METHYL *tert*-BUTYL ETHER

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

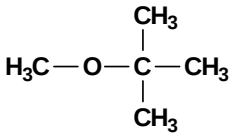
Chem. Abstr. Serv. Reg. No.: 1634-04-4

Chem. Abstr. Name: 2-Methoxy-2-methyl-propane

IUPAC Systematic Name: *tert*-Butyl methyl ether

Synonyms: *t*-Butyl methyl ether; *tert*-butoxymethane; 1,1-dimethylethyl methyl ether; methyl 1,1-dimethylethyl ether; 2-methyl-2-methoxypropane; methyl tertiary butyl ether; MTBE

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_5H_{12}O$ Relative molecular mass: 88.15

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless liquid with a terpene-like odour (Lewis, 1993; Agency for Toxic Substances and Disease Registry, 1996)

(*b*) *Boiling-point*: 55.2°C (Lide, 1997)

(*c*) *Melting-point*: –108.6°C (Lide, 1997)

(*d*) *Density*: 0.7405 g/cm^3 at 20°C (Lide, 1997)

(*e*) *Spectroscopy data*: Infrared (prism [46183], grating [31183]) and nuclear magnetic resonance (proton [19010], C-13 [4377]) spectral data have been reported (Sadtler Research Laboratories, 1980).

(*f*) *Solubility*: Soluble in water (48 g/L); very soluble in ethanol and diethyl ether (Budavari, 1996; Lide, 1997)

(*g*) *Volatility*: Vapour pressure: 3.26×10^4 Pa at 25°C (Budavari, 1996); relative vapour density (air = 1), 3.1 (Environmental Protection Agency, 1994)

(*h*) *Explosive limits*: Upper, 8.4 %; lower, 1.65%, by volume in air (Scholz *et al*., 1990)

(*i*) *Octanol/water partition coefficient (P)*: log P, 0.94 (Hansch *et al*., 1995)

(*j*) *Conversion factor*: mg/m^3 = 3.60 × ppm

1.1.4 *Technical products and impurities*

The typical purity of commercial methyl *tert*-butyl ether is 98–99 wt %. The contaminants may include *tert*-butanol and diisobutenes, residual methanol and, depending on the quality of the C-4 feedstock mixture, also C-5 and C-6 hydrocarbons. The typical composition of methyl *tert*-butyl ether adopted for use in fuels is: purity, 98–99 wt %; alcohols (methanol, *tert*-butanol), 0.5–1.5 wt %; hydrocarbons (C-5 and C-6, diisobutenes), 0.1–1.0 wt %; water, 50–1500 mg/kg; total sulfur (max.), 10 mg/kg; and residue on evaporation (max.), 10 mg/kg. For special applications, 99.95% pure methyl *tert*-butyl ether is marketed under the trade name Driveron S (Scholz *et al*., 1990).

1.1.5 *Analysis*

Pure methyl *tert*-butyl ether is analysed by gas chromatography, preferably in capillary columns with a highly polar stationary phase, e.g. 1,2,3-tris(2-cyanoethoxy)propane, Carbowax 20 M or DX-1. For gas chromatographic analysis of methyl *tert*-butyl ether-containing fuels, an oxygen-specific flame ionization detector or a column combination technique can be used (Scholz *et al*., 1990). The National Institute for Occupational Safety and Health recommends Method 1615 for sampling and analysis of methyl *tert*-butyl ether, which involves sampling with standard-sized coconut charcoal tubes, desorbing the sample with carbon disulfide, and analysis by gas chromatography–flame ionization detector; the estimated limit of detection is 0.02 mg/sample (Palassis, 1994).

Method 524.2 of the Environmental Protection Agency (1992) is a general-purpose purge-and-trap gas chromatography–mass spectrometry method for the identification and simultaneous measurement of purgeable volatile organic compounds, including methyl *tert*-butyl ether, in surface water, groundwater and drinking-water in any stage of treatment. The limit of detection for methyl *tert*-butyl ether is 0.09 μg/L. The United States Geological Survey (1995) recommended a similar method for determining methyl *tert*-butyl ether in whole water, with a detection limit of 0.06 μg/L.

Methyl *tert*-butyl ether is readily analysed in a variety of direct reading instruments, which can be used for real-time analysis and for the determination of instantaneous air concentrations. Direct reading instruments that have been successfully used to measure methyl *tert*-butyl ether are combustible gas indicators, infrared spectrophotometers, flame ionization detectors and photoionization detectors (Arco Chemical Co., 1993).

1.2 Production and use

1.2.1 *Production*

Extensive studies during the Second World War demonstrated the qualities of methyl *tert*-butyl ether as a high-octane fuel component; however, it was not until 1973 that the first commercial plant was in operation in Italy. Reduction in the lead content of gasoline in the mid-1970s led to a drastic increase in the demand for octane enhancers, and methyl *tert*-butyl ether is used increasingly in this way (Scholz *et al.,* 1990).

In 1987, the production volume of methyl *tert*-butyl ether in the United States was 1.6 million tonnes (Scholz *et al.*, 1990), and by 1995 it was 8.0 million tonnes (Kirschner,

1996). The production and consumption of methyl *tert*-butyl ether in 1995 and 1996 in Asia are presented in Table 1.

Table 1. Production and consumption of methyl *tert*-butyl ether in Asia in 1995 and 1996 (barrels/day)

Country or region	Production/consumption	
	1995	1996
China	5200/4500	6295/5100
Taiwan	2500/8750	3480/10 700
India	200/250	500/500
Indonesia	0/200	0/800
Japan	6100/6000	7500/6900
Republic of Korea	5900/7000	10 800/8500
Malaysia	4900/200	6199/238
Philippines	0/100	0/300
Singapore	1600/3000	2200/3500
Thailand	0/2000	0/3500
Asia Pacific Region	26 400/32 000	36 974/40 038

From Anon. (1997)

Methyl *tert*-butyl ether is currently produced by the acid-catalysed addition of methanol to isobutene. Suitable catalysts are solid acids such as bentonites and, especially, macroporous acidic ion-exchange resins. In 1990, 54 methyl *tert*-butyl ether plants with a total installed capacity of 7.3 million tonnes were in operation worldwide (Scholz *et al.*, 1990).

Information available in 1994 indicated that methyl *tert*-butyl ether was produced in 21 countries (Chemical Information Services, 1995).

1.2.2 *Use*

Methyl *tert*-butyl ether was first used commercially in Europe in 1973 for gasoline blending. It has been used in the United States since 1979, mainly as an octane enhancer in gasoline. It is the main oxygenate, which was present in 1997 in more than 30% of gasoline sold in the United States. It typically represents about 15% of the content of oxygenated fuels sold during winter months to reduce carbon monoxide in areas where there is heavy pollution by carbon monoxide (Piel, 1995; Stern & Kneiss, 1997). After 1992, it represented approximately 12% of the content of reformulated gasolines sold year-round in 37 areas with ozone pollution associated with emissions of volatile organic compounds.

More than 95% of the methyl *tert*-butyl ether produced is used as a component of gasoline. The market for fuels, amounting to approximately 100 million tonnes/year in

western Europe and 320 million tonnes/year in the United States, has a capacity for methyl *tert*-butyl ether that will exceed production for some time to come (Scholz *et al*., 1990). Methyl *tert*-butyl ether is used extensively in the Republic of Korea, Taiwan and Thailand, where the oxygenate content and environmental concerns are both intense. It is also used in significant quantities in China and Japan (Miller, 1998).

In Canada, where methylcyclopentadienyl manganese bicarbonyl is used as an octane enhancer, methyl *tert*-butyl ether-blended gasoline (6.5–9.6% content) accounts for only 2% of the total unleaded gasoline used (Government of Canada, 1992).

The importance of methyl *tert*-butyl ether is based primarily on its exceptionally good octane-enhancing properties when used as a gasoline blendstock. Depending on the composition of the base gasoline, blend octane numbers of 115–135 (research octane number) and 98–120 (motor octane number) can be achieved. The highest blend values are obtained with saturated, paraffin-rich gasolines and the lowest with olefin-rich gasolines. The lead and aromatics content also influence the blend octane numbers of methyl *tert*-butyl ether (Scholz *et al*., 1990).

Besides increasing the octane number, methyl *tert*-butyl ether also reduced the fuel vapour pressure (Reid vapour pressure), so that the vapour emissions during automobile fuelling and operation are reduced. Addition of methyl *tert*-butyl ether reduces exhaust emissions, particularly carbon monoxide, unburnt hydrocarbons, polycyclic aromatics and particulate carbon. Although methyl *tert*-butyl ether has a somewhat lower heat of combustion than gasoline, addition of up to 20 vol% neither impairs motor power nor increases fuel consumption (Scholz *et al*., 1990).

Methyl *tert*-butyl ether is also used in the petrochemical industry. Production of isobutene from the splitting of methyl *tert*-butyl ether is the only application that has been exploited on an industrial scale. By reversing its formation reaction, methyl *tert*-butyl ether can be cracked to isobutene and methanol on acidic catalysts at temperatures above 100°C. The methanol obtained as a co-product is recycled to synthesize methyl *tert*-butyl ether. Methyl *tert*-butyl ether can also be used in a number of chemical reactions, for example the production of methacrolein, methacrylic acid and isoprene. The lack of acidic hydrogen atoms makes methyl *tert*-butyl ether a suitable solvent for chemical reactions such as Grignard reactions. Because of its negligible tendency to form peroxides, its high ignition temperature and its narrow explosion limits, methyl *tert*-butyl ether is a good solvent for analytical use. It is also used as an extractant, for example in solvent dewaxing of hydrocarbon oils (Scholz *et al*., 1990).

Methyl *tert*-butyl ether is being evaluated for clinical use to dissolve gallstones (Agency for Toxic Substances and Disease Registry, 1996).

1.3 Occurrence

1.3.1 *Natural occurrence*

Methyl *tert*-butyl ether is not known to occur naturally.

1.3.2 *Occupational exposure*

Occupational exposure to methyl *tert*-butyl ether may occur by inhalation and dermal absorption during its production, formulation, distribution, use and disposal, either as pure methyl *tert*-butyl ether or blended into gasoline (Agency for Toxic Substances and Disease Registry, 1996). The estimated numbers of exposed workers in the United States are 900 000 professional drivers, 300 000 mechanics, 150 000 gasoline station workers, 7700 distribution workers, 1500 transport workers, 1800 blending workers and 880 manufacturing workers (Brown, 1997).

Tables 2 and 3 present the concentrations of methyl *tert*-butyl ether in worksite air collated by petroleum industry associations in Europe and the United States. In the European companies, the average full-shift concentrations to which workers in gasoline-related activities were exposed were 1.1–2.8 mg/m^3; the average shorter-term concentration was ≤ 86 mg/m^3 for top loading, which was four times higher than that for bottom loading. Even higher concentrations were measured during maintenance. In activities in which workers were exposed to undiluted methyl *tert*-butyl ether, ship-loading operations were associated

Table 2. Occupational exposure to methyl *tert*-butyl ether in the European petroleum industry; personal monitoring, 1981–95

Job or activity	Sampling (min)	No. of samples	Arithmetic mean (mg/m^3)	Range (mg/m^3)
From gasoline				
Driver bottom loading	480	49	2.8	0.01–10
Supervisor		45	2.2	≤ 14
Maintenance worker		13	2.3	≤ 20
Laboratory technician		10	1.1	≤ 3.2
Tetraethyllead operator	126–420	10	< 3.6	≤ 3.6
Area operator		6	< 3.6	< 3.6
Ship loading		7	< 3.6	< 3.6
Bottom loading	2–99	14	21	7.2–36
Top loading		6	86	29–160
Sampling		6	< 3.6	< 3.6–36
Filter change laboratory		2	23	14–32
From undiluted methyl *tert*-butyl ether				
Plant operator	100–390	10	2.4	0.08–19
Plant operator		5	< 3.6	< 3.6
Ship loading		2	46	45–46
Plant operator	15–40	3	< 3.6	< 3.6
Check tank levels		2	2.7	1.2–4.2
Hose disconnection		2	23	8.3–38

From McKee & Molyneux (1997)

Table 3. Occupational exposure to methyl *tert*-butyl ether in the United States petroleum industry, 1983–93

Operation	Exposure type	No. of samples	Geometric mean (mg/m^3)	Range (mg/m^3)
Manufacture, routine operations	Short-term[a]	27	2.4	0.58–28
	8-h TWA[b]	76	0.22	0.04–900
Manufacture, routine maintenance/turnaround	Short-term	8	4.0	1.8–26
	8-h TWA	4	0.47	0.14–2.5
Blending: undiluted methyl *tert*-butyl ether	Short-term	35	17	0.00–350
	Task[c]	13	7.4	0.76–260
	8-h TWA	12	6.2	0.14–320
Blending: fuel mixtures	Short-term	98	1.5	0.07–360
	Task	19	0.43	0.11–7.1
	8-h TWA	112	0.36	0.07–50
Transport: undiluted methyl *tert*-butyl ether	Short-term	66	43	1.1–3800
	Task	27	8.4	0.14–2500
	8-h TWA	10	1.1	0.11–2600
Transport: fuel mixtures	Short-term	64	14	0.00–1800
	Task	92	1.8	0.07–210
	8-h TWA	42	0.58	0.04–94
Distribution: fuel mixtures	Short-term	129	1.7	0.00–50
	Task	10	3.6	0.93–15
	8-h TWA	87	0.43	0.04–7.9

From McCoy & Johnson (1995); TWA, time-weighted average
[a] Duration, < 30 min
[b] Duration, 6–9 h
[c] Duration, 30 min–6 h

with an average exposure of 45 mg/m^3 (McKee & Molyneux, 1997). In a study of gasoline road-tanker drivers in Finland, top loading (without vapour recovery) was associated with the highest short-term (15–40 min) levels, with a mean of 91 mg/m^3, whereas that for bottom loading was 13 mg/m^3. During unloading at service stations, the corresponding mean levels were 16 mg/m^3 in northern and 71 mg/m^3 in southern Finland (Hakkola & Saarinen, 1996). Essentially similar results were obtained during a later study by the same group (Saarinen *et al.*, 1998).

In the United States, the highest shift-long exposure was in blending undiluted methyl *tert*-butyl ether (mean, 6.2 mg/m^3), while the highest short-term exposure was in transporting undiluted methyl *tert*-butyl ether (mean, 43 mg/m^3). In general, the short-term concentrations were 3–10 times higher than the shift-long concentrations. Operations involving exposure to undiluted methyl *tert*-butyl ether resulted in concentrations 3–20 times higher

than those involving exposure to fuel mixtures. Of the short-term exposures, transport involved higher concentrations than blending activities. Methyl *tert*-butyl ether manufacture was associated with the lowest exposures during routine operations, while the concentration increased during routine maintenance and turnaround operations and were highest during spills, leaks and upsets (McCoy & Johnson, 1995). A series of 38 personal air samples (15 min) taken in a petroleum refinery to evaluate the geometric mean of the concentrations of methyl *tert*-butyl ether in operations where there were potentially high exposures during short periods was 8.8 mg/m^3 (< 3.2–130 mg/m^3); concentrations > 36 mg/m^3 were found during sampling of railroad cars and connecting and disconnecting valves to them. The average full-shift concentration was 2.1 mg/m^3 (< 0.15–6.3 mg/m^3; $n = 9$). Individual exposures to > 3.6 mg/m^3 were found during laboratory testing and unloading of methyl *tert*-butyl ether from railroad cars (Lillquist & Zeigle, 1998).

Table 4 presents the concentrations to which workers in the United States are exposed in occupations related to automobile refuelling and servicing. As expected, exposure was higher when oxygenated fuels were used. The mean exposure of service station attendants, the most heavily exposed, during a full shift was < 3.6 mg/m^3, and individual values were rarely > 0.5–1 mg/m^3. In areas where methyl *tert*-butyl ether is used at a small percentage in gasoline, the concentrations to which service station attendants were exposed were usually below the limit of detection (about 0.11 mg/m^3). Workers who spent most of their work day in a vehicle had no detectable exposure, even in areas of oxygenated fuel use. This finding is consistent with the evaluation of Brown (1997) of a geometric mean exposure of 40 µg/m^3 for professional drivers in areas of the United States where methyl *tert*-butyl ether is used. Few data are available on peak exposures. Short-term (< 30 min) exposure was found to be an order of magnitude greater than the 8-h values for refuelling activities (McCoy & Johnson, 1995). Real-time video monitoring of total exposure to hydrocarbons indicated that peak concentrations of methyl *tert*-butyl ether (> 100 times the average for 1–2 s) occur during refuelling, even in the presence of vapour recovery systems (Cook & Kovein, 1997). The effect of spills has not been quantified (Hartle, 1993), while the effect of vehicle exhaust emissions seems to be minimal as engines are shut off during refuelling (Cook & Kovein, 1997).

The concentration of methyl *tert*-butyl ether in blood at the end of a shift and the difference between post- and pre-shift concentrations have been found to correlate with the concentrations in air (Moolenaar *et al.*, 1994; Mannino *et al*., 1995; White *et al.*, 1995). In an area where oxygenated fuels were used, the median concentration in the blood of gasoline pump attendants was approximately 15 µg/L, which was 10 times higher than that of car repair workers and 100 times higher than that of commuters (White *et al*., 1995). A decrease from 1.8 to 0.24 µg/L in the median blood concentration of methyl *tert*-butyl ether was observed in Alaskan workers exposed to gasoline vapours and engine exhausts after discontinuation of the use of oxygenated fuels (Moolenaar *et al*., 1994). Saarinen *et al.* (1998) reported that the time-weighted average exposure was strongly related to the urinary concentration of methyl *tert*-butyl ether in samples collected 1–3 h after a workshift, whereas urinary *tert*-butyl alcohol was not a reliable indicator of exposure.

Table 4. Occupational exposure to methyl *tert*-butyl ether in United States service stations and automobile repair centres

Occupation/type of fuel	Year, location	Air concentration (mg/m^3)		Sample type and duration	No. of samples	Reference
		Mean	Range			
Service station attendants and operators	1990			Personal 4 h		Hartle (1993)
Low methyl *tert*-butyl ether (0.03–0.13%)	Cincinnati, OH		ND–0.58[a]		32	
Oxygenated fuel (12–13% methyl *tert*-butyl ether)	Phoenix, AZ	1.1	0.14–14		41	
Equipped with stage II vapour recovery (0.03–2.1% methyl *tert*-butyl ether)	Los Angeles, CA	0.50	0.07–2.6[b]		48	
Various jobs, oxygenated fuel (13–17% methyl *tert*-butyl ether)	1993, Stamford, CT			Personal 8 h		Buchta (1993a)
Mechanics		0.40 (GM)	< 0.11–43		28	
Commuters[c]		ND	ND		7	
Supervisors		0.18 (GM)	< 0.11–0.54		4	
Various jobs, methyl *tert*-butyl ether up to 10%	1993, Albany,			Personal 8 h		Almaguer (1993)
Mechanics	NY	0.11 (median)	< 0.11–0.50		8	
Parking-lot attendants			< 0.11		8	
Service station attendants, oxygenated fuel (15–18% methyl *tert*-butyl ether)	1994, Newark, NJ	1.4 (GM)	0.29–4.6	Personal 3–10 h	21	Cook & Kovein (1995)
Various workers exposed routinely to motor vehicle exhaust or gasoline fumes	1992, 1993, Fairbanks, AK			Area 8 h		Moolenaar *et al.* (1994)
During oxygenated fuel programme (15% methyl *tert*-butyl ether)		0.37 (median)	0.02–2.9		18	
After oxygenated fuel programme (0.4–5% methyl *tert*-butyl ether)		0.13 (median)	ND–0.51		28	

Table 4 (contd)

Occupation/type of fuel	Year, location	Air concentration (mg/m^3)		Sample type and duration	No. of samples	Reference
		Mean	Range			
Various workers, low methyl *tert*-butyl ether (< 1%)	1993, Fairbanks, AK			Personal, full-shift		Buchta (1993b)
Mechanics		0.22 (GM)	< 0.11–1.6		26	
Commuters[c]			< 0.11		6	
Service and parts advisors			< 0.14		5	
Refuelling activities, various fuels	1983–93, USA			Personal and area		McCoy & Johnson (1995)
		2.8 (GM)	0.32–120	8 h	13	
		17 (GM)	0.58–490	< 30 min	11	

ND, not detected; GM, geometric mean

[a] Only one of 32 samples above the limit of detection

[b] Only 15 of 48 samples above the limit of detection

[c] Workers spending most of the work day inside a vehicle

Gasoline is a complex mixture, and workers exposed to methyl *tert*-butyl ether in occupations with exposure to gasoline or engine exhaust are exposed concurrently to several substances. Correlations were found in various studies between the air or blood concentrations of methyl *tert*-butyl ether and those of benzene, toluene, ethylbenzene, xylene and carbon monoxide (Moolenaar *et al*., 1994; Mannino *et al*., 1995; White *et al*., 1995). Exposure of service station attendants to benzene does not seem to be affected by the addition of up to 13% methyl *tert*-butyl ether to gasoline (Hartle, 1993). 1,3-Butadiene was not detected in a bulk sample of methyl *tert*-butyl ether collected from a petroleum refinery storage tank (Lillquist & Zeigle, 1998).

1.3.3 *Environmental occurrence*

Methyl *tert*-butyl ether enters the environment (principally air and water) during all phases of the petroleum fuel cycle, which includes production refinery stack releases, storage tank releases, pipeline leaks and significant releases from underground storage tanks, evaporative losses from gasoline stations and vehicles and, to a much smaller degree, from small gasoline engines in lawn mowers and recreational watercraft. Methyl-*tert*-butyl ether has been reported (generally at low concentrations) in air, rainwater, surface water, groundwater, drinking-water and human tissues (Environmental Protection Agency, 1994; Environment Canada, 1995; Agency for Toxic Substances and Disease Registry, 1996; Environmental Protection Agency, 1996; Health Effects Institute, 1996; National Research Council, 1996; National Science and Technology Council, 1996; Zogorski *et al*., 1996; Brown, 1997; National Science and Technology Council, 1997; National Library of Medicine, 1998; Squillace *et al*., 1998; WHO, 1998). Human exposure to methyl *tert*-butyl ether has been estimated by modelling multiple exposure pathways (Long *et al*., 1994; Agency for Toxic Substances and Disease Registry, 1996; Health Effects Institute, 1996; Brown, 1997; Stern & Tardiff, 1997; WHO, 1998).

(*a*) *Air*

Total industrial releases of methyl *tert*-butyl ether from refineries and manufacturers in Canada in 1994 were approximately 28 000 kg, the bulk of which (98.1%) was released into the air (Environment Canada, 1995).

In 1994, 190 industrial facilities in the United States reported air emissions of methyl *tert*-butyl ether to the Environmental Protection Agency Toxic Chemical Release Inventory, totalling 1.4 million kg, which represents 96.2% of the total methyl *tert*-butyl ether releases from these sources (National Library of Medicine, 1998). Industrial releases of methyl *tert*-butyl ether reported in 1993 totalled about 1.7 million kg, about 84% of which were from refineries (Zogorski *et al*., 1996).

Methyl *tert*-butyl ether discharged into the air remains principally in air, with smaller amounts entering water (Agency for Toxic Substances and Disease Registry, 1996; Zogorski *et al*., 1996; WHO, 1998). Because of dispersion, mixing and the relatively short half-life of methyl *tert*-butyl ether in the atmosphere (1–11 days), the concentrations in the atmosphere and in precipitation would be expected to decrease with

distance from the source. Methyl *tert*-butyl ether in air tends to partition into atmospheric water, including precipitation, and thus contributes to its concentrations in surface and groundwater (Zogorski *et al*., 1996; Squillace *et al*., 1998).

The presence of methyl *tert*-butyl ether in ambient air and microenvironments has been reported since its introduction into reformulated gasolines, especially from Canada and the United States and to a much lesser degree from Europe (in particular Finland), reflecting the principal use patterns (Agency for Toxic Substances and Disease Registry, 1996; Health Effects Institute, 1996; Zogorski *et al*., 1996; WHO, 1998; Zogorski *et al*., 1998).

(i) *Ambient air*

In Porto Alegre, Brazil, the concentrations of methyl *tert*-butyl ether in ambient air between March 1996 and April 1997 ranged from 0.72 to 62 μg/m^3 (average, 24 ± 16 μg/m^3). The rate of emission of methyl *tert*-butyl ether from vehicle exhausts was estimated to be 1700 ± 190 tonnes per year since 15% of the vehicles in the area run on fuels containing methyl *tert*-butyl ether (Grosjean *et al*., 1998).

The concentrations of methyl *tert*-butyl ether in ambient air at various locations in nine Canadian cities (Edmonton, Halifax, Montreal, St John, Stouffville, Toronto, Vancouver, Windsor and Winnipeg) between 1995 and 1996 were reported. The locations included petroleum refineries, gasoline processing and storage plants, pipeline transfer points and urban areas. The concentrations of methyl *tert*-butyl ether in the urban areas were generally very low, ranging from the detection limit (0.1 μg/m^3) to < 0.4 μg/m^3 . In the vicinity of petroleum refineries, methyl *tert*-butyl ether concentrations ranged from 0.81 to 11 μg/m^3 in Edmonton and from 0.23 to 1.5 μg/m^3 in Montreal. In the vicinity of Vancouver gasoline processing and storage plants, the concentrations were generally in the range 0.39–3.4 μg/m^3. The methyl *tert*-butyl ether concentrations at the boundary of a petroleum refinery in St John during a period of complaints about odours in 1995 ranged from 15 to 280 μg/m^3 in four sampling periods (WHO, 1998).

The results of monitoring of methyl *tert*-butyl ether in air in the United States are considered inadequate to characterize the concentrations to be expected in ambient air (Zogorski *et al*., 1996). The annual mean methyl *tert*-butyl ether concentration in ambient air in the United States during the late 1980s was estimated to be < 0.7 μg/m^3 (Environmental Protection Agency, 1994; Agency for Toxic Substances and Disease Registry, 1996). Twenty-four-hour ambient air sampling in 1990–91 at various sites in Boston, MA, and Houston, TX, where methyl *tert*-butyl ether was used at < 5% volume in gasoline showed concentrations of < 0.7–1.8 μg/m^3 and < 0.7–10 μg/m^3, respectively. In both Boston and Houston, the median concentration was < 0.7 μg/m^3 (Kelly *et al*., 1993).

An analysis of indoor and ambient air samples was undertaken in Fairbanks, Alaska, during the winter of 1992–93 after a series of complaints of ill health after the introduction of methyl *tert*-butyl ether as an oxygenate in gasoline. Both ambient outdoor air and air in workplaces, schools, post offices and one residence were sampled in December 1992 when methyl *tert*-butyl ether was introduced and in February 1993 when it was no longer used in gasolines. At a major intersection in Fairbanks, the mean concentrations

in ambient air were 16 mg/m^3 in December 1992 and 4.0 mg/m^3 in February 1993. The mean concentrations at those times were 17 and 1.9 μg/m^3 at an elementary school, 27 and 3.6 μg/m^3 in a private residence, 1100 and 220 μg/m^3 in some garage and 300 and 41 μg/m^3 inside vehicles (Gordian & Guay, 1995).

The median concentration of methyl *tert*-butyl ether in the ambient air of Fairbanks, AK, Milwaukee, WI, Albany, NY, Stamford, CT, Boston, MA, and Houston, TX ranged from 0.47 to 17 μg/m^3, with the highest median value measured in Fairbanks. When the value for Fairbanks was excluded, the maximum concentration measured in ambient air was 15 μg/m^3 in Milwaukee, and the median ambient air concentrations in the five cities other than Fairbanks were < 3.6 μg/m^3 (1 ppb). The concentrations of methyl *tert*-butyl ether in air near gasoline stations, roadways, parking lots, garages and blending and distribution facilities were higher than those in ambient urban air (Health Effects Institute, 1996; Zogorski *et al*., 1996).

The results of two monitoring surveys carried out in 1995–96 indicated that the average ambient air concentrations of methyl *tert*-butyl ether after 3-h sampling at four southern California locations were 2.2–26 μg/m^3 and those at seven California locations after 24-h sampling were 4.7–17 μg/m^3 (Poore *et al*., 1997; WHO, 1998).

A regional study of air from the Houston Regional Monitoring Corporation, which included the Houston Ship Channel industrial complex in Texas and some of the largest methyl *tert*-butyl ether manufacturing facilities, during the period September 1987 to September 1988 showed a mean ambient air concentration below the detection limit of 0.7 μg/m^3 (0.2 ppb) in 24-h time-averaged samples. The total yearly emissions of methyl *tert*-butyl ether in the Harris and Chambers counties were suggested to be 280 tonnes (LaGrone, 1991).

In a study of ambient air in Milwaukee, WI, where reformulated gasoline containing approximately 11% by volume of methyl *tert*-butyl ether was used, 11 weekly 24-h samples collected at an air sampling station from January to March 1995 showed concentrations of methyl *tert*-butyl ether ranging from < 0.36 to 15 μg/m^3; the concentration in 45% of the samples was below the detection limit of 0.36 μg/m^3 (0.1 ppb). The median concentration was 0.47 μg/m^3 (0.13 ppb). The concentrations in control samples from the nearby cities of Madison and Green Bay where reformulated gasoline was not mandated were below the detection limit (WHO, 1998). In the same study, the mean concentrations of methyl *tert*-butyl ether in air samples were 1.9 μg/m^3 in three samples collected near a freeway interchange, 3.8 μg/m^3 in two samples from a busy intersection and 1.8 μg/m^3 in two samples from a roadway in Milwaukee (Allen *et al*., 1996; WHO, 1998).

Measurements at an enclosed parking ramp in Milwaukee were conducted in February 1995 to determine the effect on ambient concentrations of methyl *tert*-butyl ether of starting cold engines. Concentrations of < 72 μg/m^3 with a mean of 7.4 μg/m^3 were found in eight samples. The highest concentrations were found when a large number of vehicles were started while cold within a short period (WHO, 1998).

At one refinery in the United States, the 24-h concentration of methyl *tert*-butyl ether was 20 μg/m^3 in one of nine samples taken downwind from the perimeter of a rural

refinery, which was reported to release approximately 33 tonnes of methyl *tert*-butyl ether into the air yearly. During the same period, methyl *tert*-butyl ether was not detected in 26 other downwind and upwind samples. Methyl *tert*-butyl ether was not detected (detection limit, 6 μg/m^3) in 54 24-h samples taken at two other refineries [the annual emissions from these refineries to the air were not provided] (American Petroleum Institute, 1989).

(ii) *Refuelling operations*

Non-occupational and consumer exposures to methyl *tert*-butyl ether have been measured in a number of studies. The general public has the greatest exposure to methyl *tert*-butyl ether during vehicle refuelling. The concentrations are generally higher at service stations where there is no vapour recovery system, and the concentrations usually decrease from the personal breathing zone of the customer or attendant to the pump island to the station perimeter. The heaviest exposure tended to be short. The median concentrations in the customer breathing zone during refuelling were typically 1.1–22 μg/m^3 and occasionally higher. Concentrations of 0.04–0.36 μg/m^3 were measured inside vehicles during this time, reflecting potential exposure of passengers (Allen *et al.*, 1996; Health Effects Institute, 1996; Zogorski *et al*., 1996; WHO, 1998).

In April 1993, air samples were taken inside vehicles during refuelling and suburban commuting in New Jersey, New York and Connecticut (United States), where gasoline containing 10–15% by volume methyl *tert*-butyl ether was sold. The concentrations of methyl *tert*-butyl ether inside vehicles immediately before, during and after refuelling were 24–110 μg/m^3, 130–310 μg/m^3 and 31–150 μg/m^3, respectively, in three cars, with average concentrations of 54, 200 and 72 μg/m^3, respectively. Short-term peak concentrations of methyl *tert*-butyl ether occurred during refuelling. The 60-min air concentrations of methyl *tert*-butyl ether inside 20 suburban commuter vehicles in stop–start traffic ranged from 4 to 580 μg/m^3 with a mean of 21 μg/m^3, most values being < 20 μg/m^3 and higher values being associated with the use of high-emission vehicles (Lioy *et al.*, 1994).

Finland is the only European country where methyl *tert*-butyl ether is used in reformulated gasoline as an octane enhancer and oxygenate source at 11% of gasoline blend throughout the year since 1994. The concentrations of methyl *tert*-butyl ether at the perimeter and pump island of two self-service stations (one at an urban roadside and one at a simple roadside equipped with 'stage I' vapour recovery systems) were ascertained during the period May–June and October, 1995. The service stations studied represented typical Nordic stations in size, location and design. The measurements in the customer breathing zone showed a wide distribution, the lowest exposures being the most frequent. Measurements in the breathing zone showed concentrations of < 0.2–240 mg/m^3 in 313 individual samples. On average, customers were exposed to a concentration of 6 mg/m^3 during a 1-min refuelling time. The average range in perimeter air samples at both service stations was 0.5–120 μg/m^3 methyl *tert*-butyl ether. The mean concentrations measured at the centre of the pump island ranged from 250 to 1350 μg/m^3 (n = 15) (Vainiotalo *et al*., 1996a,b). An additional study to assess the exposure of customers at service stations to

methyl *tert*-butyl ether from gasolines with lower concentrations (average, 2.7%) showed an overall average concentration in the breathing zone of 3.3 mg/m^3 (0.02–51 mg/m^3; $n = 167$), which was higher than that expected from studies of gasoline containing 11% methyl *tert*-butyl ether (Vainiotalo *et al*., 1997).

Exposure to methyl *tert*-butyl ether in 1991–92 at 16 service stations in Italy belonging to a single company was compared with that at 42 service stations belonging to all companies operating in Italy in 1995. The overall arithmetic mean concentrations, taken as a conservative estimate of personal exposure, were: 710 µg/m^3 in summer ($n = 76$) and 370 µg/m^3 in winter ($n = 128$) in 1991–92 and 260 µg/m^3 in summer ($n = 347$) in 1995 (Giacomello, 1996).

(*b*) *Water*

Methyl *tert*-butyl ether has been found in storm-water, groundwater, reservoir water and drinking-water, especially in areas where it is used extensively in gasoline and where methyl *tert*-butyl ether could be released more readily to air and water (Agency for Toxic Substances and Disease Registry, 1996; Davidson, 1996; Delzer *et al*., 1996; Environmental Protection Agency, 1996; Health Effects Institute, 1996; National Science and Technology Council, 1996; Squillace *et al*., 1996; Zogorski *et al*., 1996; National Science and Technology Council, 1997; Squillace *et al*., 1997; WHO, 1998; Zogorski *et al*., 1998). Although methyl *tert*-butyl ether released from non-point sources (e.g., precipitation and small surface spills) can enter water, the primary concern with regard to contamination of water by this chemical is substantial surface spills and leakage from underground storage tanks. Because it is highly soluble in water, methyl *tert*-butyl ether can partition readily from gasoline into water, resulting in high aqueous concentrations. In shallow groundwater below underground storage tanks, concentrations up to 200 000 µg/L have been found (Davidson, 1996; National Research Council, 1996; National Science and Technology Council, 1997).

Methyl *tert*-butyl ether was detected in storm-water runoff in about 7% of 592 samples from 16 United States cities with populations greater than 100 000 during 1991–95. The concentrations ranged from 0.2 to 8.7 µg/L with a median of 1.5 µg/L (limit of detection, 0.2 µg/L). Eighty-three per cent of the detectable methyl *tert*-butyl ether was found during winter. It was detected both in cities where oxygenated gasoline was used to reduce carbon monoxide concentrations and in cities presumed to have used methyl *tert*-butyl ether in gasoline for octane enhancement (Zogorski *et al*., 1996).

Storm-water runoff may be an important non-point source of methyl *tert*-butyl ether to groundwater. In a United States Geological Survey, storm-water runoff samples were collected in Phoenix, AZ, Denver/Lakewood, CO, and Colorado Springs, CO. Methyl *tert*-butyl ether was detected in 17% of the 94 storm-water samples collected between October 1991 and September 1994 during the summer, with a median concentration of 1.5 µg/L (Squillace *et al*., 1996).

Methyl *tert*-butyl ether is a potentially important groundwater contaminant because of its mobility and persistence. It persists in groundwater under both aerobic and anaerobic

conditions because it resists physical, chemical and microbial degradation (Squillace *et al*., 1996; Zogorski *et al*., 1996; National Science and Technology Council, 1997; Squillace *et al*., 1998; WHO, 1998; Zogorski *et al*., 1998).

Methyl *tert*-butyl ether was the second most frequently detected of 60 volatile organic chemicals in samples of shallow ambient water collected from urban areas in the United States during 1993–94 as part of the Geological Survey's National Water-Quality Assessment Program. Only concentrations of ≥ 0.2 μg/L were reported. It was detected more frequently in shallow groundwater in urban areas (27% of 210 wells and springs sampled in eight urban areas) than in shallow groundwater in agricultural areas (1.3% of 549 shallow agricultural wells sampled in 21 areas) or deeper groundwater in major aquifiers (1% of 412 wells sampled in nine areas). Methyl *tert*-butyl ether was most frequently detected in shallow groundwater in Denver, CO, and in urban areas in New England (Squillace *et al*., 1996; Zogorski *et al*., 1996, 1998).

In shallow urban groundwater, methyl *tert*-butyl ether is generally not found with benzene, toluene, ethylbenzene or xylene which are commonly associated with gasoline spills, as methyl *tert*-butyl ether is much more soluble in water (Squillace *et al*., 1996: Zogorski *et al*., 1996). Measurements of methyl *tert*-butyl ether and benzene between 1993 and 1998 in a shallow, sandy aquifer located near Beaufort, SC, suggested that the concentrations of methyl *tert*-butyl ether are lower than those of benzene because of the natural attenuation processes of dilution and dispersion in less contaminated groundwater rather than biodegradation at this point-source of gasoline release (Landmeyer *et al*., 1998).

In an analysis of data on methyl *tert*-butyl ether in surface and groundwater systems of Long Island, NY, and New Jersey, methyl *tert*-butyl ether was one of the most frequently detected volatile organic compounds. Point and non-point sources of contamination are distinguished by seasonal patterns of detection, frequent detection of low concentrations and associations with land use and population size. When only concentrations ≥ 0.5 μg/L were reported, methyl *tert*-butyl ether was the third most frequently detected volatile organic compound (9%) in 208 wells monitored in Suffolk County, NY, with concentrations ranging from 0.6 to 47 μg/L, and was the second most frequently detected volatile organic compound in streams, occurring in 29% of 93 streams in Suffolk County at concentrations ranging from 0.6 to 20 μg/L. It was detected more frequently in samples collected during winter (33%) than summer (26%), corresponding to the expected increase in both the use of oxygenated fuels and the concentrations of methyl *tert*-butyl ether in precipitation during winter (Stackelberg *et al*., 1997). Methyl *tert*-butyl ether was detected in all of 42 surface water samples collected from streams on Long Island, NY, and in New Jersey during 27–30 January 1997. The median and maximum concentrations detected were 0.36 μg/L and 8.7 μg/L, respectively. The highest concentrations of methyl *tert*-butyl ether were measured in the most intensely developed parts of the area, in streams draining basins with the highest percentages of urban land use (O'Brien *et al*., 1997).

In an analysis of methyl *tert*-butyl ether in public groundwater systems in five states where the compound was being used, 2.5% of the 2500 systems sampled had concen-

trations above the detection limit but below 10 μg/L, but one system had concentrations of 10–20 μg/L; the median limit of detection was 0.5 μg/L (Davidson, 1996).

According to the Environmental Protection Agency's Toxic Release Inventory, about 93.5% of the methyl *tert*-butyl ether released from industries in the United States in 1992 was released into the atmosphere, 3.5% was discharged into surface water and 2.5% was injected into wells (Environmental Protection Agency, 1994). In 1994, 190 facilities in the United States reported the discharge of 41 tonnes of methyl *tert*-butyl ether into surface water (National Library of Medicine, 1998).

Although methyl *tert*-butyl ether has been detected in public and private drinking-water supplies derived from groundwater in the United States, the available data are inadequate to characterize its occurrence in drinking-water nationwide, since the Federal Government does not require routine monitoring of methyl *tert*-butyl ether in drinking-water. However, it was detected in 51 public drinking-water systems in all states that provided information (Colorado, Iowa, Illinois, New Jersey and Texas). The concentration of methyl *tert*-butyl ether in nearly all these systems (47 of 51; 92%) was < 20 μg/L (Zogorski *et al*., 1996).

In an analysis of groundwater used as a drinking-water supply in six sampling areas in the lower Susquehannna River Basin (in the states of Pennsylvania and Maryland) in 1993–95, methyl *tert*-butyl ether was the most commonly detected of 60 volatile organic compounds. It was found in 16/118 wells at concentrations ranging from 0.11 to 51 μg/L (Daly & Lindsey, 1996).

No data on methyl *tert*-butyl ether in drinking-water were available from other countries (WHO, 1998).

(*c*) *Soil and sediments*

As methyl *tert*-butyl ether sorbs only weakly to subsurface solids, sorption does not substantially retard its transport by groundwater (Squillace *et al*., 1997). No quantitative estimates of the release of methyl *tert*-butyl ether to soil or sediment were available (Agency for Toxic Substances and Disease Registry, 1996; WHO, 1998).

In 1994, about 1000 kg of methyl *tert*-butyl ether were released onto the land from 190 industrial facilities in the United States, representing < 1% of the total environmental releases from these facilities (National Library of Medicine, 1998).

(*d*) *Human tissues and secreta*

The concentration of methyl *tert*-butyl ether in the blood of commuters in Fairbanks, AK (United States) decreased from 0.18 μg/L (range, 0.05–0.3 μg/L) to 0.09 μg/L (range, < 0.05–0.41 μg/L) after discontinuation of the use of oxygenated fuels (Moolenaar *et al.*, 1994).

The exposure of 14 commuters to methyl *tert*-butyl ether from oxygenated gasolines in Stamford, CT (United States), was measured in 1993. The median blood concentration was 0.11 μg/L and the range was < 0.05–2.6 μg/L. The blood concentrations correlated strongly with those in personal breathing zone samples, with estimated correlation

coefficients of 0.80 between air and blood for methyl *tert*-butyl ether and 0.70 between methyl *tert*-butyl ether in air and *tert*-butyl alcohol in blood (White *et al*., 1995).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (1997) recommended 144 mg/m^3 as the 8-h time-weighted average (TWA) threshold limit value for exposure to methyl *tert*-butyl ether in workplace air. The TWA in the Czech Republic is 100 mg/m^3, with a short-term exposure limit (STEL) of 200 mg/m^3. The STEL in the Russian Federation is 100 mg/m^3. The 8-h TWA in Sweden is 180 mg/m^3, and the STEL is 250 mg/m^3 (United Nations Environment Programme, 1998). The 8-h TWA in Finland is 180 mg/m^3 (Finnish Institute of Occupational Health, 1998).

No international guidelines for methyl *tert*-butyl ether in drinking-water have been established (WHO, 1993).

2. Studies of Cancer in Humans

No data on exposure to methyl *tert*-butyl ether itself were available to the Working Group. Exposure to gasoline and in petroleum refining has been evaluated in previous monographs (IARC, 1989).

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

Rat: Groups of 60 male and 60 female Sprague-Dawley rats, eight weeks of age, were given gastric instillations of 0, 250 or 1000 mg/kg bw methyl *tert*-butyl ether (purity, > 99%) in 1 mL olive oil once a day on two days with one day's rest and for another two days with two days' rest, each week for 104 weeks and were kept under observation until they died. The survival rate of males at the high dose was increased beyond 80 weeks after the start of treatment and was dose-dependently decreased in females beyond 16 weeks after the start of treatment [statistical significance not indicated; mean survival times not given]. No relevant differences in male and female body weights were observed. At necropsy, multiple organs were examined histopathologically, and a statistically significant increase ($p = 0.05$) in the incidence of Leydig-cell testicular adenomas was found in males at the high dose: control, 2/26; low dose, 2/25; high dose, 11/32 [group sizes indicate the number of rats alive at 96 weeks of age, when the first Leydig-cell tumour was observed]. A dose-related increase in the incidence of lymphomas and leukaemias was seen in female rats: control, 2/58; low dose, 6/51; high dose, 12/47 ($p < 0.01$ at both doses) [groups sizes refer to the number of rats alive at 56 weeks of age, when the first leukaemia was observed]. There was no increase in the incidence of lymphomas or leukaemias in males: control, 10/59; low dose, 9/59; high dose, 7/58

(Belpoggi *et al*., 1995, 1998). [The Working Group noted that the dosing schedule was unusual, that animals were allowed to live out their natural lifespan and that mortality-adjusted analysis was not performed; therefore, estimates of effective group numbers and tumour incidences were difficult to analyse.]

3.2 Inhalation exposure

Mouse: Groups of 50 male and 50 female CD-1 mice, seven to eight weeks of age, were exposed to 0, 400, 3000 or 8000 ppm [0, 1400, 11 000 and 29 000 mg/m^3] methyl *tert*-butyl ether vapour (purity, > 99%) in air for 6 h a day on five days per week for 18 months, when the experiment was terminated. The daily doses were estimated to be 340, 2600 and 6800 mg/kg bw at the three exposure levels, respectively. Males and females at the high dose had reduced body-weight gain and earlier mortality due to toxicity. The survival time decreased from 510 days in control males to 438 days in animals at the high dose and in females from 519 to 489 days. The incidence of hepatocellular adenomas was increased in females at the high dose: control, 2/50; low dose, 1/50; intermediate dose, 2/50; high dose, 10/50 ($p < 0.01$). The incidence of hepatocellular carcinoma was not increased. In males, no significant changes in hepatocellular tumours (adenomas and carcinomas) were noted, but the incidence of carcinomas showed a tendency to increase: control, 2/49; low dose, 4/50; intermediate dose 3/50; high dose, 8/49 (Bird *et al*., 1997; Mennear, 1997). [The Working Group noted that mortality-adjusted analysis was not performed and that therefore the tumour incidence in the high-dose group may have been underestimated. They also noted that groups at the intermediate and low doses were not subjected to complete histopathological examination unless the animals died spontaneously or were killed when moribund.]

Rat: Groups of 50 male and 50 female Fischer 344 rats, seven to eight weeks of age, were exposed for 6 h a day on five days per week to 0, 400, 3000 or 8000 ppm [0, 1400, 11 000 and 29 000 mg/m^3] methyl *tert*-butyl ether vapour (purity, > 99%) in air for 24 months. The doses were estimated to be 220, 1700 and 4400 mg/kg bw at the three exposure levels, respectively. Males at the high and intermediate doses were killed at week 82 and week 97, respectively, due to excess mortality from severe progressive nephrosis. The other groups were killed at 24 months. The mean survival times for the males at the low dose and controls were 617 and 632 days; the survival times of control females and those at the low, intermediate and high doses were 697, 683, 697 and 676 days, respectively. The incidence of renal tubular-cell tumours was increased in males at the two higher doses: adenomas—control, 1/50; low dose, 0/50; intermediate dose, 5/50; high dose, 3/50; carcinomas—control, 0/50; low dose, 0/50; intermediate dose, 3/50; high-dose, 0/50. The combined incidence in males at the intermediate dose (8/50) was statistically significantly different from that of controls and was outside the range of the historical controls. Female rats showed no significant increase in the incidence of renal tumours. The incidence and size of interstitial-cell adenomas of the testis were significantly increased in rats at the two higher doses ($p < 0.05$), with incidences of 32/50 controls, 35/50 at the low dose, 41/50 at the intermediate dose and 47/50 at the high dose

(Bird *et al*., 1997; Mennear, 1997). [The Working Group noted the unusually low incidence of interstitial adenomas of the testis in control rats when compared with the historical control incidence in that laboratory and that mortality-adjusted analysis was not performed.]

3.3 Administration with known carcinogens or modifying factors

Mouse: In a model of liver carcinogenesis, groups of 12 female B6C3F_1 mice, 12 days of age, received a single intraperitoneal injection of 5 mg/kg bw *N*-nitrosodiethylamine or saline. Beginning at eight weeks of age, mice were exposed by inhalation to 0 or 8000 ppm [29 000 mg/m^3] methyl *tert*-butyl ether (purity, > 99.95%) in air for 6 h per day on five days per week and were killed after 16 or 32 weeks. Exposure to methyl *tert*-butyl ether for 16 or 32 weeks after treatment with *N*-nitrosodiethylamine did not enhance the development of altered hepatic foci or increase the numbers of hepatocellular adenomas or carcinomas. No hepatic foci occurred in the group receiving methyl *tert*-butyl ether alone. (Moser *et al*., 1996a).

3.4 Carcinogenicity of metabolites

Mouse: Groups of 60 male and 60 female B6C3F_1 mice, approximately seven weeks of age, were given 0, 5, 10 or 20 mg/mL *tert*-butyl alcohol in their drinking-water for two years, providing average daily doses of approximately 540, 1000 and 2100 mg/kg bw *tert*-butyl alcohol to males and approximately 510, 1000 and 2100 mg/kg bw to females. The survival rate of males at the high dose was significantly lower than that of controls, but the final mean body weights of exposed males were similar to those of controls. The mean body weights of females at the high dose were 10–15 % lower than those of controls from 13 weeks to the end of the study. The incidence of thyroid gland follicular-cell hyperplasia was significantly increased in all exposed male groups and in females at the two higher doses. The incidence of follicular-cell adenoma or carcinoma (combined) was higher in males at the intermediate dose but was not significantly increased (control, 1/60; low dose, 0/59; intermediate dose, 4/59; high dose, 2/57). The incidence of follicular-cell adenoma was significantly increased in females at the high dose: control, 2/58; low dose, 3/60; intermediate dose, 2/59; high dose, 9/59 ($p = 0.039$) (Cirvello *et al*., 1995; National Toxicology Program, 1995).

Rat: Groups of 60 male and 60 female Fischer 344/N rats, approximately seven weeks of age, were given 0, 1.25, 2.5 or 5 mg/mL (males) or 0, 2.5, 5 or 10 mg/mL (females) *tert*-butyl alcohol in their drinking-water for two years, providing average daily doses of approximately 90, 200 and 420 mg/kg bw for males and 180, 330 and 650 mg/kg bw for females. Ten rats per group were evaluated after 15 months of treatment. The survival rates of males and females at the high dose were significantly lower than those of controls, due to toxicity. The final mean body weights of exposed males were 15–24 % lower than those of controls, and the final mean body weight of females at the high dose was 21% lower than that of controls. Water consumption was increased dose-dependently in males and decreased in females. The incidence of renal adenomas and

carcinomas combined, based on a single section of each kidney was not increased, being 1/50 (control), 3/50 (low dose), 4/50 (intermediate dose) and 3/50 (high dose). When step-sections including the single section were used, the kidney tumour incidences were increased significantly in males at the intermediate dose: 8/50 (control), 13/50 (low dose), 19/50 (intermediate dose; $p < 0.01$) and 13/50 (high dose). The incidence of focal renal tubule hyperplasia was also increased in males at the high dose (Cirvello *et al*., 1995; National Toxicology Program, 1995).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

The metabolism of methyl *tert*-butyl ether has been reviewed (WHO, 1998). A scheme for the metabolism of methyl *tert*-butyl ether is presented in Figure 1.

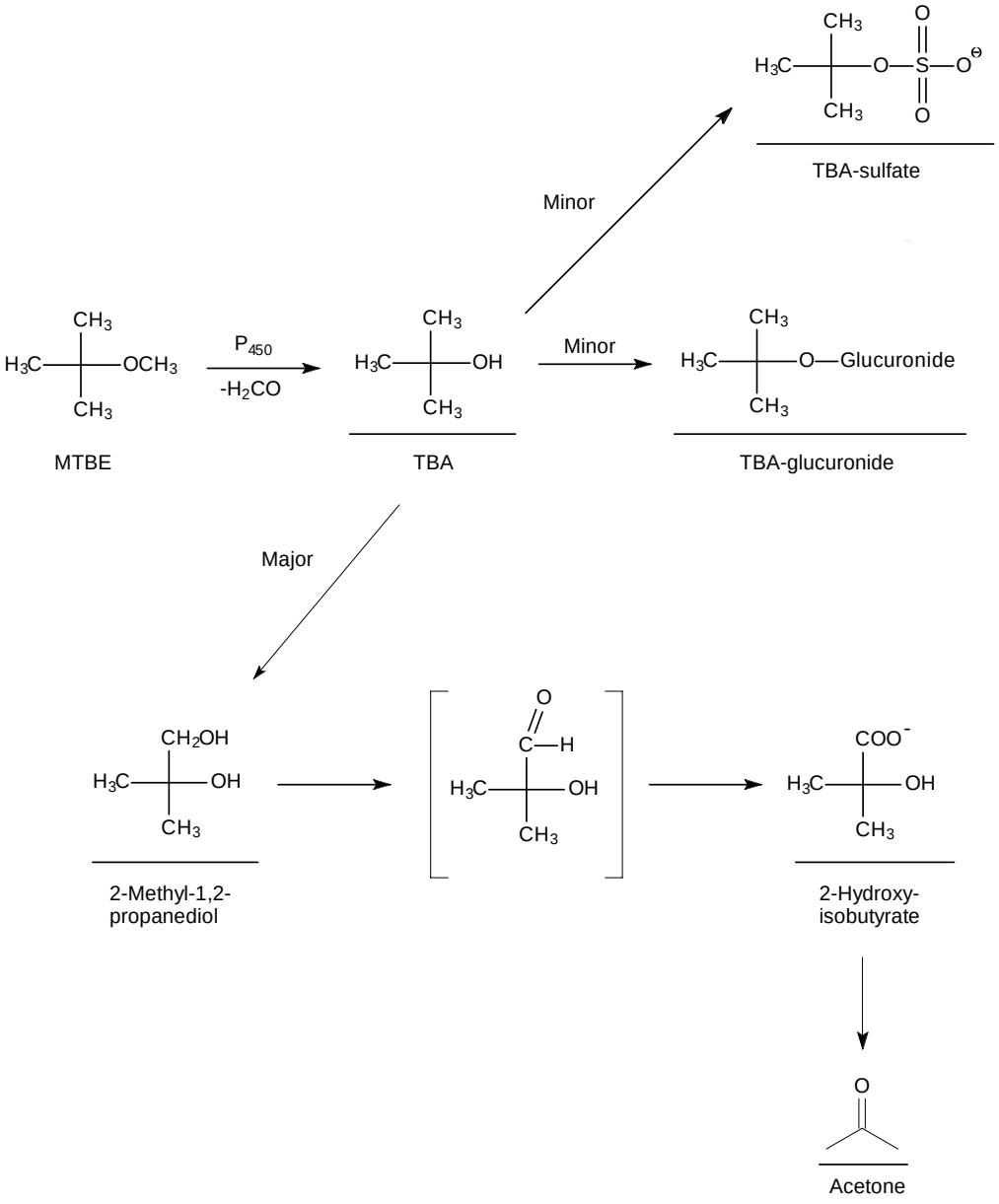
4.1.1 *Humans*

One 25-year-old man weighing 102.5 kg with a ventilation volume of 10.82 L/min and one 21-year-old woman weighing 66.5 kg with a ventilation volume of 8.65 L/min were exposed to 5.01 mg/m^3 methyl *tert*-butyl ether vapour for 1 h. Breath, blood and urine samples were collected before and up to 580 min after exposure. The blood concentrations of methyl *tert*-butyl ether at the end of exposure were 8.2 μg/L in the man and 14 μg/L in the woman. The concentrations in breath and blood decayed rapidly after exposure but were still elevated 7 h after exposure when compared with those before exposure. The blood concentration of *tert*-butyl alcohol, a metabolite of methyl *tert*-butyl ether, increased gradually during exposure and remained elevated up to 7 h after exposure; the highest concentrations measured were 9.5 μg/L in the man and 10 μg/L in the woman. Urinary elimination accounted for < 1% of the total methyl *tert*-butyl ether eliminated (Buckley *et al*., 1997).

Cain *et al*. (1996) exposed two men and two women, aged 18–26 years, to 1.7 ppm [6.1 mg/m^3] methyl *tert*-butyl ether for at least 1 h. Blood samples were taken before, during and after exposure and analysed for methyl *tert*-butyl ether. The mean concentration in blood at the end of exposure was 17 μg/L.

Ten men aged 23–51 years and weighing 70–90 kg were exposed to 5, 25 or 50 ppm [18, 90 and 180 mg/m^3] methyl *tert*-butyl ether during 2 h of light exercise (50 W) on three occasions separated by at least two weeks. Methyl *tert*-butyl ether and *tert*-butyl alcohol were monitored in exhaled breath, blood and urine. The average concentrations of methyl *tert*-butyl ether in blood were proportional to the exposure and were 1.4, 6.5 and 15 μmol/L [120, 570 and 1100 μg/L] at the end of exposure to the three concentrations, respectively. Elimination of methyl *tert*-butyl ether in blood occurred in four phases with half-lives of 1 min, 10 min, 1.5 h and 19 h. The integrated area under the curve of the blood concentration of methyl *tert*-butyl ether over time was linearly related to the exposure, suggesting

Figure 1. Metabolism of methyl *tert*-butyl ether



From Bernauer *et al.* (1998); metabolites excreted in urine are underlined.
TBA, *tert*-butyl alcohol; MTBE, methyl-*tert*-butyl ether

linear kinetics up to 50 ppm. Elimination of methyl *tert*-butyl ether in urine occurred in two linear phases with half-lives of 20 min and 3 h. The amount of methyl *tert*-butyl ether excreted in urine over 22 h represented ~0.1% of the uptake. Linear kinetics was observed for *tert*-butyl alcohol in blood at doses up to 50 ppm. The elimination half-lives of *tert*-butyl alcohol in blood and urine were 10 and 8.2 h, respectively. The blood concentration of *tert*-butyl alcohol, unlike that of methyl *tert*-butyl ether, increased slowly during exposure and remained high for several hours after exposure. Renal clearance of *tert*-butyl alcohol was calculated to be low, suggesting extensive blood protein binding or extensive tubular reabsorption. The 22-h cumulative excretion of *tert*-butyl alcohol in urine represented approximately 1% of the uptake of methyl *tert*-butyl ether (Nihlén *et al*., 1998a).

A single subject was exposed by inhalation to 1 ppm [3.6 mg/m^3] methyl *tert*-butyl ether for 10 min. Approximately 0.9% of the amount of the inhaled dose was excreted unchanged in urine, with 2.4% excreted as *tert*-butyl alcohol within 10 h after exposure (Lee & Weisel, 1998).

One male volunteer aged 44 and weighing 80 kg was given [^{13}C]*tert*-butyl alcohol orally in a gel capsule at a dose of 5 mg/kg bw (Bernauer *et al*., 1998). His urine was collected at 12-h intervals for 48 h and analysed by ^{13}C nuclear magnetic resonance. 2-Hydroxyisobutyrate (α-hydroxybutyric acid) and 2-methyl-1,2-propanediol were identified in the urine samples as major metabolites; minor urinary metabolites were *tert*-butyl alcohol and *tert*-butyl alcohol glucuronide. The sulfate conjugate of *tert*-butyl alcohol was present only in trace amounts.

White *et al*. (1995) obtained blood samples from 44 people in Stamford, CT, United States, who were either occupationally exposed to methyl *tert*-butyl ether or exposed to it while commuting. The blood levels of methyl *tert*-butyl ether ranged from a median of 15 μg/L (7.6–29 μg/L) for gasoline service station attendants to 1.7 μg/L (0.17–37 μg/L) for car repair workers and 0.11 μg/L (0.05–2.6 μg/L) for commuters. The *tert*-butyl alcohol levels reflected the same trend. The concentrations of methyl *tert*-butyl ether in blood correlated strongly with those in the breathing zone (correlation coefficient, 0.8; $p = 0.004$).

4.1.2 *Experimental systems*

(*a*) *Whole animals*

A number of studies of the pharmacokinetics and disposition of methyl *tert*-butyl ether conducted in male and female Fischer 344 rats after intravenous, oral or dermal administration of methyl *tert*-butyl ether or by inhalation were described by Miller *et al*. (1997). With few exceptions, the pharmacokinetics and disposition of methyl *tert*-butyl ether were the same in male and female rats after all types of administration, but only data for male rats were reported. In one study, rats received methyl *tert*-butyl ether either by intravenous injection into the caudal vein (40 mg/kg bw), by oral gavage (40 or 400 mg/kg bw), by dermal application (40 or 400 mg/kg bw in occluded chambers), by a single nose-only 6-h exposure to 400 or 8000 ppm [1400 and 29 000 mg/m^3] or by repeated exposure to 400 ppm for 15 days. Plasma samples were analysed for methyl *tert*-butyl ether and

tert-butyl alcohol by gas chromatography at various times after exposure to methyl *tert*-butyl ether, and the data collected were used to assess pharmacokinetics. Comparisons of the integrated area under the blood concentration–time curve for methyl *tert*-butyl ether after intravenous or oral administration indicate that methyl *tert*-butyl ether is rapidly and completely absorbed from the gastrointestinal tract. Dermal absorption represented approximately 16 and 34% of the low and high dose, respectively. Metabolism did not appear to be saturated after oral or dermal doses of 40 and 400 mg/kg bw; however, the data suggested that the metabolism of methyl *tert*-butyl ether was saturated after exposure by inhalation to 8000 ppm for 6 h. The pharmacokinetics of methyl *tert*-butyl ether and *tert*-butyl alcohol were similar after intravenous, oral and inhalation exposure and were best described by an open one-compartment model. The half-lives for the clearance of methyl *tert*-butyl ether from plasma after intravenous and oral (40 mg/kg bw) administration and inhalation ranged from 0.45 to 0.57 h. After oral administration of 400 mg/kg bw methyl *tert*-butyl ether, its half-life was 0.79 h. Plasma elimination of methyl *tert*-butyl ether after dermal application was best described by a two-compartment model, and the elimination half-life was 1.8–2.3 h. The half-lives for elimination of *tert*-butyl alcohol ranged from 0.92 after intravenous injection to 3.4 h after inhalation. Repeated exposure to methyl *tert*-butyl ether for 15 days had no effect on its clearance from plasma.

Miller *et al*. (1997) also described the disposition of [^{14}C]methyl *tert*-butyl ether in male Fischer 344 rats up to seven days after intravenous injection of 40 mg/kg bw or dermal application of 40 or 400 mg/kg bw, and in male and female rats after a single nose-only exposure by inhalation to 400 or 8000 ppm [1400 or 29 000 mg/m^3] or after repeated exposure by inhalation to 400 ppm [^{14}C]methyl *tert*-butyl ether for 6 h per day for 15 days. Total radiolabel was determined in tissues, urine, faeces and exhaled air, and the composition of the radiolabelled material was analysed in exhaled air and urine samples. Relatively little difference was observed between male and female rats in the disposition of [^{14}C]methyl *tert*-butyl ether after inhalation. The total recovery of ^{14}C measured in excreta, expired air and tissues of rats 48 h after exposure represented 91–105% of the dose. Most of the absorbed radiolabel (86–98%) was recovered in expired air and urine within 48 h, and only a small amount (< 2%) was excreted in faeces. Within the first 3 h after exposure, the proportion of radiolabel that was eliminated in exhaled air was 60% after intravenous dosing, 9–19% after dermal application, 21–54% after a single inhalation dose and 17% after repeated inhalation. Most of the exhaled radiolabel was associated with methyl *tert*-butyl ether itself: > 95% after intravenous and dermal administration and 66–80% after inhalation. Methyl *tert*-butyl ether was metabolized first to *tert*-butyl alcohol, which was either exhaled or further metabolized and eliminated in the urine. A dose-dependent shift in metabolism and route of elimination was observed after inhalation, with a greater proportion of the dose recovered in expired air as parent compound after the high dose and a larger proportion of the dose recovered in urine after the low dose. Repeated exposure to methyl *tert*-butyl ether did not affect its disposition. Of the four metabolites identified in urine, α-hydroxybutyric acid accounted for approximately 70% of the total urinary radiolabel found after inhalation, and 2-methyl-1,2-

propanediol accounted for approximately 14%. Two unidentified metabolites accounted for about 10 and 5% of the excreted radioactivity. Neither methyl *tert*-butyl ether nor *tert*-butyl alcohol was detected in urine samples from male and female Fischer 344 rats exposed to methyl *tert*-butyl ether.

Bernauer *et al*. (1998) identified urinary metabolites of methyl *tert*-butyl ether and *tert*-butyl alcohol in rats exposed to 2000 ppm [2-^{13}C]methyl *tert*-butyl ether for 6 h. Urine was collected up to 48 h after exposure and analysed by ^{13}C nuclear magnetic resonance and gas chromatography–mass spectrometry. The metabolism of *tert*-butyl alcohol was evaluated in rats given the unlabelled compound or [^{13}C]*tert*-butyl alcohol by gavage at a dose of 250 mg/kg bw in corn oil. Urine was collected up to 72 h after dosing. 2-Methyl-1,2-propanediol, 2-hydroxyisobutyrate (α-hydroxybutyric acid) and an unidentified conjugate of *tert*-butyl alcohol presumed to be a sulfate were the major urinary metabolites of methyl *tert*-butyl ether; small amounts of *tert*-butyl alcohol and its glucuronide were also identified. Rats dosed with [^{13}C]*tert*-butyl alcohol eliminated [^{13}C]acetone, *tert*-butyl alcohol and its glucuronide as minor metabolites.

Male ddY mice were given a single intraperitoneal dose of 50, 100 or 500 mg/kg bw methyl *tert*-butyl ether in corn oil. The amount of methyl *tert*-butyl ether exhaled depended on the dose administered and ranged from 23 to 69% of the dose. More than 90% of the methyl *tert*-butyl ether excreted through the lungs was eliminated within 3 h (Yoshikawa *et al*., 1994).

Male Wistar rats were exposed to 50, 100 or 300 ppm [180, 360 or 1100 mg/m^3] methyl *tert*-butyl ether vapour for 6 h per day on five days per week for 2, 6, 10 or 15 weeks. The rats were killed immediately after exposure, and their blood, cerebral hemispheres and perirenal fat were analysed for methyl *tert*-butyl ether and *tert*-butyl alcohol. The liver and kidneys were also excised and microsomes were prepared. The blood concentrations of methyl *tert*-butyl ether were dose-dependent and did not change with the number of weeks of exposure. The *tert*-butyl alcohol concentrations in blood were dose-dependent and were highest after six weeks of exposure. Methyl *tert*-butyl ether, but not *tert*-butyl alcohol, was detected in perirenal fat. The exposure caused a transient increase in microsomal UDP-glucuronosyltransferase activity in liver and kidneys, but no effect on liver or kidney microsomal 7-ethoxycoumarin *O*-deethylase activity and minor, transient induction of kidney microsomal NADPH-cytochrome c reductase activity (Savolainen *et al*., 1985).

(*b*) *In vitro*

Human liver microsomes (eight samples) were found to metabolize methyl *tert*-butyl ether to *tert*-butyl alcohol with activities ranging from 86 to 175 pmol formed per minute per milligram of total protein (Hong *et al*., 1997a). The metabolizing activity of methyl *tert*-butyl ether was approximately twofold greater in rat and mouse liver microsomes (284–288 pmol *tert*-butyl alcohol formed/min per mg of protein) than in human microsomes. Human cytochrome P450 (CYP) 2A6 and CYP 2E1 cDNAs were individually co-expressed with human cytochrome P450 reductase by a baculovirus expression system,

and the expressed enzymes (microsomal preparations of infected Sf9 cells) were used to assess the metabolism of methyl *tert*-butyl ether. The expressed CYP 2A6 was found to be more active than CYP 2E1 in metabolizing methyl *tert*-butyl ether to *tert*-butyl alcohol.

The metabolism of methyl *tert*-butyl ether to formaldehyde and *tert*-butyl alcohol was evaluated in liver microsomes prepared from male Sprague-Dawley rats treated with acetone or phenobarbital and in controls. Acetone and phenobarbital induce CYP 2E1 and CYP 2B1, respectively. Equimolar amounts of *tert*-butyl alcohol and formaldehyde were formed. Both acetone and phenobarbital induced the metabolism of methyl *tert*-butyl ether. A monoclonal antibody to CYP 2E1 inhibited the metabolism of methyl *tert*-butyl ether by liver microsomes prepared from acetone-induced rats by 35%. Methyl *tert*-butyl ether treatment resulted in a 50-fold increase in liver microsomal pentoxyresorufin dealkylase activity with no change in *N*-nitrosodimethylamine demethylase activity, suggesting an increase in CYP 2B1 but not in CYP 2E1 activity. The activities of these enzymes concord with the results of immunoblot analysis, which showed higher activity of CYP 2B1 and no change in that of CYP 2E1 when compared with controls (Brady *et al.*, 1990). In liver microsomes prepared from male Sprague-Dawley rats and exposed to purified rat CYPs (2B1, 2E1, 2C11, 1A1), CYP 2B1 was the main enzyme involved in the oxidation of methyl *tert*-butyl ether, CYP 2E1 having a lesser role (Turini *et al.*, 1998).

Microsomes prepared from nasal mucosae, including olfactory and respiratory epithelium, and liver, lung, kidney and olfactory bulbs of male Sprague-Dawley rats were used to compare the metabolic activity of these tissues towards methyl *tert*-butyl ether (Hong *et al*., 1997b). The activity was measured *in vitro* by analysing *tert*-butyl alcohol headspace concentration by gas chromatography. The olfactory mucosa showed the highest activity in metabolizing methyl *tert*-butyl ether, and the activity was 46-fold higher than in liver. No detectable activity was found in microsomes prepared from lungs, kidneys or olfactory bulbs of the brain. [The Working Group noted that measuring *tert*-butyl alcohol levels in the headspace by gas chromatography is not a sensitive method for assessing the metabolism of methyl *tert*-butyl ether in tissues with low enzyme activity.]

tert-Butyl alcohol, a metabolite of methyl *tert*-butyl ether, was found to be oxidatively demethylated, producing formaldehyde in liver microsomes prepared from Sprague-Dawley rats (Cederbaum & Cohen, 1980). Casanova and Heck (1997) demonstrated that the metabolism of methyl *tert*-butyl ether to formaldehyde in hepatocytes prepared from female CD-1 mice, male $B6C3F_1$ mice and male Fischer 344 rats approached saturation at concentrations below 0.33 mmol/L. Formaldehyde production in the metabolism of methyl *tert*-butyl ether was evaluated by measuring the formation of DNA–protein cross-links and RNA–formaldehyde adducts. No increases were detected at concentrations of methyl *tert*-butyl ether up to 6.75 mmol/L. Induction of methyl *tert*-butyl ether metabolism did not change the yields of either of these adducts, and no species or strain differences were seen.

4.2 Toxic effects

The toxicity of methyl *tert*-butyl ether has been reviewed (WHO, 1998).

4.2.1 *Humans*

(*a*) *Controlled studies*

Nineteen men and 18 women were exposed to 1.39 ppm [5.0 mg/m^3] methyl *tert*-butyl ether for 1 h on several occasions, each separated by at least one week, and each subject completed a questionnaire on symptoms before and during exposure. Cognitive testing and objective measures of ocular and nasal irritation were also evaluated. There was no significant effect upon headache, nasal irritation or odour intensity, and no evidence of ocular inflammation was apparent as measured by polymorphonuclear neutrophils on the eye surface, tear film break-up time and mRNA coding for interleukin-6 or interleukin-8 in cells removed from the eye. The numbers of inflammation mediators and neutrophils were not significantly different in the nasal lavage fluid of control and treated volunteers. The subjects did not report any adverse symptoms due to this exposure (Prah *et al.*, 1994).

Of 43 people who were evaluated for the acute effects of exposure to 1.7 ppm [6 mg/m^3] methyl *tert*-butyl ether for 1 h, 22 men aged 18–32 and 21 women aged 18–34 remained throughout the study. Symptoms such as irritation, headache and mental fatigue were evaluated, and eye irritation (by tear-film breakup, eye redness) and nasal inflammation (by measurement of polymorphonuclear neutrophilic leukocytes) were measured before and after exposure. No increase in such symptoms was observed (Cain *et al.*, 1996).

Ten white men aged 23–51 years were exposed by inhalation to 5, 25 or 50 ppm [18, 90 and 180 mg/m^3] methyl *tert*-butyl ether vapour for 2 h on three occasions, with an interval of at least two weeks between exposures, during 2 h of light (50 W) physical exercise. The subjects rated the degree of irritative symptoms, discomfort and central nervous system effects before, during and after exposure on a questionnaire. The only rating noted was that of solvent smell, which increased greatly as the subject entered the chamber and with exposure concentration. Ocular changes (redness and tear film break-up time, conjunctival epithelial damage and blinking frequency) and nasal measurements such as peak expiratory flow, acoustic rhinometry to assess nasal swelling (5 and 25 ppm) and levels of inflammatory markers in nasal lavages (50 ppm) were evaluated. No effect on any of the eye measurements was associated with exposure to methyl *tert*-butyl ether. Although some nasal changes where reported, they were not related to the concentration. Nasal airway resistance, calculated from peak expiratory flows, increased significantly after exposure, but the increase did not exhibit any relationship to concentration. Overall, this study showed no or minimal acute effects of methyl *tert*-butyl ether at these concentrations (Nihlén *et al.*, 1998b).

(*b*) *Occupational exposure*

The relationships between exposure to methyl *tert*-butyl ether and acute human health effects have been reviewed (Borak *et al.*, 1998).

A study was conducted to assess neuropsychological symptoms among 101 road tanker drivers in Finland exposed to gasoline containing 10% methyl *tert*-butyl ether. The

control group in this study consisted of 100 milk delivery drivers from the same locations. Interviews based on standardized symptom questionnaires were carried out before and at the end of the same work week. Tanker drivers were found to have a higher fatigue score then the control groups, and 20% of the tanker drivers reported headaches or nausea (Hakkola *et al*., 1997). [The Working Group noted that specific exposure to methyl *tert*-butyl ether was not evaluated in this study.]

In New Jersey (United States), 237 garage workers were evaluated to determine whether a higher prevalence of acute adverse health effects was associated with exposure to methyl *tert*-butyl ether. The workers were divided into those with low and high exposure to methyl *tert*-butyl ether on the basis of the region of New Jersey from which they came; thus, 122 workers exposed after oxygenated fuels had been phased out were considered to have low exposure, and 115 workers who were exposed during implementation of the oxygenated fuels programme were considered to have high exposure. The workers completed questionnaires including questions on symptoms experienced during the previous 30 days. No adverse health effects were attributed to methyl *tert*-butyl ether (Mohr *et al.*, 1994).

A study was conducted to determine whether symptoms associated with exposure to methyl *tert*-butyl ether were reported at an increased rate among 14 people with 'multiple chemical sensitivities', five with 'chronic fatigue syndrome' and six controls in situations where exposure was likely to be highest (i.e. in service stations and while driving a car). The participants were interviewed by telephone. Enclosed shopping centres elicited the most symptoms among the patients; while a significant rate of methyl *tert*-butyl ether-associated symptoms was reported by the patients when they were in service stations, similar rates were seen in other situations, such as in grocery shops. Thus, the study did not provide clear evidence that an usually high rate of symptoms occurred only where methyl *tert*-butyl ether was most prevalent (Fiedler *et al.*, 1994).

The percentage of apoptotic cells in peripheral blood lymphocytes of 60 men and women exposed to methyl *tert*-butyl ether and benzene from water that had been contaminated for five to eight years was reported to be greater than that in a group of people who had no exposure to these chemicals. The concentrations of methyl *tert*-butyl ether and benzene in the water samples were reported to be 1–76 and 0.2–14 μg/L, respectively. The proportions of apoptotic lymphocytes were 26 ± 1.8 (SE)% in the exposed and 12 ± 1.3% in the unexposed groups, respectively (Vojdani *et al*., 1997a). [The Working Group noted that the concentrations were not measured over the period in which the water was reported to have been contaminated. Furthermore, exposure to methyl *tert*-butyl ether and benzene was not characterized, so that the response observed cannot be attributed to either chemical.]

The generation of immunoglobulin (Ig)G, IgM, IgA and IgE antibodies against methyl *tert*-butyl ether was investigated in 18 men and six women who had been employed as gasoline service station attendants for at least two years and in eight men and four women otherwise employed. Significant increases in IgG and IgM antibodies against methyl *tert*-butyl ether were noted in seven exposed and one control person. The antibody titres did

not correlate with the severity or number of reported adverse symptoms, i.e. headaches, shortness of breath, burning eyes, nose and throat, muscle fatigue, memory loss and difficulty in concentrating (Vojdani *et al*., 1997b).

Effects on the immune system were measured by monitoring plasma interleukin-6 at the beginning and end of a single workday in 22 mechanics exposed to automobile emissions derived from fuels containing methyl *tert*-butyl ether. Interleukin-6 is involved in the differentiation of B cells to IgG-secreting plasma cells and is also an inducer of acute-phase proteins and cytotoxic T cells. No change in interleukin-6 was detected (Duffy, 1994). [The Working Group noted that exposure to methyl *tert*-butyl ether was not characterized in this study.]

Blood samples were obtained from volunteers in Fairbanks, Alaska (United States), and methyl *tert*-butyl ether was analysed by gas chromatography–mass spectrometry. The first phase of the study, involving 18 people, was conducted in early December 1992 during implementation of the oxygenated fuels programme, in which methyl *tert*-butyl ether constituted about 15% w/v of gasoline, and the second, involving 28 people, was conducted in February 1993, two months after the programme had been discontinued. The concentrations of methyl *tert*-butyl ether in the blood of workers (including service station attendants, garage workers, drivers and mechanics after a work shift were approximately seven times higher during phase I (median, 1.8 μg/L; range, 0.2–37 μg/L) than during phase II (median, 0.24 μg/L; range, 0.05–1.4 μg/L; $p = 0.0001$). As expected, the blood concentrations were higher in workers at the end than at the beginning of a workshift. The highest concentration measured was 37 μg/L in a worker at the end of a shift in phase I. Higher blood concentrations correlated with heavier exposure. Standardized questionnaires were administered to the workers at the end of the workshift on the same day that blood samples were obtained, eliciting information on key symptoms that have been associated with exposure to methyl *tert*-butyl ether, such as headache, eye irritation, burning of the nose or throat and cough, and other specific health complaints. A much higher prevalence of these symptoms was noted during phase I than phase II; however, the relationship between blood concentrations of methyl *tert*-butyl ether and symptoms was not statistically significant. The authors recognized several limitations to this pilot study (Moolenaar *et al*., 1994).

(*c*) *Instillation into the gall-bladder*

A number of studies of the potential use of methyl-*tert*-butyl ether to dissolve gall-bladder stones have been reported and reviewed (Borak *et al*., 1998). Dissolution of gall-bladder stones in humans involves injection through a catheter into the gall-bladder. In one study in which the concentrations of methyl *tert*-butyl ether in blood were measured, the peak concentrations in patients with gall-bladder stones were about 1000-fold higher than those in workers exposed by inhalation (Leuschner *et al*., 1991). Although, methyl *tert*-butyl ether and its metabolite *tert*-butyl alcohol were measured in the blood and urine of these patients and elimination took several days, no clinical reactions were reported.

4.2.2 *Experimental systems*

The lethality of methyl *tert*-butyl ether has been studied in rats and rabbits. The oral LD_{50} in rats was 4 mL/kg bw, the inhalation LC_{50} in rats was 86 mg/L (4 h), and the dermal LD_{50} in rabbits was > 10 mL/kg bw (Clayton & Clayton, 1981).

The neurotoxicity of methyl *tert*-butyl ether was evaluated in nine-week-old male and female Fischer 344 rats exposed to 0, 800, 4000 or 8000 ppm [0, 2900, 14 000 or 29 000 mg/m^3] methyl *tert*-butyl ether for 6 h, with evaluation of their behaviour 1, 6 and 24 h later. At 1 h after exposure, animals exposed to the highest dose showed a variety of sensorimotor changes indicative of central nervous system depression. The most frequent findings were ataxia, duck-walk, increased lachrymation, laboured respiration, decreased muscle tone, lowered body temperature and decreased hind-leg grip strength. No changes were observed 6 or 24 h after exposure. In a longer study, animals were exposed to 0, 800, 4000 or 8000 ppm methyl *tert*-butyl ether for 6 h per day on five days a week for 13 weeks. Any neurobehavioural changes were neither persistent nor cumulative. The body and brain weights of rats at the highest dose were decreased, but no histological changes were seen in the brain or peripheral nervous tissue. The authors concluded that any neurotoxic effects caused by methyl *tert*-butyl ether exposure at concentrations up to 8000 ppm were minimal (Daughtrey *et al*., 1997).

Five-week-old Fischer 344 rats were exposed to 0, 800, 4000 or 8000 ppm [0, 2900, 14 000 or 29 000 mg/m^3] methyl *tert*-butyl ether for 6 h a day on five days a week for 13 weeks. Animals at the high dose had decreased body weights throughout the study. The activities of aspartate aminotransferase and alanine aminotransferase were decreased in all exposed males and in females at the high dose. Increased corticosterone levels, indicative of stress, were found in male rats at the high dose, but there was no exposure-related effect on the levels of aldosterone and adrenocorticotropic hormone. The absolute and relative weights of the liver, kidney and adrenal gland were significantly increased and brain weights were significantly decreased in male and female rats at the high concentration. No histological changes were observed, with the exception of a mild increase in hyaline droplet formation in the kidneys, increased haemosiderosis in the spleen and an increased incidence of hyperplasia in the lymph nodes in exposed male rats (Lington *et al.*, 1997).

Groups of 10 male and 10 female Fischer 344 rats and CD-1 mice were exposed to 0, 400, 3000 or 8000 ppm [0, 1400, 11 000 and 29 000 mg/m^3] methyl *tert*-butyl ether for 6 h a day on five days a week for four weeks, with additional groups of five rodents of each species and each sex assigned to the control and high-dose groups and retained for a 16-day recovery period. Osmotic mini-pumps containing 5-bromo-2′-deoxyuridine were implanted 24 and 48 h before necropsy in rats and mice, respectively, to assess DNA synthesis on study day 5 and at the end of the exposure. Absolute body weight and body-weight gain were decreased in female mice after 1 week and in male and female rats throughout study in groups receiving the high dose. Increased renal DNA synthesis was found in male rats exposed to 3000 ppm on study day 5 and in those at 3000 and 8000 ppm methyl *tert*-butyl ether at the end of the study. No changes in DNA synthesis

were observed in the kidneys of exposed female rats or in male or female rats at the end of the 16-day recovery period. In mice, the labelling indices in the liver were increased significantly following five days of exposure to 8000 ppm methyl *tert*-butyl ether, but there was no significant increase in male mice. No effects were observed at the end of the treatment period or after the 16-day recovery period (Bird *et al.*, 1997).

In a study of the ability of methyl *tert*-butyl ether to induce protein droplet accumulation, α_{2u}-globulin accumulation and renal-cell proliferation, male and female Fischer 344 rats were exposed to 0, 413, 1516 or 3013 ppm [0, 250, 5500 and 11 000 mg/m^3] methyl *tert*-butyl ether for 6 h a day for 10 consecutive days. Microscopic lesions in the kidneys of exposed male rats were characterized by epithelial-cell necrosis, protein droplet accumulation and karyomegaly within the proximal tubules; in addition, occasional epithelial cell exfoliation into the tubular lumen was observed. In male rat kidney sections stained with Mallory Heidenhain stain, protein droplet accumulation increased in a concentration-related manner. Immunohistochemical staining of kidney sections from male rats for α_{2u}-globulin showed greater amounts in exposed male rats than in controls, but the exposure–response relationship was not linear. A statistically significant positive trend was found by enzyme-linked immunosorbent assay in the exposure-related increase in renal α_{2u}-globulin concentration, and this change was significant in male rats exposed to 3013 ppm methyl *tert*-butyl ether when compared with unexposed males. The labelling indices, measured by 5-bromo-2′-deoxyuridine incorporation, indicated an exposure-dependent increase in cell proliferation in the renal cortexes of male but not female rats. A strong positive correlation (r = 0.994) was demonstrated between the mean labelling index and the mean α_{2u}-globulin concentration. The results of this study indicate that methyl *tert*-butyl ether is a mild inducer of α_{2u}-globulin nephropathy and enhanced renal-cell proliferation in male but not female rats (Prescott-Mathews *et al.*, 1997).

Groups of 12-week-old male and female Sprague-Dawley rats were given 0, 357, 714, 1071 or 1428 mg/kg bw methyl *tert*-butyl ether orally in corn oil. Mild anaesthesia and diarrhoea were observed in treated animals. All treated females had decreased lung weights, with increased blood urea nitrogen and decreased creatinine concentrations at the highest dose. Males had an increased creatinine concentration at the highest dose and increased serum aspartate aminotransferase and lactate dehydrogenase activities at doses ≥ 1071 mg/kg bw. Nephropathy, characterized by increased hyaline droplets within the cytoplasm of proximal tubular epithelial cells, was recorded in 88% of the males given the highest dose and in 40% of the male controls. [The Working Group noted that the slides were stained with haematoxylin and eosin. Although droplets can be visualized with this stain, it is not specific for protein. Also, the criteria for scoring these lesions were not presented.] In a longer study, rats were treated with 0, 100, 300, 900 or 1200 mg/kg bw methyl *tert*-butyl ether in corn oil. The blood urea nitrogen concentration was decreased and that of cholesterol increased in all treated females, whereas the blood urea nitrogen concentration was decreased in treated male rats. The relative kidney weights of female rats were significantly increased at doses ≥ 300 mg/kg bw. There was a trend to increased liver and kidney weights in treated male rats, and chronic

nephropathy was common in both controls and males at the high dose. The tubular degeneration that characterizes nephropathy was graded as more severe in the treated rats. [The Working Group noted that the authors did not distinguish between chronic nephropathy and hyaline droplet nephropathy.] Fifty per cent of the male rats at the highest dose had a small number of tubules plugged with granular casts, and all had slightly increased numbers of cytoplasmic hyaline droplets in proximal tubular epithelial cells. After either 14 or 90 days of treatment, significant microscopic findings were restricted to the kidneys of male rats (Robinson *et al.*, 1990).

Eight-week-old female B6C3F$_1$ mice were exposed to 7814 ppm [28 000 mg/m^3] methyl *tert*-butyl ether for 6 h a day on five days a week for 3 or 21 days. The relative weight of the uterus was decreased in both treated groups, and the relative liver weight was higher after three days but not after 21 days. The activity of pentoxyresorufin-*O*-dealkylase, a marker enzyme for the CYP 2B family which is commonly induced by many tumour promoters, was increased by 5- and 14-fold after 3 and 21 days of exposure to methyl *tert*-butyl ether, respectively. 7-Ethoxyresorufin activity was increased two- to threefold at both 3 and 21 days. The hepatic labelling index, as measured by 5-bromo-2′-deoxyuridine incorporation, was significantly increased in exposed mice at 3 but not at 21 days. This transient increased occurred in the absence of hepatotoxicity, indicating that methyl *tert*-butyl ether is a hepatic mitogen. Mild centrilobular to midzonal swelling of hepatocytes was also observed. In the same report, it was shown that the rate of 17β-oestradiol metabolism to water-soluble metabolites was significantly increased in hepatocytes isolated from female B6C3F$_1$ mice treated by gavage with methyl *tert*-butyl ether at 1800 mg/kg bw per day for three consecutive days (Moser *et al.*, 1996b).

Exposure of female B6C3F$_1$ mice to 8000 ppm [28 000 mg/m^3] methyl *tert*-butyl ether by inhalation for 6 h per day on five days per week for three days or 3, 16 or 32 weeks caused a significant decrease in body weight at 16 and 32 weeks when compared with controls. Treatment also significantly increased the liver weight and hepatic microsomal P450 activity, with no indication of cytotoxic or hepatic necrosis. Other changes observed were decreased ovary, pituitary and uterine weights after 16 and 32 weeks of exposure; increased length of the oestrous cycle (numbers of days in both oestrus and non-oestrus stages) after 32 weeks; a decreased number of uterine glands and decreased uterine glandular and luminal epithelial DNA synthesis after 3 or 21 days or 16 or 32 weeks; and a decreased number of epithelial layers in the cervix and vagina at all times. Neither methyl *tert*-butyl ether nor its metabolite *tert*-butyl alcohol inhibited the binding of [^{3}H]17β-oestradiol to a recombinant human receptor. Treatment of HepG2 cells with methyl *tert*-butyl ether did not induce oestrogen receptor activity or antagonize a maximally inducing dose of 17β-oestradiol. In mice exposed to methyl *tert*-butyl ether, oestrogen levels in serum were not affected. The authors suggested that these results indicate that methyl *tert*-butyl ether-induced endocrine effects are not mediated through the oestrogen receptor (Moser *et al.*, 1998).

Male Wistar rats, 12 weeks of age, were exposed to 50, 100 or 300 ppm [180, 360 or 1100 mg/m^3] methyl *tert*-butyl ether for 6 h a day on five days a week for 2, 10 or

15 weeks, and microsomes were prepared from liver and kidney. A transient increase in UDP-glucuronosyl transferase activity was found in liver and kidney microsomes, but there was almost no effect on the hepatic cytochrome P450 concentration and only minor induction of renal cytochrome P450. Muscle creatine kinase activity, which is associated with contractile capacity, was decreased after two weeks of exposure, had returned to control levels at 10 weeks and then increased after exposure to 100 or 200 ppm for 15 weeks (Savolainen *et al.*, 1985).

Male and female Fischer 344 rats and CD-1 mice were exposed to 0, 400, 3000 or 8000 ppm [0, 1400, 10 000 or 28 000 mg/m^3] methyl *tert*-butyl ether for 6 h a day on five days a week for either 24 months (rats) or 18 months (mice). At the highest concentration, clinical signs of prostration, eye twitching, hypoactivity, lack of startle reflex and ataxia were observed in both mice and rats. Body-weight gain was significantly reduced by the end of the study in animals at the high dose, with decreases of 16% in male mice, 24% in female mice, 29% in male rats and 22% in female rats. At necropsy, a statistically significant decrease in the incidence of cystic endometrial-cell hyperplasia was seen in female mice and an increase in hepatocellular hypertrophy in mice of each sex at 3000 and 8000 ppm. An exposure-related increase in the incidence and severity of renal changes associated with chronic progressive nephropathy was seen in all treated male rats and to a lesser extent in female rats at 3000 and 8000 ppm. In male rats at 3000 and 8000 ppm, chronic progressive nephropathy was the major cause of death (Bird *et al*., 1997).

Eight-week-old male and female Sprague-Dawley rats were given 0, 250 or 1000 mg/kg bw methyl *tert*-butyl ether in olive oil by gavage on four days a week for 104 weeks and were maintained until they died. Body weights were unaffected. After 88 weeks of age, the survival rate of male rats treated with 1000 mg/kg bw was increased, and the survival rate of females showed a dose–dependent decrease. There was no evidence of behavioural changes, and no relevant non-neoplastic changes were detected either grossly or histologically (Belpoggi *et al*., 1995).

Toxicity of metabolites

Male and female Fischer 344 rats and B6C3F$_1$ mice were exposed to *tert*-butyl alcohol in their drinking-water for 94–95 days at doses of 0, 0.25, 0.5, 1, 2 or 4% (w/v) [providing doses of approximately 240–3600 mg/kg bw per day for rats and approximately 320–7500 mg/kg bw per day for mice] (Lindamood *et al*., 1992). Of the 10 animals per sex at the highest dose, all of the males and six of the females died before the end of the study. Body-weight gain was depressed in male rats at all doses and in female rats and male and female mice at the highest dose. Ataxia and hypoactivity were observed in treated animals. Treated mice showed hyperplasia of the transitional epithelium and inflammation of the urinary bladder. In rats, gross lesions were also observed in the urinary tract, accompanied by urinary tract calculi, dilatation of the urethra and renal pelvis and thickening of the urinary bladder mucus; they also had increased severity of mineralization of the kidney. A treatment-associated increase in

hyaline (protein) droplets was seen in male rats at 0.25–2% *tert*-butyl alcohol and a decrease in rats at 4%. Male rats at 1 or 2% *tert*-butyl alcohol showed a significant increase in proliferating cell nuclear antigen-stained S-phase nuclei, but those at 4% showed a significant decrease. The results for proliferating cell nuclear antigen-positive nuclei in female kidneys were inconclusive.

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Groups of 30 pregnant CD-1 mice and 25 pregnant Sprague-Dawley rats were exposed to methyl *tert*-butyl ether (purity, 95.03–98.93%) by inhalation at target concentrations of 0, 250, 1000 or 2500 ppm [0, 9000, 3600 and 90 000 mg/m^3] on gestation days 6–15; the fetuses were examined by routine teratological techniques on day 18 (mice) or 20 (rats) of gestation. In rats, the only significant effect seen in either dams or offspring was a transient reduction in food consumption at the start of exposure; fetal body weight was stated to be unaffected. Pregnant mice showed a slight increase in the frequency of lachrymation but no significant dose-related reduction in food consumption or body weight. No significant effects were observed in the fetuses in terms of viability, growth or morphology (Conaway *et al*., 1985). [The Working Group noted that no quantitative data were presented.]

Groups of 30 pregnant CD-1 mice and 15 pregnant New Zealand white rabbits were exposed to methyl *tert*-butyl ether (purity, 99%) vapour by inhalation at 0, 1000, 4000 or 8000 ppm [0, 3600, 14 000 and 28 000 mg/m^3] for 6 h per day on gestation days 6–15 and 6–18, respectively. The high dose represented 50% of the lower explosive limit. The pregnant females and their fetuses were examined by routine teratological techniques. In mice, maternal toxicity was seen at 4000 ppm (hypoactivity and ataxia) and 8000 ppm (hypoactivity, ataxia and reduced food consumption and body-weight gain). Late resorptions and dead fetuses and the incidence of cleft palate were increased at 8000 ppm, while fetal body weight was lower, and the incidence of skeletal variations (poorly ossified phalanges, vertebral arches and centra, reduced number of caudal segments) was increased at 4000 and 8000 ppm. Post-implantation deaths were seen mainly among male offspring. The authors noted that maternal stress may have contributed to the developmental effects, as exposure to similar concentrations is known to increase corticosterone activity, which, in turn, could produce similar outcomes. In rabbits, no effects on development were observed, although maternal weight gain and food consumption were reduced at the two higher doses and relative liver weights were reduced at 8000 ppm (Bevan *et al*., 1997a).

Groups of 15 male and 30 female CD rats, approximately eight weeks old, were exposed to measured concentrations of methyl *tert*-butyl ether (purity, 95–99%) of about 0, 300, 1200 or 2900 ppm [0, 1100, 4400 and 10 000 mg/m^3] for 6 h per day for 12 and

3 weeks, respectively, prior to breeding. Exposure of males was continued during the mating period, while females were exposed on seven days a week for 6 h per day on days 0–20 of gestation and on days 5–20 of lactation. The offspring were not directly exposed. A second mating was conducted after the first litter had been weaned to yield an F_{1b} generation. Four of 30 dams at 300 ppm and 5/30 at 2900 ppm had dilated renal pelvises, while the incidences were 1/30 in controls and 0/30 at 1200 ppm. No effects were reported on growth, the weights of the reproductive organs, the histological appearance of the gonads of animals of either sex or reproductive performance and fertility in the parental generation. There were no significant effects on the growth of offspring in the F_{1a} or F_{1b} litters, although there was a slight but significant decrease in pup viability in F_{1a} litters at the low and intermediate doses between days 0 and 4 of lactation. The incidence of dilated renal pelvis was slightly elevated in the F_{1a} offspring at the low and intermediate doses that were examined at weaning (Biles *et al*., 1987).

In a two-generation study, groups of 25 male and 25 female Sprague Dawley rats were exposed to 0, 400, 3000 or 8000 ppm [0, 1400, 11 000 and 29 000 mg/m^3] methyl *tert*-butyl ether for 6 h per day for 10 weeks before mating. Parental females were exposed during mating, gestation and from day 5 of lactation. F_1 animals were exposed from day 28; after eight weeks, adults were mated within treatment groups to yield an F_2 group. F_1 and F_2 animals at the high dose showed ataxia, hypoactivity and reduced body weights; the effects were less severe and/or transient at the intermediate dose. In the F_1 generation, increased liver weights were reported in animals of each sex at the high dose and in the males at the intermediate dose. The histological appearance of the liver was reported to be unchanged by exposure. The number of dead F_2 pups was increased on postnatal day 4, and the growth of F_1 and F_2 pups at the two higher doses was decreased during the preweaning period (Bevan *et al.*, 1997b).

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 5 for references)

Methyl *tert*-butyl ether was not mutagenic to *Salmonella typhimurium* TA98, TA100, TA104 or TA1535 in the presence and absence of an exogenous activation system. Methyl *tert*-butyl ether induced gene mutation in mouse lymphoma L5178Y $tk^{+/-}$ cells in the presence of exogenous activation. The mutagenicity was eliminated when formaldehyde dehydrogenase was added to the assay system.

Methyl *tert*-butyl ether did not induce sex-linked recessive lethal mutation in *Drosophila melanogaster*. It did not induce unscheduled DNA synthesis in the liver of mice exposed by inhalation and did not induce micronuclei in mouse bone marrow or chromosomal aberrations in rat bone marrow. Negative results were also obtained for micronucleus formation in mice treated by intraperitoneal injection with doses near the lethal concentration.

Table 5. Genetic and related effects of methyl *tert*-butyl ether

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Salmonella typhimurium TA100, TA98, TA104, TA1535, reverse mutation	–	–	7400 µg/plate	Kado *et al*. (1998)
Drosophila melanogaster, sex-linked recessive lethal mutations	–		0.3% feed	McKee *et al*. (1997)
Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	NT	+	740 µg/mL	Mackerer *et al*. (1996)
Unscheduled DNA synthesis, male and female CD-1 mouse hepatocytes *in vivo*	–		8000 ppm inh, 6 h/d × 2 d	McKee *et al*. (1997)
Micronucleus formation, male and female CD-1 mouse bone-marrow cells *in vivo*	–		8000 ppm inh, 6 h/d × 2 d	McKee *et al*. (1997)
Micronucleus formation, male and female Swiss-Webster mouse bone-marrow cells *in vivo*	–		1750 ip × 1	Kado *et al*. (1998)
Chromosomal aberrations, male and female Fischer 344 rat bone-marrow cells *in vivo*	–		8000 ppm inh, 6 h/d × 5 d	McKee *et al*. (1997)

[a] +, positive; –, negative; NT, not tested

[b] LED, lowest effective dose; HID, highest ineffective dose; unless otherwise stated, in-vivo test, mg/kg bw per day; inh, inhalation; d, day; ip, intraperitoneal

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Methyl *tert*-butyl ether is a volatile synthetic chemical that has been used widely since the 1980s in proportions up to 15% as a component of gasolines for its octane-enhancing and air pollution-reducing properties. Exposure to methyl *tert*-butyl ether may occur through inhalation and skin contact during its production, formulation, distribution and use, either as methyl *tert*-butyl ether or in gasoline. In the petroleum industry, the average exposure is generally below 5 ppm (20 mg/m^3), although higher exposure occurs during some operations. In service stations where fuels containing > 10% methyl *tert*-butyl ether are delivered, the average concentration to which attendants are exposed is about 0.5 ppm (2 mg/m^3). The ambient air concentrations in regions where methyl *tert*-butyl ether-rich gasoline is used are usually 1–5 ppb (4–20 μg/m^3), while in other regions they are below 1 ppb (4 μg/m^3). During self-service refuelling, individuals may be exposed to levels up to 10 ppm (40 mg/m^3) or more for a few minutes. Methyl *tert*-butyl ether has been detected in a small percentage of drinking-water samples in the United States.

5.2 Human carcinogenicity data

Although methyl *tert*-butyl ether has been in commercial use for gasoline blending since the 1970s, no analytical epidemiological studies have addressed a possible association of methyl *tert*-butyl ether with human cancer.

5.3 Animal carcinogenicity data

Methyl *tert*-butyl ether was tested for carcinogenicity in a non-standard protocol in rats by gavage. The incidences of Leydig-cell tumours of the testis in males and of lymphomas and leukaemias combined in females were increased. Methyl *tert*-butyl ether was tested by inhalation in one experiment in mice and in one experiment in rats. It increased the incidence of hepatocellular adenomas in female mice and that of renal tubular tumours in male rats in a non-dose-related manner.

tert-Butyl alcohol, a metabolite of methyl *tert*-butyl ether, marginally increased the incidence of follicular-cell adenomas of the thyroid in female mice.

5.4 Other relevant data

Methyl *tert*-butyl ether is metabolized in humans and rodents to *tert*-butyl alcohol. In both species, methyl *tert*-butyl ether is cleared from blood rapidly whereas *tert*-butyl alcohol accumulates and is cleared at a slower rate than the parent compound. In rats exposed to methyl *tert*-butyl ether, the metabolites identified in urine include *tert*-butyl alcohol, its sulfate and glucuronide conjugates, 2-methyl-1,2-propanediol and 2-hydroxyisobutyrate.

No significant acute effects on human health were seen after exposure of volunteers by inhalation to methyl *tert*-butyl ether itself or of service-station attendants to gasoline.

In male rats, methyl *tert*-butyl ether-induced kidney lesions were associated with α_{2u}-globulin nephropathy, a male rat-specific response. Exposure of female mice to 8000 ppm [29 g/m^3] methyl *tert*-butyl ether in air was mitogenic to the liver and caused changes in oestrogen-regulated tissues.

Methyl *tert*-butyl ether did not induce developmental toxicity in rats or rabbits exposed via inhalation to concentrations that affected maternal food consumption. In one study in mice, increased incidences of postimplantation loss and cleft palate were seen at doses that also induced hypoactivity, ataxia and reduced food consumption in the dams. Another study in mice, conducted at lower doses that were less toxic to dams, did not provide evidence of developmental toxicity.

No data were available on the genetic and related effects of methyl *tert*-butyl ether in humans. The few available data indicate that methyl *tert*-butyl ether is not genotoxic in experimental systems.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of methyl *tert*-butyl ether.

There is *limited evidence* in experimental animals for the carcinogenicity of methyl *tert*-butyl ether.

Overall evaluation

Methyl *tert*-butyl ether is *not classifiable as to its carcinogenicity to humans (Group 3).*

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