weather roofs have bottom water problems as well (frequent need for watering).

<u>Aquatic PEC local, intermittent release from tank bottom waters</u>

Because there is a large number of terminal sites in the EU storing and handling petrol a generic emission estimate is made for tank bottom waters. Some of the sites do not have actual waste water treatment systems for tank waters (except water/oil separators and API pools).

In a simplified realistic worst case emission scenario a rather high concentration of TAME in storage tank bottom water is drained directly (via water/oil separator) to surface water in a short period of time. If this happens just a few times a year, releases can be regarded as intermittent. Intermittent release is defined in the TGD as "intermittent but only recurring infrequently i.e. less than once per month and for no more than 24 hours" and PEClocal is calculated on the basis of a daily release rate. For intermittent releases to the aquatic compartment a dedicated PNEC, derived from acute ecotoxicity test data is used in risk characterisation.

Here, a intermittent PEClocal 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. The 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.

In oil and fuels industry TAME is not purified but always handled as a component in mixture of petrol hydrocarbons. The solubility of TAME into water from petrol is approximately 2,400 mg/l (US EPA 1999).

If released directly to surface water (or via a water/oil separator like API pool) as a realistic worst case situation 300 m^3 water and 720 kg TAME in it is released in a short period of time. If released during 24 hours the flow rate is 0.0035 m^3/s.

SAMS, screening assessment model system (OECD 1992), can be used for a crude estimation of PEC$_{local}$ at the recipient (TGD 2.3.8.3). SAMS – river is a 50 box steady state model for chemical transport in rivers. A flow rate, of 20,000 m^3/day (0.232 m^3/s), was selected for the river, which is 10 times the 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 (300 m^3) was released to the river in constant 0.0035 m^3/s flow (24 hours) and initial TAME concentration was 2,400 mg/l. As a result of SAMS calculation, concentration PEClocal was 35 mg/l at 400 m from the release point, which is regarded as a reference point here. (In comparison the estimated concentration was 18 mg/l at 5 km from the release point). Hence, calculated PEC local for surface water from depot tank bottom water is 35 mg/l (PECregional$_{surfacewater}$ 0.0005 added).

$$PEC_{local\_intermittent} = 35 \text{ mg/l (dissolved)}$$

In large depot areas releases may happen 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 generic PNEC for surface water has to be used in deriving the PEC/PNEC ratios.

3.1.3.1.4 Calculation of PEC$_{local}$ for private use

PEC$_{local\_boating}$

TAME is released directly to surface water as an unburnt petrol component from most petrol fuelled water crafts (boats, water-jets etc.). Especially older two stroke engines, common as outboard motors, are inefficient in fuel combustion. Even > 25% of petrol hydrocarbons can be released unburnt into the water.

A minor part of the substances in engine exhaust gas 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 are released to atmosphere as the exhaust bubbles enter the water/air interface. Test results not for TAME but 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).

Assuming a petrol consumption of 0.5 l/km (approximately 375 g/km) of a boat and a TAME concentration 10 wt-% in petrol and 25% emission leads to 375 g/km · 0.40 (EFpartitioning) · 0.25 (EF$_{engine}$) · 0.10 (TAME wt% in petrol) = 3.8 g/km TAME emission. Assuming continuous heavy boat traffic, 100 boats per hour passing the detection point on a 10 m wide boat lane (depth 1 m, length 1 km)) would lead to continuous 38 mg/m^3/hour TAME emission to surface water.

Non-equilibrium, steady state model simulation (EQC v1.0 level III) can be used to estimate steady state PEC in the water course after continuous constant emission. Simulation takes into account primary loss mechanisms, volatilisation, advection, adsorption and degradation. Using a constant emission rate of 38 mg/m^3/h for TAME directed to surface water, a steady state concentration of 13 µg/l in surface water is achieved.

Table 3.15 EQC v.1 Level III Phase volumes, rates and steady state concentrations for TAME

Phase	Air	Water	Soil	Sediment
Bulk vol m^3	$1 \cdot 10^{14}$	$2 \cdot 10^{11}$	$1.8 \cdot 10^{10}$	$5 \cdot 10^8$
Emission mg/m^3/h	0	38 mg/m^3/h	0	0
Degradation t½ h	96	no degr.	no degr.	no degr.
Concentration g/m^3	$2.9 \cdot 10^{-6}$	0.013	$3.7 \cdot 10^{-5}$	0.011

This EQC calculation contains high emission rate assumptions and it therefore obviously gives a worst case concentration of 13 µg/l estimation for TAME in surface water for boating. Adding the calculated PECregional$_{surfacewater}$ (0.5) gives a PEClocal$_{boating}$ (dissolved) =

$$PEC_{local\ boating} = 13.5\ µg/l$$

Existing monitoring data (see Section 3.1.3.2) shows that concentrations normally are far below of (< 20 times) the calculated worst case concentration. Normally dilution factors are higher and traffic intensity lower. The calculated value should be regarded as a worst case scenario which is not realistic for open waters, but might be realistic only in marinas and very narrow and shallow heavy traffic boat lanes having very poor dilution conditions. For more open waters, application of an additional dilution factor, at least 10, is justified.

3.1.3.2   Aquatic monitoring data

Even if TAME is a high volume chemical and has "open" use as a petrol component, there seems to be a rather limited set of environmental monitoring data available. The extent of monitoring data available are not capable to describe well the actual exposure situation.

A total of 249 stormwater samples were collected from 46 different sampling locations in North Carolina over an approximate 1-year period and analyzed to identify land use types where fuel oxygenates and aromatic hydrocarbons may be present in higher concentrations and at greater frequency. TAME was detected in < 10% of samples, typically < 1 µg/l. All of the locations with significantly higher contaminant concentrations were associated with direct runoff from a gas station or discharge of contaminated groundwater from a former leaking underground storage tank (Borden et al. 2002).

<u>Lakes and streams</u>

US Geological Survey detected Volatile organic compounds in 42 surface-water samples collected from streams on Long Island, New York, and in New Jersey, January 27-30, 1997. TAME was detected in 11 samples (26%). The median concentration in all detections was 0.02 µg/l and the maximum concentration in all detections was 0.08 µg/l (USGS 1997).

In Lake Tahoe (USA) TAME was measurable in three samples from the nearshore, boat-trafficked area (0.20, 0.14 and 0.14 µg/L relative to the 0.11 µg/L LOD) (Reuter et al. 1998).

In four lakes in Byram Township, Sussex County, NJ, in the summer of 1998, concentrations of TAME in water samples ranged from 0.07 to 0.43 µg/l on June 24 and from 0.2 to 0.69 µg/l on September 8. Lakes are surrounded by densely populated communities where the use of gasoline-powered watercraft is prevalent (Baehr and Zapecza 1998).

3.1.3.3   Comparison between predicted and measured levels

In general, comparison between measured and calculated values is difficult. Concentration of TAME in petrol and used total volumes in the region were needed if full comparison were possible. However, measured levels are rather low and generally at the same order of magnitude as calculated ones. An exception is the boating scenario, which is known to be a realistic worst case scenario. Actual measured levels from US lakes are approximately 20-200 times lower.

3.1.4   Terrestrial compartment

3.1.4.1   Calculation of PEC$_{local}$

Generic EUSES estimations has been carried out for relevant life-stages of TAME and results are tabled below in the relevant sub-sections.

There are specifically three exposure routes to be considered when estimating PEC$_{local}$ in soil:

- direct (point source) release of TAME during petrol storage and refuelling tanks and vehicles;
- STP sludge field application;

- dry and wet deposition from the atmosphere (infiltration of stormwater runoff and precipitation).

The first issue, soil contamination in petrol stations and storage depots, is difficult to express quantitatively. It is often, but not always a question of accidental spillages, but continuous slight contamination of storage and delivery area soil. However, in the long term, accidental spillages, like leaking under ground storage tanks (USTs), may have a remarkable contribution on contamination of soil. This kind of contamination has not directly been taken into account in local PEC calculations. PEC_{local} soil for petrol stations has not been calculated for normal refuelling leaks. No probabilistic approach for the number of leaking UST or accidents has been carried out. Instead, a set of monitoring data from contaminated sites is presented in Section 3.1.4.2 Measured levels in soil and ground-water.

Two latter issues are taken into account as modelling output. The EUSES model takes into account both the application of STP sludge on agricultural soil and the deposition from air for the calculation of TAME concentrations in the terrestrial compartment. **Table 3.16** gives the terrestrial PECs at a local scale (i.e. the concentration measured 30 days after sludge application).

3.1.4.1.1 Calculation of PEC_{local} for production, formulation and industrial use

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

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 PEC $regional_{natural\ soil}$ which is $5.3 \cdot 10^{-6}$ mg/kg wet weight.

Table 3.16 Local PECs in soil, concentrations of TAME in agricultural soil and grassland EUSES calculations

	Life cycle step	PEC_{local} terrestrial Concentration in grassland > 180 days (mg/kgwwt)	PEC_{local} terrestrial Concentration in agricultural soil > 30 days (mg/kgwwt)
A1	Production 1	0.0038	0.034
C1	Industrial use 1	0.0014	0.028
C2	Industrial use 2	0.0008	0.021

3.1.4.1.2 PEC_{soil} for petrol stations

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

During the refuelling of motor vehicles at service stations leaking of petrol to the pavement of a pump island is estimated to be 0.14 kg/tonne (CONCAWE 1978). In the past at filling stations spilled fuel could penetrate the pump island pavement causing continuous soil contamination. New and sanitised stations get closed pavement with drainage to an oil/water separator and soil contamination caused by normal refuelling operation is prevented.

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 ground water in large areas.

The intrinsic chemical properties and use pattern of TAME are very close or similar to MTBE, known ground water contaminant (properties like chemical structure, water solubility, log Kow, Koc, biodegradability, taste and odour threshold, etc. Reference to sections 1 and 3.1.2 of this report and MTBE risk assessment (European Commission, 2001).

In many of the contaminated petrol station areas in Finland both MTBE and TAME have been detected. Finland is a region where both of these substances have been in use simultaneously for almost ten years. When remediation of the petrol station soil has been carried out in recent years in Finland, both of these substances has often been found in the soil. In the case that the groundwater has been polluted by petrol oxygenates in larger areas (outside the station area) both of the substances TAME and MTBE have been often measured indicating similar mobility and persistency in soil.

Consumption volume of TAME is expected to increase continuously in coming years adding a risk to general ground water quality. In that respect, some regions in the EU are more vulnerable areas than others because of their geomorphology.

A small set of data dealing with TAME occurrence in soil and groundwater is presented in the next section.

3.1.4.2   Measured levels in soil and ground-water

Terrestrial monitoring data

All data comes from Finland and has been compiled from various sources. The data set presented here is not representative even for Finland, but rather indicative of concentrations found in some contamination/remediation cases, few years back.

Majority of the data are monitoring data from contaminated sites, mainly petrol stations. These often high concentrations are mostly caused by leaking joints in underground tank pipings. In some cases these levels are caused by accidental larger or more frequent (slight) overfilling of underground storage tanks in connection to insufficient pavement isolations at underground storage tank refilling points at the petrol stations.

Due to lack of routine monitoring programs of TAME in Finland or any other EU country, there are no known background detection or concentration trends in time. A pilot program for regular monitoring of background concentration of TAME in groundwater in Finland is under way, and the first results are available. The pilot survey covers 9 groundwater areas.

Monitoring Data - Background concentrations in groundwater

In a pilot monitoring study in Finland, background concentrations of TAME and MTBE in groundwater were investigated in November 2003. The intention was to clarify the influence of road traffic TAME/MTBE emissions in precipitation to the general groundwater quality. Nine sites for groundwater well sampling were selected in the vicinity of roads and remote areas. All

of the sampling sites were far from refueling stations to avoid direct influence of such point sources.

Most samples were taken from public water supply groundwater wells/boreholes in service or in reserve. Determination limits were 0.08 μg/l for TAME and 0.1 μg/l for MTBE.

Nine samples were taken on 25-28/Nov/2003. The concentration of TAME was below the determination limit in all of the samples. In two samples, MTBE was detected at 0.48 μg/l and 0.20 μg/l concentrations. These values are well below the odor and taste threshold).

The data set available at the moment is so limited, that any firm conclusions can not be drawn. However, it seems that TAME in precipitation may not have much influence in general on groundwater quality.

(Additional information: Site parameters for 0.48 μg/l concentration sampling site: Community groundwater well 200 m from the road having traffic intensity 12,000 vehicles per day. Groundwater level at 10 m in sandy soil. The surface area of the groundwater area is 6.3 km^2

Site parameters for 0.20 μg/l concentration sampling site: Community groundwater well 1,000 m from the road having traffic intensity 10,000 vehicles per day. Groundwater level at 5.4 m in sandy soil. The surface area of the groundwater area is 10.9 km^2).

Monitoring Data - Concentrations affected by point sources

Table 3.17 shows a set of data concerning TAME concentrations in soil and groundwater. Since this is risk assessment for TAME, only the measured concentrations of TAME are reported here. Even if not reported, the other petrol components, like aliphatic- and BTEX-hydrocarbons are often, and MTBE almost frequently, present and measured together with TAME in the water samples. Since the oxygenates are exceptionally mobile and poorly biodegradable, they are detected more frequently far from known point sources compared to sole hydrocarbons.

In a number of cases, the first sign of an under ground accidental spillage, has been sense perception of tertiary ether oxygenates in drinking water of private wells.

Removal rate of TAME in groundwater is mainly dependent on dilution properties of the aquifer. As can be seen from the monitoring data, it may take several years until the aquifer can be regarded practically taken clean after a severe contamination has taken place.

Table 3.17 Monitoring data in soil and groundwater

Location	Site type	Conc μg/l	Year
Ilomantsi. Finland	Petrol station soil	1,100	1997
	and groundwater close to petrol station	700	
Kuusaa, Finland	Groundwater close to petrol station	5,200	1997
Pyhäselkä, Finland	Groundwater/wells close to petrol station	900-4,000	1998
Kirkkonummi, Finland	Large groundwater area	5-50	1995-2000
Salo, Finland	Petrol station groundwater	100-600	1997
Turku, Finland	Petrol station groundwater	30	1998
Espoo, Finland	Petrol station groundwater, potable well	21,000	2002

Table 3.17 continued overleaf

Table 3.17 continued Monitoring data in soil and groundwater

Location	Site type	Conc µg/l	Year
Karjaa, Finland	Groundwater source: petrol station	20-30	96-98
Tuusula, Finland	Large contaminated area, source petrol station	73,000 – 150,000 potable well 50 – 24,000 groundwater area	1999->
Tampere Finland	Groundwater close to petrol station	20-30	2001
Nastola, Finland	Service station, petrol leak (approximately 1,000 liter in 1995)	max. 14,000 (in groundwater)	1995-2002
Hausjärvi, Finland	In the vicinity of a service station area	max 3,700 in groundwater	2000-2002
Loppi, Finland	Detections in groundwater and community drinking water abstraction well	max 23	1996-2003
Jokioinen, Finland	Contamination of groundwater in the vicinity of petrol station (caused mainly by diffuse emissions)	max 20,000 in groundwater	1997
Hämeenlinna, Finland	Dontamination of groundwater in the vicinity of petrol station (caused mainly by diffuse emissions)	max 3,500	1995-2002
Jyväskylä, Finland	Community drinking water extraction well, pollution source leaking UST, released amount unknown	550 (in 1987 and slowly decreasing until clean in 1995)	1987-1995
Huhdasjärvi, Finland	Private well contamination caused by accidental car petrol tank leak 25 m aside from the well	47	2002
Jaala, Finland	Private drilled well contamination caused by accidental car petrol tank leak 10 m aside from the well	2,400	2001

3.1.4.3   **Comparison between predicted and measured levels**

Since background data from soil or groundwater is not yet available, a comparison between calculated and measured values is not possible.

Measured concentrations from contaminated sites do represent site specific case by case measurements and no modell predictions (PEC calculations) for leaking underground storage tanks or other similar sources has not been carried out here. Anyway, some of the measured levels from groundwater indicate clearly local contamination of groundwater by TAME.

3.1.5   **Atmosphere**

3.1.5.1   **Calculation of PEC$_{local}$**

Local atmospheric PECs are derived for the following emission sources: the generic EUSES calculations and site specific calculations for production, formulation and industrial use 1 and 2. In addition a generic local PEC calculation for petrol station, the concentration 100 m from a point source, has been carried out.

3.1.5.1.1 Calculation of PEClocal for production, formulation and industrial use EUSES calculation

The concentration of the substance in air is estimated according to the TGD at a distance of 100 meters 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.

Table 3.18 EUSES calculations, PECs in air from production, formulation and industrial use

	Local concentration in air during emission episode (mg/m³)	Annual average conc. In air, 100 m from point source (mg/m³)	Annual PEClocal in air (mg/m³) (local + regional)
Production 1	0.062	0.059	0.060
Industrial use 1	0.109	0.105	0.105
Industrial use 2	0.002	0.002	0.003

3.1.5.1.2 Site specific PEC$_{local\_air}$ calculations for production, formulation and industrial use 2

There are site specific data available from five sites. The emission factors for the sites in **Table 3.19** range from 0.0000002 to 0.001. The default value according to the Technical Guidance Document is 0.005. The annual average concentrations in air range from 0.033 to 111 µg/m³ and the annual average predicted environmental concentration in air ranges from 0.777 µg/l to 439 µg/l.

According to the TGD concentration of the substance in air is estimated at a distance of 100 meters from a point source. In the calculation of PEC_{local} for air, both emission 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}.

$$Clocal_{air} = max\ (Elocal_{air}, Estp_{air}) \cdot Cstd_{air}$$

where $Clocal_{air}$ = local concentration in air during emission episode, mg/m³

$Elocal_{air}$ = local direct emission rate to air during episode (kg/day)

$Estp_{air}$ = local indirect emissions to air from STP during episode (kg/day)

$Cstd_{air}$ = concentration in air at source strength of 1 kg/d ($2.78 \cdot 10^{-4}$ mg/m³)

Table 3.19 Site specific local concentrations in air and deposition fluxes from production and production/formulation sites (values received from industry in bold)

	Site 1 Production Formulation	Site 2 Production Formulation	Site 3 Production Industrial use 2	Site 4 Production Formulation	Site 5 Production Formulation
Local direct emission to air Elocalair (kg/day)	**51.6**	**28.7**		**3**	15
Local indirect emission to air from STP Elocalstp (kg/day)		16.9 (from aq. emiss. data)		5.3 (from aq. emiss. data)	n.d.

Table 3.19 continued overleaf

Table 3.19 continued Site specific local concentrations in air and deposition fluxes from production and production/formulation sites (values received from industry in bold)

	Site 1 Production Formulation	Site 2 Production Formulation	Site 3 Production Industrial use 2	Site 4 Production Formulation	Site 5 Production Formulation
Local concentration in air Clocalair (Annual average Temission =350) ($\mu g/m^3$)	16.2 (15.5)	7.9	< 100	1,5	0.3
Annual average predicted environmental concentration in air (regional = 0.34 $\mu g/m^3$) PEClocalair,ann ($\mu g/m^3$)	16.5	8.2	100	1.8	62.6

Site 1

Continuous process. TAME emissions to air calculated from VOC emissions. No TAME monitoring in ambient air.

Site 2

Continuous process. Emission to air from TAME equipment leaks 677 kg/year. Emission to air from TAME storage tanks 85 kg/year. Emission to air: monitoring concentration in ambient air < 400 $\mu g/m^3$ Sampling protocols not given. GC analysis.

Site 3

Continuous process, 24 hours/day, 365 days/year Emission to air not given. Concentration in ambient air sampling indicates concentrations of well below 0.1 mg/m^3. Sampling and analysis protocols not given.

Site 4

Continuous process. Estimated emissions to air 1,1 tonnes of TAME per year (3 kg/day), estimated from total VOC emissions. No TAME monitoring in ambient air.

Site 5

Continuous process, 24 hours/day, 365 days/year. Emissions to air estimated 5,500 kg/year. Concentration in ambient air sampling indicates low concentrations below 1 $\mu g/m^3$.

3.1.5.1.3 Calculation of PEC$_{local}$ for industrial/professional use 1

Car refuelling causes evaporative emissions of TAME. Total evaporative losses of petrol components to air during refilling of cars is on average 0.15-1.5 kg/tonne petrol depending on if a vapour recovery system is used or not (uncontrolled or Stage I and II controls).

TAME concentration at pump island of two service stations during refuelling of vehicles has been measured. The median values) obtained were 1.1- 4.9 mg/m^3. The highest measured value was 29.1 mg/m^3 (Vainiotalo et al. 1999). The content of TAME in petrol handled was about 8.5%.

<u>Estimation of local PEC$_{local\ air}$ according to TGD (100 m from point source):</u>

This estimation is a generic calculation assuming still that TAME is used in high %-proportion in petrol in the region. A large size petrol station delivers annually 10,000 tonnes petrol. Using an emission factor of 1.54 kg/tonne petrol the emission would be 15,400 kg petrol. Reid vapour pressure (RVP) of TAME is approximately 1/5 of the RVP of the whole petrol mixture (on average). The emitted annual amount of TAME in petrol containing on average 10%-wt TAME, would be 15,400 kg/10/5=308 kg.

Clocalairann = max (Elocalair) . Cstdair = 308 kg/365 days . 2.78 . 10-4 mg/m^3 = 0.23 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 $\cdot$ 10^{-4} mg/m^3

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

PEC localair,ann = Clocalairann + PEC regionalair =

0.23 µg/m^3 + 0.34 µg/m^3 = 0.57 µg/m^3

3.1.5.1.4   Calculation of PEC$_{local}$ for private use

Local concentrations due to car exhaust can be estimated with computer models e.g. the CAR-model. This estimation has been done in the Risk Assessment of Existing substances for some substances present in exhaust gases (cyclohexane, pentane). Calculation for TAME has not been carried out.

3.1.5.2   Atmospheric monitoring data

No European studies of TAME peak concentrations in urban air or average background concentrations have been located.

Instead a summary of the New Jersey air quality data for 2000 reports annual maximum TAME concentrations of 0.05 and 0.07 ppb (vol) and annual average 0.01 ppb. (0.21 µg/m^3, 0.30 µg/m^3, 0.04 µg/m^3 correspondingly) (NJ 2002). TAME levels are low compared to concentrations reported for MTBE in the same report (maximum 8.99 ppb and annual average 1.79 ppb).

3.1.5.3   Comparison between predicted and measured levels

Referring to the New Jersey air quality study, information on consumption volumes of TAME at the region is not available. The comparison between calculated background values is therefore difficult to interpret. However, the calculated TAME background concentrations are at the same level as the highest annual values measured in New Jersey. Therefore, most obviously the real regional TAME consumption intensity in New Jersey is lower than the regional consumption intensity of TAME in the current risk assessment's regional EUSES calculation.

3.1.6   Secondary poisoning

Concentrations of TAME in fish and worm (EUSES calculation, local and regional combined) are given in **Table 3.20**.

Table 3.20 PECs in fish and worm

Site	Life cycle step	PEC worm mg/kg	PEC fish mg/kg
A1	Production	0.011	0.88
C1	industrial use 1	0.007	0.78
C2	industrial use 2	0.005	0.57
D1	private use	$2 \cdot 10^{-5}$	0.002

3.1.7   Calculation of regional concentrations PEC$_{regional}$ and PEC$_{continental}$

Table 3.21 shows the calculated regional concentrations PEC$_{regional}$ for air, water and soil. PEC-continental values are not regarded important here, since practically taken almost all of the consumed volume of TAME is consumed regionally. Only some production takes place outside the region.

Table 3.21 Regional PECs in air, water and soil

Compartment	PEC regional
Surface water (total), µg/l	0.52
Surface water (dissolved), µg/l	0.52
Air (total), mg/m³	0.34
Agricultural soil (total), mg/kg (wwt)	$9.3 \cdot 10^{-6}$
Pore water of agricultural soils, mg/l	$1.7 \cdot 10^{-5}$
Natural soil (total), mg/kg (wwt)	$5.3 \cdot 10^{-6}$
Industrial soil (total), mg/kg (wwt)	0.007
Sediment (total), mg/kg (wwt)	0.0005

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

3.2.1 Aquatic compartment (incl. sediment and micro-organisms)

3.2.1.1 Toxicity test results

There is a full base set available on the aquatic toxicity of TAME. There are two valid studies on fish, 3 valid studies on aquatic invertebrates and two valid studies on algae. An acute toxicity test on bacteria is also available. In addition there is a chronic study on Mysid. Only results of the studies that are considered valid are cited in the tables.

A general problem in testing the toxicity of TAME to aquatic organisms is the volatility of the substance. The vapour pressure shows TAME to be highly volatile and according to the Henry's law constant the volatility from water is also very high. Volatilisation has been prevented as much as possible in the test designs and measured concentrations are essential when validating the tests.

3.2.1.1.1 Fish

Acute toxicity

The TAME short-term toxicity studies for fish are summarised in **Table 3.22**.

Table 3.22 Short-term toxicity data for fish

No.	Type of test	Species	LC_{50} * mg/l	Exposure period	Method	Test substance	Reference
1	Flow through	Oncorhynchus mykiss	580 (m)	96 hours	EPA OTS 797.1400	98.8% TAME	American Petroleum Institute (1995c)
2	Semistatic	Oncorhynchus mykiss	>100 (n), (limit test)	96 hours	OECD 203	> 96% TAME	Mattock (1995b)

* Nominal concentrations (n);
Measured concentrations (m)

Test number 2 is a limit test showing that a concentration of > 100 mg/l had no toxic effects on fish during a 96 hour test. The concentration stated is nominal but the measured concentrations seem to be very close to nominal ones in this study (102 – 109 mg/l). Measurements were done for the 0 hour, 24 hour (old), 24 hour (new) and 48 hour (old) test media. The fact, that the test vessels in this semistatic test were fully filled with no headspace and sealed with glass tops, did not seem to have an adverse effect to the standard test conditions monitored during the test.

Test number 1 is a 96-hour flow-through test giving a LC_{50} of 580 mg/l. Test vessels were not covered during the exposure period. Mean measured concentrations averaged 79% of the nominal and coefficients of variation averaged 12% for all mean measured concentrations. The measurements were done at the beginning and at the end of the test and consequently the test is considered valid.

Since there are no chronic fish tests available, the LC_{50} value from this test on *Oncorhynchus mykiss* will be taken into consideration for the derivation of PNEC for the aquatic environment.

3.2.1.1.2   Aquatic invertebrates

Acute toxicity

The TAME short-term toxicity studies for aquatic invertebrates are summarised in **Table 3.23**.

Table 3.23 Short-term toxicity data for aquatic invertebrates

No.	Type of test	Species	EC_{50} * mg/l	Exposure period	Method	Test substance	Reference
1	Static	Daphnia magna	>100 (n) (limit test)	48 hours	OECD 202	>96% TAME	Mattock (1995a)
2	Flow through	Daphnia magna	100 (m)	48 hours	EPA OTS 797.1300	98.7-98.8% TAME	American Petroleum Institute (1995a)
3	Static renewal	Mysidops is bahia	LC_{50}: 14 (m)	96 hours	EPA OTS 797.1930	98.7-98.8% TAME	American Petroleum Institute (1995b)

* Nominal concentrations (n);
  Measured concentrations (m)

Test 1 is a static limit test. The test vessels were completely filled with no headspace and covered with screw tops. The toxicity value is based on the nominal concentration. The mean measured concentration of TAME in the test media containing a nominal concentration of 100 mg/l was 94 mg/l. At the highest concentration tested, 100 mg/l, none of the *Daphnia magna*s were immobilised after 24 and 48 hours exposure.

Test 2 is a flow-through test in which *Daphnia magna*s are exposed to five concentration levels of TAME. Mean measured concentrations averaged 19% (max) from the nominal concentrations. The relatively low recovery obtained for the tested treatment levels is most likely due to the volatility of the substance. The maintenance of the test substance from 0 hours to 48 hours was without one exception within 80%. The concentration measurements were performed at the beginning and at the end of the test. The result of the test is a 48-hour EC_{50} value of 100 mg/l.

The test organism in test 3 is a marine invertebrate *Mysidopsis bahia* (new name *Americamysis bahia*). The test is a static renewal test using seawater diluted with freshwater as test media (salinity 17-23%). The test duration was 96 hours which is the test duration required in the test guideline used (TSCA 797.1930) US EPA guideline 2007.0 Acute Toxicity Test for Mysid, Mysidopsis bahia in Methods for Measuring the Acute Toxicity of Effluents and Receiving Waters to Freshwater and Marine Organisms gives an option to choose the test duration from 24, 48 or 96 hours (US EPA, 2002). The purpose of this method, however, differs from testing of chemicals. Test vessels were completely filled with no headspace and covered with a metal screw-top lid to minimize evaporation and loss of test substance. Still, the concentration of the test substance has not been maintained within 80% (lowest 67%) in all treatment levels. The concentration measurements have been made only at the beginning and at the end of the test. The result of the test was a 96-hour LC_{50} value of 14 mg/l based on measured concentrations.

Result above indicates that TAME might be more toxic to marine invertebrates than to fresh water invertebrates. Consequently, the 96-hour LC_{50} value of 14 mg/l for *Mysidopsis bahia* will be taken into consideration in the derivation of PNEC for the aquatic environment.

It was concluded in a chronic flow-through toxicity test to the Mysid, *Americamysis bahia* that survival at the highest concentration tested, 65.1 mg/l, was greater than 50% and all LC_{50} values are therefore greater than 65.1 mg/l (Fortum 2004). This test result shows a greater LC_{50} value for Americamysis bahia than in the older test described above. Both tests are considered valid.

Chronic toxicity

A chronic flow-through toxicity test was performed on Mysid *Americamysis bahia*, formerly known as *Mysidopsis bahia*. The species appeared to be the most sensitive in acute aquatic tests and was, therefore, chosen for chronic testing. The test was a flow-through chronic toxicity test. The first experiment showed that the mean measured concentrations of the test substance ranged from 54 to 65% of the nominal concentrations despite the renewal of the test solutions 2.3 times per hour. Nominal concentrations were then corrected for the loss of TAME and mean measured concentrations increased from 73 to 88%. Mean control survival at the end of the test was 85% and each control replicate produced offspring. Mean offspring production averaged 12 young per female in the control and 100% of the retained control offspring survived to the end of the test. No sublethal effect were noted in the control during the test. The salinity range was 19 to 20%, the pH ranged from 7.7 to 8.0, the temperature ranged from 23 to 26.8ºC, and the dissolved oxygen concentration was 7.5 to 8.5 mg/l.

Table 3.24 Chronic toxicity data for aquatic invertebrates

No.	Type of test	Species	Results (mg/l)	Exposure period	Method	Test substance	Reference
1	Flow-through	Americamysis bahia	LOEC[1]: 9.14 [2] NOEC[1]: 3.39[2] MATC[1]: 5.57[2]	28 days	OPPTS 850.1350	TAME	Fortum (2004)

1) Based on the number of offspring produced by first generation mysids
2) Based on mean measured concentration of TAME

The results based on the most sensitive parameter, the number of offspring produced by first generation mysids are shown in **Table 3.24**. Other measured biological parameters were the survival of first and second generation mysids, sublethal effects of first and second generation mysids, the length of surviving first and second generation mysids, and the weight of surviving first and second generation mysids. Survival at 65.1 mg/L, the highest tested concentration, was greater than 50%, and all LC_{50} values from this test, including the 28-day LC_{50}, are therefore greater than 65.1 mg/l.

The 28-day NOEC value 3.39 mg/l will be taken into consideration in the derivation of PNEC for the aquatic environment.

3.2.1.1.3 Algae

Acute toxicity

The TAME short-term toxicity studies for algae are presented in **Table 3.25**.

Table 3.25 Short-term toxicity data for algae

No.	Species	E_bC_{50} * E_rC_{50} * mg/l	Exposure period	Method	Test substance	Reference
1	Pseudokirchneriella subcapitata	> 100 (n) (limit test)	72 hours	EC - C.3 + specific test design	TAME	Fortum (2003b)
2	Pseudokirchneriella subcapitata	E_bC_{50}: 280 (n); 230 (m) E_rC_{50}: 870 (n); 780 (m) NOEC: 100 (n); 77 (m)	72 hours	EC – C.3 + specific test design	TAME	Fortum (2003c)

*   Nominal concentrations (n);
     Mean measured concentrations (m)

The volatility of TAME from test media was found to be critical in algae studies. A new test was needed. The new limit test (test 1) was performed according to the European Commission Guideline C.3 with specific arrangements to prevent volatilisation. Advise for the test design was taken from a scientific article handling with the development of a closed test system for volatile chemicals (Mayer et al., 2000). The volatilisation was minimised testing in completely filled flasks without headspace. In order to prevent inhibition of growth due to restriction of gaseous exchange, additional sodium bicarbonate was added to the culture medium to provide a source of carbon dioxide for algal growth. The cell density at initiation of the test was $3 \cdot 10^3$ cells per ml, lower than the standard cell density $1 \cdot 10^4$ cells per ml. An additional control and test material vessel were prepared and incubated alongside the definitive test to provide control from vessels that had not been opened throughout the test period. The pH was determined at the beginning (pH 8.0) and at the end (pH 9.2) of the test.

The concentration and stability of the test material was verified at the beginning and at the end of the test. Measured test concentrations ranged from 85% to 87% of nominal and the results are based on nominal test concentration only. The result of the limit test is that no effect on the growth of algae is observed at the concentration of 100 mg/l.

The dose-response test was performed according to the same guideline with similar modifications. Exposure of *Pseudokirchneriella subcapitata* to TAME gave an 72-hour E_bC_{50} value of 280 mg/l and an E_rC_{50} value of 870 mg/l. The 72-hour NOEC value was 100 mg/l. There was a decline in concentration of TAME in the test vessels. At 0 hours the measured concentration ranged from 83% to 100% of nominal values. After 72 hours the concentrations were 77% to 91% of nominal values. Analysis from samples taken from vessels that had not been opened during the test period gave measured concentrations of 82% to 94% of nominal values. It was therefore considered that the decline in measured test concentrations is the result of losses due volatility. The 72-hour E_bC_{50} based on the geometric mean measured test concentrations was 230 mg/l and the E_rC_{50} was 780 mg/l. The 72-hour NOEC was 77 mg/l.

A 96-hour EC_{50} of 0.11 mg/l for *Selenastrum capricornutum* (now *Pseudokirchneriella subcapitata*) is reported in (American Petroleum Institute, 1995d). Due to the volatility of TAME the exposure conditions were modified e.g. test vessels were completely filled and capped and 500 mg/l sodium bicarbonate was added. The test is, however, considered invalid. The maintenance of the test concentration was, however, unacceptable, only 28% from 0 hours to 96 hours at some concentrations. In addition the cell concentration in the controls in all replicates was smaller after 72 hours than after 48 hours.

Consequently, the 72-hour NOEC of 77 mg/l will be taken into consideration when deriving the PNEC for the aquatic environment. The E_rC_{50} value of 780 mg/l for *Pseudokirchneriella subcapitata* will be taken into consideration in the derivation of intermittent PNEC. E_rC_{50} (estimated from specific growth rate) is preferred to E_bC_{50} (estimated from biomass growth) following the guidance in the Technical Guidance Document. The reason of not using the E_bC_{50} is that direct use of the biomass concentration without logarithmic transformation cannot be applied to an analysis of results from a system in exponential growth.

3.2.1.1.4 Micro-organisms

The test on TAME toxicity to micro-organisms is presented in **Table 3.26**.

Table 3.26 Toxicity data for micro-organisms

No.	Type of test	Species	Endpoint mg/l	Exposure period	Method	Test substance	Reference
1	Cell multiplication inhibition test	Pseudomonas putida	EC_{10}: 29 (n); 25 (m) EC_{50}: 580 (n); 510 (m)	16 hours	ISO 10712	TAME	Fortum (2003a)

*   Nominal concentrations (n);
 mean measured concentrations (m)

The test was performed according to ISO guideline 10712 with some exceptions. Due to the volatility of the test substance the study was conducted using sealed test vessels and chemical analysis of the test preparations were performed at the beginning and at the end of the test. Chemical analysis of the test preparations showed that at all concentrations the measured concentrations were 77% or higher of nominal values throughout the test period. At all concentrations in excess of the statistically determined NOEC the measured concentrations were 80% or higher of nominal values and therefore the results are calculated as nominal concentrations alone. The measured values are calculated in terms of the mean measured test concentrations. The use of completely filled test vessels in order to minimise losses of test material due to volatilisation was investigated, however bacterial growth in completely filled test vessels failed to satisfy the validation criteria for multiplication.

The results of the test are EC_{10} of 29 mg/l and EC_{50} of 580 mg/l as nominal concentrations. The corresponding measured concentrations are EC_{10} of 25 mg/l and EC_{50} of 510 mg/l. The EC_{10} of 25 mg/l is used for PNEC derivation.

3.2.1.1.5 QSAR calculation for aquatic organisms

QSAR calculations in **Tables 3.26**, **3.27** and **3.28** compared with the aquatic test results seem to indicate that TAME acts by a non-specific mode of action. The ECOSAR (EPIWin, 2000) calculation in **Table 3.27** shows more toxic effect to marine organisms, which is seen in the aquatic test results also.

Table 3.27 Aquatic toxicity of TAME calculated with QSARs for non-polar narcosis in TGD[1]

Species	Endpoint	Result in mg/l
Pimephales promelas	96-hour LC_{50}	200
Brachydanio rerio Pimephales promelas	28-32-day NOEC, ELS test	20.6
Daphnia magna	48-hour EC_{50}, immob.	165
Daphnia magna	16-day NOEC, growth, reproduction	34.0
Selenastrum capricornutum	72-96-hour EC_{50}, growth	170

1)   log Kow 1.55, molecular weight 102.18 g/mol

Table 3.28 Aquatic toxicity of TAME calculated with QSARs for polar narcosis in TGD[1]

Species	Endpoint	Result in mg/l
Pimephales promelas	96-hour LC_{50}	58.1
Daphnia magna	48-hour EC_{50}, immob.	22.5

1)   log Kow 1.55, molecular weight 102.18 g/mol

Table 3.29 Aquatic toxicity of TAME calculated with ECOSAR (version 0.99g) [1]

Organism	Duration	Endpoint	Predicted mg/l
Fish, fresh water	96 hours	LC_{50}	200
Fish, fresh water	14 days	LC_{50}	338
Fish, fresh water	30 days	ChV [2]	24.0
Fish, salt water	96 hours	LC_{50}	36.9
Daphnid	48 hours	LC_{50}	208
Daphnid	16 days	EC_{50}	8.77
Green algae	96 hours	EC_{50}	126
Green algae	96 hours	ChV [2]	9.78
Mysid Shrimp	96 hours	LC_{50}	79.7

1)   Chemical class Neutral Organics, measured water solubility 11,000 mg/l,
      molecular weight 102.18 g/mol, melting point –80 deg C, log Kow
      measured 1.55

2)   ChV = chronic value

The Danish EPA QSAR database estimates a 48-hour LC_{50} value of 73 mg/l for Daphnia magna. It gives negative prediction for specific toxicity in the 96-hour LC_{50} model for fish (1,000 mg/l or above) and negative prediction in the algae model (72-hour EC_{50} > 100 mg/l). Estimates of polar/non-polar narcosis LC_{50} for fish based on lethal body burden and Syracuse/Bintein BCF's suggest that the minimum toxicity (LC_{50}) is in the order of 30-140 mg/l.

3.2.1.1.6   Avoidance behaviour

In relation to the risk assessment of MTBE (tert-Butyl methyl ether) a need for better information to adequately characterise the risks to the aquatic ecosystem regarding the emission

of the substance to surface water was identified. Consequently, an avoidance behaviour test with fish was performed.

Because the inherent taste characteristics in water for humans for TAME and MTBE are similar and the measured odour thresholds are slightly different, but at the same order of magnitude, it is seen possible that the same concern for surface water might arise for TAME.

The target of the MTBE test was to investigate if there would be environmental, in this case, avoidance, effects at a concentration of 30 µg/l which was the threshold value for tainting of fish (*Oncorhynchus mykiss*) in a MTBE tainting study (Petersen and Möller 2001). The avoidance test performed with eels (*Anguilla anguilla*) at the actual measured concentration of approximately 16 µg/l showed that the eels did not avoid MTBE although there was a significant difference in the distribution of eels between the control and impact study. In fact, the eels were more present in the MTBE impact zone than in the clean water zone (Petersen, 2003).

The conclusion of the MTBE test was that there would be no additional concern from surface water emissions to avoidance behaviour which would not be covered by the threshold value for tainting.

Consequently, it is not seen necessary to investigate the avoidance behaviour within the risk assessment of TAME.

3.2.2 Calculation of Predicted No Effect Concentration (PNEC)

3.2.2.1 Aquatic compartment (incl. sediment and micro-organisms)

There is a complete base set of acute toxicity data for TAME. The acute toxicity value for fish is a LC_{50} of 580 mg/l. The acute toxicity tests for invertebrates show an EC_{50} of 100 mg/l for Daphnia and a LC_{50} of 14 mg/l for *Mysidopsis bahia* which is a marine invertebrate. The acute E_rC_{50} value for algae is 780 mg/l. The NOEC from this algae test is 77 mg/l. In addition, the chronic test performed on *Americamysis bahia*, formerly known as *Mysidopsis bahia*, gives a 28-day NOEC of 3.39 mg/l.

According to the TGD an assessment factor of 50 applies to the lowest of two NOECs covering two trophic levels when such NOECs have been generated covering that level showing the lowest $L(E)C_{50}$ in the short-term tests. In the case of TAME there is a 72 hour NOEC on algae of 77 mg/l and a NOEC on the invertebrate *Americamysis bahia*, which is the most sensitive species in acute testing. Consequently, an assessment factor of 50 is used for the chronic invertebrate NOEC value of 3.39 mg/l to derive a PNEC for aquatic environment.

$AF_{aquatic}$ = 50

$PNEC_{aquatic}$ = 0.0678 mg/l

There are some arguments for the use of an assessment factor of 10. *Mysidopsis bahia* is the most sensitive species from the base set. In addition there is a long-term NOEC for algae. It would, in some cases, be possible to draw a conclusion from the base set that the long-term fish test result would not be lower than the Mysidopsis NOEC and, therefore, an assessment factor of 10 could be used without having the chronic fish test result. In this particular case the conclusion can, however, not be supported because of the limited dataset.

For intermittent releases an assessment factor of 100 is normally applied to the lowest $L(E)_{50}$ of at least three short-term tests from three trophic levels according to the TGD. In case of TAME the QSAR calculations, however, indicate that there is no specific mode of toxic action in aquatic species. According to the test results the most sensitive group of organisms is invertebrates. Since there is information on the marine invertebrate species which is more sensitive than the fresh water Daphnia, an assessment factor of 10 is seen sufficient to provide adequate protection. The assessment factor of 10 is used for the acute marine invertebrate, *Americamysis bahia*, LC_{50} value of 14 mg/l.

$AF_{aquatic, intermittent}$ $= 10$

$PNEC_{aquatic, intermittent}$ $= 1.4$ mg/l

In the absence of any ecotoxicological data for sediment-dwelling organisms, the $PNEC_{sediment}$ is calculated using the equilibrium partitioning method. EUSES calculation using $PNEC_{aquatic}$ of 0.0678 mg/l gives a $PNEC_{sediment}$ of 0.0713 mg/kgwwt.

However, no data are available on the occurrence of TAME in sediment. According to the physico-chemical properties currently known, there is nothing indicating that TAME accumulates in sediment. Therefore a quantitative risk assessment seems not to be necessary for this compartment.

The value of EC_{10} of 25 mg/l is used to calculate the $PNEC_{micro-organisms}$. According to the TGD an assessment factor 1 is used for an EC_{10} from a growth inhibition test with *Pseudomonas putida* following the ISO 10712 Guideline. Consequently the $PNEC_{micro-organisms}$ is 25 mg/l.

3.2.2.2   Terrestrial compartment

There are no tests on the effects of TAME to terrestrial compartment. In the absence of any ecotoxicological data for terrestrial organisms, the $PNEC_{soil}$ is calculated using the equilibrium partitioning method. EUSES calculation using $PNEC_{aquatic}$ of 0.0678 mg/l gives a $PNEC_{soil}$ of 0.0354 mg/kgwwt.

3.2.2.3   Atmosphere

The is no data available on direct effects of TAME on biota through atmospheric exposure.

In a review off effects of airborne volatile organic compounds on plants (Cape, 2003) only formaldehyde was raised as a potential damaging substance on plants amongst short–chain oxygenated hydrocarbons. For formaldehyde 90 $\mu g/m^3$ is mentioned as a concentration that would be phytotoxic to some species. Measured concentrations, from all exposure scenarios in the TAME environmental risk assessment (local PECs and measured annual averages) are well below this concentration and therefore it is unlikely that TAME would directly cause phytotoxic effects. The current approach in the environmental risk assessments (793/93 EC) has been that there should be strong hints of possible high phytotoxicity before a test can be requested. Known high phytotoxicity from structurally similar substances (e.g. within the group of pthalates) has sometimes been a trigger for further testing requests. A high aquatic toxicity to algae may also give some hints on high phytotoxicity in higher plants. In this view TAME would not have high potential for phytotoxicity.

Indirect effects through tropospheric ozone forming potential and formaldehyde (formaldehyde in exhaust gases) are expected to be the most pronouncing atmospheric effects of TAME.

In general, hydrocarbons and vehicular hydrocarbon emissions are the major contributor to the formation of low level (tropospheric) ozone. As a group, all hydrocarbons (except methane) are considered ozone precursors. Therefore hydrocarbons (HC) from motor vehicles are regulated pollutants in the EU and emissions standards have been addressed to the mass of total hydrocarbons (THC) or non-methane hydrocarbons (NMHC). Using oxygenates in fuel decreases the ozone forming potential of exhaust hydrocarbons in general (lowering HC emissions). However, releases of TAME (unburnt and evaporative) to air are remarkable because of its wide use and high tonnages as a fuel component.

One study examined the contribution of TAME to ozone forming potential in a complex VOC/NOx mixture. The authors concluded that TAME has an incremental reactivity that is higher than that of alkanes and similar to that of lower aromatics (Bowman and Seinfield 1995).

According to Derwent et al. (1998) the photochemical ozone creation potential (POCP) of structurally close substance MTBE is 15.2 relative to ethylene as 100 (compared to ethane at 12.3 which is a negligible contributor to low-level ozone) (Derwent et al., 1998). On this basis MTBE is considered to be a low to negligible contributor and it can be assumed (with restrictions) that this conclusion holds true for TAME as well.

3.2.3 Secondary poisoning

Estimated BCF's calculated by EUSES for fish (4.1) and earthworm (2.7) indicate that secondary poisoning is not likely and it is not required to carry out a risk characterisation for secondary poisoning.

3.2.4 Marine Risk Assessment

TAME is released to marine environment directly from several production sites. In addition TAME is a fuel component that can reach marine surface water during the use of petrol in water craft engines.

The basic principles in marine risk assessment according to the TGD (2003) is the concern that hazardous substances may accumulate in parts of the marine environment and that the effects of such accumulation are unpredictable in the long-term. Even if TAME is persistent, it has low potential to cause secondary poisoning. The bioaccumulation potential of TAME is low as indicated earlier in this risk assessment. TAME is not regarded as a PBT substance. However, TAME needs further consideration regarding marine environment according to the TGD. Because of poor adsorptivity and low bioaccumulation potential, specific assessments for sediment and secondary poisoning are not regarded important for TAME for the marine environment.

3.2.4.1 Partitioning

Environmental partitioning of TAME is not expected to be very different in marine water compared to fresh water. TAME is a non-dissociating substance and there is no change of chemical structure in salt-water or water with alkaline sea-water (pH approximately 8). The

water solubility of TAME is rather high and "salting-out" effect may have only a slight effect on partitioning (no study data available).

Volatilization from water to atmosphere is expected to be the main removal process from marine environment. However, no further modeling work has not been carried out here to determine more precisely environmental distribution of TAME in marine environment.

However, for saline water (physiological saline), a measured dimensionless air/water partition coefficient of 0.084 value at room temperature is available (corresponding to a value of 200 Pa m^3mol^{-1}) (Nihlen et al., 1997). This value gives an indication that TAME is more easily volatilized from saline water to air compared to fresh water (calc. fresh water value 0.035 at 20°C 83.5 Pa m^3mol^{-1}).

3.2.4.2   Degradation

Existing fresh water/sediment biodegradation studies clearly show that TAME is persistent. There is no data available on standard or non-standard degradation test of TAME in marine water or marine sediment. Neither studies have been located describing observations of enhanced biodegradation of TAME in marine water.

Very poor biodegradation of TAME in fresh water most obviously holds true in marine water as well and the degradation rate is obviously still lower compared to fresh water. Only specific microbial strains can degrade TAME and the number of potentially competent degraders in marine water is expected to be extremely low. The adaptation pressure is low in marine water and therefore TAME can be classified as persistent in marine water as well.

3.2.4.3   Exposure assessment for the local marine environment.

Three of five of the TAME production sites distribute their waste waters directly to sea via WWTP. Local PEC calculations are carried out in Section 3.1.3.1.1 and release to sea has been taken into account in local PEC calculations.

A more generic local exposure assessment for certain use patterns is carried out in this section.

Generic local concentration in sea water is determined using the formula (formula no: 83 in TGD 2003):

Clocal seawater   = Clocal eff /(1 + Kp susp [SUSP water · 10^{-6}]) · DILUTION

for TAME it is   => Clocal eff /(1 + 2.27 l/kg · 15 · 10^{-6} kg/l) · 100

Generic local concentration in freshly deposited bulk sea sediment is determined using the formula (formula no: 87 in TGD 2003):

PEClocal sed   = (Kp susp - water / RHO susp) · PEClocalwater · 1,000

= 2.27 l/kg/1.150 · PEClocalwater · 1,000

For secondary poisoning, the concentrations in predators and top predators have been estimated using the following equations (formula no: 92 and 94 in TGD 2003).

$PEC_{oral, predator}$ = 0.5 · ($PEC_{local, seawater, ann}$ + $PEC_{regional, seawater, ann}$) · BCF_{fish} · BMF_1

$$PEC_{oral, top\ predator} = (0.1 \cdot PEC_{local,seawater,\ ann} + 0.9 \cdot PEC_{regional,\ seawater\ ann}) \cdot BCF_{fish} \cdot BMF_1 \cdot BMF_2$$

For TAME BMF1 and BMF2 are set to 1 since low log Kow –value (<< 4.5 the trigger value) and the structure of TAME indicates that biomagnification is unlikely. BCF=4.14. The daily emission is diluted into 200,000 m^3. The regional PECs are set to 0 for technical reasons (calculation method/software was not yet available).

Table 3.30 Local Exposure for the Marine Environment

Emission scenario	Emission FACTOR	Daily emission, kg	Release days/ year	PEC local_sea, (mg/l)	PEC local, seawater, annual (mg/l)	PEClocal, sediment (mg/kgw wt)	PEC oral predator mg/kg fw food	PECoral top-predator mg/kg fw food
Production (default emission factors)	0.003	1,520	350	7.59	7.27	19	0.0151	0.0030
Industrial Use 1, default	0.0005	19.8	350	0.1	0.1	0.25	0.0002	0.00004
Industrial Use 1, intermittent release	saturated solution (2,400 mg/l)	700	1	24	0.07	62	0.0001	0.00003
Industrial Use 2, default	0.0005	14.3	350	0.07	0.07	0.18	0.0001	0.00003

TAME used as a component in petrol is a relevant emission source to marine environment from petrol fueled water crafts. Emission may happen in coastal areas, marinas and in open sea as well. The most pronounced and highest concentration of TAME may be found in marinas and boat lines. Typically petrol fueled water crafts are rather small work or pleasure boats. A worst case PEC of 13.5 µg/l (dissolved) local calculation has been carried out for the fresh water in Section 3.1.3.1.4. Since adsorption of TAME to suspended material is poor, no additional adsorption correction for TAME is regarded necessary. Especially in marine environment, the calculated worst case PEC is an overestimation, since almost minimal dilution was expected. Higher dilution factors are needed if this scenario were carried out further.

3.2.4.4 Effects assessment for the marine environment

Aquatic

The most sensitive species tested in aquatic environment is a marine invertebrate mysid *Americamysis bahia (former name Mysidopsis bahia)*. Other taxa tested, marine and freshwater, seems to be less sensitive. The *Mysidopsis* test is described in detail in Section 3.2.1.1.2. The result of the 96-hour LC$_{50}$ test is 14 mg/l.

The mysids appeared to be the most sensitive in acute aquatic tests and was, therefore, chosen for chronic testing. For the same species *Americamysis bahia*, a chronic 28 day toxicity test has been performed. The salinity range was 19 to 20%, the pH ranged from 7.7 to 8.0. Based on the most sensitive end-point, the number of offspring produced by the first generation mysids, a NOEC of 3.39 mg/l was derived. The test is described in detail in Section 3.2.1.1.2.

At the moment, it is expected that TAME and other small molecule size tertiary ethers have no specific mode of toxic action in aquatic species. QSAR calculations in **Tables 3.27**, **3.28** and **3.29** in comparison with the aquatic test results seem to indicate that TAME acts by a non-specific mode of action. The ECOSAR (EPIWIN 2000) calculation in **Table 3.29** shows more toxic effect to

marine organisms, which is seen in the test results also. All acute test results for fresh water algae and fish species are greater than 100 mg/l.

For the derivation of $PNEC_{marine}$, the lowest chronic aquatic test result is used and assessment factor 500 applied (= 10 fold the fresh water assessment factor).

$$PNEC_{marine} = 3.39 \text{ mg/l}: 500 = 0.0068 \text{ mg/l}$$

In the absence of any ecotoxicological data for sediment-dwelling organisms, the $PNEC_{sediment}$ 0.00713 mg/kgwwt is calculated using the equilibrium partitioning method from the $PNEC_{marine}$.

The PNEC $_{sediment}$ is 0.00713 mg/kg wwt.

For intermittent releases, the PNEC $_{aquatic,\ intermittent}$ is 1.4 mg/l (see Section 3.2.2.1).

$\underline{PNEC_{oral}}$

The PNEC oral is based on the 28 day NOAEL for rats 125 mg/kg. The NOEC is calculated using the conversion factor of 20 according to the formula

$NOEC_{mammal,\ food\_chr} = NOAEL_{mammal,\ oral\_chr} \cdot CONV_{mammal} = 0.000125 \cdot 20 = 0.0025 \text{ kg} \cdot \text{kg}_{food}^{-1}$

where $NOEC_{mammal,\ food\_chr}$ = NOEC for mammals (kg·kg$_{food}^{-1}$)

$NOAEL_{mammal,oral\_chr}$ = NOAEL for mammals (kg·kg bw·d^{-1})

$CONV_{mammal}$ = conversion factor from NOAEL to NOEC (kg bw·d·kg$_{food}^{-1}$) = 20 (rats, > 6 weeks) (Table 22 in TGD)

The PNEC oral is calculated from the $NOEC_{mammal,food\_chr}$ of 0.0025 $\underline{\text{kg·kg}_{food}^{-1}}$ using the following formula and the assessment factor of 300 which is recommended in the TGD for a 28 day $NOEC_{mammal,\ food\_chr}$ (Table 23).

$PNEC_{oral} = NOEC_{mammal,\ food\_chr} : AF_{oral} = 0.0025 \text{ kg} \cdot \text{kg}_{food}^{-1} : 300 = 8.33 \text{ mg} \cdot \text{kg}_{food}^{-1}$

The resulting $PNEC_{oral}$ is 8.33 mg·kg$_{food}^{-1}$.

3.2.5   PBT-assessment

3.2.5.1   Conclusion for the PBT-assessment

According to existing data and assessment of inherent PBT -properties it can be concluded that TAME can not be regarded as a PBT-substance since it does not meet all of the three criteria. This conclusion has been drawn based on the following evaluation:

3.2.5.2   Persistence-criteria

According to existing biodegradation study results ready biodegradation may occur only if special strains of microbes are used and degraders are well adapted. In environmental conditions TAME has high resistance against biodegradation leading to high inherent persistency. In this risk assessment TAME is considered to be not biodegradable. Hence it meets the screening criteria for P and vP.

3.2.5.3 Bioaccumulation-criteria

There are no bioaccumulation study results available for TAME. The measured octanol/water partition coefficient value is 1.55 (log Kow). All predicted BCF values from log Kow are < 10 (see Section 3.1.3.3) and therefore TAME does not meet the B-criteria (> 2000) for bioaccumulation.

3.2.5.4 Toxicity-criteria

The lowest NOEC is 3.39 mg/l. This clearly exceeds the T-criteria of 0.01mg/l. Hence TAME does not meet the T criteria. Neither, based on the human health toxicity data, does TAME not fulfill the T-criterion.

3.3 RISK CHARACTERISATION

3.3.1 Aquatic compartment (incl. sediment)

Table 3.31 summarises the generic PEC/PNEC ratios for the aquatic emission scenarios. There are EUSES calculation results for the sediment as well. No further quantitative risk assessment seems to be necessary for the sediment compartment (poor adsorption to sediment and no effects data to sediment organisms) and the surface water assessment is expected to be protective for sediment also.

The Predicted No Effect Concentration for surface water $PNEC_{aquatic}$ is 67.8 µg/l. The PNEC for aquatic species is derived using assessment factor of 50. The PNEC for sediment is 71.3 µg/kg wwt. For intermittent releases, the PNEC $_{aquatic, intermittent}$ is 1.4 mg/l.

Table 3.31 Local PEC/PNEC Ratios for Surface Water and Sediment

Process/Scenario	PEC/PNEC water	PEC/PNEC sediment	Site code
Production, TGD default assessment	6.58	7.98	Generic, TGD
Industrial use 1. transportation, storage and delivery of petrol	5.83	7.08	Generic, TGD
Industrial use 1. (tank watering at terminal sites, direct discharge)*	25	-	Generic
Boating (exhaust/worst case)	0.19	-	Generic
Industrial use 2. Intermediate in chemicals industry, TGD default assessment (note: measured values in Table 3.32)	4.22	5.12	Generic, TGD
Regional	0.0077	0.0065	

*   Intermittent releases (PNEC = 1.4 mg/l)

The generic assesment for production and industrial use 2 has a PEC/PNEC ratio greater than 1. However, there are site specific data available which overrules the generic calculations (see site specific data in the **Table 3.32**). Due to the presence of the site-specific data the final risk characterisation will not be based on the generic scenario.

Industrial use 1 (processing 1 in EUSES nomenclature) has two calculations for PEC and PNEC derivation. First one is a generic assessment using TGD default emission factors, and the second calculation is for intermittent releases of tank watering at terminal sites. Both of these scenarios have a PEC/PNEC ratio greater than 1. **Conclusion (iii)**. In addition, if intermittent emissions are discharged to sewage system and to biological waste water treatment plant, this may cause problems to microbial populations at the WWTP (if $PNEC_{micro-organisms}$ will be exceeded remarkably).

Table 3.32 Aquatic and WWTP Risk Characterization Ratios for the production sites

	Producer 1	**Producer 2**	**Producer 3**	**Producer 4**	**Producer 5**
Site specific emission data	yes	yes	yes	yes	Yes
Removal rate in WWTP (%)	40	40	40	40	40
WWTP effluent flow	site specific	site specific	site specific	site specific	site specific
Receiving water	river	sea	river	sea	Sea
Dilution	default 10	default 100	default 1,000	site spec. 70	default 100
RCR for WWTP Ceffluent/PNEC micro-organisms	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1
PEC surface water (mg/l)	0.0005	0.0015	0.0001	0.0015	0.0005
RiskCharacterisation Ratio (RCR) for fresh water	< 1	< 1	< 1	< 1	< 1
PEClocal/PNECaquatic	0.007	0.22	0.001	0.22	0.07

Local Site Specific Risk Characterisation

None of the production/formulation sites have a surface water PEC higher than PNEC. **Conclusion (ii)**. Industrial use 2 is taking place in one of the production sites listed in **Table 3.32**. Therefore it can be concluded that **conclusion (ii)** applies to industrial use 2 as well.

The PECwwtp for the production/formulation sites of TAME does not exceed the PNEC for micro-organisms in any cases. **Conclusion (ii)**.

Regional Risk Characterisation

The regional surface water PEC/PNEC ratio is 0.0077. This ratio indicates that there is no risk at regional level in surface water or sediments. **Conclusion (ii)**.

Conclusions to the risk assessment for the aquatic compartment

Conclusion (ii).

Conclusion (ii) applies to following scenarios:

1.   Boating scenario

2.   Production of TAME in existing production sites in EU. On-site/off site formulation.

3.   Industrial use 2. Scenario: use of TAME as a process intermediate in chemicals production. One of the production sites is the industrial use 2 site and no risks were identified (see **Table 3.32**) except using the default emission factors (see **Table 3.31**). Measured values are used for the risk characterisation according to the TGD.

4.   Regional PEC for surface water and sediment

Conclusion (iii).

1.   **Conclusion (iii)** applies to intermittent release scenario for storage tank bottom waters at terminal sites. The currently applied risk reduction measures have proved not to be effective enough to reduce the risk for surface waters to an acceptable level.

2.   **Conclusion (iii)** applies also to generic assessment for industrial use 1, terminal sites, under use of default TGD emission factors. (No representative monitoring data is available from these sites since the number of sites at EU level is very high).

It is believed, that terminal site tank bottom waters may still be one of the most pronounced source of TAME to surface waters from these sites not only as intermittent emission parameter (point 1), but as a more continuous emission source (point 2). In large depot areas with many tanks, bottom water releases may happen monthly 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 (PNEC derived from long term tests have to be used in deriving the PEC/PNEC ratio).

If risk reduction measures are applied for intermittent emissions of tank bottom waters, it is believed, that these actions might remove or decrease the expected, intermittent and continuous emission (industrial use 1) risks in many real sites.

Conclusion (i) is not chosen for these scenarios since further testing leading possibly to the lowering the assessment factor to 10 would not remove the concern.

No account has been taken in this environmental risk assessment as regards the low odour and taste thresholds including the possibilities of behavioural effects of wild life (avoidance or attraction) or for example tainting of fish.

Conclusions to the risk assessment for micro-organisms in waste water treatment plants

The PNEC$_{micro-organisms}$ is 25 mg/l.

Conclusion (ii).

This conclusion applies to all production/formulation and industrial use 1 and 2 sites.

(Note: however, this conclusion may not apply to intermittent releases, if directed to WWTP in high >> PNEC concentrations).

3.3.2   Terrestrial compartment and groundwater

Conclusions to the risk assessment for the terrestrial compartment:

Conclusion (ii).

This conclusion applies to all generic production/formulation and processing sites and use of TAME as an intermediate in chemicals industry. This conclusion applies also to private use of TAME as a component in petrol.

Conclusions to the risk assessment for the groundwater

Conclusion (iii).

Conclusion (iii) applies to overall quality of groundwater. The conclusion is reached because of concern of potability of groundwater in respect to taste and odour as a consequence of exposure rising from leaking underground storage tanks and tank piping, as well as spillage from overfilling the tanks.

Conclusion (iii) is not based on concerns of ecotoxicological endpoints, but more on intrinsic properties of TAME and general groundwater protection. The instrinsic properties of TAME show high persistency in soil and groundwater. TAME is water soluble and has a high mobility in soil and has the tendency to leach to groundwater. TAME is highly odorous and has low taste threshold in water.

The consumption volume of TAME is expected to increase continuously in the coming years adding risk to the general ground water quality. In that respect, some regions in the EU are more vulnerable areas than others because of their geomorphology.

3.3.3   Atmosphere

Conclusion (ii).

Conclusion (ii) applies to direct effects of atmospheric emissions of TAME from all assessed environmental scenarios.

A PNEC has not been calculated for the atmosphere. Therefore direct PEC/PNEC ratio for the environment can not be derived. Specific endpoints like phytotoxicity have not been tested in this risk assessment process.

Any specific problem regarding TAME emissions into the atmosphere has not been identified in this environmental risk assessment. Based on calculated and measured atmospheric concentrations, a direct effect on biota at these concentrations is not expected, even if there is lack of substance specific effects data for terrestrial plants. These expectations are based on general knowledge that these kinds of substances are not expected to have a specific mode of action in plant cells and ambient concentrations would not have a *direct* effect on the vegetation. There may be indirect effects, but this issue must be seen in a more general, larger scope of air quality issues.

Conclusion (ii) in this risk assessment applies to the atmospheric compartment. However, this conclusion does not apply directly to general air quality issues. TAME is an atmospheric pollutant. Emissions of TAME to the atmosphere are high in terms of emitted volumes. More than 7,000 tonnes (approximately 2.5% of total volume) are emitted annually to the atmosphere as evaporative and unburnt exhaust emissions. The reasons for high emissions to the atmosphere are high consumption volume and technical issues related to vehicular emissions in road traffic in general.

TAME emissions are a part of the complex issue of ozone and smog formation and general air quality. TAME itself is not regarded as a chemical of high strength ozone forming potential (POCP). TAME is not expected to contribute to the ozone peak values significantly compared to more reactive compounds in petrol and TAME is added as an oxygenate to reduce the ozone forming potential of petrol.

However, it has been concluded here, that atmospheric TAME emissions should not be handled separately in the ESR (793/93) program, but in the general scope of air quality issues in the EU.

3.3.4   Secondary poisoning

Conclusion (ii).

This conclusion applies to all environmental compartments and assessment endpoints.

3.3.5   Marine environment

The local risk characterisation ratios for sea water, PEClocal/PNECmarinewater, are presented in **Table 3.33**.

Table 3.33 Marine Risk Characterisation Table for the Industrial Emission Scenarios

Emission scenario	PEClocal seawater,mg/l	RCR = PEC/PNEC
Production default	7.59	1,116
Industrial Use 1, default	0.1	14
Industrial Use 1, intermittent release	24 daily	3,530 (daily)
Industrial Use 2, default	0.07	10.3

The risk characterisation ratios (RCR) show local aquatic (and sediment) risk for all of the industrial scenarios, if default emission factors are used. However, this conclusion does not apply to the actual production and industrial use 2 plants, since measured PECs are below the marine PNEC value. **Conclusion (ii)**.

Industrial use 1 and intermittent release scenarios at terminal sites exhibit local risk in marine water and sediments. **Conclusion (iii)**. (This conclusion applies to the fresh water environment as well, see Section 3.3.1).

The PEC/PNEC ratio is 1.9 for the boating scenario in marine environment entirely (since the PNEC marine is 10 times lower than for the fresh water environment). However, it is realised that the boating scenario exhibited clearly some realistic worst case assumptions (exceptional high boat traffic & very poor water course dilution). Even if the conditions described in the boating scenario may sometimes/somewhere in marinas and narrow boat lines hold true, it is however believed, that in average situations concentrations may fall clearly below the calculated PEC value (13 μg/l). For these reasons, **Conclusion (ii)** is regarded the most relevant conclusion for boating scenario in marine environment.

Secondary poisoning via the marine food chain is unlikely. PECoral/PNECoral ratios for predators and top predators are both << 1. **Conclusion (ii)**.

Regional risk characterisation has not been carried out since regional PECs have not been calculated.

Conclusion (ii).

Conclusion (ii) applies to the following scenarios:

1.   Secondary poisoning in marine food chain

2.   Production of TAME in existing production sites in EU.

3.   Industrial use 2. Scenario: use of TAME as a process intermediate in chemicals production.

4.   Boating scenario

Conclusion (iii).

1. **Conclusion (iii)** applies to intermittent release scenario for terminal site storage tank bottom waters.

2. **Conclusion (iii)** applies also to generic assessment for industrial use 1, terminal sites (see risk characterisation for fresh surface water).

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 General discussion

Ether- and alcoholoxygenates are used in gasoline as octane enhancing agents. Ethers are superior to alcohols for gasoline blending; they have good octane numbers, their vapour pressures are considerably lower than those of alcohols and their phase separation properties in the presence of water are better (Kivi et al., 1991). Furthermore, the oxygen containing fuel additives improve the combustion process, resulting in a substantial decrease in hydrocarbon and carbon monoxide emissions.

Currently, MTBE (methyl *tert* butyl ether; CAS 1634-04-4) is the predominant chemical being added to gasoline. Other ether oxygenates used are ETBE (ethyl *tert* butyl ether, CAS 637-92-3) and TAME (*tert* amyl methyl ether). TAME is rarely used as the primary oxygenate; more frequently it is present as a secondary oxygenate along with MTBE in reformulated gasoline (EPA web site 2000). Greater volumes of TAME compared to MTBE are needed to achieve the same level of oxygenate and octane properties (see **Table 4.1**) (Lawrence et al., 1994).

Table 4.1 Typical gasoline-related properties for ethers used in gasoline

Property	MTBE	TAME
Research octane number (RON)	118	112
Motor octane number (MON)	102	99
(RON + MON)/2	110	105.5
Boiling point (°C)	55	86
Reid vapour pressure, kPa	55	22
Oxygen, wt %	18.2	15.7

The Finnish oil and gas company Fortum started a process in 1995, where isoamylenes are reacted with methanol to form TAME (Chang, 1997). The end product NExTAME consists of TAME, as well as other C5–C6-alkylmethylethers mixed with 60% fuel hydrocarbons (Ova-tietotokanta, 1999). This NExTAME mixture is blended into the gasoline at the refinery. TAME is produced by a similar procedure by Agip/Totalfinaelf. Transport and distribution of TAME in both cases occur only as a gasoline blend.

TAME is also used as an on-site intermediate, when it has to be isolated in neat form by distillation after being produced (industry information).

The future need of TAME on the petrol market will depend on potential legislative developments regarding oxygenate use as well as its price compared to other important alternatives. In USA 1997 the use of TAME and ETBE as a fuel additive amounted to only 6% of the corresponding

MTBE use. The use of TAME is restricted to reformulated gasoline, the share of which represented about one third of all gasoline sold in the United States (EIA, 2000).

Exposure risk from neat TAME is negligible. In production of TAME for use as an on-site intermediate an automated closed system is used. Otherwise, the potential of exposure is comprised of handling TAME containing fuel mixtures, both as an occupational and non-occupational source.

The number of people who are potentially occupationally exposed to gasoline is in Finland nearly 2,500, mostly drivers, production personnel, and tanker crews (Saarinen et al., 1998). In Finland the number of workers employed by service stations has decreased from about 15,000 (1990) to less than 10,000 (2000) due to increased automation. By the end of 2000, there were 1,855 petrol stations in Finland, of which 571 were automated self-service stations (Finnish gas and oil federation, 2000).

Occupational TAME-exposure is due to handling fuel mixtures during manufacturing, transportation, distribution or refuelling. The manufacturing process is an automated closed system, but some exposure may occur at routine operation and maintenance, special risk is involved with spills, leaks and process upsets.

In Finland, transportation to 20 depot terminals is carried out with tank vessels, road tankers or rail tank cars. This work implies besides supervision the loading and unloading operations, specific short-term exposure generating tasks like connecting/disconnecting cargo lines, opening/closing hatches and valves as well as sample taking and their analysis in the laboratory. Rail car loading operation occurs once a week, while coastal depot workers usually with a long work-shift are employed with unloading once or twice a month. Maintenance workers are potentially exposed in connection with tasks, such as cleaning, draining and gas freeing venting.

Distribution involves loading road tankers at the terminal and delivering the cargo at service stations. The loading/unloading lasts on average 30 minutes and typically 2-3 loadings/deliveries are performed per day. Potential for exposure has decreased with time due to different technical developments, such as conversion from top- to bottom-loading, controlled loading rate to avoid splashes and vapour recovery systems on loading facilities. The European Union implemented furthermore in 1994 a directive (94/63/EC) according to which storage installations, loading/unloading equipment at service stations must be designed and operated in accordance with technical provisions to reduce emissions of volatile organic compounds. This vapour recovery system called Stage I will be in use at all service stations in the European Union by the end of the year 2004. Stations with annual throughput over 1,000 m^3 should have already been repaired before the beginning of 1999 (Claydon et al., 2000). At present, one half of the stations are equipped with Stage II recovery systems, which means in practice that all vapour during the unloading at the service station is returned to the tanker for regeneration at the terminal (Hakkola et al., 1998a).

Refuelling of cars lasts on average one minute and is nowadays in Finland performed exclusively on a self-service basis by customers comprising both ordinary consumers and professional drivers. This means that if truck and taxi-drivers, not have vehicles with diesel fuel, they may be exposed to TAME during the self-refuelling. There are yet no EU-directives regarding vapour recovery systems during refuelling automobile tanks (Stage II). Thus, the introduction of Stage II shows large regional variations in Europe. The development depends on the throughput of dispensed gasoline. In Finland, only 5% of the service stations in 1998 were equipped with Stage II recovery systems, but they are currently installed whenever new stations are built or old stations are renewed (Hakkola et al., 1998b) and at present half of the pump pistols are equipped

with vapour recovery systems (industry information). The personnel at service stations have duties other than fuel dispensing, like cashier work, keeping a coffee shop or selling car accessories. Exposure of the employees can anyhow occur to some extent, due to possible exposure from spills and leaks or fugitive emissions from equipment. The mechanics doing automobile repair work at service stations and auto repair shops represent in Finland a workforce of about 8,000. This work is connected with a minor potential for exposure to TAME, because of possible emission of residual gasoline in the fuel tank and work tasks with interventions on components of the fuel supply system.

Forest, agri- and horticultural workers should also be considered, due to their use of gasoline-powered equipment. Potential sources for exposure are filling and routine use of for example chain saws and trimmers. Drivers using motorboats and sleighs equipped with 2-stroke engines are furthermore a specific group of exposure. According to an estimate, the percentage share of fuel used for motor sleighs was 0.8 of the total amount of fuel sold (2000) in Finland (Anon., 2000). The potential to be exposed is greatest in a situation where driving occurs after another sleigh, due to exposure of the exhaust gases coming from the sleigh in front.

Data and its handling

The exposure data collected from the European companies date from 1996 to 2001.

The results were complemented with data from the Finnish database and some research studies, published in peer-reviewed articles. A few data from USA studies performed 1994 by American Petrol Institute (Hinton et al., 1995) were also included.

The personal measurements consist depending on the work task of data measured approximately half an hour or over the whole work-shift. If the duration of the sampling was known, which mostly was the case, the short term-data was time-weighted averaged to 30 minutes (TWA 30 minutes) or to eight hour (TWA 8 hours) depending on type of work. The main part of the loading based samples were lasting about half an hour (range 9-110 minutes) and therefore time-weighted to 30 minutes. TWA 8 hours values are usually based on 6 to 8 hour measurements, with some short (1-2 hours) and long (up to 17 hours) exceptions. The last one mentioned represents unloading at coastal depots with work–shifts lasting an average of 13 hours. No corrections were made for the refuelling data; the sampling times represent the actual duration of the refuelling (23–207 seconds). For the area samples, TWA 8 hours values were calculated. According to the measurement reports usually no personal respiratory protective equipment was used, except sometimes gloves.

The content of TAME in fuel, if not otherwise mentioned, is expressed as volume percentage. The air concentration is expressed as mg/m^3, if given as ppm the conversion was performed by multiplying with a factor 4.24 ($4.24 \cdot ppm = mg/m^3$).

The task-based results are presented in the tables as median, range and maximum measured peaks. Range is expressed as the smallest to the largest measured value, except for data from producer 2, which were reported as the difference of these values. Furthermore, one-sided 90th percentiles of both normal and log normal distribution were calculated to assess the reasonable worst-case (RWC) exposure level for the different work scenarios. Some of the data sets given are below the recommended number of 12 for statistical evaluation, but due to scarcity of the over all data RWC values for some of these are anyhow presented (shaded values). In case of "non-detectable" data, a value half of the detection-limit has been used for the statistical assessments. Due to the skew distribution of the results, the 90th percentile of lognormal

distribution data was used as an estimator for the reasonable worst-case exposure in the summary of exposure estimates of TAME.

Exposure was also evaluated by the use of EASE-modelling (The EASE Model, Estimation and Assessment of Substance Exposure, EASE Windows Version 2.0). In EASE-modelling the use-pattern was closed system and the pattern-of-control full containment for the manufacturing process. For the transport and the distribution work scenarios the modelling parameters were non-dispersive use and the pattern-of-control direct handling with dilution ventilation. As TAME occurs mainly as a mixture, correction for dilution was reduced by the percentage of TAME in the mixture of concern or with the use of an estimated partial vapour pressure. Partial vapour pressure value was calculated in accordance with Raoult´s law, for which the activity coefficient was obtained with the UNIFAC calculator (Choy et al., 1996). For the calculation following model fuel mixture was applied: MTBE 7%, TAME 5%, xylene 35%, butane 7%, hexane 15% and decane 31%.

The dermal exposure was estimated by the use of EASE-modelling. The EASE-parameters used were non-dispersive use with either incidental or intermittent direct handling, except for maintenance, which was handled with wide-dispersive use and intermittent handling. No corrections due to use of PPE were made, although gloves were generally used, because of insufficient knowledge of their protective efficiency.

4.1.1.2   Occupational exposure

Exposure scenarios

The scenarios for industrial and occupational exposures to TAME, presented in **Table 4.2**, were selected on the basis of the data reported by the industry and information found in the literature.

Table 4.2   Occupational exposure scenarios defined for TAME

Scenarios	Industrial category	Use category / source of exposure	Additional information
1. Exposure from production			
1.1. Manufacturing and waste handling	Refinery based process	Fuel oxygenate and octane enhancer/routine operations and maintenance, handling of waste water	TAME is not isolated in neat form. 20-25% TAME is mixed in the hydrocarbon stream for blending into gasoline
1.2. TAME production	Production in closed automated system	Onsite intermediate use/ production plant operations	isolated in neat form for immediate subsequent use
2. Exposure from formulation			
2.1. Transporting operation	Transporting of gasoline from the refinery to the depot-terminals	Loading and unloading rail cars, road tankers and tank vessels	specific exposure generating tasks are connecting or disconnecting cargo lines, sample taking and analysis

Table 4.2 continued overleaf

Table 4.2 continued Occupational exposure scenarios defined for TAME

Scenarios	Industrial category	Use category / source of exposure	Additional information
2.2. Distribution operation	Transporting of gasoline from the depot terminal to service stations	Exposure of road tanker drivers in connection with loading or unloading	Recent technical developments has decreased the exposure potential
3. Exposure from end uses			
3.1. Service station operation	Refuelling cars	Exposure to gasoline emission and exhaust gases	Refuelling only by customers on self- service basis
3.2. Mechanics	Repairing car motors	Exposure to gasoline emission and exhaust gases	Potential of dermal exposure risk
3.3. Mechanics	Repairing fuel pumps	Exposure to gasoline emission	Potential of dermal exposure risk
3.4. Other work-groups (forest, agri- and horticultural work, boat and motor sleigh driving)	Use of gasoline powered vehicles and equipments with 2-stroke engines	Exposure to gasoline emission and exhaust gases	Exposure potential for both work and leisure time

Occupational exposure limits

ACGIH (American Conference of Governmental Industrial Hygienists) has in 2002 adopted a threshold limit value TWA 8 hours 20 ppm (84.8 mg/m^3) for TAME. No limit value is assessed in Europe.

Exposure measurements and determination of airborne concentrations

The main part of the air samples seemed to be collected in connection with specific work tasks and performed as active sampling on activated charcoal or chromosorb with pumps. Passive sampling with diffusive samplers was preferably used for measurements over the whole work-shift (Hakkola et al., 2001), (Saarinen et al., 2002). The road tanker drivers were trained to perform the passive sampling by themselves. In these cases sampling was not only concentrated to the loading and unloading operations, but continued during the driving interval as well. The diffusive samplers used were Perkin-Elmer ATD-400 sampler tube filled with Tenax GR adsorbent.

The passive samplers were thermally desorbed and cold trapped with Chrompack Purge and Trap Injector and analysed by GC/MS (Hakkola et al., 2001), (Saarinen et al., 2002). Activated charcoal tubes were after sampling desorbed in the laboratory either with carbon disulphide (Vainiotalo et al., 1996b) or *N,N*-dimethylformamide (Saarinen et al., 1998), while the chromosorb samples were thermally desorbed and cryofocalized (Producer 2). For the analysis gas chromatographs, usually equipped with flame ionisation detectors were used. Identification of the compounds was validated by dual column/detection systems or by the use of mass spectrometer screening. The carbon tubes used were packed with two subsequent sections, to enable separate analysis for checking possible breakthrough of compounds sampled. The limits of detection for active sampling and liquid desorption varied from 0.1 to 0.42 mg/m^3. With active sampling and thermal desorption the detection limit was as low as 0.0001 mg/m^3.

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4.1.1.2.1 Occupational exposure from production

Ethers, such as MTBE and TAME, are made by a catalytic process from methanol and the corresponding isomeric olefin. TAME is produced with the NExTAME process, which is described as a high conversion technology producing methyl ethers from C5-C7-tertiary olefins, yielding besides TAME tert. hexyl methyl ethers and tert. heptyl methyl ethers. The share of the higher homologues in the end product depends on the composition of the etherified naphtha stream. The process is anyhow regulated so that the content of C6 -homologues does not exceed 10% and C7-homologues 1%, respectively (industry information). Vainiotalo et al., (1999a) has determined the amount of different ethers in the gasoline. The total amount of ethers in the 95 RON brand was 14.5%, TAME being the main component (7.7-9.5%), while the C6-homologues amounted to 3%. Only MTBE (12.2%) was found in the 98/99 RON brand, whereas in another study this brand was reported to contain small amounts (0.2-0.25%) of TAME.

Inhalation exposure for manufacturing and waste handling

Measured data

Measurement data concerning production was provided from four companies producing TAME as a blending component for gasoline. The manufacturing procedure is described as a continuous, automated and closed system, with negligible opportunity for exposure. NExTAME process is utilised, which yields a product, containing 35 to 45% of TAME mixed with unreacted hydrocarbons. Another producer informs that their plant manufactures a TAME-rich naphtha stream with an average content of 13% (w/w) of TAME. These mixtures are directly used in suitable amounts as a component in reformulated gasoline. In the petrol industry TAME does not occur in neat form at all (Neste engineering web site). No exposure to the product is expected under conditions of normal handling and use due to the closed nature of the process. Personal protective equipment is used as needed during product sampling and exposure generating routine maintenance operations. Waste handling exposure levels are measured at the wastewater plant. Accidental leakage to the drainage system may increase the exposure potential for TAME. The median exposure value 0.46 mg/m³ for on-site operation of company 1 representing typical exposure of the NExTAME-process described above is taken forward to risk characterisation. The corresponding calculated 90th percentile value 1.8 mg/m³is chosen to represent the RWC-exposure.

Table 4.3   Production and waste handling; exposure levels are expressed as mg/m³

Data provided by companies									Calculated at 90th percentile		
Sampling		Personal short-term ST (TWA 30 minutes)		Personal long-term TWA 8hours		Area long-term TWA 8 hours		Measured worst exposure		Personal St (TWA 30 minutes) [TWA 8 hours]		Reference
Site, task, year		median	range (n)	median	range (n)	median	range (n)	Peak	Long-term	normal	log-normal	Company
Production												
1997-1998	On-site operation			0.21	< 0.42-2.1 (8)	0.21	< 0.42-16.2 (48)			[1.4]	[1.0]	4
2001	Work on the plant			0.05	< 0.1-0.35 (5)		< 0.1 (60)			[0.38]	[0.42]	3
2001	On-site operation			0.46	< 0.13-1.7 (8)					[1.4]	[1.8]	1
2001	Topping				< 0.0001 (101)		< 0.0001 (163)					2
2001	On-site operation				0.067		0.073					2
2002	0n-site operation			0.005	< 0.005 0.29 (18)						[0.11]*	5
Waste handling												
1996-1997	Waste water handling					0.21	0.05-3.8 (26)					4
2000	Waste water handling					0.028	0.104 (5)					2
2000	Waste water handling		< 0.42 (1)	0.21	< 0.42 (28)	0.21	< 0.42-0.42 (65)					4

 In the case of "non-detectable" data a value half of the detection limit has been used for the statistical assessments

*   95th percentile

Modelled data

The EASE 8 hours estimate for closed process of 40% TAME resulted in 0-0.42 mg/m³, which agree well with the measured values.

Inhalation exposure of TAME production

The manufacturing procedure is described as a continuous, automated and closed system, with negligible opportunity for exposure (producer 3). TAME is isolated by distillation and used immediately further in the process. The measured values from work on the plant are included in **Table 4.3**.

Modelled data

The EASE 8 hours estimate for closed process of 40% TAME resulted in 0-0.42 mg/m^3, which agree well with the measured values.

Summary/statement of the exposure level

The main part of the data consisted of area samples, which mostly were below detection limit. This was the case too with the personal exposure levels measured in connection with routine maintenance. The personal TWA 8 hours maximum value of 2.1 mg/m^3 was measured during a shutdown period, when the operator was occupied with draining and vaporising the system. During the work respiratory protective equipment was used. Personal and area measurement data has also been reported from wastewater treatment. The RWC of 1.8 mg /m^3, based on the highest calculated 90th percentile of available data, is taken forward to risk characterisation. As the process is closed and remotely controlled, no skin contact in liquid form can be expected to occur in the production scenario (industry information). The personal measurements concerning this work scenario were all below detection limit. The highest area TAME level, 3.8 mg/m^3, was measured beside the aeration basin.

4.1.1.2.2 Occupational exposure from formulation

Occupational exposure to the formulation occurs in connection with transporting of gasoline from the refinery to the depot terminals and the further distribution from terminals to service stations.

Inhalation exposure from transporting operations

Measured data

Exposure levels of concerned transportation processes were provided from two companies, from the literature and from the Finnish database. Because Finland until now has been the only European country in large scale using TAME as a fuel-blend component, most data available originates from measurements performed in Finnish environmental conditions. In Finland, transportation of fuel to depot terminals occurs either by ship, railway or road tankers. The company-provided data concern area measurements during loading procedures, while personal unloading values are derived only from literature data. The few personal exposure levels measured during rail car loading with vapour recovery system were below the detection limit. The main part of the TWA 8 hours samples from the breathing zone of the pier and ship operators did not have measurable amounts of TAME. Some short-term (ST) exposure peaks, up to 2.5 mg/m^3, were noticed for ship operators in connection with tasks like draining and connecting/ disconnecting pipes. A one-hour work task comprising assembly of a pipeline with blind flange resulted in such a high peak exposure that the over all measured TWA 8 hours level was 1.1 mg/m^3.

Table 4.4 Transporting operations; exposure levels are expressed as mg/m³

Data provided by companies										Calculated at 90th percentile		
Sampling		Personal short-term ST (TWA 30 minutes)		Personal long-term TWA 8 hours		Area long -term TWA 8 hours		Measured worst exposure		Personal ST (TWA 30 minutes) [TWA 8 hours]		Reference
Site, task, year		median	range (n)	median	range (n)	median	range (n)	Peak	Long-term	normal	log-normal	Company
1996	Rail car loading v.r.			0.21	< 0.42 (3)	0.21	< 0.42-0.76 (13)					4
1996	Ship operator		(0.43-0.75) (2)	0.21	< 0.42-1.1 (9)	0.21	< 0.42-2.5 (25)	2.5 (9 min)		[0.72]	[0.62]	4
1996	Pier					0.42	< 0.42-1.4 (10)					4
2000	Ship operator		4.7	0.21	< 0.42-0.42 (5)	0.21	< 0.42-1.7 (15)					4
2000	Depot tank farm					0.031	0.156 (9)					2
2000	Depot pump room					0.192	0.318 (3)					2
2000	Depot open space					0.218	1.04 (6)					2
2000	Depot offices					0.09	0.14 (8)					2
2001	Tank farm					0.003	0.09 (8)					2
2001	Depot inside locations					0.0005	0.007 (10)					2
2001	Depot surroundings					0.0008	0.001 (5)					2

Table 4.4 continued overleaf

Table 4.4 continued Transporting operations; exposure levels are expressed as mg/m³

Data provided by companies									Calculated at 90th percentile		
Sampling		Personal short-term ST (TWA 30 minutes)		Personal long-term TWA 8 hours		Area long -term TWA 8 hours		Measured worst exposure	Personal ST (TWA 30 minutes) [TWA 8 hours]		Reference
Site, task, year		median	range (n)	median	range (n)	median	range (n)	Peak	Long-term	normal	log-normal	Company
2000	Field operator			0.041	0.42 (16)						[0.31]*	2
2000	Field supervisor			0.046	0.16 (6)							2
2002	Road tanker loading			0.008	> 0.005 -2.03 (9)						[1.84]*	5
2002	Ship tanker loading			0.005	< 0.005 -0,14 (12)						[0,12]*	5
Data from literature											
1996, west, 14-20 °C	Ship unloading 10%	0.83 (1.4)	0.19-2.2 (0.13-7.9) (5)					2.2 (7.9)		1.9 (6.4)	2.2 (7.7)	(Vainiotalo, 1996)
1997 10-15°C	Ship unloading	0.85 (0.85)	< 0.2-3 (< 0.2-3.6 (8)									Finnish database
1998, east 11-22 °C	Depot unloading/ railcar and tanker, n.v.r.4-8%			0.23	< 0.1-2.6 (13)				2.6	[1.5]	[1.2]	Hakkola et al. (2001)

In the case of "non-detectable" data a value half of the detection limit has been used for the statistical assessments.

* 95th percentile

Modelled data

EASE 8 hours prediction with non-dispersive use and direct handling with dilution ventilation for loading and unloading is 21-30 mg/m³ for fuel with 5% TAME. The corresponding result obtained by the use of specific partial vapour pressure value for 5% of TAME in a fuel mixture is 42–84 mg/m³.

Summary/statement of the exposure level

The ship off-loading data available concerns task-based ST-measurements performed during sampling and connecting/disconnecting pipes (Vainiotalo, 1996). The greatest measured 30 minutes TWA was 7.9 mg /m³. The fuel handled had an exceptionally high amount (10%) of TAME. Results from the Finnish database concerning ship unloading varied from < 0.2-3.6 mg/m³. Another study performed by (Hakkola et al., 2001) represents unloading from both ship and rail car. Measurements were performed over the whole work-shift with passive sampling. The TAME content of the fuel handled was reported to be 4-8%. The highest measured 8-hour TWA value was 2.6 mg/m³. The calculated 8-hour RWC value for this set of measurements is 1.2 mg/m³ with a median value of 0.23 mg/m³. These values were taken forward to risk characterisation as they are representative for the whole work-shift. The somewhat lower exposure level reported by producer 2 can be explained by their use of lower TAME content (0.2-1.5%) in the gasoline. The overestimation of modelled data compared to measured ones can be explained by the fact that the main part of the loading or unloading work-time is spent with tasks with only minor or no exposure potential at all, as the modelling suppose exposure to occur all the time.

Dermal exposure from transportation operations

Modelled data

The predicted EASE dermal exposure potential of palms of both hands (420 cm²) for transportation operations of fuel containing 5% TAME with following parameters: non-dispersive use, direct handling and incidental contact is 0.005 mg/ cm²/day, derived from 0-0.1 mg/cm²/day. This value gives a daily dermal exposure dose of 2.1 mg.

Inhalation exposure from distribution operations

Measured data

Petrol is distributed from the depot by road tankers. Worker groups having exposure potential are except the road truck drivers, operators employed at the terminal. Distribution exposure figures were received from one company and several literature reports. The results delivered by the company concerns loading measurements performed 1997 and 2000. In both cases, vapour recovery system was in use during the loading procedure.

Table 4.5 Distribution; results are expressed as mg/m^3

Data provided by companies									Calculated at 90th percentile		
Sampling		Personal short-term ST (TWA 30 minutes)		Personal long-term TWA 8 hours		Area long -term TWA 8 hours		Measured worst exposure		Personal ST (TWA 30 minutes) [TWA 8 hours])		Reference
Site, task, year median		median	range (n)	median	range (n)	median	Range (n)	Peak	Long-term	Normal	log-normal	Company
1997	Tanker driver, loading^{bo}	0.6	< 0.42-26.2(13)			0.21	< 0.42-0.63(12)	32.3 (4 min)		12	4.8	4
1997	Delivery unit operation			0.21	< 0.42-0.7 (14)					[0.41]	[0.35]	4
1997	Maintenance			0.21	< 0.42-0.42 (3)							4
1997	Instrument fitter, electrician			< 0.42	< 0.42 (12)							4
2000	Tanker driver, loading^{bo} v.r.	0.26	< 0.42-1.2 (6)			0.41	< 0.42-3.5 (5)					4
2000	Delivery unit operator		11.4	0.21	< 0.42-0.84 (3)			38.0 (9 min)				4
2001	Loading dock^{top}					0.002	0.022 (4)					2
2001	Loading dock^{bo}					0.007	0.072 (4)					2
2001	Delivery unit operator			0.0008	0.014 (5)							2
2001	Delivery unit supervisor			0.003	0.006 (7)							2
2001	Tanker driver			0.005	0.007 (6)							2
2001	Lab technician			0.003	0.001 (3)							2
2001	Technical supervisor etc.			0.0006	0.004 (11)						[0.003]*	2

Table 4.5 continued overleaf

Table 4.5 continued　Distribution; results are expressed as mg/m^3

Data provided by companies										Calculated at 90th percentile		
Sampling		Personal short-term ST (TWA 30 minutes)		Personal long-term TWA 8 hours		Area long -term TWA 8 hours		Measured worst exposure		Personal ST (TWA 30 minutes) [TWA 8 hours])		Reference
Site, task, year median		median	range (n)	median	range (n)	median	Range (n)	Peak	Long-term	Normal	log-normal	Company
Data from literature												
1995, south, 8-18°C	Loading[bo] v.r. 0.2 – 6%	0.94 (1.2)	0.18-6.9 (0.25-8.7) (20)					6.9 (8.7)		3.8 (4.4)	3.8 4.1)	Vainiotalo et al. (1999a)
1996, west, 12-19°C	Loading[bo] n.v.r. < 1 – 9%	0.52 (0.72)	0.15-1.6 (0.13-2.0) (7)					1.6 (2.0)		1.4 (1.7)	1.7 (2.2)	Vainiotalo et al. (1999a)
1996, west, 12-19°C	Unloading 5 with v.r. 2 with n.v.r. < 1 – 9%	0.36 (0.44)	0.08-2.0 (0.08-1.1) (7)					2.0 (1.1)		1.4 (0.9)	1.2 (0.9)	Vainiotalo et al. (1999a)
1995, 10-15°C	Loading[bo] v.r. < 1 - 9%	0.1 (0.1)	< 0.2 – 1.3 (< 0.2-1.7) (14)					1.3		0.7 (1.0)	0.5 (0.6)	Saarinen et al. (1998)
1995, 10-15°C	Unloading, n.v.r. < 1 - 9%	0.1 (0.1)	< 0.2 – 2.5 (< 0.2-2.0) (19)					2.5		1.4 (1.3)	1.3 (1.1)	Vainiotalo et al. (1999a)
1994-1999, south and central 9–26°C	Unloading n.v.r. 4 - 5% 1.2% in air	0.5 (0.4)	< 0.2 – 14 (0.08 - 14) (14)					14		8.4 7.2	6.4 5.2	Saarinen et al. (2002)*

Table 4.5 continued overleaf

Table 4.5 continued Distribution; results are expressed as mg/m³

Data provided by companies									Calculated at 90th percentile		
Sampling		Personal short-term ST (TWA 30 minutes)		Personal long-term TWA 8 hours		Area long-term TWA 8 hours		Measured worst exposure		Personal ST (TWA 30 minutes) [TWA 8 hours])	Reference
Site, task, year median		median	range (n)	median	range (n)	median	Range (n)	Peak	Long-term	Normal	log-normal	Company
Data from literature												
1994 – 1999 south and central 10-19ºC	Unloading v.r. 4-5% 1.7% in air	0.2 (0.2)	< 0.2 – 2.0 (< 0.2 - 2.7) (14)					2		1.2 1.8	1.0 1.4	Saarinen et al. (2002)*
1997 east 4-24ºC	Tanker driver, loading and unloading 4-8%			0.12	< 0.02– 1.3 (29)				1.3	[0.7]	[0.6]	Saarinen et al. (2002)*

In the case of "non-detectable" data a value half of the detection limit has been used for the statistical assessments.
* 95th percentile

Modelled data

EASE 8 hours prediction with non-dispersive use and direct handling with dilution ventilation for loading and unloading road tankers is 21-30 mg/m³ for fuel with 5% TAME. If the estimation is based on partial vapour pressure, the value will be 42-84 mg/m³.

Summary/statement of the exposure level

TAME-exposure (TWA 30 minutes) varied from < 0.42 to 26.2 mg/m³ with a median value of 0.6 mg/m³. The level depends on type and total amount of gasoline loaded. The 95 RON brand, compared to 98 and 99 contained higher amount of TAME. The measured worst exposure (TWA 30 minutes) was 26.2 mg/m³ representing a loading procedure of 48,500 L including only 95 RON brand. Some leakage during the procedure was also reported. Corresponding results found in literature show levels from < 0.2-8.7 mg/m³ (Vainiotalo et al. 1999a), (Saarinen et al., 1998). Vainiotalo et al. (1999a) has also measured bottom loading with no vapour recovery, when the 30-minute TWA range was 0.13-2.0 mg/m³ and the median 0.72 mg/m³. Calculated 30-minute RWC value for bottom loading with vapour recovery is 4.1 mg/m³ and without vapour recovery 2.2 mg/m³. The unexpected lower result obtained for loading without recovery system compared to the one with can be explained by differences in the quality of gasoline loaded. In the latter case, the main part of the gasoline handled was 98 and 99 RON brands, containing only 0.2% TAME. The exposure level of the delivery unit operators and the maintenance workers was quite low. The exposure level of the delivery unit operators and the maintenance workers was quite low. From a dataset of 14 samples (company 4) concerning a delivery unit operation the calculated median value is 0.21 mg/m³ and the corresponding calculated 8-hour RWC value 0.35 mg/m³.

The 30-minute TWA range for unloading without vapour recovery is 0.08-4 mg/m³ and < 0.2-2.7 mg/m³ with vapour recovery (Saarinen et al., 2000). The corresponding calculated RWC values are 5.2 and 1.4 mg/m³.

Saarinen et al. (2002) has also measured the exposure over the whole work-shift including both loading and unloading procedures with passive sampling, whereby the 8-hour TWA varied between 0.02 and 1.3 mg/m^3 with a median value of 0.12 mg/m^3 representing typical exposure. The calculated 8-hour RWC 0.6 mg/m^3 is taken forward to risk characterisation. This value is chosen because the measurements were performed during over the whole work-shift and the number was enough for statistical evaluations.

Dermal exposure from distribution operations

Modelled data

The predicted dermal exposure with EASE modelling for palms of both hands (420 cm^2) with non- dispersive use, direct handling and incidental contact is 0.005 mg/cm^2/day for fuel blend with 5% TAME. This value gives a daily dermal exposure dose of 2.1 mg.

4.1.1.2.3   Occupational exposure from end uses

Inhalation exposure from refuelling

Measured data

Literature data measured during refuelling is based on two Finnish studies. Hakkola and Saarinen (2000) studied the influence of introduction of vapour recovery system on exposure levels. Vainiotalo (Vailiotalo et al., 1996b) has measured exposure of customers to fuel emissions during refuelling cars on self-service basis. The measurements were carried out during 4 days in summer 1996 at two self-service stations with Stage I vapour recovery systems. The measurements were grab-sampling lasting as long as the refuelling time, on average 63 seconds. American Petrol Industry has 1995 measured the gasoline exposure of service station personnel in United States (McCoy and Johnson, 1995).

Summary/statement of the exposure level

The short term median values obtained were 1.1-4.9 mg/m^3 (Vailiotalo et al., 1996b). The highest measured ST-value was 29.1 mg/m^3 and the calculated ST-RWC value 23.6 mg/m^3. Hakkola and Saarinen (2000) have studied the influence of vapour recovery by measuring before and after installation of the system. Without recovery, the median value was 1.3 and with the recovery system installed 0.1 mg/m^3. The corresponding calculated ST-RWC values were 5.8 and 1.7 mg/m^3. The only measurements performed on service station attendants showed negligible exposure levels of TAME. Evaluation of the results is impossible as the work-tasks as well as the blending rate of TAME are not mentioned. Overall, the present work specifications for service station attendants are not clear enough for relevant exposure assessment. The refuelling exposure levels presented for customers can anyhow be representative for attendants for that part of the working day refuelling is performed. At least in the South Europe refuelling is still to some extent handled by service station attendants while the time spent in refuelling is supposed to be 20% of the working time as a worst case. Other possible work tasks with less exposure potential must be taken in account in evaluating the overall exposure level. With these assumptions a RWC-exposure level of 2.8 mg/m^3 is taken forward to the risk characterisation (estimated from the average RWC short-term exposure of 14 mg/m³). The corresponding typical exposure value is 0.5 mg/m³. The calculations are based on values obtained from refuelling with

pump pistols without recovery system. With recovery system installed (Stage II), which also will be the future practice, the exposure level is only one tenth compare to no recovery installed.

Table 4.6 Refuelling; results are expressed as mg/m³

Data from literature										Calculated at 90th percentile		
Sampling		Personal short-term (refuelling time 23-207 s)		Personal long-term task based		Area long -term		Measured worst exposure		Personal ST		Reference
Year, site tempera-ture	Task, TAME content (%)	median	range (n)	median	range (n)	median	range (n)	Peak	Long-term	normal	log-normal	
Self service refuelling												
1998, south, 10-16ºC	Stage I n.v.r. 5%	1.3	< 0.2-7.3 (10)					7.3		4.5	5.8	Hakkola and Saarinen (2000)*
1998, south, 10-17ºC	Stage II v.r. 5%	0.1	< 0.2-2.6 (10)					2.6		1.6	1.7	Hakkola and Saarinen (2000)*
1996, south, 19-25ºC	Stage I n.v.r. < 1-8%	3.2	0.18-10.9 (20)					10.9		7.7	10.2	Vainiotalo et al. (1999b)
1996, south, 20-25ºC	Stage I n.v.r. < 1-.9%	4.9	< 0.08-29.1 (21)					29.1		16.2	23.6	Vainiotalo et al. (1999b)
1996 , 20–24ºC	Stage I n.v.r. < 1–9%	3.2	< 0.04 -17.7 (21)					17.7		9.4	15.5	Vainiotalo et al. (1999b)
1996, 18-25ºC	Stage I, n.v.r. < 1–9%	2.1	0.04 -8.4 (21)					8.4		5.9	8.8	Vainiotalo et al. (1999b)
1996, south 17–21ºC	Stage I n.v.r. < 1–10%	3.2	0.01 -18.7 (21)					18.7		10.7	22.0	Vainiotalo et al. (1999b)

Table 4.6 continued overleaf

Table 4.6 continued Refuelling; results are expressed as mg/m^3

Data from literature										Calculated at 90th percentile		
Sampling		Personal short-term (refuelling time 23-207 s)		Personal long-term task based		Area long-term		Measured worst exposure		Personal ST		Reference
Year, site temperature	Task, TAME content (%)	median	range (n)	median	range (n)	median	range (n)	Peak	Long-term	normal	log-normal	
Self service refuelling												
1996 south 17-19ºC	Stage I n.v.r. < 1–9%	2.0	0.01 - 26.9 (21)					26.9		12.8	10.8	Vainiotalo et al. (1999b)
1996 south 17-19ºC	Stage I n.v.r. < 1–8%	1.8	0.06 - 13.7 (21)					13.7		9.3	13.6	Vainiotalo et al. (1999b)
1996 south 15-21ºC	Stage I n.v.r. < 1–8%	1.1	0.02 - 15.3 (21)					15.3		11.1	17.3	Vainiotalo et al. (1999b)
Attendant refuelling												
1994 Winter 6-16ºC	Refuelling attendants < 0.1-3.7%		< 1 (8)		< 0.08 (12)							Hinton et al. (1995)
1994 Summer 23-26ºC	Refuelling attendants < 0.1-2.2%		< 1 (14)		< 0.08 (10)							Hinton et al. (1995)

In the case of "non-detectable" data a value half of the detection limit has been used for the statistical assessments

* TAME-exposure levels are not presented in the publication, but they were received directly from the author

Dermal exposure

Modelled data

For the estimation of dermal exposure of palms of both hands (420 cm^2) the same parameters are used as for transportation and distribution (wide dispersive use, direct handling and intermittent contact) resulting in a predicted value of 0.05–0.25 mg/cm^2/day for a fuel blend containing 5% of TAME. The daily calculated worst exposure total dose is 100 mg.

Inhalation exposure from car motor repair and maintenance

Measured data

The only exposure levels available are from the service station measurements performed by API 1994 (Hinton et al., 1995).

Modelled data

EASE 8-hour prediction with non-dispersive use and direct handling with dilution ventilation for inhalation exposure is 21-30 mg/m^3 for fuel with 5% TAME. If the estimation is based on the partial vapour pressure of TAME, the estimation will be 42-84 mg/m^3

Summary/statement of the exposure level

Of the totally 20 work-shift measurements concerning exposure of mechanics work only two showed measurable amounts of TAME. The levels of these were low; 0.06 and 0.07 mg/m^3 8-hour TWA. The exposure for TAME is unclear as the actual work-tasks was not described. Possible exposure in these cases is connected to the fact that the measurements were performed at areas, which used low amounts (< 0.1-3.7%) of TAME as a component in gasoline. EASE 8-hour prediction 21-30 mg/m^3 seems, however, quite high in comparison with the airborne benzene concentrations, TWA$_{8h}$ 0.3-1.5 mg/m^3 obtained with an actual benzene concentration in gasoline of 2.0-2.5% (v/v) in the breathing-zone of car mechanics reported by (Laitinen et al., 1994). Benzene and TAME have almost identical vapour pressures and therefore these analogous data seem justified to be used. The highest short-term exposure level 12 mg benzene/m^3 was measured in connection with changing fuel filter. The durations of the various repair tasks were reported to last from 1-2.5 hours. With these assumptions a RWC value of 1.5 mg/m³ based on expert judgement from Laitinen's analogous data is taken forward to risk characterisation. Accordingly a concentration of 1.0 mg/m³ is chosen as typical exposure value.

Dermal exposure from car motor repair and maintenance

Modelled data

Car motor repairs comprise, however, several such work phases where the likelihood for dermal exposure is more prominent. (Laitinen et al., 1994) evaluated skin to represent up to 80% of the exposure route in car repairing work. This concerned specially tasks, like changing of filter to fuel pump, adjustment of electronic injection, renewal, adjustment and gathering of carburettor and adjusting of spraying nipples. For the estimation of dermal exposure with EASE modelling following parameters were used: inclusion onto matrix with direct handling and extensive contact the prediction resulted in 0.05-0.25 mg/cm^2/day. The petrol residues with 5% TAME are expected to occur mostly in matrices of motor oil, with a skin area of both hands (840 cm^2), which could sometimes be even more extensive, giving a daily total dose of 210 mg.

Table 4.7 Car motor repair and other work groups; results are expressed as mg/m³

Data from literature										Calculated at 90th percentile		
Sampling		Personal short-term ST (TWA 30 minutes)		Personal long-term TWA 8 hours		Area long -term		Measured worst exposure		Personal ST (TWA 30 min) [TWA 8 h]		Reference
Year, site temperature	Task, TAME content (%)	median	range (n)	median	range (n)	median	range (n)	Peak (TWA 30 min)	Long-term	normal	log-normal	
Car motor repair												
1992	Mechanics	6.5	0.4-12 (8)					12*				Laitinen et al. (1994)
1994 Summer	Mechanics		< 1 (15)	0.04	< 0.08-0.07 (8)							Hinton et al. (1995)
1994 Winter	Mechanics	0.5	< 1-0.84 (7)	0.04	< 0.08-0.06 (12)					[0.05]	[0.05]	Hinton et al. (1995)
Other work-groups												
2000, north 2-7°C	Forest work 7%			0.19	0.04-0.21 (3)				0.21			Lapinlampi et al. (2000)

In the case of "non-detectable" data a value half of the detection limit has been used for the statistical assessment
*   The measured value is for benzene, but it can be used for evaluation of TAME exposure.

Inhalation exposure from fuel pump repair and maintenance

Fuel pump repair is mostly carried out at the service stations outdoors. The work includes gauge repair, gauge and hose replacements and test runs. Exposure to TAME by inhalation may occur especially when the gasoline is drained from the gauge. The workers estimated that they are occupationally exposed to gasoline on 50-100 days per year and daily for 0.5-2 hours at a time. Calibration of the fuel meters is based on periodic inspections at the service stations.

During testing, the minimum of 55 litres of gasoline per pump pistol is used. The test is carried out using a slow flow rate and a measuring vessel of 5 l and repeated with both a slow and a high flow rate and two vessels of 25 l. After testing, the vessels are emptied into a container, which is unloaded into underground tanks at the service station. The inspectors estimated that they are occupationally exposed to about 100 days per year and on average 5.5 hours per day.

Measured data

Results from altogether 10 measurements were obtained for the work scenario including fuel pump repair and replacements as well as calibration at service stations (Pekari et al., 2004). The measurements were performed from April to June 2004 in Southern Finland. The 8-hour time-weighted exposure varied from < 0.01-5.5 mg/m³ with a median value of 0.9 mg/m³ representing typical exposure. The highest concentration was measured in connection with pump

repair indoors. The calculated 90th percentile was 3.5 mg/m³, which is taken forward to risk characterisation to represent the RWC exposure.

Modelled data

EASE 8-hour prediction with non-dispersive use and direct handling with dilution ventilation is 21-30 mg/m^3 for fuel with 5% TAME. If the estimation is based on partial vapour pressure, the value will be 42-84 mg/m^3.

Dermal exposure from fuel pump repair and maintenance

Modelled data

For fuel pump repair, the predicted dermal exposure potential concerns palms of both hands (420 cm^2). For the estimation of dermal exposure with EASE modelling following parameters were used, non-dispersive use with direct handling and extensive contact the prediction result in 0.05-0.25 mg/cm^2/day for petrol residues containing 5% of TAME, giving a daily total dose of 100 mg.

Inhalation exposure from gasoline powered equipments

Measured data

Other work groups concerned are those using gasoline-powered equipment's and vehicles with 2-stroke engines. Lapinlampi et al. (2000) has in 2000 measured the exposure of forest workers for TAME. Depending on the TAME content of gasoline used in the chain saws with fuel containing 7% TAME the exposure level (8-hour TWA) varied from non-detectable to 0.21 mg/m^3. These equipments can however be used with gasolines without oxygenates or with only MTBE.

Lapinlampi (Lapinlampi and Anttonen, 1998) has in 1998 measured gasoline components over the whole work-shift for estimation of five reindeer breeders´ exposure to motor sleigh exhaust gases. The fuel used was 98 or 99 RON brands with only small content of TAME resulting in air concentrations of it below detection limit.

Dermal exposure from gasoline powered equipments

Modelled data

The predicted dermal exposure with EASE modelling for palms of both hands (420 cm^2) with non- dispersive use, direct handling and incidental contact is 0.005 mg/cm^2/day for fuel blend with 5% TAME. This value gives a daily dermal exposure dose of 2.1 mg.

4.1.1.2.4 Summary of occupational exposure

Almost all exposure levels available originate from Finnish studies or industry reports, which make it difficult to evaluate the representativeness of the data for other EU-countries. Exposure assessment is generally evaluated based on studies, in which the average content of TAME in fuels handled was about 5%. In Finland 95 RON gasoline nowadays typically contain 7-8% and in 98 grade about 2%, respectively. Therefore, the use of estimations based on 5% seems justified and furthermore as the remaining European level is below 4%.

TAME is not an unambiguous chemical exposure agent; exposure to TAME occurs almost exclusively as a blending component in fuel. The amount used varies from one brand (95, 98 or 99 RON) to another, with divergences even within the same brand due to production circumstances. Furthermore, it should be noted that the type of content of a fuel brand is nationally restricted. Thus, for example Sweden started 2001 to blend 95 RON brand only with ethanol oxygenate, while the same brand in Finland is typically a TAME-rich product (Statens Petroleum Industry, 2001).

All the work scenarios described comprise handling of fuels with variable amounts (0-10%) of TAME and the work-task presented implies usually all fuel brands. For normal road tanker loading procedures the share of the TAME-richest brand, 95 RON, reported to vary between 11 and 100% (or from 5 to 48.6 t, n=19). The level of exposure naturally depends on the type of fuels handled and cannot thus be predicted without knowledge of its composition. This means on the other hand that for some work-groups e.g. motor sleigh drivers for which the exposure now was reported to be negligible might have shown higher exposure levels with other types of fuel. For mechanics, the risk of contamination and thus penetration through the skin has been shown to be the most significant route (80%) of exposure, which should be considered in the risk assessment of car mechanics (Laitinen et al., 1994). For this kind of work tasks, the residual amount of TAME in petrol is surely variable and unpredictable. Maintenance operations are furthermore needed through all the scenarios from petrol production to delivery, distribution and service stations. TAME exposure measurements of maintenance operators are only available in connection with production, where the levels showed to be negligible. Although the main part of the exposure in petrol connected work scenarios has been minimised due to changes in operating practices, maintenance and repair work is still and will be in future undertaken in a similar manner to previously. The tasks have to be performed manually, with obvious potential of dermal exposure risk, due to direct contact of the workers hands with petrol product. The mechanics are daily exposed during removal of pumps and repairing repellers, during replacement of railroad drybeak couplings, and while repairing and calibrating fuel meters at service stations. Overall, two little information about the nature of task based dermal exposure is available, which makes it difficult to evaluate possible transfer of chemicals to workers from contaminated surfaces of equipments handled.

The uncertainty concerning the estimation of inhalation exposure potential by EASE modelling depends on the TAME percentage chosen for the modelling and reflects thus that average situation. The other fuel components furthermore influence the evaporative emission characteristics of TAME, which in fact would provide a real comprehensive modelling for correct estimation.

The data sets were often scanty for statistical evaluation. A great deal of the exposure levels reported was below detection limit, which cannot be explained by insensitive analytical methodology. Rather it depends on minor exposure potential. The few occasionally occurring tasks with exposure potential seem not to be enough to change the overall low exposure trend. The main cause for this is the poor evaporative emission characteristics of TAME in comparison with the other fuel components. The phenomenon can partly also be ascribed to a lot of recent technical improvements aiming at reducing emission and exposure in connection with transportation and distribution operations

with the other fuel components. The phenomenon can partly also be ascribed to a lot of recent technical improvements aiming at reducing emission and exposure in connection with transportation and distribution operations

The main route of exposure is to be inhalation. This conclusion is based on the fact that due to technical developments skin contact to liquid fuel has been minimised in most work tasks. The EASE-estimation of dermal exposure may therefore be unrealistic. An exception is manual work tasks like car motor and fuel pump repair, as well as accidental spill in connection with transfer of fuel from small jerry cans to tanks of 2-stroke engines. Evaluating the potential dermal exposure resulting from e.g. splashes (100 mg equals 1-2 droplets depending on drop size) on the skin or clothing the loss due to evaporation should be accounted for. TAME is a medium volatile compound, which means that it will take 8 s for 1 mg/cm² to evaporate from the skin and accordingly the dermal exposure will be reduced because of the shortened retention time of the substance on the skin.

The EASE-estimation of inhalation exposure for the transportation and distribution seemed to be overestimated in comparison with the measured exposure levels. This is supposed to depend on the fact that the main part of these work procedures is supervision with only minor exposure potential.

In **Table 4.8**, the work scenarios identified for occupational exposure to TAME are summarised. The duration and frequency of exposure, numerical values for measured typical inhalation exposure (calculated median value) and reasonable worst case (calculated 90th percentile) are given. Modelled EASE estimation of inhaled and dermal exposure is also presented. For each work scenario except for refuelling the statistical value best representing the exposure was selected. For the selection, one decisive criterion was sampling time in relation to the time of a work day. For refuelling median and RWC-values are average values of all measured refuelling results (see **Table 4.6**). The lower exposure level measured at Stage II was excluded, thus the summary result represent only Stage I refuelling.

Table 4.8   Summary of the occupational exposure assessment

Scenario	Activity [1]	Frequency Days/year	Duration Hours/day	Inhalation				Dermal			
				Reasonable worst case 90th percentile		Typical concentration		Reasonable worst case		Daily dose	
				TWA 8h, mg/m^3	Method2	TWA 8h, mg/m^3	Method [2]	mg/cm^2/d	Method [2]	mg	Method [2]
Production	Long term	200	2	1.8	Measured	0.46	Measured	Negligible			
Formulation											
Transporting	Long term	50	4	1.2	Measured	0.23	Measured	0.-0.0055 (5 vol %)	EASE	2.1	EASE
Distribution	Long term	200	3	0.6	Measured	0.12	Measured	0-0.005 (5 vol %)	EASE	2.1	EASE
Uses											
Service attendants (refuelling)	Short term Long-term	200	2	14 2.8	Measured Estimated	2.5 0.5	Measured Estimated	0.05-0.25 (5 vol %)	EASE	100	EASE
Car motor repair	Long term	150	3	1.5	Measured*	1.0	Measured*	0.05-0.25 (5 vol %)	EASE	210	EASE
Fuel pump repair	Long-term	100	4	5.5	Measured	0.9	Measured	0.05-0.25 (5 vol %)	EASE	100	EASE
Other	Long- term	150	3	0.21	Measured	0.19	Measured	0.0.005 (5 vol %)	EASE	2.1	EASE

1) Full shift, short term, etc.
2) Measured, EASE, Expert judgment, Calculated, etc.
* Evaluated from benzene exposure of car repair from Laitinens study

4.1.1.3   Consumer exposure

4.1.1.3.1   Introduction

Except occupational exposure, humans are exposed to TAME via the environment. Consumers who refuel their cars are also exposed, but to a lesser extent than the professional attendants. Oral and dermal exposure may result from drinking and bathing water contaminated by TAME.

TAME is released from petrol stations, (due to unloading of lorries, refuelling, spillage, leakage's and car exhausts) and elevated air concentration can occur in their neighbourhood. Significantly elevated air concentrations of MTBE have been measured near petrol stations, but so far no analytical data concerning TAME are available. In the end of 1998 in Finland, there were 1,762 petrol stations, of which 529 were automated self-service stations. In 1999, the number of service stations in EU-countries was 111,950 (Personal information from Finnish Oil and Gas Federation). Thus, a large group of population is potentially exposed to elevated concentration of TAME in ambient air.

Engineering control (Saarinen and Hakkola, 1996) of petrol exposure at dispensing stations is carried out with vapour recovery systems. Type Stage I vapour recovery system means vapour recovery during delivery (unloading) and Stage II vapour recovery means vapour recovery during refuelling. It has been observed that customer exposure to constituents of petrol during refuelling is clearly decreased by Stage II technique (Hakkola and Saarinen, 2000). About two thirds of the Finnish stations are now equipped with Stage I gas recovery systems and Stage II vapour recovery systems are installed, when new stations are built and old stations are renewed. In other EU-countries (informed only from 7 countries), 55.3% (range 38-90%) of stations are equipped with Stage II recovery systems. In Switzerland, Stage II vapour recovery systems are installed in 91% and in Norway 1% of service stations (Hakkola et al., 1998b).

The major oxygenate concentrations in the atmosphere (HEI, 1996) are mainly derived from evaporative emissions from petrol and from petrol combustion. The major points of evaporation from automobile are the exhaust pipe, the petrol tank when the fuel is excessively hot, and the leaking of fuel lines. Only minor concentrations are generated from other sources.

To put the estimates of consumer exposure into perspective, it has to be recognised that prospects for TAME consumption trends indicate an almost two-fold increase in the production of TAME, from 175,000 tonnes in 2001 to approximately 348,000 in the year 2005 (Dewitt and Company, 2001). This is due to compensation of octane loss and aiming to meet the 98/70/EC requirements concerning total aromatics in EU countries.

TAME is a constituent of oxygenated petrol in some European countries. Usually the blending rate is below 5%, but occasionally at least in Finland it is up to 10%. Taking into account the blending rates reported by major producers and formulators in Europe, 5% was selected as a representative figure, which is used below, in case no measurements are available and the concentrations of TAME have to be estimated. No consumer product containing TAME other than petrol has been identified.

Exposure, which takes place during car refuelling, is included in this section. Exposure at pump island of service stations, in cars, in perimeter of gasoline stations etc. are dealt with in Section 3 "Indirect exposure via the environment". The use pattern and the exposure scenarios concerning TAME are very similar to those of MTBE. Therefore, the recently prepared risk assessment of

MTBE was carefully considered for the risk assessment of TAME. To allow comparisons between the two oxygenates, their physical-chemical properties are given in **Table 4.9** below. Most important parameters in terms of consumer exposure scenarios are the vapour pressure and water solubility. The former affects e.g. the evaporation of TAME during refuelling and the later is one of the determinants of the potential contamination of ground water and drinking water by TAME.

Table 4.9   Comparison of physical, chemical and other key properties of TAME and MTBE

Property/Parameter	TAME	MTBE
Molecular weight	102.18	88.15
Percentage in petrol	7.7-9.5% in 95 grade petrol, and 0% 12.2 in 98/99 grade petrol, in Finland (Vainiotalo et al., 1999b)	1.7-4.0% in 95 grade petrol, and 12.2 in 98/99 grade petrol, in Finland (Vainiotalo et al., 1999b)
Vapour pressure	90 hPA at 20°C	270 hPA at 20°C
Water solubility	11 g/l at 20°C	42 g/l at 20°C
Odour threshold in water [1]	Odour detection (average): 194 µg/l Odour recognition threshold (average): 443 µg/l (Vetrano et al., 1993)	15 µg/l, lower threshold level identified and used for the risk characterisation of MTBE (Finnish Environment Institute 2001)
Taste threshold in water [1]	Taste detection threshold (average): 128 µg/l (Vetrano et al., 1993)	15 µg/l, lower threshold level identified and used for the risk characterisation of MTBE (Finnish Environment Institute 2001)
Odour average threshold in air (Vetrano et al., 1993)	Detection: 0.12 mg/m^3 (0.027 ppm) Recognition 0.20 mg/m^3 (0.047 ppm)	Detection 0.053 ppm (0.19 mg/m^3) Recognition 0.08 ppm (0.29 mg/m^3)

[1]   These estimates are based on test in distilled water under laboratory conditions from one set of tests. Therefore, it does not reflect the natural environmental situation, where e.g. water hardness, temperature, chlorinating or other contaminants influence to taste and odour. Thus, the concentration, at which the taste or odour makes water unacceptable for consumers, may vary greatly. In addition, the thresholds values differ between various persons. Values cited above are just indicative and refer only to one study.

4.1.1.3.2   **Refuelling**

Inhalation exposure

In some gasoline stations, gasoline is unloaded at the station without collection of volatilised gasoline. At Stage I stations, during unloading from tank truck to station tank, vaporised gasoline is collected, which reduces the release to the air and limits the customer and occupational exposure. At Stage II stations, vaporised gasoline is collected also during refuelling by an inlet, which is attached to the gasoline pistol. This decreases the exposure of consumer to TAME vaporised during refuelling.

The proportion of Stage II stations is 38-90% in the six most advanced European countries. In Finland, the proportion of Stage II stations was only 5% in the year 1998 (Hakkola et al., 1998b).

Vainiotalo et al. (1999b) measured the customer exposure to TAME during refuelling in two self-service gasoline stations during summertime. The stations were adjacent to main roads with high traffic density. The mean wind speed was 1.4 m/second and the mean air temperature was 21ºC. Samples were collected in the breathing zone of the customer. Stage I vapour recovery

systems were operational at the stations. The gasoline pistols had rubber "splash collars". The sampling started, when the pump pistol was inserted in the tank and ended when the pump pistol was replaced in its holder. The 95-grade petrol, which contained about 8.5% of TAME contributed by 75% to the volume refuelled during the study; the rest of the gasoline was 98/99 grade containing no TAME (but 12.2% of MTBE). The geometric mean concentrations of TAME at the two stations were 2.2 mg/m^3 (0.03-29.1 mg/m^3) and 1.7 mg/m^3 (< 0.02-27.0 mg/m^3). The average refuelling times were 63 and 74 seconds. The overall geometric mean (n=167) for an adjusted 1-min refuelling time was 1.9 mg/m^3.

The concentration of TAME in petrol is higher in Finland than in most EU countries. Furthermore, Stage II vapour recovery, which means recovery during refuelling, is more frequent in many European Countries than in Finland. For these two reasons, the measurements reported above do not represent the European average, but maximum levels.

Hakkola and Saarinen (2000) found that the MTBE exposure level of customers at Stage II stations during refuelling was 20-25% of the exposure at Stage I service stations. The conditions at these stations were equal and the results were not affected by other confounding factors such as leaks or spills. A similar reduction of customer exposure is estimated to be achieved for the level of TAME in air at service stations. Thus, taking the geometric mean at Stage I stations (1.9 mg/m^3) and 20-25% of that concentration, an estimate of maximum breathing zone concentration of TAME at Stage II stations would be 0.38-0.48 mg/m^3.

In general, compound with odour thresholds below 1,000 mg/l are considered highly odorous. TAME's odour was described like sweet, rubbery, fruity, ether-like and paint-like (Vetrano et al., 1993).

Dermal exposure caused by refuelling

Refuelling of a car or a boat motor may cause dermal contact with TAME. No measurements are available of this scenario and route of exposure. The reasonable worst case scenario presented below is based on assumptions.

When both hands are exposed to gasoline, during careless refuelling, the volume of gasoline on the skin is assumed 100 mg (e.g. a few drops of petrol on hands without glows). This accounts for 5 mg of TAME, when the gasoline contains 5% of TAME. When this exposure occurs, significant increase of the TAME exposure would follow (compare with **Table 4.2**). However, since this exposure is not regular and since no measured data is available this exposure is not considered in the estimates of combined exposure below.

4.1.1.4 Indirect consumer exposure via the environment

In Central Europe, the average TAME concentration of common grades of gasoline is not known. In Finland, the normal TAME content in gasoline is 8.5% (wt) (Vainiotalo et al., 1999a). In this assessment, 5% was selected as a representative figure.

4.1.1.4.1 Exposure via drinking water

TAME enters surface water and ground water as a result of fuel leaks and spills and from corroded tanks and pipelines mostly at the service stations. When contaminated ground water is used as drinking water, people are exposed to TAME.

According to EUSES modelling the local (near production and processing sites) and regional PECs of TAME in surface water are 0.1-450 μg/l and 0.52 μg/l, respectively (see Section 3.1.3 Aquatic compartment, e.g calculation of local PECs.) Most likely, the water near the five identified production and formulation sites (local PEC) is not used as drinking water, and the estimated concentrations therefore are not relevant in terms of human exposure. Moreover, the actual concentrations tend to be lower than those retrieved by EUSES estimation. The only figure based on *measured* TAME content in effluent was 1 μg/l (see **Table 3.19**). The regional estimate may be relevant for estimation of exposure due to drinking water, which is taken from regionally contaminated surface water.

Apart from the few analyses of ground water concentrations in Finland, no measured concentrations of TAME in drinking water were available. In the studies reviewed in Section 3.1. (Environment part) in more detail, concentration of TAME in surface waters was analysed (see **Table 4.10**). These concentrations are used here for normal background concentrations, as it is assumed that similar types of surface waters can be used as potable water sources. Furthermore, it is assumed that water treatment processes do not significantly decrease the concentration of TAME.

Exhausts and leaks from boat engines

Boating causes release of TAME to surface water. Local PEC, i.e., concentration of TAME in marinas and coastal waters with heavy boat traffic, is 13 μg/l (see the respective section in the environmental part). This estimate is based on the following: the fuel combustion in outboard motors is inefficient; even > 25% of petrol hydrocarbons can be released unburned into the water. Furthermore, continuous heavy boat traffic i.e. 100 boats per hour passing the detection point on a 10 m wide boat lane was assumed. The figure (13 μg/l) seems to be an overestimate, since in two studies made in USA, lake water contaminated by heavy boat traffic contained only 0.69 μg/l at the maximum (see **Table 3.1**). These waters are seldom used as sources of drinking water and therefore, the PEC estimate is not used for the reasonable worst-case scenario. Small leaks and spills are common e.g. when a gasoline 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 doses of TAME. Since outboard motors release substantial amount/percentage of unburned gasoline, yachters may be exposed to TAME in the air of marinas, as well. No measurements of TAME in the air of marinas or in boats are available.

The studies summarised in **Table 4.10** have been accomplished in the USA. No similar studies made in Europe are available. In two of these studies, releases from boating are an obvious reason to slightly elevated concentration. Therefore, normal concentration in surface waters as well as in drinking waters is lower, probably < 0.1 μg/l in most cases.

Table 4.10 Measured concentration of TAME in surface waters

Sampling site	Concentrations µg/l	Number of samples or sampling sites	References
North Carolina, storm water	Detected in < 10% of the samples, typically < 1 µg/l	249 samples from 46 sites	Borden et al. 2002
Long Island, New York, surface water	Median 0.02 µg/l Maximum 0.08 µg/l	42 samples	US Geological Survey 1997
Lake Tahoe, near shore, boat-trafficked area	0.2, 0.14, 0.14 µG/L	3 samples	Reuter et al. 1998
Byram Township, N.J., lake water, lot of watercraft around the lake	0.07-0.43 in June, 0.2-0.69 in September	-	Baehr and Zapecza 1998

TAME in ground water

The physical and chemical properties of TAME increase the possibility of contamination of ground water: The water solubility of TAME is 11 g/l at 20°C (for MTBE the value is 42 g/l at 20°C). Furthermore, TAME is generally resistant to biodegradation in ground water. As with MTBE, releases of TAME to the environment 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). TAME released from underground storage tanks (UST) and spills that take place during unloading operation at the gasoline station may contaminate the ground water and nearby wells.

As indicated in Section 3.1.4.2, high concentrations of TAME have been measured in a number of ground waters in Finland. These pollution cases are caused by releases from petrol stations. The concentration range was 5-150,000 µg/l in ten petrol station sites. Analytical data from other EU member states are presently not available. Since the higher concentration range is much above the odour and taste threshold of TAME, it is assessed that consumers would be exposed to the high concentrations only temporarily (i.e. a few days before a new drinking water source is arranged). Therefore, the value below odour and taste threshold i.e. 100 µg/l, is carried to the reasonable worst-case scenario (see **Table 4.12**).

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, which has become more common in recent years, diminishes the risk of leaks, but the percentage of these modern tanks in not known (oral communication, representative of petroleum industry 1999).

Regulations on tank monitoring

In the United Kingdom, Guidelines for Petrol Filling Stations given by Health and Safety Executive stipulate 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 take place showing gains or losses for each tank or compartment and connected pipeline system. The Guidelines provide 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. Nonetheless, 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. (Information submitted by Fortum, email of Sandrine Dixson-Decleve forwarded by Hilkka Vahervuori 7 September 1999).

In July 1998, a decision was adopted by the Ministry of Trade and Industry, which describes the requirements for new UST 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.

4.1.1.4.2   Exposure via air

TAME is released to air during loading and unloading of gasoline 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, which consumers are exposed to, are presumably during refuelling of cars. Consumers are indirectly exposed to TAME 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 TAME in the ambient air.

There are not many studies on air concentrations of TAME and therefore EUSES results and rough estimates are used for the exposure assessment below.

Pump island of service stations

Vainiotalo et al. (1999b) measured concentration of TAME at the pump island in two self-service gasoline stations during summertime. The stations were adjacent to main roads with high traffic density. The mean wind speed was 1.4 m/second and mean air temperature was 21ºC. Customers spend about 5 minutes (on the average) at the pump island, as compared with about 1 minute that the refuelling takes. The mean concentrations (and standard deviation) of TAME at the pump islands of the two stations were 0.031 mg/m^3 (0.021) and 0.031 mg/m^3 (0.013).

Perimeter of gasoline stations

Due to the lack of analytical data on TAME, studies, in which MTBE concentrations were measured, are used to retrieve a crude estimate of the likely concentration level of TAME in the perimeter of gasoline stations. Vainiotalo et al. (1998) measured MTBE concentration in the vicinity of 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 these 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. From other of the service stations, there were apartment houses within that distance. The concentration range of individual samples was 0.5-121 μg/m^3. 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 (Vainiotalo et al., 1998).

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 summer 1996 (Heudorf and Ullrich, 1998). The persons had the sampler with them all the day. In the neighbourhood of the station, the geometric mean and the maximum concentration were 3.8 and 9.9 $\mu g/m^3$, respectively. For the controls, the respective figures were 8.4 and 20.1 $\mu g/m^3$. The person giving this maximum value (20.1 $\mu g/m^3$) 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.

First taking the range of these two studies, 3.8-14.1 $\mu g/m^3$ and assuming that the concentration of TAME is related to its lower vapour pressure, 1.3-4.7 $\mu g/m^3$ would represent the concentration range of TAME in the perimeter of gasoline stations. Second, the amount to TAME released form service stations also depends on the concentration of TAME in the gasoline, and 5% is used here. Using the blending rates of MTBE and TAME, i.e. 11 and 5% it is estimated that the concentration of TAME in the perimeter of petrol station is 0.6-2.1 $\mu g/m^3$. It is assumed that in the normal scenario, there is no service station near to the residential houses (see **Table 4.12**). For calculation of the reasonable worst-case scenarios, it is assumed that long-term indoor concentration in the neighbourhood of service stations is 0.6-2.1 $\mu g/m^3$.

Commuting in car

Combustion of TAME containing fuel results in tail pipe emission. Density of the traffic, car type, season and fuel has an effect on the concentration of TAME that the car-driver and passengers are exposed to. No data are available on measured or estimated concentrations of TAME in cars

To obtain an estimate for TAME, data on MTBE concentrations in cars are used: Concentration of MTBE was measured in a car cabin for one hour (Lioy et al., 1994). Samples were collected in New Jersey and Connecticut where MTBE concentration in gasoline is 13-15%. The geometric mean concentration was 21 $\mu g/m^3$ (0.006 ppm) with a range of 4-580 $\mu g/m^3$ (0.001-0.16 ppm). The cabin concentrations were dependent on the type of vehicle. The higher interior concentrations were measured in the car that also had higher rate of VOC emissions. Pre-fuelling concentrations in cabin were about 36 $\mu g/m^3$ (0.01 ppm), in three cars studied, about 180 $\mu g/m^3$ during and about 54$\mu g/m^3$ after refuelling.

Rhodes et al.(1999) measured 2-hour integrated concentrations of MTBE in vehicles on roadways. Average in-vehicle concentrations ranges were 3-90 $\mu g/m^3$. This concentration range is close to 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 gasoline was not reported.

Exposure to MTBE in buses, private cars and in ambient air was compared in a Korean study [Jo, 1998 #90]. The samples were collected in buses and cars, during rush hours of the winter season. In gasoline, the concentration of MTBE was 6-7%. In private cars, median MTBE levels of 48.5 $\mu g/m^3$ were measured. MTBE concentrations were about 3.5 times higher in a car with carburettor engine than in the three electronic fuel-injected cars. Summarising the three studies, 15-70 is taken as a typical concentration range of MTBE in cars.

Base on lower vapour pressure of TAME (see **Table 1.1**), and the blending rate relation (TAME 5% and MTBE 11%), it is assessed that in cars and in buses, the realistic range of TAME concentration that passengers are exposed to during commuting is 2.3-10.4 $\mu g/m^3$.

Areas polluted by production and formulation sites

The EUSES estimation indicates that average air concentration of TAME near point sources varies from 0.73 to 94 µg/m^3. Near to refineries and factories, where TAME is produced and/or gasoline is formulated, the concentration of TAME in ambient air can be elevated. The site specific measured average concentrations in air, reported by industry, range from 0.033 to 111 µg/m^3. For dose estimation it is suggested that typical concentration in areas polluted by refineries would be 1-100 µg/m^3. It is assumed that people living near these sites are exposed for 12 hours/day (see **Table 4.12**).

The number of persons living near to production sites of contaminated areas is not known, but is probably small. Only few European data are available at present. This source of exposure is considered relevant in terms of assessing the reasonable worst-case scenario. It appears 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, although the range is larger.

Urban background

A summary of the New Jersey air quality data for 2000 reports annual maximum TAME concentrations of 0.2 µg/m^3 and 0.3 µg/m^3 and an annual average of 0.04 µg/m^3. The levels are low compared to concentrations reported for MTBE in the same report: the maximum was 33 µg/m^3 and the annual average 6.5 µg/m^3. (New Jersey Department of Environmental Protection, 2000). No analytical data on TAME in ambient European air are available.

Exposure estimates

Based on the current data, the highest air concentrations (1,900 µg/m^3) that consumers are exposed to are due to refuelling of cars. The duration refuelling is short, i.e. about one minute. Higher than ambient concentration have also been measured in pump island at the gasoline station, at immediate vicinity of them and also in cars. Generalised from the analytical data and from our estimates, scenarios related to gasoline stations and refuelling are presented in **Tables 4.11** and **4.12**.

Indirect exposure to TAME is also caused by car exhausts and releases from the gasoline stations. People living in the houses adjacent to the gasoline station, are exposed to slightly elevated air concentration of TAME. Parameters, which affect the concentrations of TAME, are e.g. the concentration of TAME in gasoline, technique applied for emission control at the station (no control, Stage I or Stage II), wind direction and distance from the source of release.

To support some of the percentages in **Table 4.11** and the time budgets, the data from the US Bureau of Census (1995) is presented. That data indicates that 1 hour per day is a reasonable estimate for time spent in vehicles per day for the driving population. While refuelling, customers may spend 5 minutes or more at the gasoline service station, the average time near the pump island being lower. Reasonable estimate of an average refuelling time (refuelling and stay in the pump island) is 3 min and frequency of refuelling is 70 events per year. Commuting and refuelling are considered to be moderate activities in terms of physiological characteristics and thus, the average breathing rate would be 1.35 m^3/hour. For other exposures, a daily average rate of 0.75 m^3/hour is appropriate for both adults and children.

It was estimated that, of the population in USA:

        83%   do not live near a TAME facility

        6.4%   live near a gasoline service station

9.6%   live near a gasoline storage facility

1.1%   live near a manufacturing or blending facility

72%   are drivers and gasoline station customer

41%   are commuters

The first four categories are mutually exclusive whereas the others are not.

Table 4.11 Exposure to TAME via inhalation; the representative concentration ranges are based on published data and on estimates presented above. In case no analytical data is available, a blend rate of 5% was assumed and read-across to MTBE data has been applied

Relevant area/scenario	Source of MTBE	Duration of exposure Hours/day	Typical concentration µg/m³	Percentage of population
Urban background	Car exhausts, rain (?)	12/24 hours/day	0.1	about 98%
Perimeter of production and formulation plants	Industry	12 hours/day	1-100	< 1%
Perimeter of gasoline stations	Gasoline stations, car exhausts	12-24 hours/day	0.6-2.1	< 1%
Commuting in car or bus	Car exhausts, refuelling	1-2 hours/day	2.3-10.4	?
Pump area of gas station	Refuelling, spills, cars	1-5 min./d, 2-3 visits/week	31	15%
Refuelling, Stage I station [1]	Gasoline pistol, car exhausts	1 min./d, 2-3 visits/week	1,900	15%

1)   Adjacent roads with high traffic density may contribute to the TAME levels observed

4.1.1.5   Total exposure via drinking water and via air - normal and reasonable worst case scenario

Inhalation of TAME that evaporates during refuelling and unloading operations of gasoline at service stations, exposure to car exhausts and ingestion of TAME in the drinking water are the main exposure scenarios. The normal scenario concerns a person, who commutes in car of bus regularly and visits service stations but does not refuel to car, and is exposed to ambient urban air concentration of TAME. The scenario also includes some exposure via tap water caused by minor contamination of water source, which is due to precipitation of TAME with the rain water. The total dose of the normal scenario is 0.10-0.29 µg/kg bw/day (see **Table 4.12**).

Most analytical data used for this section originates from Finland or from USA, where higher TAME level in gasoline (up to 11%) are used, than in most EU countries. While there are no sufficient analytical data from Central Europe, it is preliminarily assessed that the dose of TAME to which consumer is exposed to in normal EU scenario is about 30% of the dose ranges calculated in **Table 4.12**.

Table 4.12 Exposure to TAME via inhalation and via tap water, normal scenario and reasonable worst case scenario (car drivers living in perimeter of a production or formulation plant or gasoline station). For this table, the typical concentration levels are selected based on available analytical data to represent the situation in Finland. In case no analytical data is available, blend rate of 5% and read-across of MTBE data has been applied

Relevant area/scenario	Source of TAME	Duration of exposure, normal/RWC	Normal Concentration µg/m³	Normal Dose µg/day [1]	Concentration used to calculate RWC dose µg/m³	RWC Dose µg/day [1]
Inhalation						
Urban background	Car exhausts, rain (?)	22/10 hours/day	0.1	1.8	0.1	0.83
Perimeter of production and formulation plants	Industry	0/12	-	-	1-100	10-996
Perimeter of gasoline stations	Gasoline stations, car exhausts	0/12 hours/day	-	-	0.6-2.1	6.7-20.9
Commuting in car or bus	Car exhausts	2 hours/day	2.3-10.4	3.8-17.3	2.3-10.4	3.8-17.3
Pump area of gas station	Refuelling, leaks, cars	1-5 min./d, 2-3 visits/week	31	0.1-0.9	31	0.1-0.9
Refuelling, Stage I station	Gasoline pistol	1 min./d, 2-3 visits/week	-	-	1,900	7.6-11.4
Tap water ingestion						
Urban background in the normal and petrol station in the RWC scenario	Car exhausts, rain, leaks and spills at petrol stations	-	< 0.1µg/l	< 0.2	100µg/l	200
Total exposure µg/kg/bw/day [2]				**0.10-0.29**	**3.27-17.82**	

1) Respiratory volume is about 20m³/24 hours=0.83 m³/hour=0.014m³/minute (uptake % not considered). It is assumed that ingestion of tap water is 2 l/day.
2) Dose of an adult (70 kg) is calculated.

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 Vainiotalo et al. (1999b). Other durations of exposure presented in **Table 4.11** are based on our assessment and reasoning. The percentage of the population exposed in various scenarios (see **Table 4.11**) are preliminary estimates, probably indicating the correct order of magnitude. These figures have to be substantiated later.

A reasonable worst-case scenario concerns a person, who is exposed to TAME at the gasoline station during and after refuelling of the car and who also lives near a gasoline station (50 m). Commuting in a car or in a bus is also considered. The total dose for a reasonable worst case scenario is 3.27-17.8 µg/kg of bw/day (see **Table 4.12**). In some cases, the same person might also be exposed to an elevated concentration of TAME in the tap water. It is reasonable to assume that in some cases these two scenarios, i.e. 1) high inhalation exposure due to vicinity to a production or formulation plant or a service station and 2) elevated TAME concentration in contaminated tap water might coincide. The total dose of TAME, which concerns the reasonable worst-case scenario, is based on the currently available data. It is not possible to present an accurate estimate on the percentage of population, which is exposed to this dose level. It is suggested that this percentage of the population is much below 1%.

High concentrations of TAME (5-150,000 µg/l) have been observed in ground water in Finland near petrol stations. Since the higher concentration range is much above the odour and taste threshold of TAME, it is assessed that consumers may only temporarily be exposed to the high concentrations. Therefore, these data are not used in the reasonable worst-case scenario (see **Table 4.12**). However, these measurements do give rise to concern of unacceptable ground-water contamination and will be discussed in the risk characterisation section. This conclusion is similar to that drawn in the RAR of MTBE.

4.1.2 Effects assessment: Hazard identification and dose (concentration)- response (effect) assessment

4.1.2.1 Toxicokinetics, metabolism and distribution

4.1.2.1.1 Studies in animals

In vivo studies

Inhalation and Oral

Study 1: Human and Rat – Kinetics and biotransformation

Method

TAME metabolism was compared in man and F-344 rats exposed to TAME (> 97%) in respired air (Amberg et al., 2000). Three male human volunteers and five male and female rats were exposed to 4 and 40 ppm TAME for 4 h in a dynamic exposure system. Volunteers did not smoke and refrained from alcohol use and did not refuel two days before and during the experiment. Urine samples were collected for 72 hours at 6 hour intervals. In humans, TAME and tert-amyl alcohol (TAA) were determined from blood samples taken regularly for 48 hours. In urine, TAME metabolites quantified (GS/MS) were: TAA, 2-methyl-2,3-butanediol, 2-hydroxy-2-methylbutyric acid and 3-hydroxy-3-methylbutyric acid.

Results - Humans

The urine samples of the human volunteers contained a small background concentration of 2,3-methyl-2,3-butanediol which was present in the samples collected before exposure and the control subjects. In addition, a high and variable concentration of 2-hydroxy-2-methylbutyric acid and 3-hydroxy-3-methylbutyric acid were detected. There were no background concentrations of TAME or TAA.

The maximum TAME plasma concentrations were detected directly after the end of exposure. An average maximum TAME concentration of 0.63 µmol and 4.4 µmol were observed for 4 ppm and 40 ppm dose groups, respectively. TAME decreased rapidly and reached the limit of detection after 12 hours for both concentrations. Elimination of TAME from blood was rapid and two phases with half-lives of 1.2 hours and 3.5 hours could be distinguished. Volunteer blood samples showed detectable concentrations of TAA for 36 hours post exposure when exposed to 40 ppm. TAA was detectable only 6 hours after 4 ppm exposure. TAA clearance followed first order kinetics and was slower than that of TAME.

In the exposed individuals, a significant increase of 2-methyl-2,3-butanediol was noted in all urine samples collected until 72 hours after the exposure to both 4 and 40 ppm TAME concentrations. The elimination of 2-methyl-2,3-butanediol was slow and it was still present at the end of the observation period. Statistically significant increases of 2-hydroxy-2-methylbutyric acid concentrations were detected only 0 to 30 hours after the end of the 40 ppm exposure. The urine level of 3-hydroxy-3-methylbutyric acid was significantly elevated only 12 hours after the exposure to 40 ppm. Neither 2-hydroxy-2-methylbutyric acid nor 3-hydroxy-3-methylbutyric acid were significantly increased in urine after exposure to 4 ppm TAME due to high and variable background.

Based on the recovered amounts of excretory metabolites, 2-methyl-2,3-butanediol (261.3 µmol after 40 ppm), 2-hydroxy-2-methylbutyric (291.8 µmol after 40 ppm) acid and 3-hydroxy-3-methylbutyric acid (330.9 µmol after 40 ppm) were the major metabolites. Free (5.7 µmol) and conjugated TAA (13.6 µmol) and TAME (1.5 µmol) were only minor metabolites in urine. The volunteers showed large variations in the extent of TAME biotransformation between individuals and the rates of excretion and the urinary concentrations of 2-hydroxy-2-methylbutyric acid and 3-hydroxy-3-methylbutyric acid. No statistically significant differences were noted in the excretion of metabolites between the tree individuals. The half-lifes of elimination were not significantly different in the two exposure groups.

Results - Rats

The results showed that rats had higher TAME blood levels (9.6 µmol after 40 ppm and 1.3 µmol after 4 ppm) than humans. This was probably due the higher ventilation rate in rats, which leads to greater uptake. TAME half-life from rat blood was about 1 hour or less. The TAA concentrations were not significantly different between humans and rats after 4 (8.1 µmol) and 40 ppm (1.8 µmol) TAME. Identical metabolites of TAME were formed in rats and humans. In rats, TAME is mainly excreted as 2-methyl-2,3-butanediol and its glucuronide. Further oxidation of TAA to other products is of minor importance due to rapid elimination and glucuronide formation. In humans, 2-methyl-2,3-butanediol is eliminated more slowly than in rats. In addition, TAA seems to be more efficiently oxidised to 2-hydroxy-2methylbutyric acid and 3-hydroxy-3-methylbutyric acid in humans. This metabolic pathway is of lesser importance in rats. The extent of biotransformation in humans is significantly higher when the relative urine metabolite concentrations are compared to the doses received. About 60% of the calculated TAME doses were recovered in human urine compared to 40% in rats. The rest of the TAME is probably exhaled.

Study 2: Human – Kinetics

Six male volunteers were exposed at rest in a chamber to 15 and 50 ppm for 4 hours. Chamber and exhaled air, urine and blood from antebranchial vein were analysed by IR-spectrophotometry (Johanson et al., 1997). Liquid to air partitioning coefficients were determined *in vitro* at 37ºC for blood, saline and olive oil. Because this was an abstract only, no further information was available.

TAME *in vitro* blood/air partition coefficient was 18 and that of oil/blood was 19. The net uptake as a percentage of the inhaled amount was 51% for TAME and 42% for MTBE. The percentage excreted as a percentage of net uptake was 35% of ether in breath, 0.1 of ether in urine and 0.3% alcohol (TAA) in urine. Half-life for TAME was 6.3 hours for blood and 8.0 hours for urine. The blood $t_{1/2}$ for TAA was 5.5 hours for blood and 7.6 hours for urine.

Study 3: Human – Kinetics

Six men per group were exposed in a 15 m^3 exposure chamber to 0, 15 or 50 ppm TAME for 4 hours (Pekari et al., 1997). The average age of these men was 24.2 years. The physical activity of the exposed subjects corresponded to light deskwork. Samples were taken from chamber air three times during each exposure. Biological samples were collected from the test subjects' blood and exhaled air before, during and after exposure. In addition, the subjects collected all urine during 48 hours starting from the time before exposure. The exhaled air, blood and urine samples were analysed using headspace gas chromatography. Toxicokinetic parameters, such as absorption kinetics, metabolism and extraction were determined. The study also contained recording of acute toxicity symptoms (sensory irritation and pre-narcotic signs) and posturographic (steadiness of standing) and reaction time (response to visual signal) measurement.

The blood-air-partition coefficient of TAME was 16.2. TAME blood concentration rapidly increased with a slowing at the end during the 4 hours of exposure period demonstrating an approaching steady state. At 50 ppm, TAME blood concentration reached 13.2 μmol/L and when the exposure was 15 ppm, the maximum blood concentration was 4.8 μmol/L. Independent of the air concentration, the lung retention during the 4 h exposure was 51%. The retention was greater than average in the beginning and lower than average at the end of exposure due to lowered capacity of tissues approaching steady state. The blood concentration of tert-amyl alcohol (TAA) rose to the same level as that of TAME but with a 1-hour delay. Assuming steady state at the end of the exposure a theoretical clearance of about 1 L/min can be calculated. However, based on the calculated half times, a steady state would be reached only after 25-30 hours from the start of exposure. In any case, the estimated clearance figure shows that the metabolism of TAME is not very efficient. Observing from a graph blood concentration vs. time, blood clearance appears to have 2-3 separate phases. The half-life of TAME was about 6.3 hours while for TAA it was approximately 5.5 hours. Significant individual differences were also noted between test subjects. Thirty-four percent of TAME was removed in exhaled air unchanged whereas about 2/3 was metabolised to other products. Only about 0.3% was excreted as the primary metabolite, TAA, to the urine.

Study 4: Rat/Mice - Metabolism and distribution

TAME metabolism and distribution was investigated in F-344 rats and CD-1 mice exposed by gavage or by inhalation to ^{14}C-labelled TAME (Sumner et al., 1997). The study was conducted according to GLP regulations. The gavage doses were 100 mg/kg (rats and mice) 10 mg/kg (rats) and 20 mg/kg (mice). Four animals of both sexes were used for each dose of the gavage studies. Nose only –method was used to expose rats and mice to target concentrations of 100, 500 or 2,500 ppm for 6 hours. One animal of each sex and species was used for each concentration level. Additional rats were assigned to 1-day nose only exposure of 500 ppm ^{14}C-TAME after a 4-day whole body exposure to unlabelled 500 ppm TAME. Three rats from the 1+4-days 500 ppm inhalation study and four rats from the other inhalation dosing regimes were sacrificed immediately after the 6 h exposure for the determination of the retained dose. Other four rats and mice of the gavage and nose only study were transferred to metabolism cages for the time-course collection of expired air, urine and faeces up to 48 hours. Tissues were collected 48 hours after the termination of exposure. TAME and tertiary amyl alcohol (TAA) were quantitated in blood and urine as ^{14}C-TAME equivalents and three metabolites were quantitated in urine (a direct glucuronide conjugate of TAA, an oxidation product of TAA and the glucuronide product of the oxidation product). The blood levels and half-lifes were reported as ^{14}C-TAME equivalents with a percentage of TAME and TAA combined.

TAME distributed evenly throughout the body. ^{14}C-TAME equivalents of most tissues were similar to those of blood following inhalation or gavage exposure. No sex differences were noted in the male and female rats following the 6-hour 100 or 500 ppm exposures. Male and female rats and mice exposed for 5 days had significantly greater ^{14}C-TAME equivalents in tissues, in general, as compared to the ones with one day exposure. After inhalation exposure, tissue levels displayed a supralinear relationship to exposure concentration, with disproportionately lower levels of ^{14}C-TAME equivalents found at the higher inhalation exposures. For gavage regimen, the 14C-TAME equivalents in tissues were higher than or not significantly different from blood levels. The highest levels were in the liver, kidney and intestines. There were no sex differences in the tissue of TAME equivalents in rats with gave doses. Male mice had higher equivalents in the heart, kidneys and blood following either gavage dose or inhalation.

In a respiratory exposure experiment, more than 95% of the dose was recovered. The percentage of recovered ^{14}C-TAME equivalents for male rats exposed to 2,500 ppm was greatest in urine (48%) and for expired volatiles (45%), with lower recovery in faeces (1%) and as [14]CO_2 (3%). Females had a higher percentage in expired air (57%) and a lower percentage in urine (36%) with 1% in faeces and 4% as CO_2. Male and female rats and mice eliminated > 84% within 24 hours following the inhalation or gavage exposure regimens. In 500 and 2,500 ppm inhalation exposure and assuming one compartment model, the half-life was longer in male and female rats (5-9 hours) compared to male and female mice (2-3 hours). When exposed to 100 ppm, the half-life was 18 hours in male rats, 3 hours for female rats and remained near 2 hours for mice. In the low and high dose gavage regimens the half-life was 15-16 hours for rats and 7-12 hours for mice.

For all exposure regimens, 72 to 94% of the recovered radioactivity was excreted in the urine. Following 0-1 hours the termination of exposure, TAME and TAA accounted for more than 87% of the radioactivity recovered. With increasing time, the contribution of these components decreased indicating further metabolism of TAME and TAA. The remaining radioactivity was as [14]CO_2 or was recovered in faeces. The percentage of expired radioactivity in rats was about 30% at 100 ppm and about 55% at 2,500 ppm, while the excreta percentage decreased from over 60% to more than 40%. Mice had a similar trend as the rats in the quantity of radioactivity in expired air. Rats, but not mice, had about 20% more TAME in excreta after a 5-day exposure to 500 ppm compared to 1-day exposure. This was probably due to increased oxidation of TAME to TAA, since the levels of metabolites that require oxidation of TAME or TAA were elevated after the 5-day exposure compared to the 1-day exposure. Rats had 20-40% more of radioactivity in expired air than in excreta after the 100 mg/kg gavage dose, whereas the percentages were similar at 10 mg/kg. Mice had about twice the amount radioactivity in excreta with both doses. The evaluation of metabolites in urine excreted 0 to 48 hours following termination of inhalation exposure or gavage administrations shows that the contribution of the TAA cytochrome P-450 oxidation product (2,3-dihydroxy-2-methylbutane or 2-methyl-2,3-butanediol) and its glucuronide decreases with an increase in exposure or gavage dose. This probably indicates the saturation of the urinary metabolism pathway.

Study 5: Rat/Human - Biotransformation

TAME (> 98%) biotransformation was studied in F-344 rats and one human volunteer after inhalation of [12]C- or ^{13}C-labelled (C2 position) TAME (Amberg et al., 1999). In addition, the biotransformation of the TAME metabolites, tert-amyl alcohol (TAA) was investigated in rats after gavage. Urinary metabolites were identified by GC/MS and ^{13}C-NMR. Free and glucuronidated 2-methyl-2,3-butanediol and a glucuronide of TAA were identified by ^{13}C-NMR GC/MS and LC/MS/MS as major urinary metabolites on the basis of relative intensities of the ^{13}C-NMR signals. Rats (two of each sex) were individually exposed to initial concentration of

2,000 ppm [12]C- or ^{13}C-TAME for 6 hours and urine was collected for 48 hours. The metabolites were identified using ^{13}C-NMR, gas and liquid chromatography and mass spectrometry. The human volunteer was exposed to an initial concentration of 27,000 ppm ^{13}C-TAME for 4 minutes from a 2 l gas sampling bag and the metabolites to urine. To study TAA biotransformation, three male rats were given 250 mg/kg TAA by gavage dissolved in corn oil and urine was collected for 48 hours and metabolites were determined with ^{13}CNMR. No quantification of metabolites was done.

Results - Rat

In rats, one of the major metabolites that were identified was 2-methyl-2,3-butanediol and more abundantly its glucuronide. These compounds are formed from TAME by Cytochrome P450 (CYP 450) oxidation and glucuronyltransferase. The third main metabolite was the glucuronide of TAA, which is formed via P450 hydroxylation of the ether moiety. 3-hydroxy-3-methylbutyric acid and 2-hydroxy-2-methylbutyric acid, formed via P450 oxidation to alcohol, were identified as minor metabolites. No major differences were found in the concentration of the metabolites between males and females. Moreover, the kinetics of the excretion was similar in males and females. Identical metabolites were found in urine samples collected after 24 and 48 hours, but the relative concentrations of the metabolites were different in the samples between 24 and 48 hours compared to those collected between 0 to 24 hours, indicating differences in excretion kinetics between different metabolites. The tert-amyl alcohol given by gavage to rats confirmed that the metabolites were identical to those seen in rats given TAME.

Results -Human

In the human urine samples, in contrast to rats, ^{13}C-TAA was present in significant amounts after ^{13}C-TAME inhalation. The major rat metabolite, 2-methyl-2,3-butanediol, was present only in minor amounts. All other detected metabolites were present in the human urine samples at concentrations similar to those seen in the rat urine. TAME metabolites were also detected in the urine samples collected 48 hours after TAME inhalation.

Other data

Metabolism

Liver metabolism of ETBE, MTBE and TAME was studied in 15 microsomal samples from normal human livers (Hong et al., 2001). It was noted that the formation of the major MTBE metabolite is NADPH dependent and is significantly inhibited by carbon monoxide, which inhibits P450 (CYP) enzymes. The microsomal activities metabolizing different ethers correlated well with each other, which suggests that ETBE, MTBE and TAME are metabolised by the same enzymes. CYP isoform 2A6 seemed to have the highest metabolising activity. Expressed in a baculovirus expression system, 2A6 shows a higher activity in the transformation of ETBE, MTBE and TAME than CYP isoform 2E1. Monoclonal antibody against 2A6 caused a 75-95% inhibition. In addition, the metabolism of the ethers was inhibited in a concentration dependent manner by coumarin, a known substrate for 2A6. With MTBE, the isoform 2A6 is the enzyme which is responsible for the first step in the metabolism, i.e., demethylation to formaldehyde and tert-butyl alcohol (EU risk assessment, 2001). Although there are no studies to show it, logically it is expected that the enzyme also demethylates the 2-methoxy methyl group of TAME yielding formaldehyde and tert-butyl alcohol.

Metabolism and hepatic effects were studied in Wistar rats following a single intragastric dose of 13.2-13.6 mmol/kg TAME or methyl tert butyl ether (MTBE) 13.3-14.0 mmol/kg (Elovaara et al., 1996). The rats were killed 18 hours after the treatment and were sampled for blood and liver samples. The concentrations of MTBE, tert-butyl alcohol, TAME and tert-amyl alcohol was measured with headspace gas chromatography. The induction profile of cytochrome P450 enzymes 2E1 and 2B1 was characterised by measuring the activities of n-nitrosodimethylamine demethylase (NDMAD) and 7-pentoxyresorufin O-dealkylase (PROD). The results showed that the overall rate of ether metabolism and elimination in rats was faster for MTBE than for TAME. The study also showed that cytochrome 2E1 was responsible for the metabolism of MTBE and the cytochrome isoforms 2E1 and 2B1 for the metabolism of TAME in rats.

Dermal and oral absorption

No data on dermal absorption is available for TAME. However in a study by Miller et al. (1997) dermal absorption of tert-butylmethyl ether (MTBE) was studied. 40 mg/kg and 400 mg/kg MTBE were administered using occluded dermal exposure chambers on F-344 rats. The exposure period was 6 hours. The exposed skin area was not reported. The animals were killed 10 minutes to 45 hours after the end of exposure and blood samples were collected and MTBE measured. Plasma levels of MTBE after the exposure were low; peak concentrations were achieved 2-4 hours after dosing. Based on mass balance studies, dermal absorption was estimated to be 16% and 34% at the low and high dose, respectively. This study also compared the AUC of an i.v. dose (40 mg/kg) and oral dose (40 or 400 mg/kg), which demonstrated that MTBE was rapidly and completely absorbed across the gastrointestinal tract (t_{max} plasma = 15 minutes).

Fourteen volunteers were exposed dermally for 1 hour to 51.3 ug/ml MTBE in tap water, 2.8 mg MTBE in 250 ml Gatorade (Prah J. et al., 2004). Samples were collected from blood and exhaled air. The maximum blood concentration, 0.17 umol/l, was found after 15 minutes of the end of oral exposure. Elimination was described as three-compartment model. The calculated blood half lives for each compartment were 14.9 minutes, 102.0 minutes and 417.3 minutes. The respective half lives in the exhaled air were 13.0 minutes, 63.1 minutes and 254 minutes. After dermal exposure, the maximum blood concentration was 0.05 umol/l at 65 minutes after end of exposure. The three half lives in blood were 5.5 minutes, 126.6 minutes and 403.1 minutes. Two half lives were given for the exhaled air, 58.4 minutes and 256.0 minutes. The calculated dermal permeation coefficient was 0.028 cm/hour. After 24 hours the MTBE concentrations were at or below detection level.

Inhalation absorption

Respiratory net uptake was estimated using 10 human volunteers who were exposed for 2 hours to 5, 25 or 50 ppm MTBE under a light workload (Nihlén, 1998). The absorbed dose was calculated as the sum of net respiratory uptake and exhaled air. After two hours of exposure, a concentration of 14 μmol MTBE was reached. This is higher than what seen in volunteers exposed to 40 ppm TAME for four hours (max TAME concentration = 4.4 uM). The study showed that MTBE respiratory uptake was 45%. Another study, which exposed four resting volunteers to 25 and 75 ppm for 4 hours concluded to 40% respiratory uptake. In the study described in the previous paragraph (Prah et al., 2004), the 14 volunteers were exposed also for 1 hour to 3 ppm (10.8 mg/m^3) MTBE. The maximum blood concentration was found at the end of exposure, 0.28 umol/l. MTBE concentration declined rapidly after exposure and virtually no MTBE was present in blood after 24 hours. The blood half lives in the three compartments were 1.9 minutes, 59.0 minutes and 313.7 minutes and the respective half lives in exhaled air were

30.2 minutes, 265.7 minutes. Two half lives were given for the exhaled air, 30.2 minutes and 265.7 minutes.

4.1.2.1.2   Summary of toxicokinetics, metabolism and distribution

Based on the available data, TAME is absorbed efficiently from the rat intestine. TAME is rapidly absorbed from lungs; in studies with human volunteers, the respiration net uptake is 50%. The maximum plasma concentration of humans after 50 ppm TAME exposure for 4 hours was 13.2 μmol/L. Data from an absorption study with MTBE in rat suggests that probably one third or less of a percutaneous TAME dose would be absorbed. Based on a human volunteer study with, MTBE was rapidly absorbed via skin and a dermal permeation coefficient of 0.028 cm/hour was found.

In rat, TAME is distributed evenly throughout the body and is eliminated via respiration, urine and faeces, urine being the main route of elimination while excretion in faeces is only a few percent at maximum.

The elimination from human blood was rapid after the end of inhalation exposure and it occurred in two phases. The blood half-lifes were between 1.2 and 6.3 hours with relatively big individual differences between test subjects. The limit of TAME detection was reached after 12 hours. In rat, the removal via respiration increases with higher doses. The primary enzyme responsible for the metabolism of TAME to tert-amyl alcohol in humans is cytochrome 2A6 mainly present in liver. This is the same enzyme, which converts MTBE to tert-butyl alcohol and formaldehyde. The main human urine metabolites are 2-methyl-2,3-butanediol, 2-hydroxy-2-methylbutyric acid and 3-hydroxy-3-methylbutyric acid. Free and conjugated TAA and TAME were only minor metabolites in urine.

The absorption percentages to be taken to risk characterisation are 100% for oral, 30% for dermal, 50% for inhalation exposure route.

Figure 4.1   TAME's biotransformation in mammals (Amberg et al., 2000)
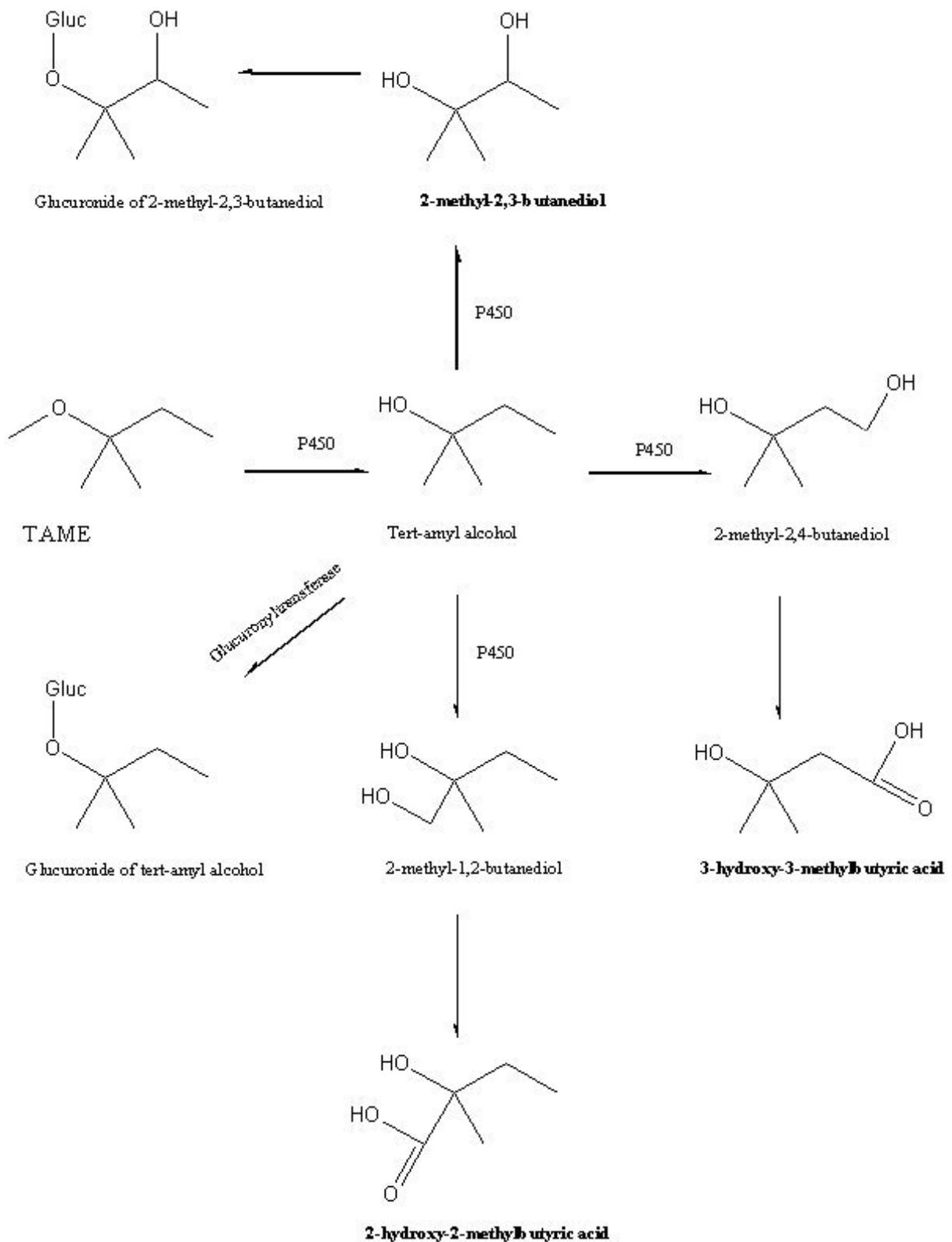
Major human urine metabolites are in bold.

4.1.2.2   Acute toxicity

4.1.2.2.1   *In vitro* studies

Acute neurotoxicity

Martin et al (2002) compared the binding of fuel oxygenates and their metabolites to the gamma-aminobutyric acid(A)-receptor. The binding was studied by measuring the inhibition of the radioligand [3H]t-butylbicycloorthobenzoate ([3H]TBOB) to the GABA receptor in membranes of rat brain. The results showed that the t-ethers TAME, ethyl-t-butyl ether (ETBE) and methyl-t-butyl ether (MTBE) and tertiary alcohols tert-amyl alcohol (TAA) and tert-butyl alcohol (TBA) inhibited binding to the convulsant site of the GABA-receptor. For molecules of the same number of carbons, the alcohols inhibited the binding more potently than the ethers. In the rank of descending binding potency the results were as follows: TAA, TAME, ETBE, TBA, MTBE and ethanol.

4.1.2.2.2   Studies in animals

Inhalation

Five male and five female Sprague-Dawley rats were assigned to a single group, which was exposed in a 1 m^3 exposure chamber to a mean TAME vapour concentration of 5,400 mg/m^3 for 4 hours (IIT, 1991). The rats were clinically observed immediately after removal from the chamber, approximately 2 to 3 hours after the exposure and at least once per day during the 14-day post exposure observation period. Rats were weighed before the exposure, one week later and before necropsy.

None of the rats died from exposure to TAME. In clinical observations, rales were seen in all rats immediately following the exposure. The rales were present in 7/10 animals about 2 hours after the exposure but 3 ¼ hours later all rats appeared normal. Redness around the nose was noticed in 7/10 rats during the study. Necropsy revealed external haemorrhagic lung foci in the lungs in seven rats. However, mostly these foci were comparable in size and number to control rat foci, with the exception of one female rat that had numerous foci and one male that had a diffuse red area on its lungs. Six rats had enlarged mandibular lymph nodes.

Other information

F-344 rats were exposed in a chamber to TAME vapour concentrations of 250, 1,500 and 3,500 ppm (Huntington Life Sciences, 1997). Exposure lasted 6h/day, 5 days/week for at least 65 exposures. Control and 3,500 ppm dose groups had initially 51 rats/sex and 250 and 1,500 ppm dose groups 41 rats/sex. Signs of acute toxicity were prominent in the high dose group. Most animals were prostrate during the exposure of TAME. Also the animals in the mid dose group were prostrate or lethargic during the first month of the exposure. The latter half of the study few animals of this group had laboured breathing and lethargy. The low dose group (250 ppm) showed no abnormal signs during the study. The observations in the high dose group during the recovery period were comparable to the control group.

As a part of the 90-day study, a satellite group of 10 rats/sex were exposed to a 6-hour exposure of TAME at 250, 1,500 or 3,500 ppm (1,060, 6,360 or 14,840 mg/ m^3) and examined using the Functional Observation Battery (FOB) (Huntington Life Sciences, 1997). A dose related

neuromuscular impairment and CNS depression were noted 1 hour after the exposure. The effects were no longer seen after 6 or 24 hour or after repeated exposure to TAME.

Using the same protocol mice were exposed to the same concentrations. Due to high mortality in the 3,500 ppm exposure group, TAME air concentration was lowered and a new high exposure group was established at 2,500 ppm together with a concomitant control group. Control and high dose (3,500 and 2,500 ppm) groups had initially 46 animals/sex and 250 and 1,500 ppm dose groups 36 animals/sex. No neurobehavioral or neuropathological study was conducted with mice. Ten male and 12 female mice died during the first week of the study. The clinical signs in the high exposure animals included mainly laboured breath and prostration. At lower doses, death incidences were similar to control group. In the 1,500 ppm group, TAME caused lethargy and some prostration during the study.

Ten Sprague-Dawley rats were exposed 6 hours daily to target TAME vapour concentrations of 0, 500, 2,000 and 4,000 ppm, 5 days per week for 4 weeks (White et al., 1995). The Functional Observation Battery was used to examine neuromuscular function and sensory perception one week before exposure and after 1, 5 or 20 exposures. Following the final exposure, the rats were fasted for 18 hours after which they were anesthetised.

The acute effects observed in this study included the death of four females and three high dose (4,000 ppm) males. The probable cause of death was due to severe central nervous system depression. Other acute effects noted in the 4,000 ppm group, which were also seen in the 2,000 ppm dose group included sedation, coma, ataxia, coldness to touch, ptosis, hyperirritability, hypoactivity and effect on posture. The FOB evaluation performed 1 hour after exposure confirmed the clinical observations: the 4,000 ppm rats showed reductions in tail pinch response, righting reflex and negative geotaxis together with reduced body temperature, impaired rotorod performance and increased hind limb splay. The signs of CNS depression were absent in animals examined 18 hours after the end of the study.

Dermal

No data available.

Oral

Five female and five male Sprague-Dawley rats per group were administered 2,000, 2,500 or 3,000 mg/kg tert-amyl methyl ether (TAME) by oral intubation (Exxon Biomedical Sciences Inc, 1989a). The test laboratory had no knowledge of the purity of the substance (Batch: MRD-89-374) but they assumed it was sufficiently pure for dosing purposes. Dose range was based on a range-finding study. The animals' symptoms were recorded at 1, 2, 4 and 6 hours after dosing and once daily for 14 days after dosing. Body weights were recorded on the day before dosing, the day of the dosing (day 0), day 7 and day 14 and at termination followed by a gross necropsy. The LD$_{50}$-value was calculated using the Litchfield-Wilcoxon method with equal weighing of the data points.

Four animals died in the 2,000 mg/kg group, seven animals in the 2,500 mg/kg group and eight animals in the 3,000 mg/kg group. One animal was found dead on day 0 but this was thought to have resulted from a dosing error. Clinical observations showed typical signs of sedation and included, for example, ataxia, emaciation, prostration, hypothermia, hypoactivity, dyspnea, hypopnea, wet and dry rales, clear and red nasal and oral discharge, staining of the fur and piloerection. These observations were most prevalent during day 0 and day 1 in all groups. None of the surviving animals showed any observable abnormalities from day 2. The animals that died

showed in gross necropsy abnormalities of the gastro-intestinal (G-I) tract and the urinary bladder, discoloration of the thymus, lungs and liver and staining of the fur. There was a single incident of enlarged heart atrium and one of dilated pelvis in both kidneys. Surviving animals had no observable abnormalities apart from a single incidence of dilated kidneys and one liver abnormality in one group. The predicted LD_{50} values were for females 1,602 mg/kg and for males 2,417 mg/kg and combined sexes 2,152 mg/kg.

4.1.2.2.3   Studies in humans

Six men per group with an average age of 24.2 years were exposed in a 15 m^3 exposure chamber to 0, 15 (64 mg/m^3) or 50 ppm (212 mg/m^3) TAME for 4 hours (Pekari et al. 1997). The physical activity of the exposed corresponded to light deskwork. Samples from blood and exhaled air were taken before, during and after exposure. In addition, the subjects collected all urine during 48 hours starting from the time before exposure. The exhaled air, blood and urine samples were analysed using headspace gas chromatography. Acute toxic symptoms (sensory irritation and pre-narcotic signs) were recorded based on subjective reporting. The answers were analysed and four closely related symptom complexes were formed, namely, "irritation", "feelings in the head", and "mood". The questionnaire was filled at one and 3 hours from the start of exposure and one hour post-exposure. Posturography (steadiness of standing) was conducted and reaction time (response to visual signal) measured. The posturographic measurements were conducted before exposure, at 1, 2.5 and 3.5 hours after start of exposure and 1 hour post-exposure. The reaction time was measured in the morning before the exposure, at 1 and 3.5 hours after the start of exposure and one hour post-exposure.

The reported symptoms were minimal. Two persons reported slight irritation of the eyes, nose and throat and drying of the mouth. One reported this only with the highest concentration, while the other reported all three irritation symptoms also on the control day. When the symptoms belonging to the complex "feelings in the head" were reported, after one hour of exposure, one person reported slight headache in both 15 and 50 ppm exposure concentrations. After three hours, one person in the 15 ppm group and two persons in the 50 ppm reported slight headache. A symptom described as "heaviness of head" was experienced by 2 persons at 1 hour and by 3 persons at 3 hours. Contrary to expectations, on exposure days, five persons reported no "heaviness of head" at 50 ppm after either 1 or 3 hours after the start of exposure. In 15 ppm exposure, three persons reported no heaviness of head at 1 hour and two at 3 hours. When mood changes were reported, one person at 15 ppm and another at 50 ppm reported negative mood. On control day nobody reported a negative mood.

TAME had no significant effect on mood, reaction time or steadiness of standing.

In summary, the reporting on the effects is somewhat inconsistent and not very firm conclusions can be drawn from the study. However, the results seem to indicate that TAME causes some mild acute toxic effects at low doses.

4.1.2.2.4   Summary of acute toxicity

The LC_{50} value via inhalation is over 5,400 mg/m^3 in rats. No dermal studies were available. The predicted oral LD_{50} in rat was for females 1,602 mg/kg, males 2,417 mg/kg and combined 2,152 mg/kg. Classification with R22 could be considered based on the predicted LD_{50} for female rats. In humans, TAME can cause slight irritation of eyes and the upper respiratory tract

and drying of mouth at air concentrations of 60 mg/m^3 but since these effects are marginal 50 ppm (212 mg/m^3) will be taken as the NOAEC for risk characterisation.

4.1.2.3   Irritation

4.1.2.3.1   Skin

Studies in animals

Skin irritation properties of TAME (98.4%) were investigated in a study conducted on three albino rabbits following Good Laboratory Practise (GLP) and OECD guideline 404 (Märtins, 1991). A semiocclusive patch was used to cover a clipped patch on the dorso-lateral area of the trunk to which 500 µl of the test substance had been applied. The patch was left in place for 4 hours after which the exposed skin area was washed carefully. The contralateral skin area acted as control. Dermal irritation was scored and the degree of erythema and oedema, together with any other lesions, was recorded. Draize scores were recorded for each animal at 24, 48 and 72 hours after the application of the substance. The index was separately calculated for erythema/eschar and oedema formation.

All scores were zero at all time points. TAME was not irritating to albino rat skin.

4.1.2.3.2   Eye

Studies in animals

Together with the above-described study a OECD protocol 405 (GLP) was followed to test the eye irritant properties of TAME (Märtins, 1991). Three albino rabbits were administered 100 µl TAME to the conjunctival sac of one eye while the other remained as an untreated control. 24 hours after instillation, the test substance of the treated eye was rinsed with saline. Eye irritation was scored according to Draize and recorded 1, 24, 48, 72 hours, 7, 14 and 21 days after administration.

Table 4.13   TAME eye irritation summarised

Observed effect/ Duration from application	Conjunctiva						Damage to Iris			Cornea Clouding		
	Redness			Swelling								
Animal number	1	2	3	1	2	3	1	2	3	1	2	3
1 hour	0	0	0	4	2	1	0	0	0	0	0	0
24 hours	2	2	2	2	0	0	0	0	0	0	0	0
48 hours	2	2	2	0	0	0	0	0	0	0	0	0
72 hours	1	1	1	0	0	0	0	0	0	0	0	0
7 days	0	0	0	0	0	0	0	0	0	0	0	0
Mean	**1.7**	**1.7**	**1.7**	**0.7**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**

4.1.2.3.3   Summary of irritation

TAME did not cause skin irritation. In the eye irritation test, slight redness and swelling of the conjunctiva were recorded. However, the effects were reversible after 7 days of instillation of the test substance. The mean 24-48-72-score does not imply classifying TAME as eye irritant. In the human volunteer study with six males described in the toxicokinetics and acute toxicity sections, slight irritation of eyes, throat and nose was reported at an air concentration of 60 mg/m^3.

4.1.2.4   Corrosivity

TAME is not expected to be corrosive based on the results of irritation tests.

4.1.2.5   Sensitisation

4.1.2.5.1   Studies in animals

Skin

In vivo studies

The skin sensitisation potential of TAME in guinea pigs was investigated in a Bühler test that followed GLP and the USEPA Toxic Substance Control Act specification (American Petroleum Institute, 1995). TAME was applied as 100% solution to twenty guinea-pigs (10/sex). The induction administration was done by placing an occluded chamber on the shaved back of the guinea-pig. About 0.3 ml of TAME was applied to the chamber, which was left in place for 6 hours. After the exposure period, the chamber and any excess material were removed. The induction treatment was performed once a week and repeated for three times. Fourteen days after the last induction exposure, the challenge was conducted in the same manner as in the induction phase, but on the opposite side of the back midline. To control for irritation reactions at challenge, 10 previously untreated animals were subjected to the same challenge procedure as the animals, which received the induction treatment. For positive control, 1-chloro-2,4-dinitrobenzene was used. See **Table 4.14** for a more detailed description of the experimental design. In the evaluation of results, redness at the challenge site clearly greater than that seen in the irritation control animals was considered an allergic response. In the absence of reaction in the challenge irritation control animals, dermal scores of 1 or greater were considered clearly sensitising. Scores of 0.5, corresponding to barely perceptible erythema, were considered equivocal, depending on the reaction of irritation control animals. Two indices were used, one for the incidence and one for the severity. The incidence index is the percentage of positive responses, i.e., the number of animals with score 1 or higher at 24 or 48 hours. The severity index is the mean value of the male and female dermal scores calculated for both, 24 and 48-hour evaluations

Table 4.14 Experimental design of the Bühler test

Group	Number of animals	Concentration (%)	
		Induction	Challenge
Light mineral oil	10	100	100
Light mineral oil irritation control c	10	-	100
DNCB	10	0.5a	0.3b
DNCB (irritation control) c	10	-	0.3b
TAME	20	100	100
TAME (irritation control) c	10	-	100

DNCB   1-chloro, 2,4-dinitrobenzene,
a)   Vehicle 80% ethanol,
b)   Vehicle acetone,
c)   Treated at challenge only. The same animals served irritation control for all three materials.

At induction, animals treated with mineral oil or TAME did not show irritation, whereas 0.5% DNCB exhibited light irritation after the first induction. At challenge, all animals induced and challenged with mineral oil and irritation control animals (no mineral oil induction) showed no dermal response. All ten positive control animals exhibited dermal responses greater in severity (24 hours: 1.8 and 48 hours: 2.1) than those seen in the irritation control animals (0.2 and 1.4). The incidence index in the positive control animals was 100%. None of the animals induced and challenged with TAME showed a dermal response, the incidence index and severity score being zero.

4.1.2.5.2   Summary of sensitisation

TAME was considered not sensitising in a guinea pig Bühler test.

4.1.2.6   Repeated dose toxicity

4.1.2.6.1   Studies in animals

In vivo studies

Inhalation

Rat, 90-days

Whole body exposure (6 m^3 chamber) was used to expose F-344 rats to TAME vapour concentrations of 250 (1,060 mg/m^3), 1,500 (6,360 mg/m^3) and 3,500 ppm (14,840 mg/m^3) (Huntington Life Sciences, 1997). The study was conducted following GLP. Exposure levels were selected based on available toxicity data and limiting the highest exposure to less than 75% of the vapour explosion limit for the test substance. Exposure lasted 6 hours/day, 5 days/week for

at least 65 exposures. Control and 3,500 ppm dose groups had initially 51 rats/sex and 250 and 1,500 ppm dose groups 41 rats/sex.

Body weights were monitored pre-test, weekly and terminally. Food consumption was recorded one week before treatment and after that weekly. Animals were monitored for viability twice daily and eyes were examined at pre-test, week 14 and treatment termination and during the recovery period. Samples for haematology evaluations were collected on weeks 5, 14 and 18 (recovery). Clinical chemistry samples were taken on weeks 5, 6, 14, and 18. Using separate animals treated similarly 5 male and 5 female rats per group were subjected to renal nephropathy and proliferation studies on weeks 1, 4 and 13 in a separate institute. For the proliferation study, the animals were surgically implanted with an osmotic pump containing 5-bromo-2'-deoxyurine. In addition, removed tissues were stained for α-2u-globulin and hyaline droplets in the proximal tubules. A satellite group of 10 rats/sex/group was evaluated based on a Functional Observation Battery after a single 6-hour exposure 1, 6 and 24 hours after the exposure. FOB was also performed to another group of 10 rats/sex/group of repeated exposure in weeks 2, 3, 5, 9 and 14. A modified version of Schulze's procedure was used to monitor motor activity in weeks 5, 9 and 14 with a group of 10 rats/sex/group. The FOB was performed to all animals before evaluation of motor activity. A neuropathology examination was performed to 6/10 animals. Necropsies and microscopic examination were performed on week 14 (16 or 10 animals/group) and for the recovery group on week 19 (10 animals/group). At week 19 low and mid dose animals were not subjected to necropsy or microscopic examination. Microscopic evaluation was conducted on 39 organs for the high dose and control groups; the lungs were examined in all groups. Adrenals, brain, heart, kidneys, liver, lungs, ovaries and testes were weighed. The following organs were collected from the animals subjected to a neuropathological examination: brain, spinal cord, sciatic nerve, sural nerve, tibial nerve, gasserian ganglia dorsal root ganglia, dorsal and ventral root fibers.

Results

Mortality and physical observations

Two high dose animals, one of both sexes, were found dead on days 36 and 33. Although the deaths occurred soon after blood sampling (day 32) they were believed to have been treatment-related. The cause of death could not, however, be determined in the post-mortem macroscopic and microscopic evaluations. In the high dose group, most animals were prostrate during the exposure of TAME. Also the animals in the mid dose group were prostrate or lethargic during the first month of the exposure. The latter half of the study few animals of this group had laboured breathing and lethargy. The low dose group (250 ppm) showed no abnormal signs during the study. The observations in the high dose group during the recovery period were comparable to the control group.

Ophthalmology

At termination of the study, there seemed to be a dose related increase of corneal scarring in the males and females of the 1,500 and 3,500 ppm dose groups. The incidences were 20% and 28% in the high dose males and females, respectively and 12.5% in the mid exposure males and females. Corneal scarring was not observed in the 250 ppm group. The control incidence was 3.8% in each group. After the 4-week recovery scarring was seen in 30% of the high exposure males and 20% high exposure females, but not in the control animals. However, corneal scarring occurs increasingly with age in F-344 rat. In this study TAME has increased the onset in the 1,500 ppm and 3,500 ppm exposure groups.

Body weights and food consumption

The mean body weight and body weight increase were significantly decreased in the 3,500 ppm dose group. The decrease was slightly more pronounced in the males than in the females: the mean body weight was 6.9% lower in females and 10% lower in males. The mean body weights were still decreased after the recovery period on week 18, with males 9.4% and females 3%. The weight gain was comparable to control. The mean body weights and mean body weight increases in the 250 and 1,500 ppm dose groups were significantly increased with about the same magnitude as they were decreased in the high dose groups, but this change is not considered to be toxicologically significant. The food consumption was statistically significantly decreased in the males and females of the high dose group during the initial 2 weeks of exposure. The low and mid dose group animals had sporadic decreases and increases in food consumption.

Neurobehavioral studies

After the single 6-hour exposure (3,500 ppm) to the satellite group of 10 rats/dose/sex dose related effects on the central nervous system and neuromuscular junction after one hour interval were described. The effects included depression of the central nervous system and neuromuscular junction impairment. The effects were no longer evident after 6 or 24 hours acute exposure and they were not seen after repeated exposure to TAME. In the 1,500 ppm dose group, these effects were only seen in male rats. The NOEL for single exposure in the Functional Observatory Battery (FOB) was 250 ppm. Only evidence of neurotoxicity was the 4-5% weight decrease in the 3,500 ppm males and females. The decrease remained at 3% in the male rats after the recovery period.

Haematology

Platelet counts were statistically significantly increased in weeks 5 and 14 in the males and females of the 3,500 ppm and 1,500 ppm dose groups. The values returned to normal after the 4-week recovery period. There other slight but statistically significant decreases were seen in haemoglobin, haematocrit and/or red blood cell counts compared to controls in all treated males. However, the authors did not consider these changes toxicologically significant since all values were within normal physiological range and changes were not related to the exposure range. In white blood cells, there were no decreases in the total count but an increase in the absolute neutrophils count in high dose males and females and a concomitant decrease in absolute lymphocyte count in high exposure males and females in week 5 and high exposure males in week 14. The authors regarded the changes as usually indicative of stress if they are not accompanied by a change in total white blood cell count. The neutrophils and lymphocyte values had returned to control level, except in the high dose females, which had slight, but statistically significant increases in total white blood cell count and absolute lymphocyte counts.

Clinical chemistry

Total protein was significantly increased in the 1,500 and 3,500 ppm male and female rats. The changes were accompanied by an increase of albumin and globulin with a decrease in albumin/globulin ratio. These changes reversed after the 4-week recovery period. Alkaline phosphatase activity was significantly decreased in all treated males at week 5 and in 250 ppm and 3,500 ppm groups also at week 14. In addition, there was a significant decrease in female alkaline phosphatase activity at 1,500 and 3,500 ppm. Apart from the high dose male group the activity levels were normal after the recovery period. The changes were within normal variability and were not considered toxicologically relevant. There was also a slight increase in blood urea

nitrogen (BUN) in low- and mid-dose males at week 5 and in high exposure males at week 19. In addition, there was a series of other sporadically and non-consistently occurring changes in clinical chemistry parameters, which were not of toxicological significance.

Organ weights and microscopic findings

A statistically significant 4-5% decrease was noted in the mean absolute brain weight of the 3,500 ppm males and females at termination of exposure. This was accompanied by a significant increase in the brain-to-body weight ratio in the 3,500 ppm males. This change remained after the recovery period in males, although the mean absolute weight increase was now at 3%. The female brain weights, absolute or relative to body weight, were normal at the end of the recovery period. The findings in the male brain weight decrease were not supported by the dimension measurements in the neuropathology animals, which had brain weights comparable to control group. However, the results were obtained by whole-body perfusion, which together with the fixation process may have caused small changes go unnoticed. Liver weights (absolute, relative to body weight and relative to brain weight) were increased in all treated males (250, 1,500 and 3,500 ppm) and females of 1,500 ppm and 3,500 ppm groups. The percent changes in absolute weight compared to control rats were 19% (250 ppm), 18% (1,500 ppm) and 22% (3,500 ppm). When expressed as relative to brain weight, the differences between control and the treated groups were 15% (250 ppm), 17% (1,500 ppm) and 26% (3,500 ppm). The liver weights returned to normal after the recovery period. No histopathologic findings were seen in the livers, which would have correlated with the weight changes. Kidney to body weight and kidney to brain weigh ratios were increased in the 3,500 ppm males and females. In females, the kidney to body weight changes to control was 15% and relative to brain weight the change was 13%. The respective male values were 21% and 13%. Absolute and relative kidney weights were increased in 1,500 ppm females. Absolute kidney and kidney to brain weight ratios were statistically significantly increased relative to control males in the 1,500 ppm (18% abs., 15% org/brn) and 250 ppm (12% abs., 8% org/brn) group males. The increase in the latter groups was consistent with the increase in terminal body weights (250 ppm: ~9% and 1,500 ppm 15% higher than the control). In microscopy, evidence of cell proliferation and male rat specific α2u-globulin syndrome were seen. These findings contributed to the weight increase in males but were not present in the females. There was also statistically significant increase in the heart to body weight in the 3,500 ppm males (15%) and females (7%), which remained increased (10%) only in males after the recovery period. Absolute heart weight was increased in the 250 ppm group (11%) and in the 1,500 ppm males, absolute (17%) and heart weight relative to brain weight was increased (14%). However, these changes were attributed to increase in body weight since the heart to body weight ratios were comparable to controls. Adrenal (absolute, relative to brain and body) weights were statistically significantly increased in the 3,500 ppm dose males (55%) and females (45%). In the 1,500 ppm group, the absolute adrenal weight increase in males was 20% and in females 16%. Also the adrenal to brain weight ratios were increased in this dose group, 17% in males and 15% in females. In the 250 ppm group, only males had an increased absolute adrenal weight (14% abs, 10% relative to brain weight). Following the four-week recovery period, the increases in adrenal weights had dropped in the high dose females to 11% increase in the absolute weights. In the high exposure recovery-group males the mean absolute adrenal weight was comparable to the control group adrenal weight. Only the adrenal to body and adrenal to brain weights were statistically significantly increased in the high dose males. This was attributed to lower terminal body and brain weight in these animals. There were no microscopic lesions found and the weight changes were attributed to stress due to exposure. There were no adverse treatment-related histopathological findings seen in either the whole body exposure or the neuropathology portion of the study.

Discussion

The increased weights in the absolute and relative adrenal weights in the 3,500 and 1,500 ppm males and females and 250 ppm males were explained by the investigators as a response to stress due to the exposure to the test material. They did not consider this a direct effect of the test material because there were no microscopic lesions in the adrenals. Only male rats showed a2u-syndrome-related cell proliferation of the kidney tubules, which could have attributed to the weight change in male kidneys at 3,500 ppm. The increase in the female kidney weights at 3,500 and 1,500 ppm could not be explained by any toxicological phenomenon. After the 4-week recovery period, the high dose males and females had increased kidney to body weights, although the absolute and kidney to brain weights were comparable to control.

Based on the liver weight increase at all dose groups, no NOEC can be set for males. The investigators set the NOEC to 250 ppm for females based on the increased liver and kidney weights at 1,500 ppm. While liver weight increase is a typical form of adaptation and could be seen as non-adverse, it is more difficult to account for the adrenal or especially the kidney or weight increases simply as adaptive. It is debatable whether, e.g., the adrenal organ weight increases with no adverse changes in microscopy or blood values can be discounted as "indirect" or "stress-related". However, although there was an 8% increase in kidney/brain weight and the 10% increase in adrenal/brain weight noted in males it is chosen that this does not qualify as a LOAEC based on the following reasoning. The weight increases were statistically significant only when presented as absolute weight or organ/brain weight values and since the body weight of the low dose males also increased (+9%) a factor that may have played a contributing or confounding role, and since there was no histopathological damage present in these animals the exposure level of 250 ppm will be considered as a NOAEC, although a marginal one.

Conclusion

A NOAEC is set to 250 ppm based on the organ weight increases in male and female liver, adrenals and kidneys.

Mice, 90-days

Whole body exposure was used to expose CD-1 mice to TAME air concentrations of 250, 1,500 and 3,500 ppm (Huntington Life Sciences, 1997). The study was conducted following GLP. Exposure lasted 6 hours/day, 5 days/week for at least 65 exposures. The test protocol was for most parts the same as the one described above for the F-344 rats. Exposure levels were selected based on available toxicity data and limiting the highest exposure to less than 75% of the explosive limit for the test substance. Due to high mortality in the 3,500 ppm exposure group, TAME air concentration was lowered and a new high exposure group was established at 2,500 ppm together with a concomitant control group. Control and high dose (3,500 and 2,500 ppm) groups had initially 46 animals/sex and 250 and 1,500 ppm dose groups 36 animals/sex. In the study with mice, a satellite group of 8 mice/sex/dose were used to examine the effect of TAME exposure on liver cell proliferation. No neurobehavioral or neuropathological study was conducted with mice.

Results

Clinical observations

At the original high exposure level 3,500 ppm, 26/46 males and 14/46 females died within three exposures to TAME. At the new exposure level 2,500 ppm, 14/46 male and 13/46 females died

compared to 3 male and 2 female control mice that died during the course of the study as a consequence of blood collection. Four deaths in the high exposure males and one death in high exposure females were associated with blood sampling. The remaining deaths were attributed mainly to TAME and occurred during the first week of the study. The clinical signs in the high exposure animals included mainly laboured breath and prostration. The mice in the 1,500 ppm were mostly lethargic and some were prostrate. At lower doses, death incidences were similar to control group.

Clinical chemistry

Alanine aminotransferase and blood urea nitrogen levels were elevated in the 2,500 ppm females at week 14, total protein was increased in males at week 5 and elevated globulin in females of 1,500 and 2,500 ppm at week 5. The changes mostly returned to normal after the 4-week recovery period.

Organ weights and microscopy

Absolute, relative to body and brain liver weight was significantly increased in the 2,500 ppm males and females and in the 1,500 ppm males. In the histological examination, hepatic centrilobular hypertrophy and increased proliferation were found, which is consistent with the liver weight increase. Liver hypertrophy was only seen in the mice of the 2,500 ppm dose groups. These changes had returned to normal after the recovery period, except for the slightly elevated liver to body and brain weight in females. In female mice, statistically significant increases in liver cell proliferation were noted at 250, 1,500 ppm and 1,500 but not at 2,500 ppm male mice, mainly only at week 1 and without dose-relationship. The effect was also seen at weeks 4 and 13 but to a smaller extent and more inconsistently. The increased labelling indices correlated with centrilobular and mid-zonal swelling of hepatocytes in mice exposed to 1,500 and 2,500 ppm.

Conclusion

Given the absence of dose-response in the female liver proliferation findings and their transient nature, the NOAEC in this study is 250 ppm, for both female and male mice.

Rat, 4 weeks

Ten Sprague-Dawley rats were exposed 6 hours daily to target TAME vapour concentrations of 0, 500, 2,000 and 4,000 ppm, 5 days per week for 4 weeks (White et al., 1995). The exposures were conducted in a 1 m^3 cubic chamber. Body weights were measured at the study initiation and termination and weekly during the study. In addition to the daily general toxicity assessment, the animals were evaluated with a Functional Observation Battery for neuromuscular function and sensory perception one week before exposure and after 1, 5 or 20 exposures. Following the final exposure, the rats were fasted for 18 hours after which they were anesthetised. Blood samples were collected for the determination of blood parameters. Necropsy was performed to 10 rats/group and the following tissues were weighed and fixed: brain, adrenal glands, gonads, heart, kidneys, liver, lungs and spleen. Only control and 4,000 ppm dose animals' organs were processed for microscopic examination.

Results

Four females and three high dose (4,000 ppm) males died. The probable cause of death was due to severe central nervous system depression. Other observations in the 4,000 ppm group which

were also seen in the 2,000 ppm dose group included sedation, coma, ataxia, coldness to touch, ptosis, hyperirritability, hypoactivity and effect on posture. The FOB evaluation performed 1 hour after exposure confirmed the clinical observations: the 4,000 ppm rats exhibited reductions in tail pinch response, righting reflex and negative geotaxis together with reduced body temperature, impaired rotorod performance and increased hind limb splay. The signs of CNS depression were absent in animals examined 18 hours after the end of the study. Body weight gain was significantly reduced only in male rats of the 4,000 ppm dose group. Mean body weight of this group was 14% lower. Relative liver weights were significantly increased in both sexes of the 2,000 and 4,000 ppm dose groups. The 4,000 ppm males had in addition relative organ weight increases of brain, lungs, testes, adrenals and kidneys. In addition to the liver weight increase, females of the 4,000 ppm group had a relative organ weight increase of the adrenals. Clinical chemistry showed minimal changes which were manifested as increased serum cholesterol in the 2,000 and 4,000 ppm males and 4,000 ppm females. Males of the 4,000 ppm group also had reduced serum triglycerides. Only a single high dose rat had increased serum alanine aminotransferase. The animal also displayed multifocal hepatocellular necrosis, which can be associated with the liver transferase increase. However, since this was an isolated incidence the toxicological significance remained unclear.

Conclusion

Based on the liver weight increase in both sexes, the NOAEC from this study is 500 ppm.

Dermal

No studies were available.

Oral

Rats, 4 weeks

Five male and five female Sprague-Dawley rats were administered 0, 125, 500 or 1,000 mg/kg TAME in corn oil by gavage (Daughtrey et al., 1995). Negative controls were given corn oil only. The dose was given once daily, 7 days a week for a period of 29 days. Rats were observed daily for clinical sings and weight was prior first dosing and weekly thereafter. Food consumption was measured weekly. Haematology and clinical chemistry parameters were determined from the blood sample collected at necropsy. Organ weights were measured for the kidneys, adrenals, liver, testes and ovaries. In addition to these organs, heart and spleen or any organs appearing abnormal were processed and stained for microscopy from the control and high dose animals.

Results

Four animals died in the high dose group. The deaths occurred between the days 6 and 9 and two of them were presumed test material related, although the precise cause of death was not identified. The majority of animals did not exhibit unusual symptoms during the experiment. Lung rales and anogenital staining was observed at low frequency in 1,000 mg/kg animals. Mean body weights were significantly lower in the 1,000 mg/kg males on 7 (-14%), 21 (-18%) and 28 (-19%). Females had mean body weights comparable to controls. Food consumption was significantly lower in the 1,000 mg/kg males and females during week 1 and also during week 2 in the 1,000 mg/kg males. A dose-related increase of relative (body) and absolute adrenal weight was noted and it was statistically significant in the 500 (mid) and the 1,000 (high) mg/kg males. The following mean adrenal weights were measured (grams): ctrl: 0.057 ± 0.010, 125 mg/kg:

0.074 ± 0.015, 500 mg/kg: 0.082 ± 0.008*, 1,000 mg/kg: 0.100 ± 0.010** (*p<0.05, **p < 0.01). The mid and high dose males also had increased relative kidney weights. The liver weights were not statistically significantly affected. Females displayed no statistically significant differences in any organ weights. The high dose males had increased activated partial thromboblastin time and increased blood glucose but the biological significance of these findings was unknown. No treatment-related tissue lesions were recorded, including the male high- and mid-dose kidneys and liver which were enlarged.

Conclusion

Based on the adrenal weight increase in the male adrenals, the 125 mg/kg dose is set as a LOAEL. Even if there appears to be a dose response with the adrenal weight increase starting already at 125 mg/kg, the effect seen at this dose was not statistically significant making it a possible chance finding. Although the LOAEL is set at this dose level, it should be noted that this LOAEL is quite debatable.

4.1.2.6.2   Summary of repeated dose toxicity

A NOAEC of 250 ppm (1,060 mg/m^3) is selected for respiratory exposure based on the organ weight increases seen in the 90 day study with male and female F-344 rats. For oral route, a LOAEL of 125 mg/kg is selected based on the dose related adrenal weight increase at dose of 125 mg/kg and higher in male rats in the 28 days study. No classification is warranted based on the effects noted.

4.1.2.7   Mutagenicity

4.1.2.7.1   *In vitro* studies

Microbial cells

Study 1

A study by Herbold (1991), investigated the ability of TAME to induce point mutations using the Salmonella/microsome test conducted according to the OECD guideline 471. TAME (98.4%) doses were 0, 8, 40, 200, 1,000, 2,000 and 5,000 µg/plate and the strains used were: TA98, TA100, TA1535 and TA1537. Doses up to and including 40 µg did not cause toxicity. At higher doses, TAME had a weak strain-specific bacteriotoxic effect. Nevertheless all the doses could be used for assessment. No indications of mutagenic effects were seen at doses up to 5,000 g/plate, with or without metabolic activation with male Sprague-Dawley liver S9 fraction.

Study 2

Another study, conducted according to GLP regulations but without mention of a specific guideline, examined TAME mutagenicity with strains TA98, TA100, TA1535, TA1537 and TA1538 (Exxon Biomedical Sciences Inc, 1989c). Doses were 0, 100, 316, 1,000, 3,162 and 10,000 µg /plate. Sprague-Dawley rat livers were used for the preparation of S9-fraction. Test substance purity was approximately 93%. Toxicity pre-test was conducted using TA98 and no toxicity was seen even at a dose of 10,000 µg/plate. The test was conducted twice. TAME was

not mutagenic to the tested Salmonella strains at doses up to and including 10,000 µg/plate with or without metabolic activation.

Study 3

In a non-guideline and non GLP study, five doses were used to examine the mutagenicity of 94.5% TAME on Salmonella strains TA98, TA100, TA1535, TA1537 and TA1538. TAME doses were 0, 100, 316, 1,000, 3,162 and 10,000 µg/plate (Daughtrey et al., 1995). No toxicity was noted at doses up to 10,000 µg/plate. No increase of mutation frequency was noted in any of the strains or doses.

Mammalian cells

CHO/HGPRT

TAME's mutagenic potential of was investigated further in Chinese hamster ovary cells by evaluating it's potential to elicit forward mutations to hypoxanthine-guanine phosphoribosyl transferase (HGPRT) gene (American Petroleum Institute, 1996b). TAME of unknown purity was added to a culture of Chinese hamster ovary cells (CHO-K1-BH4) with and without rat liver S9 activation mix at concentrations ranging from 1,000 to 5,000 (no S9) or 500 to 5,000 µg/ml (S9). These concentrations were selected based on the cloning efficiency. Cloning efficiency relative to solvent controls was 89% at 5,000 µg/ml without S9-activation and 42% with S9-activation. Cytotoxicity was evaluated by determining the cell cloning efficiency. The mutant frequency was calculated by dividing the total number of mutant colonies by the number of cells selected, corrected for the cloning efficiency of cells prior to mutant selection, and expressed as TG-resistant mutants per 10^6. Mutant frequencies generated from doses giving 10% or less survival were not considered as valid data points. The response was considered positive when there were more than 40 mutant colonies per 10^6 clonable cells. The laboratory 3 year historical control data of solvent control mutant colony frequency ranges from 0 to 20 or 0 to 24 with S9. Ethyl methane sulphate was used as a positive control.

Results

None of the treated cultures exhibited mutant frequencies greater than 40 mutants per 10^6 clonable cells in the non-activated or activated cultures and the result was concluded to be negative.

Table 4.15 Mutants frequencies per 10^6 clonable cells in the CHO/HGPRT assay

Treatment (ug/ml), exposure for 5 hours at 37 C	-S9	+S9
1,000	3.9	4.5
2,000	< 0.5	5.4
3,000	1.6	6.8
4,000	6.4	4.4
5,000	0.6	11.6

Chromosome aberrations in CHO

A study conducted according to GLP but with no reference to a guideline evaluated the clastogenic potential of TAME in Chinese hamster ovary cells (CHO) (American Petroleum Institute, 1996a). No data of test substance purity as provided. Selection of dose levels was based

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on cell growth inhibition relative to solvent control. Since at least 50% inhibition was noted at 5,000 µg/ml in both non-S9-activated and activated test systems, the doses were 313, 625, 1,250, 2,500 and 5,000 µg/ml. The average generation time was delayed at the highest dose with metabolic activation to almost 24 hours, based on which the harvest time was adjusted to 20 hours. The cell harvest time for non-activated cells was 12 hours.

Results

Toxicity was approximately 43% at the highest dose (5,000 µg/ml) evaluated for chromosome toxicity. With metabolic activation, toxicity was 72% at 5,000 µg/ml. A statistically significant increase in chromosome aberrations was seen at the 2,500 µg/ml dose level without metabolic activation. This was, however, in the range of historical control and was not considered biologically significant. With S9-fraction, statistically significant increases in the percentage of cells with aberrations were observed at the 1,250, 2,500 and 5,000 µg/ml dose levels. Based on these findings, TAME was concluded positive for the induction of chromosome aberrations in Chinese hamster ovary cells. The aberration types were mainly chromatid-type breaks and exchanges with some gaps occurring. The historical control percentage of S9-activated CHO cells was reported to range between 0 to 6%. For the analysis, 200 cells were scored.

Table 4.16 Cytogenetic analysis of CHO cells with TAME

Treatment	Mitotic index	Aberrations/Cell	Cells with aberrations (%)
Untreated (harvest 12 hours)	5.3	0.010 ± 0.100	1.0
Ethanol (harvest 12 hours)	5.7	0.000 ± 0.000	0.0
625 µg/ml TAME -S9 (harvest 12 hours)	5.0	0.010 ± 0.100	1.0
1,250 µg/ml TAME -S9 (harvest 12 hours)	5.1	0.000 ± 0.000	0.0
2,500 µg/ml TAME -S9 (harvest 12 hours)	3.1	0.040 ± 0.196	4.0**+
5,000 µg/ml TAME -S9 (harvest 12 hours)	4.3	0.015 ± 0.122	1.5
Mitomycin C 0.08 µg/ml (harvest 12 hours)	2.8	0.100 ± 0.317	9.5
Untreated (harvest 20 hours)	10.1	0.000 ± 0.000	0.0
Ethanol (harvest 20 hours)	6.3	0.005 ± 0.071	0.5
625 µg/ml TAME +S9 (harvest 20 hours)	10.2	0.020 ± 0.140	2.0
1,250 µg/ml TAME +S9 (harvest 20 hours)	5.3	0.120 ± 0.395	10.0**
2,500 µg/ml TAME +S9 (harvest 20 hours)	4.6	0.290 ± 0.631	21.0**
5,000 µg/ml TAME +S9 (harvest 20 hours)	1.1	0.900 ± 1.742	39.5**
Cyclophosphamide 10 µg/ml (harvest 20 hours)	3.2	0.630 ± 1.528	32.5**

** $p \leq 0.01$; Fisher's exact test
+   Statistically significant but within range of historical controls.

4.1.2.7.2 *In vivo* studies

In a study conforming to GLP regulations, five female and five male CD-1 mice were given a single intraperitoneal injection of 150, 375 or 750 mg TAME in corn oil per kg body weight (Exxon Biomedical Sciences Inc, 1989b). The doses were selected based on a preliminary toxicity test in which there was mortality still at 1,000 mg/kg dose. Negative control and TAME treated animals formed three different sample time groups (24, 48 and 72 hours), consisting of

five mice of each sex per group. Positive control (cyclophosphamide) mice were sampled at 24 hours only. 1,000 polychromatic erythrocytes (PCE) were examined for micronuclei and the ratio of PCE and normochromatic erythrocytes (NCE) was calculated from 1,000 erythrocytes. A standard one way analysis of variance and regression analysis were performed

Results

TAME did not induce statistically significant increases in micronucleus formation in either sex of CD-1 mice.

Table 4.17 Mouse bone marrow micronucleus assay

Sacrifice time	End point	Sex	Control	150 mg/kg	375 mg/kg	750 mg/kg
24 hours	Micronuclei [1]	M	1.6 ± 1.3	0.8 ± 0.8	1.8 ± 1.1	2.0 ± 1.4
	Micronuclei	F	1.2 ± 0.4	1.4 ± 1.1	0.6 ± 0.9	2.2 ± 1.8
	%PCE [2]	M	53 ± 6.3	52 ± 6.7	56 ± 3.6	54 ± 5.2
	%PCE	F	54 ± 5.0	60 ± 7.0	53 ± 7.9	52 ± 11
48 hours	Micronuclei	M	1.4 ± 1.3	1.6 ± 1.7	1.2 ± 0.4	1.6 ± 0.8
	Micronuclei	F	1.2 ± 1.3	1.2 ± 0.8	1.2 ± 0.8	1.6 ± 1.1
	%PCE	M	52 ± 7.7	54 ± 8.6	59 ± 6.0	61 ± 7.0
	%PCE	F	57 ± 6.3	60 ± 3.7	59 ± 5.6	61 ± 4.6
72 hours	Micronuclei	M	0.8 ± 0.4	0.8 ± 0.8	1.8 ± 1.3	0.6 ± 0.9
	Micronuclei	F	1.0 ± 0.7	2.0 ± 1.2	0.4 ± 0.5	1.0 ± 0.7
	%PCE	M	55 ± 6.2	58 ± 4.5	60 ± 3.2	65 ± 6.4
	%PCE	F	62 ± 6.6	60 ± 7.7	61 ± 4.6	65 ± 3.1

1)   Mean micronuclei ± SD per 1,000 polychromatic erythrocytes
2)   Mean percentage PCEs ± SD; PCE/(PCE+NCE) · 100

Discussion

The mutagenicity of TAME is unclear to some extent. No mutagenic activity was seen in any of the bacterial assays or in Chinese hamster ovary cell when the ability of TAME to cause point mutations was investigated. However, TAME caused a clear increase of aberrations, which increased with dose, in Chinese hamster ovary cells *in vitro* when metabolic activation was present. However, a micronucleus study conducted in mice gave a negative response at all sampling times.

According to the toxicokinetics study by Sumner et al., (1997), TAME and tert-amyl alcohol are relatively evenly distributed in CD-1 mice bodies, including femur, after oral doses of 100 or 10 mg/kg. As the aberrations occur only with S9 activation, it appears that one of the TAME metabolites causes the positive response in the chromosome aberrations assay. Cytochrome isoform 2A6, responsible for the conversion of tert-butyl methyl ether (MTBE) to tert-butyl alcohol and formaldehyde is also responsible for the oxidative demethylation of TAME. At the first stage of the metabolic pathway tert-amyl alcohol and presumably formaldehyde are formed. For MTBE the role of formaldehyde *in vitro* genotoxicity has been demonstrated by co-incubation with aldehyde dehydrogenase. In addition, MTBE tested in an *in vitro* mouse lymphoma assay, which measures the frequency of forward mutations, resulted in a positive result. This was hypothesised to have been caused by the formation of formaldehyde

extracellularly. Formaldehyde has been reported to cause chromosome aberrations *in vivo* and *in vitr*o (IARC Monograph 62). However, in this case, formaldehyde is not likely to play a significant role in an *in vivo* setting since it is cleared rapidly in human body by formaldehyde dehydrogenase present in several tissues (IARC Monograph 62). To serve academic interests, the role of formaldehyde in the mutagenesis could be studied further by an *in vitro* chromosome aberration experiment where formaldehyde dehydrogenase with its cofactor NAD is present.

Tert-amyl alcohol, which is not a major urine metabolite, displayed a blood half-life of about 7 hours after 40 ppm TAME exposure. It was detectable in blood still 36 hours after the exposure whereas TAME disappeared after 12 hours. No data on mutagenicity was available for the tert-amyl alcohol.

4.1.2.7.3   Summary and conclusion of mutagenicity

Summary

Although a clear positive result was obtained in the *in vitro* CHO clastogenicity assay in the presence of S9 activation, it is probable that the cause for this may have been formaldehyde, which is transiently formed during metabolism. However, formaldehyde is not likely to be a concern in *in vivo* because it is efficiently cleared from the tissues by formaldehyde dehydrogenase. This is supported by the result of a valid mouse micronucleus study, which showed that TAME does not cause chromosome aberrations *in vivo*. Moreover, the compound structure does not give rise to concern for mutagenic activity.

Table 4.18 Summary of mutagenicity studies

Study type	Doses	Result with S9	Result without S9	Reference
Ames	0, 8, 40, 200, 1,000, 2,000 and 5,000 µg/plate	Negative	Negative	(Herbold, 1991)
Ames	100, 316, 1,000, 3,162 and 10,000 µg/plate	Negative	Negative	(Exxon Biomedical Sciences Inc, 1989c)
Ames	100, 316, 1,000, 3,162 and 10,000 µg/plate	Negative	Negative	(Daughtrey et al., 1995)
CHO/HGPRT	to 5,000 (no S9) or 500 to 5,000 µg/ml (S9)	Negative	Negative	(American Petroleum Institute, 1996b)
CHO/chromosome aberrations	313, 625, 1,250, 2,500 and 5,000 µg/ml	Positive	Negative	(American Petroleum Institute, 1996a)
In vivo: Micronucleus in CD-1 mice (i.p.)	150, 375 or 750 mg/kg (sampling at 24, 48 and 72 h)	Negative	-	(Exxon Biomedical Sciences Inc, 1989b)

Conclusion

TAME is not considered mutagenic. No further testing is considered necessary.

4.1.2.8   Carcinogenicity

TAME (98%) was administered orally to groups of 100 male and 100 female 8 weeks-old Sprague-Dawley rats in gavage doses 0, 250 and 750 mg/kg (Belpoggi et al., 2002). A concurrent test with di-isopropyl ether (DIPE) was conducted with the TAME experiment. The

administration was given 4 days/week, for 78 weeks. The animals were maintained until spontaneous death. The experiment ended after 135 weeks of treatment with the death of the last animal, which was 143 weeks old. The publication claimed GLP, but no GLP statement was available nor was there a record of the facility in question in the OECD database. The statistical analysis was performed using the χ^2-test to evaluate differences in tumour incidences between treated and control rats. Cochran-Armitage –test was used to evaluate dose-relationship. For a more detailed description of the protocol, the publication referred to another carcinogenicity study with methyl and ethyl alcohol in the same volume Soffritti et al., (2002). The protocol used in that study is described here.

Drinking water and feed consumption were determined once a week for the first 13 weeks and twice a week for 104 weeks. The study lasted 104 weeks. Animals were weighed every 8th week until the end of the experiment. Clinical examination was performed every 2 weeks. Upon death the animals underwent necropsy in which the following tissues and organs were examined: skin and subcutaneous tissue, brain, pituitary gland, Zymbal-, parotid-, Harderian- and submaxillary glands, cranium, tongue, thyroid, parathyroid, pharynx, larynx, thymus, mediastinal lymph nodes, trachea, lung and main stem bronchi, heart, diaphragm, liver, spleen, pancreas, kidneys, adrenal glands, oesophagus, stomach, intestine, urinary bladder, prostate, gonads, urinary bladder and interscapular fat pad.

No significant differences were noted in the body weight, daily water or feed consumption, behaviour between the treated and the control rats. No test substance related signs of toxicity were reported. The male rats had a decrease in survival between the weeks 40 and 104 when compared to controls.

When all malignant tumours frequencies were compared no differences were seen between the TAME-treated and controls. The following tumours were reported in creased incidences, although most of them did not have statistical significance.

Table 4.19 Tumour incidences after oral TAME exposure

	0 mg/kg/d M	0 mg/kg/d F	250 mg/kg7d M	250 mg/kg/d F	750 mg/kg/d M	750 mg/kg/d F
Ear duct carcinomas	1/100	2/100	4/100	4/100	5/100	4/100
Interstitial tumours of the testis	0/100	-	3/100	-	4/100	-
Oligodendroglioma of the brain	0/100	2/100	4/100	2/100	3/100	2/100
Haemolymphoreticular neoplasias (lymphomas and leukaemia)	17/100	7/100	7/100	14/100 +	21/100	27/100 *+

*   p < 0.01 using χ^2-test
+   p < 0.05 using Cochrane-Armitage test for dose-relationship

When the female haemolymphoreticular neoplasias were broken down by histocytotype, in the 750 mg/kg dose group the most common tumour type was lymphoimmunoblastic lymphoma (77.8% versus 42.9% in controls), lymphoblastic lymphoma was present in 3.8% (42.9% controls) and lymphocytic lymphoma (LCL) was found in 3.7% while controls had no LCL. LCL was also seen in the mid dose females in 14.3% of the cases. Mid dose female lymphoblastic lymphoma incidence was 14.3% and the lymphoimmunoblastic lymphoma rate 42.9%. All rats had also histiocytic sarcoma (HS), which did not appear dose related. In female rats, the HS incidences were: control: 14.3%, 250 mg/kg: 28.6% and 750 mg/kg: 18.6%.

Discussion

The only significant increase in tumour incidence was seen in haemolymphoreticular neoplasia in females at 750 mg/kg. A significant dose-response was calculated for both treated female groups. In the absence of statistical significance or dose relationship, the other tumours listed as increases are likely to be chance findings. Determination of dose-response is hampered because only two treated dose levels were used.

The study lacks in reporting, e.g., no mortality figures were given, which makes the assessing of effective group number and tumour incidences difficult. Moreover, the reported lack of signs of general toxicity is difficult to assess since no data is available. Yet it is stated in the study that a decrease of mortality was seen in TAME treated males between the 56th and 88th week of the study when compared to controls.

In a study with the same design (Belpoggi, 1995), a similar increase of incidence in haemolymphoreticular tumours was noted after administration of methyl tert-butyl ether (MTBE), a substance closely related to TAME in structure. The study also found a statistically significant increase of interstitial cell adenomas of the testis, which the authors of the current study suggest were also slightly, although not statistically significantly increased with TAME. The histocytotype of the haemolymphoreticular neoplasia induced by MTBE were similar to that induced by TAME. With the highest TAME dose (Females, 750 mg/kg) the most typical neoplasia was lymphoimmunoblastic lymphoma (77.8%), while with MTBE (Females, 1,000 mg/kg) the frequency of this histocytotype was 66.7% of all haemolymphoreticular neoplasia (12/60) recorded. A 2-year study with inhaled MTBE conducted by Bird et al., 1997 did not find an increase of haemolymphoreticular tumour but they did note an increase in testicular tumours at 3,000 and 8,000 ppm. However, they did not consider this finding test substance related due to unusually low control incidence.

In the Belpoggi study with TAME or MTBE, no exact data was given on historical control incidence, but it was stated in the original MTBE report that the historical incidence of haemolymphoreticular tumours is below 10% for female rats. The TAME study stated that the same rat strain and methodology has been used in both studies.

In description of the results in the MTBE-study, 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. 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 the other group, which may lead to a false positive correlation. However, in the TAME-study, the decrease in survival was reported to have occurred only observed in the TAME-treated males between the weeks 40 and 104 and a significant increase of tumours was noted in females only.

The neoplasia were of the lymphoid origin localised in the lungs. The differentiation of pluripotent stem cells to lymphoid progenitor cells takes place in the bone marrow. The mouse micronucleus study with TAME, which measures the substance's ability to induce damage in chromosomes of the bone marrow cells, was negative. This suggests that a mutagenic mode of action is not present in the formation of tumours. Moreover, the study in mice concluded that there was no significant effect 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 lifetime studies, spontaneous and cryptogenic tumours, such as lymphomas and leukaemia, are known to occur, 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, when tested with the closely related substance, MTBE. 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. Unlike for MTBE, the TAME study had no differential analysis of the lymphoid and leukaemia tumours. US NTP guidelines recommend that neither mononuclear cell leukaemia and malignant lymphoma nor malignant lymphomas and histiocytic sarcomas should be combined for the purposes of biological or statistical evaluation. The estimation of the tumours' relevance based on the information given in this study is difficult.

As with MTBE, the molecular structure of TAME does not appear to contain such properties that would cause concern in terms of carcinogenicity. Both substances have a common metabolite, formaldehyde, but due to formaldehydes fast metabolism in most human tissues, this is not considered to be an issue. MTBE was not classified as a carcinogen in the EU or the IARC. No epidemiological data is available for TAME.

Conclusion

Results are available from a single oral carcinogenicity study. The dosing regime used to treat the animals was unusual and only two dose levels were used. Moreover, the animals were allowed to live out their natural life span and no adjustment for mortality was available. The neoplasia in this study were of lymphoid origin and derived from cells originating from the bone marrow, however, results from a mouse micronucleus study with TAME, which measure the substance's ability to induce damage in chromosomes of the bone marrow cells, was negative. The publication's reporting was inadequate in many aspects resulting in a low level of confidence of the results. Therefore, an analysis of effective group numbers and tumour incidence were difficult to analyse. Negative results from mutagenicity studies on TAME suggest that mutagenicity is not a contributing mode of action in the formation of tumours. Lack of alert from molecule structure and results of carcinogenicity testing for the related substance MTBE, suggest that carcinogenicity is not an endpoint of concern. Due to lack of confidence on the study results, risk characterisation is not performed on the carcinogenicity end-point.

4.1.2.9   Toxicity for reproduction

4.1.2.9.1   Effects on fertility

Studies in animals

2-generation reproductive toxicity study in Sprague-Dawley rats

Weanling male and female Sprague-Dawley rats (F0 generation) were exposed by inhalation to 0, 250, 1,500 and 3,000 ppm TAME vapour, five days/week for 6 hours/day for ten weeks in a 2-generation reproductive study conducted under GLP regulations (Welsch et al., 1998, Tyl et

al., 2003). Each exposure group had 30 animals/sex. Body weights, feed consumption and clinical signs were recorded daily. Vaginal cytology was evaluated for three weeks before pre-breed period. Animals were then mated randomly within treatment groups to produce F1-generation. Exposure continued 6 hours/day 7 days/week through mating, gestation and lactation. F0 males were submitted to necropsy and evaluation of reproductive and other selected organs (high and control animals) after the delivery period. An andrological assessment was conducted to all parental males. F1- litters were culled to 10 pups on post-natal day (PND) 4 and weaned on PND 28. Up to three weanlings/sex/litter were chosen for necropsy and 30 animals/sex/dose were selected as parents of the F2-generation. F0 females were then submitted to necropsy and histopathology of reproductive and other selected organs of high and control dose animals. The selected F1-weanlings were exposed 10 weeks with acquisition of vaginal patency and the assessment of preputial separation in males and vaginal cytology evaluated during the last three weeks. Results from these measurements triggered the measurement of anogenital distance in F2 offspring at birth. F1 animals were mated in a two-week mating period following the procedure used with F0 animals. At weaning 30 animals/sex/dose were selected for post-wean retention with no exposure through acquisition of vaginal patency in females and preputial separation in males. Up to three F2 weanlings/sex/litter were selected for necropsy with selected organ weights.

Results

Systemic toxicity in adult F0 and F1

Adult systemic toxicity was present in F0 and F1 animals at 1,500 and 3,000 ppm. Both sexes and generations displayed ataxia and persistently reduced body weights at 3,000 ppm. Body weights were reduced during gestation in F0 (GD 0-7, ~6%) and F1 (GD 0-20, ~9%) and during lactation in F0 (PND 0 – 4, 5-9%) and F1 (PND 0-14, 7-10%) at 3,000 ppm. Ataxia was present in the 1,500 ppm F0 animals but there were no effects on body weights or food efficiency. F1-dams had a reduction in lactation period weight gain. In necropsy, the liver weights (absolute and relative) were increased in the F0 and F1 males and less in females. In F0 males, the relative to body weight increase was at 1,500 ppm 29% and 3,000 ppm 33% and F0 females at 3,000 ppm 24%. In F1 males, the relative liver weight increase was 22% in the 1,500 ppm and 3,000 ppm dose group. In F1 females, the relative liver weight increase at 3,000 ppm was 14%. The relative kidney were significantly increased in the 1,500 F0 males (21%) and 3,000 ppm F0 males (26%) and females (9%), while male absolute kidney weight was significantly increased at all levels (8-19%) and in females only 9% at 3,000 ppm. F1 males, but not females, had increased kidney weight at 1,500 ppm (18%) and 3,000 ppm (22%). Relative but not absolute spleen weights were significantly increased in F1 males at 1,500 and 3,000 ppm. Relative and absolute adrenal weights were significantly increased at the 3,000 ppm group in males and females.

Reproductive toxicity in F0 and F1

In F0 and F1 males, minimal effect on gonads were noted at 3,000 ppm, which was expressed as increased relative but not absolute testes weight, probably due to reduced terminal body weights in this group. The absolute prostate weight was significantly reduced at 3,000 ppm for F1 males but not for F0 males. At 3,000 ppm, F1, but not F0 males had reduced sperm concentrations of the epididymis. Both the 1,500 ppm (3.13%) and 3,000 ppm (5.49%) F0 males had an increase of abnormal sperm compared to the concurrent control group (0 ppm (2.26%, 250 ppm (2.40%)), but not when compared to the historical values (range: 2.0 ± 0.3% to 6.1 ± 3.3%). The F1 males also had an increasing trend of abnormal sperm, although none of the figures was statistically

significantly over the concurrent control group (0 ppm: 2.5%, 250 ppm: 2.7%, 1,500 ppm: 3.9%, 3,000 ppm: 3.5%). The treatment had no effect on mating or survival indices, on absolute testes weight, on absolute or relative epididymides or seminal vesicles with coagulating gland, on relative prostate weight, sperm motility, or sperm production. There were no treatment-related findings in the histopathology.

In females, no treatment-related change was noted in the vaginal cyclicity, or oestrous cycle length. Gestational length was significantly longer in the F1 1,500 ppm females but this was probably of no toxicological significance, because the effect was not seen in the F1-3,000 ppm group or the F0 females. No significant changes were seen on the number implantation sites per litter, on prenatal mortality index or the number of live or dead pups on PND 0.

In the offspring, the acquisition of preputial separation was significantly delayed in the 1,500 and 3,000 ppm F1 males and F2 males at 3,000 ppm. Acquisition of vaginal patency was significantly delayed at 3,000 ppm in F1 females and at 250 and 3,000 ppm in F2 females. These effects were considered as the landmarks, which triggered the measurement of anogenital distance (AGD) in the F2 animals. The AGD was significantly decreased in both sexes of the F2 3,000 ppm rats. This was accompanied and probably caused by a significant reduction (~ 8%) in body weights/litter in the F2 pups on PND 0. Although the 3,000 ppm F1 body weights per litter were significantly lowered on the post-natal days 4, 7, 14, 21 and 28, the survival indices were not affected in the F1 offspring throughout lactation. The F1 1,500 ppm animals had reduced litter body weights on PND 4 and 7 (females) and 14, 12 and 28. The 250 ppm F1 pup body weights per litter were reduced on PND 14, 21 and 28 (28 days, males only). At 3,000 ppm, F2 offspring had reduced survival indices on PND 4 and 21 and the pup body weights were significantly reduced during lactation on PND 0, 4, 7, 14, 21 and 28. In the 1,500 ppm group significantly reduced pup weights were observed on PND 14 and 21. There were no effects on F2 pups at 250 ppm. The increased offspring mortalities at 1,500 and 3,000 ppm were thought to have been due to the "overt toxicity and the compromised status" of the dams. The observations included lethargic or hypothermic pups with little or no milk in stomach, tail chewed off, thin fur and haematomas at various locations.

Endocrine disruption potential

The authors state that TAME changes seen in the reproductive landmarks, the acquisition of preputial separation and vaginal patency cannot be interpreted as endocrine disruption activity. This is because if TAME would have androgenic or anti-androgenic or estrogenic or anti-estrogenic activity, depending on the activity and sex in question one of the landmarks would have been delayed while the other one was accelerated or not affected. For example, if TAME was an estrogenic antagonist, vaginal patency would be delayed and preputial separation unchanged. The same is true for the reductions seen in the anogenital distance. If TAME was, e.g., an anti-androgen, males only would be expected to exhibit shorter AGD, whereas females would be unaffected or have a longer AGD. Neither was true in this case. On the other hand, if the preputial separation and AGD were earlier dismissed as evidence for reproductive toxicity by the authors because the differences were said to have been caused by significantly different pup weights on PND 0, then their use as negative evidence for endocrine disruption is questionable.

Summary

TAME caused systemic toxic effects in adults at 1,500 and 3,000 ppm, which were mainly manifested as changes in liver adrenal and kidney weights and reduction in body weight. There were also general signs of toxicity to central nervous system, such as ataxia. Indications of

toxicity to male gonads were slight, expressed as a statistically significant increase of abnormal sperm count in the 1,500 ppm (3.13%) and 3,000 ppm (5.49%) F0-males. These changes were increased also in F1 males but without statistical significance. The toxicological significance of the sperm abnormalities is questionable since they are within the historical control figures of the laboratory and there was an absence of effects on reproductive function. Offspring toxicity was demonstrated at 1,500 and 3,000 ppm as reduced body weights in F1 and F2 pups during lactation, increased mortality during lactation and delayed acquisition of preputial separation in F2 males and delayed acquisition of vaginal patency in F1 and F2 females at 3,000 ppm. Moreover, both sexes had reduced anogenital distance with reduced body weight at 3,000 ppm.

Other studies

The fertilisability of oocytes was investigated following a 2-week exposure to rats via drinking water to tetrachloroethylene, trichloroethylene, ethyl tertiary butyl ether (ETBE), methyl tertiary butyl ether (MTBE) and TAME and two metabolites of MTBE and ETBE (Berger and Horner, 2003). The preceding two weeks of the oocyte recovery, young female Sprague-Dawley rats (28-45 days) were treated with 0.3% TAME, MTBE and ETBE. Controls received drinking water only. The rats were induced to ovulate with gonadotropin. After treatment, the females were killed, oviducts were removed and the oocytes isolated and transferred to fertilisation medium. The *Zona pellicuda* was removed before insemination. Oocytes (in 100 µl) were inseminated with 10 µl of sperm diluted to either $7 \cdot 10^6$ or $0.5 \cdot 10^6$ sperm/ml. Three replicates were inseminated with $7 \cdot 10^6$ sperm/ml and three replicates with $0.5 \cdot 10^6$ sperm/ml. Following 20 hours of incubation at 37°C, oocytes were rinsed and transferred to cover slips for examination. The ethers did not have an effect on the final weight of the females, but the females exposed to MTBE had lower weight gain than the control rats. The treatment did not have an effect on the oocytes fragility. However, the results showed that in the ethers treatment groups, the fertilisability of the oocytes decreased after consumption of TAME. The percentage of fertilised oocytes was 84% in the control group and 64% in the one treated with TAME. The oocytes of trichloroethylene-exposed females also had reduced ability to bind sperm plasma membrane proteins: the ratio of penetrated sperm/oocyte dropped from 1.84 in controls to 1.54 after 0.3% TAME treatment.

<u>Conclusion</u>

Although there were statistically significant changes in sperm count at 1,500 ppm and 3,000 ppm, these changes were within the historical controls. Moreover they did not affect the reproductive parameters. The NOAEC for parental toxicity was 250 ppm. The NOAEC for reproductive toxicity is set to 3,000 ppm. Toxicity to offspring was seen at 1,500 ppm leading to a NOAEC of 250 ppm for developmental effects.

In vivo administered TAME seemed to have an inhibitory effect on the fertilisability of rat oocytes *in vitro*. However, this finding was not supported by the findings in the 2-generation reproductive toxicity study. Therefore, the significance of this observation fertility is left unknown.

4.1.2.9.2   Developmental toxicity

<u>Studies in animals</u>

Rat

Sprague-Dawley rats were exposed to TAME target concentrations of 250, 1,500 and 3,500 ppm, which were selected based on a preliminary examination where 7,000 ppm resulted in excessive mortality, 4,000 ppm showed demonstrable maternal toxicity and 1,000 ppm caused only minimal maternal toxicity (Welsch and Tyl., 1997b). Twenty-five sperm-positive female rats per group were exposed for 6 hours/day. The animals were exposed through the gestation days (GD) 6 to 19, resulting in 14 days of exposure. Clinical observations were made once daily before exposure (GD 0-5) and on the exposure days before and after the daily exposure. Maternal feed consumption was evaluated on gestation days 0-6, 6-9, 9-12, 12-15, and 18-20. Animals were killed 1-1½ days before parturition and uteri were examined for implantation sites. The body, liver, and uterus of each sperm-positive female were weighed, ovarian corpora lutea and uterine contents (implantation sites, resorptions, dead and live foetuses) were recorded. Live foetuses were sexed and weighed and examined for external abnormalities, including cleft palate. Approximately half of the live foetuses per litter were examined for visceral malformations and had their sex confirmed. All foetal carcasses were eviscerated, with sex determined internally in those foetuses that did not go though visceral examination, macerated and stained for examination of skeletal malformations and variations. The study was conducted in compliance with GLP standards and following the Toxic Substance Control Act, OPPTS Draft Testing Guidelines (US EPA, 1995b).

<u>Results</u>

Maternal toxicity

No dams died aborted or delivered early. The numbers of litters (and foetuses) evaluated were 23 (330) at 0 ppm, 24 (354) at 250 ppm, 24 (349) at 1,500 ppm and 21 (298) at 3,500 ppm. Maternal body weight was significantly reduced only at 3,500 ppm on GD 12, 15, 18 and 20. Maternal weight gain was significantly reduced at 1,500 and 3,500 ppm for GD 6-9 and at 3,500 ppm for GD 6-20. Maternal absolute liver weights were equivalent across the groups, but liver weight relative to sacrificed body weight was increased in the 3,500 ppm group. At 3,500 ppm clinical signs included those typical to TAME from other experiments such as ataxia, lethargy, slow respiration and gasping and clinical weight loss ($\geq$ 5 g within a weigh period). Most of these signs were noted during the first ten days starting exposure. The dams of the 1,500 ppm group exhibited also lethargy (one each on GD 6 and 7) and piloerection (GD 15). Maternal feed consumption was significantly reduced in the 3500 ppm group for GD 6-9, 12-15, 15-18, 18-20 (exposure period) and 0-20 (gestation period). At 1,500 ppm, feed consumption was significantly reduced only for GD 9-12. In summary, based on the weight reductions in damson GD 6-9, maternal toxicity was evident at 1,500 ppm.

Developmental toxicity

There were no significant changes in the gestational parameters including number of ovarian corpora lutea, total number of uterine implantation sites, pre- or post-implantation loss, number of live foetuses per litter and sex ratio per litter (% male foetuses). Foetal body weight was significantly reduced in the 3,500 ppm dose group, when calculated for all foetuses or males and females separated. There was no treatment-related increase of visceral, skeletal or total

malformations or variations by litter or by foetus per litter. Based on the foetal body weight reduction at 3,500 ppm, the NOAEC for developmental toxicity in Sprague-Dawley rat is 1,500 ppm.

Mouse

Led by the same investigators in the same laboratory of the study described above, a developmental toxicity evaluation was conducted using CD-1 mice (Welsch and Tyl, 1997a). Exposure concentrations of 250, 1,500 and 3,500 ppm were used. Twenty-five mice per group were exposed 6 hours/day on gestational days 6-16 for a total of 11 days. Maternal body weights were taken on GD 0, 6, 9, 12, 15, and 17. The feed consumption was measured during intervals 0-6, 6-9, 9-12, 12-15 and 15-17. Ovarian corpora lutea were counted and the number of implantation sites was recorded. All foetuses were dissected from the uterus, counted, weighed, sexed and examined for external abnormalities, fixed and stained. Half of the litter from each exposure group was examined for visceral malformations and variations. The other half, which did not go to visceral examination, was examined for skeletal malformations and variations. Due to safety precautions, observation of the animals was not possible during the exposure.

Result

Maternal toxicity

Four dams of the 3,500 ppm group died. The deaths occurred on gestation days 6, 7, 8 and 9. One female at 3,500 ppm died before the start of exposure. No abortions occurred. One dam of the 250 ppm group delivered early. Maternal feed consumption was significantly *increased* at 3,500 ppm dose during GD 0-6 (as g/day and g/kg/day), but then reduced for GD 9-12, 12-15, 15-17 and 6-17 (exposure period). Maternal feed consumption was unaffected across the groups for the gestational period, GD 0-17. At 1,500 ppm, feed consumption was significantly reduced only for gestational days 6-9. When the data were expressed as g/kg/day, maternal feed consumption at 3,500 ppm was reduced only for GD 9-12 and for 1,500 ppm, feed consumption was unaffected. There were no effects related to treatment in gestational parameters. Maternal body weight was significantly decreased only at 3,500 ppm for GD 15 and 17. Maternal weight change was significantly reduced at 3,500 ppm on GD 9-12, 12-15, 15-17, 6-17 (exposure period), and 0-17 (gestation period). The 250 and 1,500 ppm dose groups had no significant changes in weight development. Treatment-related clinical observations included ataxia, prone positioning, lethargy, head tremors, eye squinted, gasping and slow respiration at 3,500 ppm. Head tremors and eye(s) half closed were also seen at 1,500 ppm, but only in one mouse on one gestation day (10). Maternal absolute and relative liver weights increased at 1,500 and 3,500 ppm. The absolute liver weight was significantly increased at 1,500 ppm but not at 3,500 ppm. The absolute liver weights were as follows: 0 ppm: 2.72 ± 0.06, 250 ppm: 2.81 ± 0.06, 1,500 ppm: $2.96 \pm 0.06*$ and 3,500 ppm: 2.86 ± 0.06. When measured relative to the sacrificed body weight the following figures were reported: 0 ppm: 5.78 ± 0.12, 250 ppm: 5.61 ± 0.05, 1,500 ppm: $6.41 \pm 0.13**$, 3,500 ppm: $6.91 \pm 0.12**$ ($*p < 0.05$, $**p < 0.01$). Overall, maternal toxicity was expressed clearly only at 3,500 ppm and only slight adaptive response was seen in the liver at 1,500 ppm group.

Developmental toxicity

All pregnant animals had one or more foetuses; the numbers of litters (foetuses) examined were: 0 ppm: 23 (252), 250 ppm: 21 (258), 1,500 ppm: 22 (244), 3,500 ppm: 19 (193). In the 3,500 ppm group, the increase of incidence of litters late foetal deaths was significantly

increased (control: 8.7%, 3,500 ppm: 36.8%) and foetal weight per litter weight decreased (-40%) compared to control group. Malformations and variations included increased incidence of cleft palate and enlarged lateral ventricles. The incidence of cleft palate at 3,500 ppm was 11 foetuses in 6 litters and at 1,500 ppm 3 foetuses in 3 litters. The incidence of enlarged lateral ventricles showed a treatment-related increase in incidence; there were at 0 ppm 8 foetuses/8 litters, at 250 ppm 6 foetuses/4 litters, 1,500 ppm 7 foetuses/7 litters and at 3,500 ppm 38 foetuses affected in 16 litters.

Discussion

The authors stated that the occurrence of cleft palates could have been related to elevated corticosterone due to stress from the anaesthetic quality of TAME at high concentrations. While maternal stress is a commonly used explanation for the cleft palates, the pathogenesis of this malformation is very complex multifactor process, which can involve xenobiotic effects of which corticosterone induction caused by maternal stress is one. However, in this study no measurements of corticosterone or other signs of stress were conducted to support this hypothesis. Moreover, in the 1,500 ppm group, there were very few clinical signs of toxicity in the dams. The only clinical signs of toxicity occurred in one dam on GD 10 reported as "half closed eyes" and "head tremors". This dam did not have foetuses with cleft palate. The three dams that had foetuses with cleft palate did not show any specific signs of toxicity that would correlate with these malformations. Because the observation of the animals was not possible during the exposure, it is plausible that some symptoms, possibly relevant to maternal stress, may have gone unrecorded. The 90-day study reviewed in the repeated toxicity section reports that most animals were lethargic and some were prostrate during the study. This may well have been the case also in the Welsch study, but since the animals' clinical signs were recorded only before and after the exposure, the signs of lethargy or prostration may have disappeared. Another hypothesis, which is sometimes associated with cleft palates, is restriction of diet (Daston et al., 1991), which can sometimes induce zinc metallothionein enzymes in liver and affect the distribution of zinc leading to malformations. When inspecting the dams, which had malformations individually, they showed no abnormally low feed consumption or weight loss during gestation. When the feed consumption data were expressed as g/kg/day, the 1,500 ppm group did not show a difference in feed consumption when compared to the control group. The role of neurotransmitters in the disturbances in palate reorientation is recognised (Zimmermann, 1985). For instance, whereas serotonin and acetylcholine stimulate the palate reorientation process, gamma-aminobutyric acid (GABA) has been shown to inhibit it. Recent studies have shown that non-neuronal, viz. palatal epithelium, GABAergic system is implicated in palate development (Homanics et al., 1997). However, the data is not sufficient to draw conclusions about the possible role of GABA or other neurotransmitter in the current situation. The laboratory historical control data sets of the study by Welsch and Tyl (1997) list the findings made from 589 control foetuses examined for any malformations in two studies in 1991 and 1993. One cleft palate was observed. In summary, in the light of current knowledge, no firm conclusions can be drawn on the possible human relevance of the mechanism of cleft palate development. However, as these malformations occur at very high doses, it is likely that they are of little relevance to humans.

The visceral variation of the cerebrum was consistent with developmental delay, since the mean foetal body weights (male and female separately and combined) were approximately 60% of the control values.

4.1.2.9.3   Summary of toxicity for reproduction

2-generation study in rats

The NOAEC for adult systemic toxicity is 250 ppm, for reproductive toxicity 3,000 ppm and for offspring toxicity 250 ppm. The effects seen with TAME were not consistent with those expected for an endocrine disrupting agent.

Developmental study in rats

Maternal toxicity was present at 1,500 and 3,500 pm and it was manifested as reduction of body weight, reduction of weight gain and various clinical signs, especially at the top dose group. The NOAEC for maternal toxicity is 250 ppm. Based on the weight reductions seen in the litters at 3,500 ppm and the absence of embryo-foetal effects at 250 or 1,500 ppm doses, 1,500 ppm is chosen as the NOAEC for developmental toxicity in Sprague-Dawley rat.

Developmental study in mice

Four dams died during the first four days of exposure in the 3,500 ppm dose group. At 1,500 (11%) and 3,500 ppm (20%), the maternal liver absolute and relative weights were significantly increased. The toxicity noted at 1,500 ppm (11% liver weight increase) is likely to represent a slight adaptation of the liver rather than significant rather than to represent such maternal toxicity, which would account for the foetal malformations. Therefore, the maternal toxicity NOAEC is set at 1,500 ppm. The NOAEC for developmental effects is set to 250 ppm based on the malformations (cleft palate) seen at 1,500 and at a higher incidence at 3,500 ppm in CD-1 mice.

Conclusion

Toxicity to fertility

NOAEC of 3,000 ppm (12,720 mg/m^3) is selected. Although a statistically significant increase of abnormal sperm counts seen in F0 male rats at 1,500 ppm and 3,000 ppm, the effects on sperm counts occurred together with considerable systemic toxicity at the same dose level and they were within the historical controls. Moreover, no other significant effects on reproductive performance were reported at this level. This end-point will not be considered in the risk characterisation.

Developmental toxicity

A NOAEC of 250 ppm (1,063 mg/m^3) is selected for developmental effects based on the malformations (cleft palate) in mice at 1,500 ppm and 3,500 ppm and based on the reduced body weights seen in the F1-offspring of the 2-generation study. Although slight maternal toxicity is seen at 1,500 ppm, this alone is not seen as sufficient to explain the malformations in mice.

4.1.3   Risk characterisation

4.1.3.1   General aspects

Exposure

Exposure to TAME occurs almost exclusively as a blending component in fuel. Worker exposure occurs during production of TAME or the formulation and use of TAME containing petrol. Consumers are exposed directly or indirectly via the environment either via respiration from TAME evaporating from petrol, mainly at petrol stations, or via ingestion through TAME-contaminated drinking water. The amount of TAME used varies from one petrol brand to another (95, 98 or 99 RON), with divergences even within the same brand due to production circumstances. Exposure assessment is generally evaluated based on studies, in which the average content of TAME in fuels handled was about 5%. In production, TAME content can vary from around 13% to 45%. A 40% assumption was used in the EASE estimations for the production scenario.

Toxicity

For the purposes of risk characterisation, oral absorption is assumed 100%, the respiration net uptake percentage is 50% and 30% percutaneous TAME absorption will be used. The maximum plasma concentration in humans after 50 ppm TAME exposure for 4 hours was 13.2 μmol/L. The elimination from human blood was rapid after the end of inhalation exposure and it occurred in two phases. The blood half-lives were between 1.2 and 6.3 hours with relatively big individual differences between test subjects. The limit of TAME detection was reached after 12 hours. TAME is metabolised to tert-amyl alcohol in humans primarily by cytochrome 2A6 mainly present in liver. The first metabolic step releases tert-amyl alcohol and formaldehyde. The main human urine metabolites are 2-methyl-2,3-butanediol, 2-hydroxy-2-methylbutyric acid and 3-hydroxy-3-methylbutyric acid. TAA and TAME are minor metabolites in urine. TAME acute toxicity is of relatively low concern. Via oral administration, it appeared slightly more toxic to female than male rats. The female LD_{50} value is below the classification limit (1,602 mg/kg) but when a predicted combined LD_{50} value is calculated a figure of 2,152 mg/kg is obtained. Based on volunteer studies with six humans, TAME caused only minor acute effects, best characterised as slight irritation of upper respiratory tract and drying of mouth. Feeling characterised as "heaviness of the head" seemed to correlate inversely with increasing TAME concentration. Concentrations up to 50 ppm did not have an effect on reaction time, balance or mood in 4-hour exposure. These results are only indicative, as the group size of the study was quite small. However, the results of this study are used for the risk characterisation of acute effects, since they reflect the real situation better than an LD_{50} value from rats. In the repeated dose toxicity, mice and rats were reported as lethargic and prostrate at doses of 1,500 ppm and higher. Based on studies conducted following OECD guidelines and Good Laboratory Practise, TAME did not cause irritation in rabbit skin or eyes. These end-points will not be considered further in the risk characterisation. There is no guideline sensitisation study. However, the available study conducted following the Bühler method is of sufficiently well quality for an assessment of the sensitisation potential. Based on that study, sensitisation is not a concern and it will not be taken further in the risk characterisation. In repeated dose toxicity studies via the inhalation, only few deaths were seen in rat at the highest used concentration (14,840 mg/m^3 or 3,500 ppm). The signs of toxicity at the lowest observable adverse effect concentration (LOAEC), 6,360 mg/m^3 or 1,500 ppm, were not remarkable. At 1,500 ppm the male and female rats showed increased liver, kidney and adrenal weights. Based on the organ weight increases in both sexes in rats, a NOAEC

is set to 250 ppm. For the oral route, a NOAEL of 125 mg/kg is selected based on the dose related adrenal weight increase in the 28 days study at 500 mg/kg. TAME was not mutagenic**.** The data for carcinogenicity end point is of limited quality. There is also very scarce information in the study available, which does not allow an assessment of the validity of the claimed tumour findings. The study was also conducted using an unusual life time exposure protocol, which makes the interpretation of tumours difficult. No risk characterisation is conducted on this end-point. Based on the available information, TAME is not considered toxic to reproduction; therefore, this end-point is not taken to the risk characterisation. Rats showed no developmental toxicity at non-maternally toxic doses. In mice, an increased incidence of cleft palates was noted at 1,500 and 3,500 ppm. There was clear maternal toxicity in the high dose animals, while the signs of toxicity were less obvious in the intermediate dose animals. Based on the 90-day study, it is likely that the animals were lethargic and prostrate during the exposure at 1,500 ppm, which could have contributed to maternal stress. However, no clear mechanism could be attributed to the malformations seen in mice. For developmental toxicity, the NOAEL used is 250 ppm or 1,060 mg/m^3.

Table 4.20 Summary of effects

Substance name	Inhalation (N(L)OAEL)	Dermal (N(L)OAEL)	Oral (N(L)OAEL)
Acute toxicity	212 mg/m^3	no data	1,602 mg/kg*
Irritation / corrositivity	Not irritating to skin or eyes.		
Sensitization	Not sensitising.		
Repeated dose toxicity (local)	No substance-related local effects were reported.	Not tested	No substance-related local effects were reported.
Repeated dose toxicity (systemic)	250 ppm	Not tested	125 mg/kg
Mutagenicity	Based on the available data, mutagenicity is not a concern.		
Carcinogenicity	No data.	No data.	Data is insufficient. This end-point was not considered in risk characterisation.
Fertility impairment	Based on the available data, toxicity to fertility is not a concern.	Not tested.	Not tested
Developmental toxicity	250 ppm	Not tested.	Not tested

*   The LD$_{50}$ calculated for females. Combined LD$_{50}$ was 2,152 mg/kg.

4.1.3.2   Workers

The exposure values taken to the worker risk characterisation are taken from the reasonable worst case values summarised in the worker exposure section. Body burdens were calculated from these exposure figures using the absorption assumptions, which were concluded in the toxicokinetics section.

4.1.3.2.1   Acute toxicity

Because ingestion is not likely, a characterisation of risks of acute toxicity via oral route is not considered relevant for the worker risk assessment. For the assessment of acute toxicity via inhalation, the rat LC$_{50}$ value is not used but rather the maximum dose (50 ppm or 212 mg/m^3) of the human volunteer study, which investigated the acute toxic characteristics of TAME in six

men. The long term exposure values were used, except for service station for which a short term value was available. The exposure time varies between 2 to 4 hours.

Table 4.21 Occupational risk assessment for acute toxicity

	Inhalation				Dermal				Combined			
	RWC TWA 8h Exposure mg/m³	NOAEC from Human volunteers mg/m³	MOS	Conclusion	Exposure	NOAEL	MOS	Conclusion	Exposure	NOAEL	MOS	Conclusion
Production	1.8	212	118	ii		No data.						
Formulation												
Transportation	1.2	212	177	ii		No data.						
Distribution	0.6	212	353	ii		No data.						
Uses												
Service station	14*	212	15	ii		No data.						
Car motor repair	1.5	212	141	ii		No data.						
Fuel pump repair	3.5	212	61	ii		No data.						
Other work groups	0.21	212	1,010	ii		No data.						

*   Short term value

4.1.3.2.2   Repeated dose toxicity

Inhalation MOS has been calculated against from the measured or EASE estimated RWC air concentration at the work place assuming an 8-hour workday. Measured air concentrations were used where available. The dose from dermal exposure was calculated taking the upper range limit of the EASE estimated reasonable worst-case skin exposure and assuming 30% absorption and 1,140 cm^2 surface area for forearms and a 70 kg person. The value from the daily dose was taken (in **Table 4.8**) considering already the exposure time per day and the surface area.

For the calculation of the systemic dose received by inhalation, it is assumed that the lung ventilation over the workday is 10 m^3 (about 21 l/minute), which corresponds to light work. 50% lung retention and a 70 kg person are assumed. When assessing the risks from dermal exposure, 30% absorption percentage was assumed. This was then compared to the oral NOAEL of 125 mg/kg. Minimal MOS inhalation exposure was calculated by including a factor of 3 for interspecies extrapolation, a factor 3 for intraspecies and a factor of 2 for subchronic to chronic extrapolation resulting to a minimal MOS of 18. For dermal and combined exposure the lower MOS limit was calculated using a factor 10 for interspecies extrapolation and allometric scaling, factor 3 for intraspecies and a factor of 4 for subacute to chronic extrapolation resulting to a minimal MOS of 120. The factor of 4 for subacute to chronic is chosen, because based on the 28 day and 90 day studies the toxicity of TAME does not appear time but rather dose dependent and, moreover, TAME does not accumulate in the body but is quite rapidly excreted.

The LOAEL values can, perhaps, be seen as somewhat debatable, because of the increases in organ weights noted already at 125 mg/kg in the oral study and at 250 ppm after respiratory exposure. However, the changes at 250 mg/kg were not statistically significant, and the changes at 250 ppm were noted in males only and were related to body weight increase. Based on the low severity of the effects at much higher dose levels (500 mg/kg and 1,500 ppm), changes in the lower dose groups are not considered of particular concern. Although it could be argued that the NOAEL for oral exposure is at 125 mg/kg due to the lack of statistical significance, this dose is set as the LOAEL, because the weight increase is quite large even at 125 mg/kg and there is a dose response with this effect.

Table 4.22 Occupational risk assessment for repeated dose toxicity

	Inhalation				Dermal				Combined			
	Dose intake/ mg/kg/day (RWC air conc mg/m³)	NOAEC mg/m³	MOS	Conclusion	DOSE (mg/kg/d), 30 % absorption	Oral NOAEL mg/kg	MOS	Conclusion	Exposure	NOAEL (mg/kg/d)	MOS	Conclusion
Production	0.13 (1.8)	1,060	589	ii	-	-	-	ii	0.13	125	962	ii
Formulation												
Transportation	0.09 (1.2)	1,060	883	ii	0.01	125	12,500	ii	0.10	125	1,250	ii
Distribution	0.04 (0.6)	1,060	1,767	ii	0.01	125	12,500	ii	0.05	125	2,500	ii
Uses												
Service station	0.2 (2.8)	1,060	379	ii	0.43	125	291	ii	0.63	125	198	ii
Car motor repair	0.11 (1.5)	1,060	707	ii	0.90	125	139	ii	1.01	125	123	ii
Fuel pump repair	0.25 (3.5)	1,060	303	ii	0.43	125	291	ii	0.68	125	184	ii
Other work groups	0.02 (0.21)	1,060	5,048	ii	0.01	125	12,500	ii	0.03	125	4,167	ii

The figures in parenthesis are RWC air concentrations. Minimal MOS inhalation exposure is 3 · 3 · 2= 18. Minimal MOS dermal and combined exposure is 10 · 3 · 4 = 120

4.1.3.2.3   **Mutagenicity**

Based on the available data, mutagenicity is not a concern **Conclusion (ii)** is drawn.

4.1.3.2.4   **Toxicity for reproduction**

<u>Developmental toxicity</u>

The NOAEC of 250 ppm was taken from the developmental toxicity study with CD-1 mice. The inhalation MOS was calculated from the RWC air concentration at the work place (in parenthesis). Measured RWC air concentrations were used where available. Dermal intake was calculated using the upper range of the RWC estimate and assuming 30% absorption and 1,140 cm^2 (TGD) surface area for forearms and a 70 kg person. For the calculation of the inhalation dose, 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 TAME in the lungs is 50% and a 70 kg person is assumed. When calculating the MOSs for dermal and combined exposure, the inhalation NOAEC 1,060 mg/m^3 (250 ppm) was converted to correspond a systemic dose using 1.5 l/hour ventilation rate, 6 hour/d exposure 50% lung retention and 37 g mouse weight (calculated from the average maternal weights on gestation days 6 to 15). An internal dose of 129 mg/kg was obtained.

Minimal MOS inhalation exposure was calculated by including a factor of 3 for interspecies extrapolation and a factor 3 for intraspecies differences, resulting in a minimal MOS of 9.

Table 4.23 Occupational risk assessment for reproductive toxicity – developmental

	Inhalation					Dermal				Combined			
	Dose intake/ mg/kg/day	Dose intake/ mg/kg/day	NOAEC mg/m³	MOS	Conclusion	DOSE intake (mg/kg/d)	Oral NOAEL mg/kg/d	MOS	Conclusion	Exposure	NOAEL (mg/kg/d)	MOS	Conclusion
Production	0.13 (1.8)		1,060	589	ii	-	-	-	ii	0.13	129	992	ii
Formulation													
Transportation	0.09 (1.2)		1,060	883	ii	0.01	129	12,900	ii	0.10	129	1,290	Ii
Distribution	0.04 (0.6)		1,060	1,767	ii	0.01	129	12,900	ii	0.05	129	2,580	ii
Uses													
Service station	0.2 (2.8)		1,060	379	ii	0.43	129	300	ii	0.63	129	205	ii
Car motor repair	0.11 (1.5)		1,060	707	ii	0.90	129	143	ii	1.01	129	128	ii
Fuel pump repair	0.25 (3.5)		1.060	303	ii	0.43	129	300	ii	0.68	129	190	ii
Other work groups	0.02 (0.21)		1,060	5,048	ii	0.01	129	12,900	ii	0.03	129	4,300	ii

The figures in parenthesis are RWC air concentrations. Minimal MOS of 9 was calculated by factoring for 3 for interspecies extrapolation and a factor 3 for intraspecies extrapolation

4.1.3.2.5   Summary of risk characterisation for workers

Acute toxicity

The smallest MOSs were the service station and fuel pump repair, with MOSs of 15 and 61 when calculated from the 50 ppm air concentration obtained from a volunteer study, where slight irritation was reported. Although the MOS at service station appears quite low it is not considered to be a concern based on the low severity of the effect. When using lethality (rat LD_{50}) as the acute toxicity end-point, the MOSs would be several magnitudes higher. **Conclusion (ii)** is drawn for all scenarios.

Repeated dose toxicity

No local effects of concern were noted in the hazard assessment. The smallest MOS in the repeated dose toxicity scenarios was found in the car motor repair (123) in dermal and combined exposure. All other combined or dermal exposure scenarios had MOSs of over 150 not causing concern. In inhalation exposure, the lowest MOS was 303 (fuel pump repair) and it was not considered to cause concern. **Conclusion (ii)** is drawn for all scenarios.

Mutagenicity

Mutagenicity is not considered a concern. **Conclusion (ii)** is drawn.

Developmental toxicity

The smallest MOS is noted in the car motor repair (128), based on a NOAEL from a developmental toxicity study in mice. This was not considered to cause concern. **Conclusion (ii)** is drawn in all scenarios.

Table 4.24 Overview of the conclusions with respect to occupational risk characterisation

		Acute toxicity		Local toxicity after single or repeated exposure			Sensitisation	Repeated dose toxicity Systemic			Mutagenicity	Reproductive toxicity (combined)
		Dermal	Inhalation	Dermal	Inhalation	Eye		Dermal	Inhalation	Combined		
Production	MOS	n.d.	118	-	-	-	-	-	589	962	-	992
	Concl.	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii
Transportation	MOS	n.d.	177	-	-	-	-	12,500	883	1,250	-	1,290
	Concl.	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii
Distribution	MOS	n.d.	353	-	-	-	-	12,500	1,767	2,500	-	2,580
	Concl.	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii
USES												
Service station	MOS	n.d.	72	-	-	-	-	291	379	198	-	205
	Concl.	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii
Car motor repair	MOS	n.d.	141	-	-	-	-	139	707	123	-	128
	Concl.	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii
Fuel pump repair	MOS	n.d.	61	-	-	-	-	291	303	184	-	190
	Concl.	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii
Other work groups	MOS	n.d.	1,010	-	-	-	-	12,500	5,048	250	-	4,300
	Concl.	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii	ii

n.d.   No data

4.1.3.3   Consumers (Combined with exposure via the environment)

Although most of the consumer exposure occurs indirectly via the environment, for the purposes of this risk assessment risks are assessed in the consumer section, because a total exposure figure comprising of both exposure types is used. Consumers can be exposed via air through several scenarios, which include pump islands at service stations, the perimeter of gasoline stations, commuting in cars, areas polluted by production and formulation sites, urban background or exhaust or leaks from boat engines. The only likely oral source of TAME could be ingestion of TAME contaminated drinking water, which would mostly occur near petrol stations with leaking underground storage tanks. Since a combination of all these exposure scenarios is possible for a theoretical consumer, the reasonable worst-case exposure figure is calculated from the highest estimated total intake via air from all the scenarios together with consumption of drinking water with a TAME content of 100 µg/l. The same toxicokinetic assumptions will apply as in the worker scenarios. The systemic dose from all respiratory exposure scenarios was calculated from the sum of the upper limit RWC concentrations and exposure times given in **Table 4.12** in the consumer section. In addition, a 70 kg person with a daily respiratory volume of 20 m^3 (833 l/hour, 14 l/minute) and 50% respiratory uptake were assumed. Thus, a total daily dose of 7.5 µg/kg is obtained for respiratory exposure. For oral exposure, a daily drinking water consumption of 2.0 l is assumed with 100% absorption resulting in a RWC daily dose of 2.9 µg/kg. Both routes calculated together, a total daily dose of 10.3 µg/kg is obtained.

The sections for environmental risks and risks for human health from physico-chemical properties identified a concern to the aesthetic quality of drinking water due to leakage of TAME to ground water from underground storage tanks. Potential risk reduction measures aiming at protection of ground water are considered sufficient in contributing to prevention of the contamination of drinking water. This section of the risk assessment will deal only with the possible health risks caused by direct or indirect exposure to TAME.

4.1.3.3.1   Acute toxicity

Inhalation

For the assessment of acute toxicity via inhalation, the highest RWC air concentration is compared to the data from the acute toxicity study with human volunteers. For this purpose, the perimeter of production and formulation plants scenario will be used, where a consumer can be exposed to a concentration of up to 100 µg/m^3 for 12 hours/day. Using the 50-ppm 4-hour exposure (212,000 µg/m^3) from the volunteer study, where no significant adverse effects were seen, apart from slight upper respiratory way irritation, a MOS of 2,120 is calculated. **Conclusion (ii)** is drawn.

Oral

For oral toxicity, the rat LD$_{50}$ value was 1,602,000 µg/kg. Compared to the estimated daily oral intake of 2.9 µg/kg, a MOS of about $5.5 \cdot 10^5$ is obtained. **Conclusion (ii)** is drawn

4.1.3.3.2   **Repeated dose toxicity**

Inhalation

For repeated toxicity via inhalation, a NOAEC of 1,060,000 μg/m^3 was taken forward. Comparing to the 12-hour exposure at a production and formulation plant perimeter to 100 μg/m^3, this will result to a MOS of 10,600. **Conclusion (ii)** is drawn.

Oral

An oral NOAEL of 125,000 μg/kg was derived. Compared to the daily intake of 2.9 μg/kg via the drinking water a MOS of approximately $4.3 \cdot 10^4$ is calculated. **Conclusion (ii)** is drawn.

4.1.3.3.3   **Mutagenicity**

Based on the available data, mutagenicity is not a concern **Conclusion (ii)** is drawn.

4.1.3.3.4   **Toxicity for reproduction**

Developmental toxicity

A NOAEC of 1,060,000 μg/m^3 was taken forward from the developmental toxicity study with mice. When this is compared to the 12-hour exposure to 100 μg/m^3 at production and formulation plant perimeter, a MOS of 10,600 can be obtained. For oral exposure (2.9 μg/kg) a MOS of over 44,400 is obtained when compared to the internal dose NOAEL of 129,000 μg/kg in mice. **Conclusion (ii)** is drawn.

4.1.3.3.5   **Summary of risk characterisation for consumers**

Due to their negligible nature, the combined risks from consumer and indirect exposure via the environement were assessed in the consumer Section 4.1.3.3. As no margin of safety lower than 2,120 was obtained, all end points resulted in **conclusion (ii)**.

4.1.3.4   **Humans exposed via the environment**

These risks are assessed in the consumer section. For combined consumer exposure and exposure via the environement, no margin of safety lower than 2,120 was obtained. Thus, all end points resulted in **conclusion (ii)**.

4.1.3.5   **Combined exposure**

Because the contribution of consumer exposure or indirect exposure via the environment is negligible compared to the occupational exposure and would practically make no change in the worker MOSs, no assessment of combined exposure is conducted.

4.2   HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

4.2.1.1   Explosivity

TAME as such is not explosive, but high concentrations of TAME vapour can ignite explosively, e.g. by static sparks. The vapour pressure of TAME is relatively high (90 hPA at 20°C), therefore, high concentrations of TAME vapours are plausible, for instance, in case of major leaks or other accidents.

4.2.1.2   Flammability

Neat TAME is flammable. Its autoflammability temperature is 430°C. The lower explosion limit is 1.0 vol% gas in the air and the upper limit 7.4 vol% gas in the air. The flash point is -11°C.

Because of its flammability, neat TAME is stored outdoors in a detached and a properly identified area, and the container materials are resistant to the product. Spark-free materials and equipment have to be used.

4.2.1.3   Oxidising potential

TAME is not expected to have oxidising properties based on the chemical structure. Peroxide formation has not been documented.

4.2.1.4   Other relevant physico-chemical properties

4.2.1.4.1   Odour and taste properties

Due to relatively high water solubility (10.7 g/l at 20°C), TAME separates from petrol and dissolves into water, if petrol is dispersed on water surface or is otherwise in contact with water. Although general odour and taste threshold values have not been determined, results from a study conducted in laboratory conditions with one set of tests and one panel show that TAME may have very low limits for sense perception for instance in drinking water.

In general, compounds with odour threshold below 1,000 μg/l are considered highly odorous. The results by Vetrano et al. (1993) are from distilled water from a test conducted in laboratory conditions from one set of tests and panel of 6 adult persons only. Therefore, these test results do not reflect the natural environmental situation, where e.g. water hardness, temperature, chlorinating or other contaminants could influence to taste and odour detection. In addition, significant interindividual differences in detection sensitivity could be expected. Thus, the concentration, at which the taste or odour becomes unacceptable for consumers, may vary greatly. Because of these shortcomings, the values sited above should be treated as indicative only.

Odour threshold in air (Vetrano 1993)

	mg/m^3	ppm
Odour detection	0.12	0.027
Odour recognition	0.20	0.047

Odour and taste threshold in water

Estimated average detection threshold values (Vetrano 1993)

	mg/l
Odour detection	0.194
Odour recognition	0.443
Taste detection	0.128

4.2.1.4.2 Viscosity

TAME is an aliphatic ether. TAME has a kinetic viscosity value of $0.5 \cdot 10^{-6}$ m^2/s (40 C). This together with a surface tension of less than 33 Nm/m would qualify classification with R65 (aspiration hazard). However, there is no data on TAME's surface tension, and therefore no conclusion can be drawn as to the need to classify for this end point. Moreover, there are no relevant scenarios for this end point in workers, consumer or in direct exposure even if it were classified.

4.2.2 Risk characterisation

4.2.2.1 Workers

Flammability could pose a fire and explosion risk in situations, where TAME vapour 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 TAME vapour and necessary precautions are normally taken to prevent ignition during storage and when transferring TAME. Moreover, the professional workers are aware of the characteristics of TAME and the entrance of outsiders to the production area is not allowed. In other scenarios concerning TAME as an additive in petrol, the risk arises from the totality of flammable elements in automotive petrol vapours, where the part of TAME is minor.

Conclusion

Flammability is not considered to cause a significant risk to workers. **Conclusion (ii)** is drawn.

4.2.2.2   Consumers

There are no relevant scenarios.

4.2.2.3   Humans exposed via the environment

TAME 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 reservoir of ground water serving as drinking water supply is contaminated, the consequences can be remarkable in terms of costs and 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

- TAME is not considered to cause adverse health or ecotoxic effects at taste and odour threshold level.

- Even the relatively small amount of TAME may render large reserves of ground water 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).

As described in the environmental part of this report the contamination of ground water is mainly caused by leaking underground storage tanks and spillage from overfilling the tanks. Therefore, it is justified to conclude that TAME is causing a risk for the aesthetic quality of drinking water.

<u>Conclusion</u>

Conclusion (iii) is drawn for indirect exposure to man via drinking water based on the risk on the aesthetic properties of drinking water.

5 RESULTS

5.1 INTRODUCTION

The risk assessment of TAME is based on current practices related to the life-cycle of the substance produced in or imported into the European Community as described in the risk assessment forwarded to the Commission by the Member State Rapporteur.

The risk assessment has, based on the available information, determined that in the European Community the substance is mainly used as a blending component of standard unleaded petrol.

Other uses are as on-site intermediate in neat form.

5.2 ENVIRONMENT

Atmosphere

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 is reached because the risk assessment shows that direct risks arising from the use of TAME are not expected. Risk reduction measures already being applied are considered sufficient. However, this conclusion does not apply directly to general air quality issues. Atmospheric TAME emissions should not be handled separately in ESR (793/93) program, but in the general scope of air quality issues in the EU.

Terrestrial ecosystem

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 is reached because the risk assessment shows that risks are not expected. Risk reduction measures already being applied are considered sufficient.

Groundwater

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

The conclusion is reached because of concerns for the potability of ground 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.

Aquatic ecosystem (incl. sediment and marine environment)

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

The conclusion is reached because of concerns for the aquatic ecosystem as a consequence of exposure arising from releases to surface water from:

- terminal site's storage-tank bottom waters (intermittent release) and

- transportation, storage and delivery of petrol at terminal sites with direct discharge.

Risk reduction measurements to the aquatic compartment should also cover possible risks to sediment.

<u>Micro-organisms in the sewage treatment plant</u>

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 is reached because the risk assessment shows that risks are not expected. Risk reduction measures already being applied are considered sufficient.

<u>Secondary poisoning</u>

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 is reached because the risk assessment shows that there is at present no need for further information and/or testing or for risk reduction measures. This conclusion applies to all environmental compartments and assessment endpoints.

5.3　　　　　　　　HUMAN HEALTH

5.3.1　　　　　　　Human health (toxicity)

5.3.1.1　　　　　　Workers

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 (ii) applies to acute toxicity, repeated dose toxicity and reproductive toxicity (development). Irritation, sensitisation or mutagenicity was not included in the risk characterisation because these endpoints were assessed not to pose a hazard. Carcinogenicity was not taken forward to the risk characterisation because of the inadequacy of the available data.

5.3.1.2　　　　　　Consumers

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 (ii) applies to acute toxicity, repeated dose toxicity and reproductive toxicity (development). Irritation, sensitisation or mutagenicity was not included in the risk characterisation because these endpoints were assessed not to pose a hazard. Carcinogenicity was not taken forward to the risk characterisation because of the inadequacy of the available data.

5.3.1.3   Combined exposure

No assessment was conducted on combined exposure, due to negligible additional contribution to risk.

5.3.1.4   Humans exposed via the environment

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.

The risk assessment shows that risks are not expected. Risk reduction measures already being applied are considered sufficient.

5.3.2   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.

Conclusion (iii) applies to drinking water contamination and 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
CMR	Carcinogenic, Mutagenic and toxic to Reproduction
CNS	Central Nervous System
COD	Chemical Oxygen Demand
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 90 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
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
SCHER	Scientific Committee on Health and Environmental Risks (DG SANCO)
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
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)

European Commission
DG Joint Research Centre, Institute of Health and Consumer Protection
European Chemicals Bureau
EUR 22236 EN   European Union Risk Assessment Report
                      2-methoxy-2-methylbutane (TAME), Volume 70

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The report provides the comprehensive risk assessment of the substance 2-methoxy-2-methylbutane (TAME). 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 humans and the environment, laid down in Commission Regulation (EC) No. 1488/94.

Part I - Environment

This part of the evaluation considers the emissions and the resulting exposure to the environment 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.

The environmental risk assessment concludes that there is concern for the aquatic ecosystem (including marine environment) because of exposure arising from intermittent releases to surface water from storage-tank bottom-waters at terminal sites and from releases to surface water from transportation, storage and delivery of petrol at terminal sites with direct discharge. Risk reduction measurements to the aquatic compartment should also cover possible risks to sediment.

There is concern for groundwater as well, in particular concern of potability of groundwater in respect to taste and odour as a consequence of exposure rising from leaking underground storage tanks and tank piping, as well as spillages from overfilling the tanks.

There is at present no concern for the atmospheric and terrestrial compartments, micro organisms in the sewage treatment plant and secondary poisoning.

Part II - Human Health

This part of the evaluation considers the emissions and the resulting exposure to human populations in all life cycle steps. The scenarios for occupational exposure, consumer exposure and humans exposed via the environment have been examined and the possible risks have been identified.

The human health risk assessment concludes that there is concern arising from the physico-chemical properties of the substance in relation to drinking water contamination and potability of drinking water in respect of taste and odour as a consequence of exposure arising from leaking underground storage tanks and tank piping as well as spillages from overfilling of the storage tanks.

There are no concerns for workers, consumers and humans exposed via the environment with respect to the toxicity of TAME.

The conclusions of this report will lead to risk reduction measures to be proposed by the Commission's committee on risk reduction strategies set up in support of Council Regulation (EEC) N. 793/93.

European Commission – Joint Research Centre
Institute for Health and Consumer Protection
European Chemicals Bureau (ECB)

European Union Risk Assessment Report

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