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Methyl *tert*-Butyl Ether
(MTBE)
Health Risk Characterisation

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SUMMARY

Use

Methyl *tert*-butyl ether (MTBE) is a colourless flammable liquid with a distinctive ethereal odour. It is used almost exclusively as a gasoline additive. It is added to unleaded gasoline in quantities between 2 and 5% (w/w), to raise the octane level, or up to 15% (w/w) to improve combustion efficiency as a measure to reduce air pollution from automotive exhaust emissions.

Minor applications include its use in clinical practice as a solvent for the dissolution of gallstones.

Exposures

Although the data on occupational exposure available to the Task Force were limited, they provided an indication of the magnitude of the potential exposure for workers. Occupational exposure may occur during MTBE production and loading, when handling gasoline containing MTBE or when working as a service station attendant or garage worker. The relevant route of such exposure is inhalation. Whereas MTBE production is associated with relatively low exposures (< 10 mg/m^3), loading operations may result in higher exposures (mean values of 20 mg/m^3, peak values of about 200 mg/m^3). Mean short-term exposure measurements for loading and delivery of gasoline containing 10-15% MTBE were between 13 and 91 mg/m^3 with a maximum of 226 mg/m^3. Since most fuels in Europe currently contain only 2 to 5% MTBE as an octane enhancer, these findings were considered by the Task Force to be a 'worst case' situation. For service station attendants and garage workers in the US, the mean exposures were < 3.5 mg/m^3 and 7.56 mg/m^3, respectively. The most likely source of consumer exposure to MTBE arises from gasoline evaporation during car refueling and its duration is very short. A study of consumer exposure in Finland measured concentrations of 6.0-7.5 mg/m^3 at service stations delivering gasoline containing 11% of MTBE.

Toxicity

Biotransformation of MTBE leads to the formation of *tert*-butanol (TBA) and formaldehyde, which in turn are further metabolised. TBA excretion proceeds relatively slowly (half-life of 8 h in humans). For formaldehyde the detoxification rate is much faster than its rate of formation from MTBE and therefore this route of metabolism is judged not to contribute to the toxic effects of MTBE discussed in this report. Toxicokinetic data do not indicate reasons for concern with regard to bioaccumulation of MTBE or any of its metabolites.

Skin and respiratory irritation are regarded as effects of prime concern following acute exposure. MTBE posesses a low order of acute toxicity in experimental animals exposed via oral, dermal and inhalation routes. LD_{50} values exceed 2,000 mg/kg for oral and dermal exposure, and the inhalation LC_{50} value is 85,000 mg/m^3 for 4 hours. Sub-lethal acute exposure evokes local irritation at the site of contact and transient clinical signs characteristic of central nervous system (CNS) depression. Skin contact with MTBE causes reversible moderate to severe irritation in rabbits whereas MTBE was found to be only slightly irritant to the rabbit eye. MTBE vapour at concentrations above 300 mg/m^3 evokes slight and transient irritation to the respiratory system of laboratory animals. For sensory and respiratory irritation an RD_{50} value (50% reduction of breathing rate) of 16,600 mg/m^3 was determined for MTBE in the mouse. The Task Force recommended that MTBE be labelled as irritant (Xi) with the corresponding R-phrase 38 (irritating to skin).

There have been no cases reported of sensitisation to MTBE in humans exposed by skin contact to the neat material or to gasoline containing MTBE. Studies in animals also failed to demonstrate skin sensitising potential on the part of MTBE, adding weight to the conclusion that MTBE is not a skin sensitiser.

MTBE caused anaesthesia in experimental animals when inhaled at concentrations of 28,800 mg/m^3. Reversible CNS effects were detected in a rat study at 14,400 mg/m^3 (LOAEL) using a functional observation battery and 6 hours of exposure. The NOAEL in this study was 2,880 mg/m^3. Observations suggesting transient CNS depression were consistently made also in animal studies using repeated inhalation and oral exposure. However, all effects were reversed when exposure ended and repeated exposure did not lead to NOAELs that were lower than for single exposure.

Principle effects observed following repeat oral and inhalation exposure of rats and mice to MTBE are local irritation, transient anaesthetic effects (as observed with many other low molecular weight ethers), chronic nephropathy and hepatocellular hypertrophy. The NOAEL for sub-chronic oral exposure is 300 mg/kg and for chronic inhalation exposure 1,440 mg/m^3. The latter value corresponds to daily retained doses (for calculation see page 29) of 102 and 113 mg/kg for male and female rats, respectively and 182 and 184 mg/kg for male and female mice, respectively.

MTBE has been tested extensively *in vitro* and *in vivo* for its genotoxic potential. The weight of evidence shows MTBE is not genotoxic . This conclusion is supported by the information for TBA, which is not genotoxic in several *in vitro* and *in vivo* tests, and formaldehyde, which though genotoxic in a number of tests, is rapidly detoxified by the body thereby removing the potential to damage the cell.

Tumours in rodents result from exposure to MTBE at doses exceeding the Maximum Tolerated Dose (MTD). An inhalation study in rats demonstrated a tumourigenic response in the male kidney at 10,800

and 28,800 mg/m^3 (corresponding to daily retained doses of 384 and 1023 mg/kg, respectively), but a non-genotoxic mechanism unique to the male rat is probably involved. An apparent increase in the incidence of Leydig cell tumours in male rats treated via inhalation was not considered to be relevant to humans. An inhalation study with mice showed an increase in the incidence of liver adenomas in female animals at 28,800 mg/m^3 (corresponding to a daily retained dose of 1824 mg/kg). A non-genotoxic mechanism is likely to be involved.

Further mechanistic studies are currently under way to clarify the mechanisms for the induction of these tumours.

Effects reported in an oral gavage study include an increase in rat Leydig cell tumour incidence and elevated combined lymphoma/leukaemia incidence in female rats. The Task Force considered the rat Leydig cell tumour findings as not predictive of hazard to humans. Furthermore, the importance of the combined lymphoma/leukaemia incidence from this oral gavage study was unclear due to deficiencies in the study report.

Overall, the Task Force concluded that the doses necessary to evoke neoplastic effects are equal to or greater than the doses that induce non-neoplastic effects in female mouse liver and male rat kidney. Therefore, protection against non-neoplastic effects should also protect from any theoretical carcinogenic effect. The Task Force concluded that MTBE is not carcinogenic according to the criteria in EU Directive on Dangerous Substances 67/548/EEC (EEC, 1993B).

Effects of MTBE vapour on reproduction and development have been evaluated in well-conducted inhalation studies with rats, mice and rabbits. Foetal toxicity and developmental toxicity were observed only at concentrations clearly toxic to the mother. MTBE was not embryotoxic or teratogenic at exposure levels not causing maternal toxicity and did not adversely affect reproduction.

Human Experience

A large body of data is available from human experience with MTBE, including case reports of clinical use of MTBE for gallstone dissolution, studies reporting subjective complaints by garage workers and service station attendants, large population studies with sophisticated study design and controlled short-term exposure of volunteers. Whereas the early studies suggested a relationship between MTBE exposure concentration and health complaints, this has not been confirmed in subsequent studies. This absence of an association is in line with short-term experimental studies that showed no specific effects at concentrations (< 3.6-180 mg/m^3) similar to or greater than those observed in the population studies. Human experimental data do not indicate irritation of the respiratory tract at concentrations of 180 mg/m^3 for two hours. Exposure to 270 mg/m^3 for three hours caused mild mucous membrane irritation in some volunteers. Objective symptoms on the CNS have not been observed in volunteer

studies up to 270 mg/m^3. Subjective symptoms at this concentration were reported by volunteers (mainly feeling of heaviness in the head). At 180 mg/m^3 no symptoms were reported.

Risk Characterisation

Table 1 on page 5 summarises the conclusions with regard to MTBE-related health effects. Irritation observed after short-term exposure in humans as well as liver and kidney toxicity observed after long-term exposure in experimental animals are considered to be the critical effects for the health risk characterisation of MTBE. Mild respiratory irritation occurred at a concentration of 270 mg/m^3 for three hours in human volunteers, whereas 180 mg/m^3 for two hours did not evoke such effects. The lowest NOAEL for liver and kidney effects after chronic inhalation exposure was 102 mg/kg/day (retained dose in male rats). The basis for the risk characterisation is a comparison of these three different doses/concentrations with occupational and consumer exposure data.

The available data on short-term peak exposure levels (about 200 mg/m^3) did not indicate concerns with regard to respiratory irritation. Comparison of the NOAEL for long-term liver and kidney effects revealed margins of safety between 180 to 300 fold for workers involved in MTBE production, about 70 fold for workers handling gasolines containing MTBE, and between 250 to 800 fold for service station attendants and garage workers. A 17,000 fold margin of safety was calculated for consumer exposure during car refuelling.

Compliance with an occupational exposure limit of 90 mg/m^3 or 25 ppm MTBE (8-h TWA) is considered by the Task Force to protect workers from any potential health hazards. This concentration corresponds to a daily retained MTBE dose of about 5.1 mg/kg for a 70-kg adult (on the basis of a ventilation volume of 10 m^3/8-h shift and a relative respiratory uptake of 40%) and provides a margin of safety of 20 when compared with the lowest NOAEL determined in chronic animal inhalation experiments. Respiratory irritation is regarded as the critical effect for higher short-term exposures. In humans, no effects were observed at a concentration of 180 mg/m^3 for 2 hours, while at 270 mg/m^3 for three hours only weak irritating effects on the mucous membranes were reported in some volunteers. Therefore, a limit of three times the TWA (270 mg/m^3 or 75 ppm) is considered to be an appropriate short-term, peak exposure limit (15-min STEL).

Conclusion

The risk characterisation for MTBE does not indicate concern for human health with regard to current occupational and consumer exposures.

Table 1: Principal effects of MTBE and NOAELs

End point	Species	Route	Exposure Time	Principal Effects	NOAEL	Remarks	Reference
acute effects	human	inhalation	2 hours (during light physical exercise)	mucous membrane irritation	180 mg/m^3	subjective symptoms (like slight irritation and heaviness in the head) were reported at 270 mg/m^3 (3 h exposure)	Johanson *et al*, 1995; Riihimäki *et al*, 1996
subchronic toxicity	rat	inhalation	90 days	liver and kidney toxicity (males)	2,880 mg/m^3	equivalent to 228 mg/kg bw/day (males)	Dodd and Kintigh, 1989
chronic toxicity and neoplastic effects	rat	inhalation	105 weeks	liver and kidney toxicity, kidney tumours (males)	1,440 mg/m^3	equivalent to 102 mg/kg bw/day (males)	Chun *et al*, 1992
	mouse	inhalation	18 months	liver tumours (females)	10,800 mg/m^3	equivalent to 669 mg/kg bw/day (females)	Burleigh-Flayer *et al*, 1992
neurotoxicity	rat	inhalation	6 hours	functional CNS effects	2,880 mg/m^3	LOAEL was 14,400 mg/m^3; effects were reversible	Gill, 1989
effects on fertility	rat	inhalation	two generations	no treatment-related effects	> 28,800 mg/m^3	for parental toxicity a NOAEL of 1,440 mg/m^3 was determined	Myhr *et al*, 1991
developmental toxicity	mouse	inhalation	gestation days 6 to 15	no direct effect on the fetus	3,600 mg/m^3	higher concentrations caused maternal toxicity and secondary developmental toxicity	Tyl and Neeper-Bradley, 1989

1. INTRODUCTION

Methyl *tert*-butyl ether (MTBE) is a colourless flammable liquid with an ethereal distinctive odour. MTBE is used as gasoline additive, with minor applications as a solvent. It is added to unleaded gasoline in quantities ranging between 2 and 5% (w/w) to raise the octane rate, although some countries (notably Canada, Finland and the USA - the latter with its "oxygenated fuel program") have implemented higher blending levels of up to 15% MTBE (w/w) to improve combustion efficiency in order to reduce car emissions.

The widespread introduction of MTBE and the public awareness of health-related issues with regard to gasoline have caused interest in the toxicological and epidemiological database on MTBE. A programme of toxicity studies was conducted in the 1980s. After the start of the oxygenated fuel programme in the USA in 1992, however, reports on health complaints in Fairbanks, Alaska, initiated a scientific and public debate in the USA on the risk/benefit of MTBE use in gasoline. This was further stimulated by a report that suggested an increased tumour incidence in rats receiving high oral doses of MTBE. In view of this discussion, ECETOC established a Task Force to review the toxicity of MTBE. In the meantime, MTBE was selected for inclusion in the third priority list of the EC existing substances program. In anticipation of the EU risk assessment, the Task Force prepared a review of the toxicological and epidemiological database, an estimation of the occupational and consumer exposures, and a risk characterisation for occupational and consumer exposures. The structure of this report on the health risk assessment of MTBE follows the general principles outlined in the EU Technical Guidance Documents (EEC, 1994).

2. IDENTITY AND CHEMICAL PROPERTIES

Common name:	Methyl *tert*-butyl ether, MTBE, *tert*-butyl methyl ether
IUPAC name:	2-Methoxy-2-Methyl Propane
CAS registry No.:	1634-04-4
EINECS No.:	216-653-1
EU-Labelling	R11 - Highly flammable + R38 - Irritant
Chemical Group:	Dialkyl ethers
Formula:	$H_3C\text{-}O\text{-}C(CH_3)_3$
Molecular mass:	88.15
Purity of the technical product:	97.0 to 99.9%
Conversion Factor (20°C, 1.018 hPa):	1 mg/m^3 = 0.277 ppm
	1 ppm = 3.6 mg/m^3

Table 2-1: Physical and Chemical Properties[a]

Parameter	Value
Boiling point	55.2 °C
Freezing point	-109 °C
Flash point	- 30 °C
Autoignition temperature	425 °C
Flammability limits in air	1.5 - 8.5%
Vapour pressure	245 mm Hg at 25 °C
	361.7 to 413.8 mm Hg at 38 °C
Relative Density	0.7405 at 20 °C
Refractive index	1.3690 at 20 °C
Colour	Colourless
Odour	Strong ethereal odour
Odour threshold	0.18 mg/m^3 (0.24 µl/l; 0.05 ppm) (Prah *et al*, 1994)
Solubility	less than 10% in water; miscible with ethanol and diethyl ether.
Partition Coeff. log P_{ow}	1.06
The technical product is stable.	
Conditions to avoid include:	open flame and other ignition sources, heat, sparks
Substances to avoid:	oxidising agents, strong acids, 2-Fluorel^R and Viton^R.

[a] From Material Safety Data Sheet for MTBE provided by ARCO Chemical Co.

3. PRODUCTION AND USE

The raw materials for the manufacture of MTBE are isobutylene and methanol. Isobutylene is obtained from either petroleum refinery sources (e.g. steam cracker operation, fluid catalytic cracker operation, butane dehydrogenation) or from dehydration of *tert*-butanol. Production is in closed systems.

Commercial production of MTBE started in Europe in 1976 and in the US in 1979. World-wide capacity has grown at a rate of 20% per year over the past decade, particularly in North America and Europe. Total world-wide production capacity in 1994 was 20.6 million tonnes and is expected to grow to 25 million tonnes. Of this amount 23% originated from steam cracker, 31.5% from fluid catalytic cracker and 32.5% from dehydrogenation operations. The remaining 13% was produced through dehydration processes. Most of the recent growth is based on butane dehydrogenation and fluid catalytic cracker units. European production of MTBE is approximately 3.5 million tonnes per annum.

MTBE has been added to gasoline blends since the second half of the 1970's, initially at low levels (2-5% w/w) to boost the octane rating of unleaded premium or high performance grades. More recently MTBE has been added at higher levels (11-15% w/w) to promote more efficient combustion of the gasoline. Blends meeting the latter specifications are widely used in North America and parts of Europe to improve air quality (oxygenated gasolines).

High purity MTBE (>99.9%) is being used as a process reaction solvent in the pharmaceutical industry, and as a gallstone dissolver in clinical practice.

4. TOXICOKINETICS

4.1 INTRODUCTION AND OVERVIEW

The information presented in this chapter has been arranged according to the processes that influence the fate of chemicals in the body, i.e. absorption, distribution, metabolism and excretion. Major studies addressing these aspects are listed in table 4-1 (studies indicated as A to J) and experimental details are described either in tables 4-2 to 4-4 or are given in the text.

MTBE has been studied extensively with regard to its toxicokinetic properties. MTBE is absorbed by all routes of exposure with quantitative differences with regard to the extent of absorption. Absorbed material is distributed uniformly in all tissues according to the relevant tissue/blood partition coefficients which for most tissues is around one. The fat/blood partition coefficient is about 10 and consequently the fat concentrations are about 10-fold higher than blood concentrations at steady state. Overall, due to rapid removal via exhalation and metabolism, there is no tendency for MTBE to accumulate. Metabolism proceeds via two principal metabolites, i.e. *tert*-butanol (TBA) and formaldehyde (see figure 4-1), both of which are further transformed and also show no tendency to accumulate. The products resulting from TBA metabolism are mainly eliminated via urine, whereas formaldehyde and its breakdown products enter the normal physiological pathways. This general description of the MTBE toxicokinetics appears to be valid for all investigated species, including man.

4.2 ABSORPTION

Information on absorption following oral, dermal and inhalation exposures is available from several studies. In study A-2 peak plasma concentrations of MTBE were reached within 1 hour after oral (gavage) administration, indicating rapid uptake from the gastrointestinal tract. The area under the plasma concentration-time curve (AUC), a measure of the total absorption of MTBE, after oral administration was greater than the AUC after intravenous administration (A1) of an approximately equivalent dose. Since the theoretical bioavailability for intravenous administration is 100% , this result was attributed by the authors to a higher proportion of MTBE being exhaled after intravenous administration. Following dermal application (A3 - closed chamber, 6-hour contact), the peak plasma concentrations were 20-fold lower than observed after oral administration and were reached about two hours after the start of the experiment. This demonstrates a slower uptake of MTBE through the skin compared with the uptake from the gastrointestinal tract. The bioavailability of MTBE after dermal administration was 20% and 39% (40 and 400 mg/kg, both routes respectively) of the oral bioavailability.

Figure 1: Major Metabolic Pathways for MTBE and MTBE Metabolites

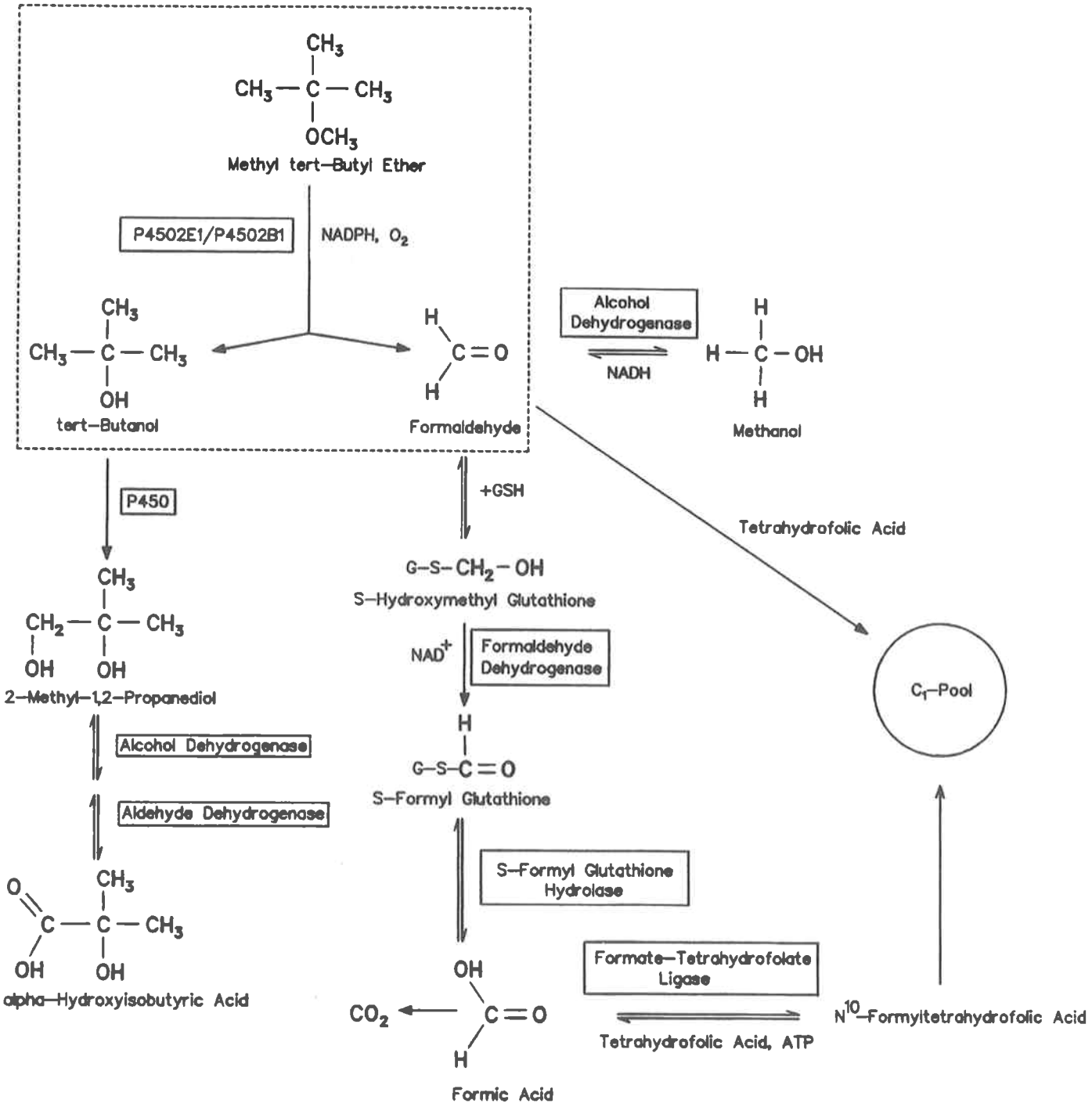

Table 4-1: Major Studies Addressing Several Aspects of MTBE Toxicokinetics

Study	Species/ Strain/Sex/ No/group	Route	Dose/ Concentration	Material	Reference	Confidence in results
A-1	rat/Fischer 344/ M+F/ 40/group	intravenous (bolus)	40 mg/kg	unlabelled MTBE	Bio-Research Laboratories, 1990a	high
A-2	rat/Fischer 344/ M+F/ 40/group	oral (gavage)	40, 400 mg/kg			high
A-3	rat/Fischer 344/ M+F/ 60/group	dermal (application chamber)	40, 400 mg/kg			high
B-1	rat/Fischer 344/ M+F/ 52/group	single inhalation (nose only, 6h)	1,440 mg/m^3 28,800 mg/m^3	unlabelled MTBE	Bio-Research Laboratories, 1990b	high
B-2	rat/Fischer 344/ M+F/ 40/group	15-day inhalation (nose only, 6h/d)	1,440 mg/m^3			high
C-1	rat/Fischer 344/ M+F/ 6/group	intravenous (bolus)	40 mg/kg	^{14}C-MTBE (label on central butyl carbon)	Bio-Research Laboratories, 1990c, 1991	high
C-2	rat/Fischer 344/ M+F/ 6/group	oral (gavage)	40, 400 mg/kg			high
C-3	rat/Fischer 344/ M+F/ 6/group	dermal (application chamber)	40, 400 mg/kg			high
D-1	rat/Fischer 344/ M+F/ 6/group	single inhalation (nose only, 6h)	1,440 mg/m^3 28,800 mg/m^3	^{14}C-label as in C-1	Bio-Research Laboratories, 1990d	high
D-2	rat/Fischer 344/ M+F/ 6/group	15-day inhalation (nose only, 6h/d)	1,440 mg/m^3	no label first 14 d, further as D-1		high
E	rat/Sprague-Dawley M+F/ 3/group (11 time points)	intraperitoneally	232 mg/kg	^{14}C-label on methyl and central butyl carbon	Zacharias and Eschbach, 1984	high
F	rat/Charles River/ M+F/ 2/gr	intraperitoneally	7.3 mg/kg 14.6 mg/kg	^{14}C-label position not indicated	Kennedy and Keplinger 1972	low
G	monkey/Rhesus / F/2/group	intraperitoneally	58.4 mg/kg	as F	as F	low
H	rat/Wistar/ M/ 5/group	15-week inhalation(whole body, 6 h/d, 5 d/w)	180 mg/m^3 360 mg/m^3 1,080 mg/m^3	unlabelled MTBE	Savolainen *et al*, 1985	high
J	rat/Wistar/ M/ 5 (8 time points)	oral (gavage)	0.379 mg/kg	unlabelled MTBE	Li *et al*, 1991	low

In study J, the peak plasma concentration of 5.9 µg/ml was reached after 0.9 h, also demonstrating rapid uptake of MTBE from the gastrointestinal tract.

During the single inhalation exposures in study B plasma levels of MTBE increased rapidly between 10 min to 2 h after the start of exposure and then more gradually up to a maximum concentration (Cmax), at approximately 4 to 6 h after the start of exposure. This indicates a rapid pulmonary absorption of MTBE.

In the mass balance study C, the percentages of the radioactive doses recovered after oral (gavage) and after the intravenous dose were about the same, demonstrating virtually complete absorption from the gastrointestinal tract. In addition, the time course for exhalation of radioactive material and for the appearance of radioactivity in the urine indicated that most of the material was absorbed from the gastrointestinal tract within 3 hours after dosing the animals. Following dermal application of 40 mg/kg, about 60% of the radioactive material was still present in the application chambers, after administration of 400 mg/kg about 35% remained in the application chambers. This demonstrated a limited dermal absorption in comparison with the oral dose. The time course for exhalation of radioactive material and for the appearance of radioactivity in the urine after dermal application showed the uptake via the skin to be much slower in comparison with the uptake after oral administration.

Data from the inhalation experiments in study D do not allow any conclusions regarding the extent of absorption of MTBE after inhalation. However, a recent publication by Borghoff *et al* (1995) described a physiologically based pharmacokinetic (PBPK) model for MTBE in the rat and reported a blood/air partition coefficient of 11.5. Johanson *et al* (1995) determined a partition coefficient blood/air of 17.7 for human blood. These values indicate efficient uptake from inhaled air, as well as excretion via exhaled air. The net uptake at steady state is dependent on the MTBE concentration and decreases with increasing MTBE concentrations. A detailed discussion is provided in chapter 4.7.

In study E radioactivity in whole blood peaked 5 min after intraperitoneal administration, decreased sharply until one hour post-treatment and then decreased more gradually during the rest of the observation period. Forty eight hours after dosing, only small amounts of radioactivity could still be detected. The half life of MTBE, calculated on the basis of the ^{14}C-labelled material in whole blood, was 60 min for male rats and 49 min for female rats. In study F using two rats of each sex, 67 to 72% of the radioactive material was excreted within 24 hours of dosing by intraperitoneal injection, suggesting rapid absorption also via this route of administration.

It is not possible to derive clear data on the uptake kinetics for monkeys after intraperitoneal injection from the results of study G. Of the radioactive material 72 to 75% was excreted via exhalation, urine and faeces within 24 hours, indicating that primates and rats show similar kinetics via this route of administration.