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DECOS and NEG Basis for
an Occupational Standard

Methyl-tert-Butyl Ether

A A E Wibowo

ARBETS MILJÖ INSTITUTET
NATIONAL INSTITUTE OF OCCUPATIONAL HEALTH

A Center for Research on Occupational Health

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Preface

An agreement has been signed by the Dutch Expert Committee for Occupational Standards (DECOS) of the Dutch Health Council and the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG). The purpose of the agreement is to write joint scientific criteria documents which could be used by the national regulatory authorities in both the Netherlands and in the Nordic Countries.

This document of health effects of Methyl-tert-Butyl Ether is a product of this agreement. The document was written by Dr AAE Wibowo from the Coronel Laboratory in Amsterdam, the Netherlands, and has been reviewed by the Dutch Expert Committee as well as by the Nordic Expert Group.

V.J. Feron
Chairman
Dutch Expert Committee

P. Lundberg
Chairman
Nordic Expert Group

Contents

1. Introduction

This report is made at the request of the Directorate-General of Labour in the Netherlands. Since the compound methyl-tert-butyl ether (MTBE) is a component of a specific type of gasoline (high octane gasoline) the reader is also advised to take notice of the document: Health based recommended occupational exposure limit of gasoline from the Dutch Expert Committee on Occupational Standards (1991).

In the on-line search of data on the health aspects due to exposure to this compound it is found that very few reports exist, which make the health assessment difficult. Therefore, appreciation is acknowledged to Dr. R.A.J. Priston from the Shell International Petroleum Co. who had made a summary of available (published and unpublished) data derived from private company's in the US.

A word of gratitude is also expressed to Mr Charles M Aur, Director Chemical Division of the US EPA for sending numerous recent data on MTBE.

The procurement of data is finalized at March, 1994.

For background material the following papers are used:

* Swedish Criteria Group: Consensus report for methyl-tert-butylether. Arbete och Hälsa 32 (1988) 35-39.

* US Environmental Protection Agency: Testing consent order on methyl-tert-butylether and response to the interagency testing committee. Federal Register 53/62 (1988) 10391-10394.

* R.A.J. Priston: HSE toxicology database. Material: methyl tertiary butyl ether. Date: 26-6-1987 (revised 1992). Shell International Petroleum Co, Den Hague, 22 pp.

2. Identity, Physical and Chemical Properties, Monitoring

2.1. Identity

MTBE at room temperature is a colourless liquid with a characteristic odour. The vapour is heavier than air and may travel along the ground; distant ignition is possible. The substance reacts with strong oxidants (16).

Purity from 97 to 99.5% by weight is given.

2.1.1. Structure

Formula: $C_5H_{12}O$ Structure: $CH_3 - O - \overset{CH_3}{\underset{CH_3}{C}} - CH_3$

2.1.2. Chemical names and synonyms/registry numbers

Name:	Methyl-tert-butylether
Systemic name:	2-Methoxy-2-methyl propane
Synonyms:	Methyl-t-butyl ether
	Methyl-1, 1-dimethyl ethyl ether
	2-Methyl-2-methoxypropane
	MTBE

CAS no. 1634-04-4.
EINECS no. 216-653-1

2.2. Physical and Chemical Properties

Molecular weight: 88.15
Boiling point (° C): 55.2
Melting point (° C): -109
Flash point (° C): -28
Spontaneous ignition temp. (° C): 460
Relative density (water = 1): 0.75
Relative vapour density (air = 1): 3.1
Relative density at 20° C of the
saturated vapour/air mixture (air = 1): 1.5
Vapour pressure (hPa, 25° C): 326

Explosive limits (vol % in air): 1-8
Solubility in water (g/100 ml, 20° C): 5.1
Conversion factors: 1 ppm = 3.60 mg/m^3
1 mg/m^3 = 0.278 ppm

2.3. Analytical Methods

2.3.1. Environmental monitoring

The NIOSH issued a protocol for the determination of MTBE (in gasoline). The method number is 1615, date of issue: 15-8-1990 (19).

The working range is 0.2 to > 35 ppm (0.75 to > 125 mg/m^3) for an 80 l air bag.

For sampling, solid absorbent tubes are used (two charcoal tubes in series; front 400 mg; back 200 mg), with a flow rate of 0.1 to 0.2 l/min.

For the analysis, a gas chromatography instrumentation with an FID detector is to be used. For other specific data see protocol.

Price and Saunders (23) described determination of airborne MTBE in gasoline athmospheres. The principal features of the method are: (1) construction and commissioning of an efficient fused - silica capillary collumn interface between an automatic two-stage thermal desorber and a gas chromatograph; (2) separation of MTBE from gasoline hydrocarbons on an OV-1701 fused-silica capillary collumn without sub-ambient or multi-ramp temperature programming; (3) the choice of Chromosorb 106 in primary and secondary traps to produce acurate and precise quantification of MTBE.

2.3.2. Biological monitoring

Biological monitoring can be performed by determination of MTBE and/or TBA (tertiary butyl alcohol) in total blood (9). The concentration can be determined by using a modified technique of gas chromatography/mass spectrometry. The minimum detection limit for MTBE was 0.05 µg/l, with a maximum linear standard of 37 µg/l. For TBA, the minimum detection limit was 0.5 µg/l with a maximum linear standard of 76.5 µg/l.

3. Sources of Exposure

3.1. Natural Occurrence

There are no data to indicate a natural occurrence of this compound.

3.2. Man-Made Sources

3.2.1. Production

The EPA (12) reported that the annual plant capacity of MTBE production was estimated at about 4 billion pounds in 1986 in the United States. The growth rate in production of MTBE was estimated to be 19 percent per year from 1985 to 1990. However, between 1982 and 1985, production increased over 140 percent.

No data exist on the production capacity in the Netherlands or elsewhere in Europe.

3.2.2. Uses

MTBE is used as a blending component in high octane gasoline in an effort to raise the octane level and promote fuel combustion. The concentration in liquid gasoline varies from 7 to 11 % (v/v) (18). In certain parts of the USA, it is being used as part of a gasoline oxygenated program to reduce tailpipe carbon monoxide emissions. It has been approved for use in gasoline at concentrations up to 15%.

Another, but limited, use of MTBE is known in experimental medicine. It is used for the dissolution of gallstones in laboratory animals and patients (1, 3, 22, 30).

4. Environmental Levels and Human Exposure

4.1. Environmental Levels

4.1.1. Water and food

In the US the EPA (12) is concerned about MTBE contamination of ground water. The rapid growth in production, transport and use of MTBE will probably contribute to an increase in incidents of contamination. MTBE is relatively water soluble compared to other gasoline components. The largest identified population affected by MTBE-contaminated water was Rockaway Township in New Jersey. The level of MTBE contamination in the township wells ranged from 25 to 40 ppb and required aeration treatment before delivery to the township's residents. A leaking underground storage tank in a rural area of Maine, US, has contaminated household wells in the vicinity with MTBE concentrations as high as 690 ppb. Maine and New Jersey have set a maximum contaminant level of 50 ppb for MTBE. There are no data on the contamination of MTBE of foodstuff.

There are no data on the environmental contamination in the Netherlands.

4.1.2. Air (Occupational)

The US EPA (12) cited a report that worker exposure to MTBE vapour measured at refineries has generally been less than 1 ppm (3 mg/m^3) for an 8-hour TWA. Limited data reported by Sanderson (personal communication) indicated that operator exposures in European refineries are below 0.2 ppm (TWA-8 h). Data from MTBE production plants in Europe and USA indicate that exposures were usually less than 3 ppm (8 h TWA), but may exceed 100 ppm (STEL) for workers engaged in barge loading. According to the EPA (12) the highest exposure level of MTBE vapour reported was a TWA of 33 ppm (100 mg/m^3) and a short-term exposure of 45 ppm (135 mg/m^3). Approximately 50 percent of the MTBE produced is shipped off-site before blending. Short-term exposure to MTBE during bulk loading and unloading operations has been estimated to be as high as 550 ppm (1650 mg/m^3). Recently the US Centers for Disease Control (9) monitored a median workplace concentration of 0.1 ppm (0.37 mg/m^3) in December of 1992 in Fairbanks, Alaska, during which period gasoline with 15% MTBE was used. In February of 1993, when the use of MTBE in gasoline was discontinued, the median workplace air concentration was reduced to 0.03 ppm (0.10mg/m^3).

Exposure to MTBE vapour during transfer of MTBE-containing gasoline has been estimated indirectly from gasoline vapour measurements, assuming 7 percent MTBE concentration by volume. During bulk loading and delivery of MTBE-containing gasoline, exposure to MTBE vapour was estimated to be short-term exposure of 8 ppm (23 mg/m^3) for the truck drivers. For service station attendants it has been estimated that they are exposed to MTBE vapour to as high as 8.6 ppm (31 mg/m^3) for an 8-hour TWA.

Total MTBE vapour release can be calculated from volatile organic carbon (VOC) emissions estimated for gasoline. Assuming MTBE accounts for 8 to 11 percent of total VOC emissions from gasoline, MTBE vapour release would be 3 to 17 million kg/yr (12).

4.2. Human Exposure

4.2.1. General population

No data exist on exposure to general population in the Netherlands or other countries in Europe. The US Centers for Disease Control reported a study (9) where biological monitoring as well as environmental monitoring had been performed in December of 1992, during which period gasoline containing 15% MTBE had been used, and again in February of 1993 in which the use of MTBE had been discontinued. The study was performed on commuters. In December the median MTBE level in blood of 7 commuters was 0.83 µg/l and in February it was reduced to 0.10 µg/l in 6 commuters. Although no control group was used in this study, it may be concluded that exposure to MTBE occurred in general population.

4.2.2. Occupational population

There are some occupational groups at risk for exposure to MTBE:

- Bulk loading and delivery operators of gasoline containing MTBE
- Service station attendants
- Refinery workers
- Truck drivers of delivery tankwagons.
- MTBE production operators
- Scientists and clinical laboratory technicians in experimental medicine.

It is of interest to point out the five basic steps involved in bringing MTBE to the market (15). Operators attending these activities are at risk for exposure to MTBE:

- Manufacturing - MTBE production at both chemical plant and petroleum refinery facilities;
- Blending - introduction of MTBE into motor gasolines which includes handling of both neat MTBE and blended MTBE fuels;
- Transportation - movement of MTBE or MTBE blended fuels via barge, tanker, railcar, truck or pipeline to points of distribution;
- Distribution - storage and movement of MTBE blended fuels from distribution terminals to the service station; and
- Service Station - storage and dispensing of MTBE blended fuels to the motoring public.

5. Guidelines and Standards

5.1. General Population

There is no standard for MTBE for general population in the Netherlands.

5.2. Occupational Population

Table 1. Occupational exposure limits in some countries.

Country	Concentration	Comments
The Netherlands (1992)	none	-
United States		
ACGIH (1992)*	none	-
OSHA (1992)	none	-
Germany (1992)	none	-
Sweden (1992)	50 ppm (180 mg/m^3)	TWA - 8 h
	75 ppm (250 mg/m^3)	TWA - 15 min
Britain (1992)	none	-
USSR (1992)	none	-

Note: There are some private oil/chemical companies in the United States who have recommended occupational exposure limits for MTBE. The Sun Refining and Marketing Co recommends an 8-h TWA exposure limit of 100 ppm (300 mg/m^3). However, Texaco Chemical Co recommends a limit of 200 pm (600 mg/m^3) for MTBE (12).

* It should be noted that ACGIH in a draft document 1993 has just proposed a TLV for MTBE of 40 ppm, TWA - 8 hour .

6. Toxicokinetics

6.1. Absorbtion

In occupational exposure, MTBE is primarily taken up by inhalation, but it may also be absorbed by the skin and through the digestive tract (17).

There are no human data on the kinetics of MTBE, but experiments on animals exposed to MTBE in inhaled air indicated a relationship between the levels in inhaled air and the levels of MTBE and its metabolite, tertiary-butanol, in blood, brain and perirenal fat tissues (26). The equilibrium in blood was reached within two weeks in rats.

6.2. Distribution

There are no available human data. Savolainen et al. (26) exposed groups of male Wistar rats to 0, 50, 100 or 300 ppm MTBE vapour, 6 h/day, 5 day/week for 2-15 weeks in dynamic 1 m^3 exposure chambers. A relationship was found between the exposed levels and the concentrations of MTBE in blood, perirenal fat and brain tissues. In case of the latter it means that MTBE could pass the blood-brain barrier. It may also be concluded that MTBE has a predilection for the perirenal fat tissue since it has the highest concentration of MTBE, and only traces of the metabolite tertiary butyl alcohol (TBA, or tertiary butanol) are found. These findings are found throughout the whole 15 weeks of exposure period. The fact that some changes occurred in specific enzyme activities of the liver, kidney and muscle tissues may indicate that MTBE is also distributed into these organs.

6.3. Biotransformation and Excretion

Experiments on rats by a single intraperitoneal injection of 14C-MTBE showed that forty-eight hours post treatment the total cumulative 14C-activity recovered averaged 103.8 % of the administered dose, the majority of the 14C-activity eliminated was found in the expired air and averaged 99.9 % of the administered dose, the radio activity in expired air was 92.5 % of the dose as volatiles and 7.4 % as CO_2 (20). 99 % Of the volatiles was the parent compound. 2.95 % Of the dose was in urine by 48 hour, of which 96.6 % as formic acid, 0,8 % of the dose was in faeces at 48 hour with most of them as formic acid. The whole blood content of radio-label peaked at 5 min, and the half-life in whole blood was 50-60 minutes.

Inhalation exposure to rats (50, 100 or 300 ppm MTBE vapour, 6 h/d, 5 d/w for 2-15 w) showed a dose-dependent increase of *tertiary-butanol* in the blood, indicating a metabolic breakdown of the ether in vivo. The blood MTBE levels decreased after 6 weeks of exposure at the 50 ppm dose level and remained unaffected at higher doses, while tertiary-butanol concentrations was increased

after 6 weeks with all doses, and began to decrease thereafter (26). In the brain tissues, the MTBE and tertiary-butanol levels followed a similar course.

Cederbaum and Cohen (8) studied the fate of tertiary-butanol in an in vitro experiment. Although it has been popularly known that tertiary-butanol is a "non-metabolizable" alcohol, they found that this compound serves as a substrate for rat liver microsomes and that it is oxidatively demethylated to yield formaldehyde. The formaldehyde production is stimulated by azide, which prevents destruction of the H_2O_2 by catalase. Hydroxyl radical scavenging agents, such as benzoate, manitol and 2-keto-4-thiomethylbutyrate suppress formaldehyde production. Therefore, according to the authors, the microsomal pathways appears to involve the interaction of tertiary-butanol with hydroxyl radicals generated from H_2O_2 by the microsomes. A portion of the tertiary-butanol is also excreted as a glucuronic acid conjugate.

Recently Brady et al. (6) studied the metabolism of MTBE by the rat hepatic microsomes in vitro. They found that the V_{max} for the demethylation of MTBE into formaldehyde increased by 4-fold and 5.5-fold after the rats had been pretreated with acetone or phenobarbital, respectively. The metabolism of MTBE (1 mM) was reduced by 35 % by monoclonal antibodies against P450IIE1, the acetone/ethanol inducible form of cytochrome P_{450}, suggesting a partial contribution by this isoenzyme.

6.4. Biological Monitoring

Biological monitoring can be performed by determination of MTBE level in blood. The US Centers for Disease Control (9) reported in 1993 a study on workers selected because they were heavily exposed to gasoline fumes or exhausts in their workplace, in Fairbanks, Alaska. In December 1992 they examined 18 workers before and after a work-shift. During that period there was 15% MTBE in the gasoline. The median post-shift MTBE in blood level was 1.8 µg/l (range 0.2 - 37 µg/l)). The median workplace air concentration was 0.1 ppm (0.37 mg/m^3). The same study was repeated in February of 1993 on 28 workers, in that period the use of MTBE in gasoline was discontinued. They found a median post-shift blood concentration of MTBE of 0.24 µg/l (range 0.05 - 1.44 µg/l). The median workplace air level of MTBE in February was 0.03 ppm (0.10 mg/m^3).

The US EPA (13) reported a pharmacokinetic study performed by the Yale University in the US, on four subjects. They were exposed to 1.68 ppm (6 mg/m^3) MTBE for one hour. The peak blood MTBE concentrations were 16.6, 14.8, 17.4 and 19.7 µg/l respectively. When a single exponential elimination curve was fitted, the mean half-life was 80 minutes. Another method for biological monitoring is the determination of TBA, a metabolite of MTBE. In the Yale experiment, the TBA concentrations in blood of the exposed subjects, at 90 minutes post-exposure, had a mean of 10.3 µg/l (range 7.9 - 13.3 µg/l). TBA has substantially a longer half-life in blood when compared to MTBE, the former is estimated to have a half-life of several hours to a few days.

7. Effects

7.1. Animal Experiments

7.1.1. Irritation and sensitization

The Patty's Industrial Hygiene and Toxicology handbook (17) classifies this compound as a mild eye irritant compound. Based on studies in rabbits, MTBE was found not to be a primary skin or eye irritant, although repeated/prolonged exposure had not been tested but can be expected to lead to irritation and or dermatitis due to defatening (private communication, RAJ Priston, 1992). MTBE was not found to be a skin sensitizer in the guinea pig.

7.1.2. Acute toxicity

The acute oral LD_{50} (rat) is 3.9 g/kg, and the acute percutaneous LD_{50} (rat) is > 5 ml/kg and that of the rabbit > 10 g/kg. Inhalation (4 h) LC_{50} is approximately 120 g/m^3. The clinical signs of exposure are: anaesthesia, ataxia and tremors (RAJ Priston, private communication). From the same source, 4-h inhalation LC_{50} for rats is 85 g/m^3 and mouse 80 g/m^3.

Paulov (21) studied the toxicity of MTBE in water on tadpoles. He found the LC_{100} was ≥ 3000 mg/l, the LC_{50} was 2500 mg/l and concentrations of ≤ 2000 mg/l were without any lethal effect. Low MTBE concentrations in water (100 mg/l) led to a marked weight increase of tadpoles and frogs, that had undergone metamorphosis, when compared to controls.

7.1.3. Short-term toxicity

Ben-Dyke et al. (4) exposed CD rats (20 male and 20 female rats per dose) to 0, 100, 300, 1000 and 3000 ppm MTBE, 6 h/d, 5 d/w for 9 days. The actual exposure concentrations as determined were 0, 134, 350, 1110 and 3240 ppm. There were no compound related mortalities and the growth rates were unaffected. Phosphorus levels in blood serum were elevated only in the 1110 and 3240 ppm groups. Urinalyses of the volume, pH, specific gravity, albumen, glucose, occult blood and microscopic examination of centrifuged deposit were normal. Increased relative liver weights were found in male and female fasted rats at 3240 ppm group. In unfasted animals this occurred only in the 3240 ppm males. Increased adrenal weights in non-fasted females at 3240 ppm was considered not to be related to MTBE. In the gross pathology, there were no MTBE-related findings. There was an increased incidence and severity of inflammation of the nasal mucosa and trachea in the 1110 and 3240 ppm male and female groups. This means that the no-observed-adverse effect level of MTBE is 350 ppm, as actually measured, and a minimal adverse effect level of 1110 ppm may be noted as well.

Savolainen et al. (26) reported an increase of the UDP-glucuronyltransferase activity in the liver microsomes of rats exposed to 50, 100 or 300 ppm MTBE, 6 h/d, 5 d/w for 2 weeks, which was dose-dependent. On week 15th no increase

was noted anymore. The same incidents also occurred in the kidney microsomes of these animals. No effect was found on the microsomal 7-ethoxycoumarin O-deethylase and NADPH-cytochrome C reductase activities and cytochrome P-450 concentrations in the liver at any time. No effect was noted in the brain or muscle succinate dehydrogenase or acetylcholine-esterase activities.

7.1.4. Long-term toxicity/carcinogenicity

Burleigh-Flayer et al. (7) reported a blind peer review of an experiment on 50 male and female CD-1 mice exposed to 0, 400, 3000 or 8000 ppm MTBE, 6 h/d, 5 d/w for 18 months. The first examinations showed an excess of benign tumours of the liver (hepatocellular adenomas) in female mice at an exposure level which caused general adverse health effects to the mice (reduced activity, prostration and dramatically decreased weight gain during the course of the study) demonstrating that the 8000 ppm exposure level is above the maximum tolerated dose for the species (14). Microscopic examinations for the peer review were performed solely for the purpose of evaluating neoplastic or preneoplastic lesions. No attempt was made to record or assess any lesions which were considered to be degenerative, inflamatory, congenital or toxic. There were no neoplasms which occurred in statistically significantly increased frequency for mice of either sex. In male mice, hepatocellular adenomas occurred in almost identical frequency in all four exposure groups, with 10 or 11 animals/group being affected. In female mice, there was a definite trend toward neoplasia, which was not statistically significant, for the high concentration group animals.

Chun et al. (10) describes the experiment on Fischer rats. Fifty animals per sex were exposed to levels of 0, 400, 3000 or 8000 ppm MTBE vapour during 6 h/d, 5 d/w for 24 months. Due to increased mortality rate in the male rats, terminal necropsies were performed during Study Week 82 (high exposure group), 97 (mid exposure group) and 104 (low exposure and control groups). Terminal necropsies for all female rat groups were performed during Study Week 105. The results showed that for the male rats a concentration-related increase of chronic nephropathy was found in the 3000 and 8000 ppm groups. There was also a slight increase in mortality and decrease in mean survival time in males from the 400 ppm group which was considered to be due to an increase in the severity of male rat nephropathy. The other major cause of deaths in the low concentration group males was large granular lymphocyte (LGL) leukemia. LGL leukemia was the main cause of deaths in the control group males. The mortality and survival time for females were equivalent in all exposure groups. Clinical signs were observed for both sexes of animals during exposures to 3000 and 8000 ppm, and included blepharospasms, hypoactivity, ataxia and lack of startle reflex. No exposure-related changes in hematologic parameters were observed. A decrease in corticosterone levels was observed for male rats from the 8000 ppm group at week 81th. Concentration-related increases in kidney and liver weights were observed for female exposed rats from the 3000 and 8000 ppm groups. The only neoplastic lesions considered to be exposure-related in this study was an increased number of renal tubular cell tumours noted in males from the 3000 and 8000 ppm

groups. The occurrence of these tumours in only the male rats, combined with the informations from previous studies, strongly suggests that the neoplasms resulted from an accumulation of a2u-globulin in renal tubular cells.

7.1.5. Mutagenicity

There are no published data on the genotoxicity of MTBE, on the other hand RAJ Priston (private communication) compiled the following summary from company-based data files:

- MTBE was not mutagenic in +/- S9 metabolic activated S.typhimurium TA1535, TA1537, TA1538, TA98 and TA100.
- MTBE was not mutagenic in +/- S9 metabolic activated S.cerevisiae D4.
- Forward mutations were not induced in the absence of S9 at a level greater than 6.25 µl/ml, it did not show toxicity in Mouse lymphoma cells assay, L5178Y TK+/- cell line. In the presence of S9, MTBE was toxic at 3.125 µl/ml and a dose-related mutagenic effect was observed. The mutant frequency increased from 3x at 0.39 µl/ml to 24x at 3.12 µl/ml.
- MTBE caused no SCE and chromosomal aberrations in mammalian cells in vitro at doses of 0.009-5.0 µl/ml.
- MTBE did not increase the incidence of chromosomal aberrations in the bone marrow cells of male and female rats following repeated inhalations at levels of 800-8000 ppm, 6 h/d, 5 consecutive days.

7.1.6. Reproduction toxicology

Schroeder and Forder (27) performed a reproductive toxicity study on pregnant CD rats. They were exposed to nominal exposure concentrations of 0, 250, 1000 and 2500 ppm (actual mean levels were 0, 260, 1100 and 3300 ppm) MTBE, 6 h/d on days 6-15 of gestation. Sacrifice was done on day 20 of gestation. No mortality and no effect on maternal body weights were found. There was no effect of treatment on the corpora lutea or uterine implantation. No effects were found on gross autopsy. No treatment-related effects were found on soft or skeletal tissues. The same authors (28) also performed these experiments on pregnant CD-1 mouse. The nominal MTBE concentrations were 0, 250, 1000 and 2500 ppm [actual levels were 0, 280, 1110 and 2710 ppm]. The exposure was 6 h/d on days 6-15 of gestation. There was no effect on the number of implantation sites. At the 280 and 2710 ppm there was an increase in the number of resorption sites and an increase in the percentage of resorption of implants. This effect was attributable to two litters in each of the high + low dose groups. The absolute and relative liver weights were unaffected by MTBE. No effects were observed post mortem. No effect on foetal weights, Crown-Rump distances, sex distribution or ossification variation data. Some malformations were observed in treated and control groups but no treatment-related effects were found in soft tissue or skeletal examination. At a later date these two studies were published by Conaway et al. (11).

Recently Tyl (31) performed a teratology study on pregnant NZW rabbits exposed to 0, 1000, 4000 or 8000 ppm MTBE (actual levels were: 0, 1021, 4058 or 8021 ppm), 6 h/d on days 6-18 of gestation. On day 29 the animals were

sacrificed. Maternal toxicity was observed in animals exposed to 4058 and 8021 ppm MTBE. Significant reductions in weight gains and food consumption during the exposure period were found at these levels and a significant increase in relative liver weight at the highest level. Gestational parameters exhibited no significant changes, including number of Corpora lutea, total nonviable or viable implantations per litter, sex ratio, pre or post-implantation loss and foetal body weights per litter. There were no changes in the incidence of any individual malformations, malformations by category (external visceral or skeletal), or of total malformations. From this study it may be concluded that the no-observed-adverse effect level (NOAEL) for maternal toxicity is about 1021 ppm MTBE.

Tyl and Neeper-Bradley (32) also performed a teratology study on pregnant CD-1 mice exposed to 0, 1000, 4000 or 8000 ppm MTBE (actual levels were: 0, 1035, 4076 or 8153 ppm), 6 h/d on days 5-15 of gestation. On day 18 the animals were sacrificed. Maternal toxicity was observed in animals exposed to 4076 and 8153 ppm MTBE. Significant reductions in body weight, weight gain and treatment-related clinical signs (hyperactivity, ataxia, prostration, laboured respiration, lacrimation and periocular encrustation) during exposure and decreased food consumption during and after exposure to 8153 ppm were found, as well as treatment-related clinical signs of hypoactivity and ataxia at exposure to 4076 ppm MTBE. Gestational parameters were affected in animals exposed to 8153 ppm, including reduced number of viable implantations/litter and increased number of nonviable implantations/litter (resorption and dead foetuses) and reduced male to female ratio. Foetal body weights were reduced significantly in animals exposed to 4076 and 8153 ppm MTBE. There was a significant increase in the incidence of cleft palate (observed both externally and viscerally when the fetal head was serially sectioned) and therefore increased incidences of pooled external and visceral malformations and of total malformations in animals exposed to 8153 ppm. There were also treatment-related increases in the incidence of individual skeletal variations at 4076 and 8153 ppm. From this experiment it may be concluded that the incidence of cleft palate of the fetus in maternal exposure to 8153 ppm MTBE is concomitant with profound maternal toxicity and a no-observed-adverse effect level (NOAEL) of 1035 ppm for both maternal toxicity and developmental toxicity may be indicated.

Schroeder and Forder (29) reported a single generation reproduction study on rats. The actual exposure levels were 0, 290, 1180 or 2860 ppm MTBE for male rats and 0, 300, 1300 or 3400 ppm MTBE for female rats. Premating period of exposure for males were 6 h/d, 5 d/w for 12 consecutive weeks and for females 6 h/d, 5 d/w for 3 consecutive weeks. During the mating period the animals were exposed for 6 h/d, 15 days. In the post-mating period the female rats were exposed for 6 h/d, 7 d/w on days 0-20 of gestation and from days 5-12 of lactation of the litters (F1a). There was no treatment between day 21 of gestation and day 4 of lactation periods. A second litter (F1b) was produced under the same mating and post mating exposure regimen. No adverse effect of treatment was observed in the adult animals (F0) throughout the in-life portion of the study. The only

remarkable finding was an increased incidence of dilated renal pelves in the low- and high-dose females (F0). All gonad weights, male accessory reproductive organ weights, organ-to-body weight ratio's and reproductive organ histopathology were unremarkable upon comparison of treated animals with air sham controls. The mating indices and fertility indices in exposed animals for both mating intervals (F1a and F1b) were not significantly different from controls. Pregnancy rates were comparable between treated and control females for the first litter interval (F1a) but were slightly lower than control on the second latter interval (F1b). Treated animal mean gestation length and the mean number of pups at birth were not statistically different form controls. The pups viability indices at birth (an indication to denote a stage of development) were comparable for control and treated groups for the F1a generation, but the mid- and high-dose groups displayed a slight statistically significant decrease in the F1b generation; the decrease was not considered to be treatment-related. Litter survival indices were comparable between control and treated groups for both litter intervals. Pups of mid- and high-dose females had slightly lower mean weights at days 14 and 21 of lactation but this was not considered treatment-related. The most frequent post-mortem observation for pups sacrificed at day 21 of lactation was dilated renal pelves. This did not appear to be related to treatment. It was seen at comparable frequencies in high dose and control groups with a slightly lower frequency at low and mid dose. This is a frequent observation in this rat strain and in weanlings, according to the authors. The authors concluded that MTBE exposure by inhalation showed little adverse reproductive toxicity as shown in one generation reproduction assay. This study is later published by Biles et al. (5).

7.2. Observation in Man

Although the strong odour of MTBE may lead one to think that very high concentrations of it are in the air, this is not necessarily true. The US EPA (13) reported recent experimental study of MTBE odour thresholds indicate that this compound can be detected at concentrations around 0.05 ppm (0.18 mg/m^3) and recognized (identified) at levels around 0.09 - 0.13 ppm (0.32 - 0.47 mg/m^3), depending on the purity. When MTBE and gasoline are mixed together (15% MTBE in gasoline), then the threshold for detection will be 0.09 - 0.26 ppm (0.32 - 0.94 mg/m^3) and for recognition 0.19 - 0.69 ppm (0.68 - 2.48 mg/m^3).

Direct exposure of the skin, eyes and other tissues to MTBE causes irritation similar to that of conventional gasoline. Prolonged or frequent contact may result in drying, chapping or cracking of the skin (13).

Very few data exist on systemic effects in workers occupationally exposed to MTBE. Some information was received from experimental medicine where MTBE was used for dissolution of gallstones. Ponchon et al. (22) had attempted this procedure in 8 highly selected patients -five women and three men. The volume of MTBE used was calculated at 5 ml less than the volume of the respective gallbladder but not more than 10 ml. The procedure lasted 7 hours in five patients. A severe complication was observed in one patient, who went into

coma with an odour of MTBE on the breath. The coma reversed after 4 hours but acute renal failure with anuria had developed. Haemolysis was suspected as the cause of the renal failure.

Whether this accident has any implication on the assessment of health risk due to occupational exposure to MTBE is not known at present. The dosis is probably too high and many confounding factors are interrelated to be of use in the assessment.

In a criteria document from Exxon (JP Sanderson, private communication) it was reported that from their experience in occupational medicine, workers handling bulk drum quantities of MTBE claimed to experience headaches, slight nausea, watery and/or burning eyes and loss of breath. Time of exposure varied from 1 to 8 hours with a frequency of once per month to once per year. Contractors working approximately 100 meter downwind from a separation tank at which vacuum trucks were discharging a combined mixture of diesel and MTBE complained of headaches and sore throats. During barge open loading, MTBE exposure exceeding 100 ppm has caused some workers to complain of odour, nausea, headache and respiratory tract irritation.

In 1993, the US EPA (13) performed a study on 37 healthy non-smoking subjects, ages between 18 and 35 years. Each subject was exposed to 1.4 ppm (5 mg/m^3) MTBE or clean air for one hour, on different days. Blood concentration of MTBE rose rapidly, but did not plateau during exposure. Peak concentrations in two subjects were 8.2 and 14.1 µg/l, respectively. There was no effects on the reporting of headache and nasal irritation symptoms, using either the computerized questioinaire or the analog approach. The neurobehavioral test battery (symbol-digit substitution, switching attention and mood scales) showed no effect of MTBE exposure. No markers of nasal and eye inflammation showed a statistically significant response from the MTBE exposure.

Also in 1993, investigators of the Yale University, US, replicated the EPA study (13). A total of 43 subjects between the ages 18 and 34 years participated. The MTBE exposure concentration was slightly higher, 1.68 ppm (6 mg/m^3). In addition to a clean air and MTBE exposure for one hour at 75°F, each subject also underwent a one hour exposure to a complex mixture of volatile organic compounds (VOC's) commonly found in gasoline. When MTBE exposure was compared to clean air exposure, the Yale study found essentially the same results as the EPA study (i.e., MTBE exposure had no statistically significant effect on symptoms, the neurobehavioral test battery, nasal inflammation, eye inflamation, eye redness and tear film breakup times). After exposure the subjects had peak blood MTBE concentrations of 16.6, 14.8, 17.4 and 19.7 µg/l in four subjects determined.

Raabe (24) reported a study initiated by the American Petroleum Institute (API) in 16 company-members. Sixty one occupational complaints and nine consumer complaints were reported. Headache, dizziness and nausea accounted for the majority of the symptoms reported. The number of complaints appears to be unrelated to both average short-term exposures and average time-weighted

average exposures. Examination of these complaints suggested factors other than MTBE exposure may have influenced the reporting of complaints.

7.3. Summary

- Acute toxicity studies on experimental animals indicated signs of depression of the central nervous system (anaesthesia, ataxia and tremors).
- Short-term toxicity studies in rats showed increased incidence and severity of chronic inflammation of the nasal mucosa and trachea at 1110 and 3240 ppm MTBE, with a NOAEL of 350 ppm. At level of 3240 ppm, an increased relative liver weights was noted.
- Long-term exposure experiments indicate induction of benign liver tumours in female mice, but not in male mice, at exposure level of 8000 ppm which was well above the MTD level for this species. In male rats a concentration-related increase of chronic nephropathy was found at exposure to 3000 and 8000 ppm MTBE, which was associated with an increase in the number of renal tubular cell tumours. It was considered that the increased incidence is a result of accumulation of a2u-globulin in renal tubular cells which is a specific mechanism in male rat. In the control group as well as the low concentration exposed groups there were an increase of the large granular lymphocyte leukemia. Clinical signs in both sexes of rats during exposures to 3000 and 8000 ppm included blepharospasms, ataxia and lack of startle reflex.
- MTBE is not mutagenic on S.typhimurium and S.cerevisiae D4, and it does not induce SCE and chromosomal aberrations in mammalian cells. On the other hand mutagenic effect is found on the Mouse Lymphoma Cell assay. (These results are not published.)
- In the teratology studies on rats and mice no treatment-related effects are found in animals exposed up to 3000 ppm. In rabbits, reductions of maternal weight gains and food consumption are found at exposure to 4058 and 8021 ppm MTBE, and an increase of maternal relative liver weights at exposure to 8021 ppm. It is teratogenic at maternal toxic dose. From this study it may be concluded that the NOAEL for maternal toxicity is about 1021 ppm MTBE.
- In a different study on reproduction of mice clinical signs of maternal and foetal toxicity are found in animals exposed to 8153 ppm. Foetal body weights are reduced at exposure to 4076 ppm. The NOAEL for maternal and developmental toxicity is estimated at 1035 ppm MTBE.
- A single generation reproduction study on rats shows little reproductive toxicity when the animals are exposed to MTBE at levels of 300 up to about 3000 ppm.
- There are very little data available on systemic effects in workers occupationally exposed to MTBE. Complaints of headaches, nausea, irritation of the eyes and upper respiratory tracts were reported from operations involving exposure to levels around 100 ppm MTBE.

8. Previous Evaluation by (Inter)National Bodies

According to Sanderson (private communication) there is no ACGIH Threshold Limit Value for MTBE currently, though the American Industrial Hygiene Association (AIHA) Workplace Environmental Exposure Level (WEEL) Guide in 1991 recommended 100 ppm (8-h TWA).

The rationale of AIHA (2) was as follows. MTBE has low acute toxicity and is mildly irritating to the eyes and skin. Results from several developmental toxicity studies in mice, rats and rabbits suggest that the NOAEL is about 1000 to 2500 ppm. The weight of evidence from subacute and subchronic inhalation studies in rats and monkeys indicate that the NOAEL is 800 ppm or higher. A work-place environmental exposure level (WEEL) guide of 100 ppm for an 8-hour TWA is recommended for MTBE to protect against effects from repeated exposure.

Recently the ACGIH in a draft document (1993) recommended a TLV-TWA of 40 ppm for MTBE. This level was based on the NOAEL of 400 ppm in rats from a two-generation study, as well as the renal toxicity noted in rats, both in the dams and offsprings, after inhalation of 300 and 3400 ppm. It should be noted that the NOAEL of 400 ppm was attained from an abstract of a symposium, and the complete study was never published, as far as known.

At November of 1987, the Swedish Criteria Group (SCG) published a Concensus Report on MTBE. They concluded that from animal experiments, the critical effect of exposure to MTBE is irritation of the nose and respiratory passages. At high exposure levels, MTBE affects the central nervous system. The current Occupational Standards for MTBE in Sweden are 50 ppm (180 mg/m^3), TWA-8 h, and 75 ppm (250 mg/m^3), TWA-15 minutes.

9. Evaluation of Human Health Risk

9.1. Groups at Extra Risks

No groups at extra risks can be selected.

9.2. Assessment of Health Risks

The assessment of health risks in workers occupationally exposed to MTBE is difficult because limited human data are available and the lack of long-term animal exposure studies. There are three organs/systems which are found to be the target organs in exposure by inhalation: the upper respiratory tract, the central nervous system and the liver.

From the accumulated data the following **dose-effect relationship** may be constructed in exposure by inhalation (preliminary report data are not included):

Table 2. Effects of exposure to MTBE.

Level of exposure in ppm (mg/m^3)	Exposure duration	Effects (animal species/humans)
>100 (360)	unknown	Upper respiratory tract irritation (humans)
350 (1260)	6 h/d, 5 d/w, 9 exposures	NOAEL for irritation of the upper respiratory tract (rats)
1021 (3676)	gestation period	NOAEL for maternal signs of toxicity (rabbits)
1035 (3726)	gestation period	NOAEL for maternal and developmental toxicity (mice)
1110 (3996)	6 h/d, 5 d/w, 9 exposures	Irritation of the upper respiratory tract (rats)
3240 (11664)	6 h/d, 5 d/w, 9 exposures	Increased relative liver weights (rats)
4058-8021 (14609-28876)	gestation period	Reduction of maternal weight gain and food consumption (rabbits)
4076 (14674)	gestation period	Reduced fetal body weights (mice)
8021 (28876)	gestation period	Increased maternal liver weight (rabbits)
8153 (29351)	gestation period	Maternal and fetal signs of toxicity and signs of teratogenic effects (mice)

From these data it may be concluded that the most prominent NOAEL for systemic effects lies about 1000 ppm (3600 mg/m^3) as found in rabbits and mice. For local effects such as irritation of the upper respiratory tract the NOAEL is about 350 ppm in rats

On the other hand the available human data indicate that exposure exceeding 100 ppm may lead to complaints of headaches, nausea, irritation of the eyes and upper respiratory tract to some workers.

10. Recommendations for Research

- Long-term animal studies by inhalation exposure are needed.
- Epidemiological studies in workers occupationally exposed to MTBE
- Occupational exposure data.
- Quantitative determination of the absorption through the skin.
- Pharmacokinetic studies.

11. Summaries

11.1. Summary in English

Wibowo AAE: DECOS and NEG Basis for an Occupational Standard. Methyl-tert-Butyl Ether. Arbete och Hälsa 1994:22, pp 1-21.

Methyl tertiary Butyl Ether (MTBE) is a colourless liquid with a characteristic odour. It is used almost exclusively as a blending component in high octane gasoline in an effert to raise the octane level. Occupational exposure to MTBE at refineries are generally less than 3 ppm for an 8 hour TWA but may exceed 100 ppm for short-term exposure in barge-loading activities.

In occupational exposure; MTBE is primarily taken up by inhalation, but it may also be absorbed by the skin and through the digestive tract. It is distributed into the blood, perirenal fat and brain. The MTBE is metabolized into tertiary butanol, the latter is further on probably oxidatively demethylated into formaldehyde. A portion is also excreted as glucuronic acid conjugate. Biological monitoring can be performed by determination of MTBE or its metabolite, tertiary butanol, in blood.

MTBE is classified as a mild eye irritant compound. High level short-term exposures in rat induce inflammation of the nasal mucosa and trachea. The no-observed adverse effect level is estimated at 350 ppm. Long-term exposures to mice produce a non-significant excess of benign liver tumours in female mice at concentrations which also caused general health effects, but it is not found in male mice. In male rats an increase of chronic nephropathy was found at exposures to 3000 and 8000 ppm MTBE, 6h/d, 5D7W, for two years. It is considered that the nephropathy is a result of mechanism specific to the male rat. In teratologic studies on rats and mice no treatment-related effects are found in animals exposed up to 3000 ppm MTBE. In rabbits, reductions of maternal weight gains and food consumptions are found at exposures to 4058 and 8021 ppm MTBE, an an increase of maternal relative liver weight was found at exposures to 8021 ppm. The NOAEL for maternal toxicity is estimated at 1021 ppm MTBE. There are very little data available on systemic effects of MTBE on workers exposed to this compound. Complaints of headache, nausea, irritation of the eyes and upper respiratory tracts are reported from occupational operations involving exposure levels around 100 ppm MTBE.

Key words: Criteria document, Irritation, Methyl-tert-butyl ether, MTBE, Occupational exposure limit, Teratogenicity.

11.2. Sammanfattning på svenska

Wibowo AAE: DECOS and NEG Basis for an Occupational Standard. Methyl-tert-Butyl Ether. Arbete och Hälsa 1994:22, sid 1-21.

Metyl-tert-butyleter (MTBE) är en färglös vätska med karakteristisk lukt. Den används huvudsakligen för att höja oktantalet i bensin. Yrkesmässig exponering för MTBE vid raffinaderier är vanligen lägre än 3 ppm som 8 timmars medelvärde, men kan överstiga 100 ppm vid korttidsexponering vid lastning.

Vid yrkesmässig exponering tas MTBE primärt upp vid inandning, men kan absorberas via hud och mage. Det distribueras till blod fett runt njurar och hjärna. MTBE biotransformeras till tertiär butanol, vilken troligen oxidativt demetyleras till formaldehyd. En del utsöndras som glukuronsyrekonjugat. Biologisk monitorering kan utföras genom bestämning av MTBE eller tertiär butanol i blod.

MTBE har klassats som milt ögonirriterande. Hos råtta ger höga kortvariga exponeringar inflammation i näs别mhinna och svalg. NOAEL har bedömts vara 350 ppm. Vid långtidsexponering erhöll mushonor benigna levertumörer vid koncentrationer som även orsakade allmäna hälsoeffekter. Detta ses ej hos mushanar. Hanråttor erhåller kronisk nefropati vid exponering för 3000 och 8000 ppm MTBE, 6 tim/dag, 5 dag/vecka i två år. Nefropatin anses vara resultat av en för råtta specifik mekanism. Vid teratologistudier med råtta och mus sågs inga effekter vid exponering upp till 3000 ppm MTBE. Hos kanin sågs minskad viktökning och födokonsumtion vid exponering för 4058 och 8021 ppm MTBE och en ökad relativ levervikt hos mödrarna vid den högre dosen. NOAEL för toxicitet hos modern beräknas till 1021 MTBE. Det finns få data över systemeffekter av MTBE hos yrkesexponerade. Vid exponering för omkring 100 ppm MTBE har huvudvärk, illamående och irritation i ögon och luftvägar rapporterats.

Nyckelord: Hygieniskt gränsvärde, Irritation, Kriteriedokument, Metyl-tert-butyleter, MTBE, Teratogenicitet.

12. References

1. Adam G, Knuechel R, Vorwerk D, Held C, Guenther RW. Tissue response of the biliary and digestive system of rabbits after MTBE infusion into the gallbladder. *Invest Radiol* 1990;25:58-61.
2. AIHA (American Industrial Hygiene Association). Workplace environmental exposure level guide. Methyl tert-butyl ether. AIHA, 345 White Pond Drive. P.O.Box 8390, Akron, 1992, pp 4.
3. Allen MJ, Borody TJ, Bugliosi TF, May GR, Larusso NF, Thistle JL. Cholelithiasis using methyl tertiary butyl ether. *Gastroenterol* 1985;88:122-125.
4. Ben-Dyke R, Decker CA, Hoffman CA. A nine day inhalation toxicity study of methyl-t-butyl ether in the rat. Bio/dynamics Inc., proj no 80-7452 (1984) Registered in API as Medical Res Publ: 32-30235.
5. Biles RW, Schroeder RE, Holdsworth CE. Methyl-tert-butyl ether inhalation in rats: a single generation reproduction study. *Toxicol Ind Health* 1987;3:519-534.
6. Brady JF, Xiao F, Ning SM, Yang CS. Metabolism of methyltertiary-butyl ether by rat hepatic microsomes. *Arch Toxicol* 1990;64:157-160.
7. Burleigh-Flayer HD, Chun JS, Kintigh WJ. Methyl tertiary butyl ether: Vapour inhalation oncogenicity study in CD-1 mice. Bushy Run Research Center. Pennsylvania, USA, 1992.
8. Cederbaum AI, Cohen G. Oxidative demethylation of t-butyl alcohol by rat liver microsomes. *Biochem Biophys Res Comm* 1980;97:730-736.
9. Centers for Disease Control (CDC). *An investigation of exposure to methyl tertiary butyl ether in oxygenated fuel in Fairbanks*, Alaska. Preliminary findings, July 27th, 1993.
10. Chun JS, Burleigh-Flayer HD, Kintigh WJ. *Methyl tertiary butyl ether: Vapor inhalation oncogenicity study in Fischer 344 rats*. Bushy Run Research Center. Pennsylvania, USA, 1992.
11. Conaway CC, Schroeder RE, Snyder NK. Teratology evaluation of methyl tertiary butyl ether in rats and mice. *J Toxicol Environ Health* 1985;16:797-809.
12. Environmental Protection Agency (EPA). Testing concent order on methyl tert-butyl ether and response to the interagency testing committee. *Federal Register* 1988;53:10391-10394.
13. Environmental Protection Agency (EPA). *Assessment of potential health risks of gasoline oxygenated with methyl tertiary butyl ether (MTBE)*, Research Triangle Park, NC 27711,November 1993, 51 pp.
14. Gann M., Priston B. *Methyltertiarybutylether and mouse carcinogenicity studies*. Information note from HSE/2 Division, 10 August 1992.
15. Hinton J. Occupational exposures - MTBE. American Petroleum Institute. July 27, 1993, pp 4.
16. Hymans, Ingen, Wibowo (eds), *CKB (Chemiekaarten Boek)*, 6th ed, 1990, Samson HD Tjeenk Willink Co, Alphen a.d. Rijn.
17. Kirwin Jr CJ, Sandmeyer EE. Ethers. In: Clayton and Clayton (eds) *Patty's Industrial Hygiene and Toxicology*. Vol 2A, 3rd ed.New York: Wiley-Interscience Publ, 1981:2491-2565.
18. Lundberg P (Ed). Scientific Basis for Swedish Occupational Standards. Consensus report for methyl-t-butyl ether. *Arbete och Hälsa* 1988;32:35-39.
19. National Institute for Occupational Safety and Health. Methyl tert-butyl ether. Method: 1615, Issued: 8/15/90. In: NIOSH *Manual of Analytical Methods*. US Dept Health & Human Sciences, Cincinnati, Ohio 1990.
20. O'Gronick J, Esbach JC, McPartland RP, Zacharias SB. *Metabolic fate of methyl-t-butyl ether following an acute intraperitoneal injection*. Bio dynamics Inc., proj 80089, 1984. Registered in API as Medical Res Publ: 32-30238.

21. Paulov S. Action of the anti-detonation preparation tert-butyl methyl ether on the model species Rana temporana. *Toxicol Abstr* 1987;12:41 (abs)
22. Ponchon T. Barond J, Pujol B, Valette PJ, P errot D. Renal failure during dissolution gallstones by methyl-tert-butyl ether. *Lancet* 1988;II:276-277.
23. Price JA, Saunders KJ. Determination of airborne methyl tert-butyl ether in gasoline athmospheres. *Analyst* 1984;109:829-834.
24. Raabe G. API questionaire study. In letter to the EPA from S.D. Larson, Sr Program Coordinator, Texaco Inc., October 1993.
25. Savolainen H. Renal failure during dissolution of gallstones by methylbutyl ether. *Lancet* 1988;II:515.
26. Savolainen H, Pfäffli P, Elovaara E. Biochemical effects of methyl-tertiary-butyl ether in extended vapour exposure of rats. *Arch Toxicol* 1985;57:285-288.
27. Schroeder RE, Forder JD. *An inhalation teratology study in rats with methyl-t-butyl ether*. Bio/dynamics Inc., proj no 80-2515 . Registered in API as Medical Res Publ: 32-30236, 1984.
28. Schroeder RE, Forder JD. *An inhalation teratology study in mice with methyl-t-butyl ether*. Bio/dynamics Inc., proj no 80-2516 . Registered in API as Medical Res Publ. 32-30237, 1984.
29. Schroeder RE, Forder JD. *A single generation inhalation reproduction/fertility study in rats with methyl-t-butyl ether*. Bio/dynamics Inc., proj no 80-7453. Registered in API as Medical Res Publ: 32-30239, 1984.
30. Teplick SK, Haskin PH, Goldstein RC, Corvasce JM, Frank EB, Sammon JK, Hofman AF. Common bile duct stone dissolution with methyl tertiary butyl ether: experience with three patients. *Am J Rontgenol* 1987;148:372-374.
31. Tyl RW. *Developmental toxicity study of inhaled methyl tertiary butyl ether in New Zealand White rabbits*. Report of study conducted for MTBE Toxicology Committee, Washington 1989 by Bushy Run Research Centre (Project Rep 51-628, May 12, 1989).
32. Tyl RW, Neeper-Bradley TL. *Developmental toxicity study of inhaled methyl tert-butyl ether in CD1-mice*. Report of study conducted for MTBE Toxicology Committee, Washington by Bushi Run Research Centre (Project Rep 52-526, July 20, 1989).

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