NTP CHEMICAL NOMINATION BACKGROUND

Methyl tert-butyl ether
CAS No. 1634-04-4

SUMMARY OF DATA FOR CHEMICAL SELECTION

CHEMICAL IDENTIFICATION

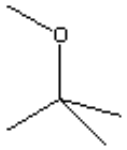
CAS Registry Number: 1634-04-4

Name: Methyl *tert*-butyl ether

Chem. Abstr. Name: 2-Methoxy-2-methylpropane (9CI)

Synonyms: MTBE; tert-butyl methylether (8CI); methyl 1,1-di-methylethyl ether

Structure, Molecular Formula, and Molecular Weight:



$C_5H_{12}O$ Mol. wt.: 88.15

Chemical and Physical Properties

Description: Colorless liquid (1)

Melting Point: -109^{o}C (2)

Boiling Point: 55.2^{o}C (2)

Density: 0.745 (2)

Solubility: Soluble in ether and ethanol (2); slightly soluble in water (4.8 g/l at 25^{o}C) (3); MTBE in water 4.8 weight% (6); water in MTBE 1.5 weight% (4).

Technical Products and Impurities

MTBE is available from US manufacturers typically in 97.0-97.45 weight % compo- sitions. Specifications for the minimum concentration of MTBE range from 95.0 - 97.0 weight % (4,1). Methanol is allowed in concentrations not to exceed 0.5% (1) or 0.7% (4). Water may be present in less than 0.15% concentration by weight (4,1). Other typical contaminants include diisobutylene, triisobutylene and t-butyl alcohol (0.56%); C_4hydrocarbons (1.10%) and C_5 hydrocarbons (0.35%) by weight (1).

BASIS OF NOMINATION TO THE CSWG

Methyl tert-butyl ether was nominated in joint discussions between NCI, TJ, and TRI personnel at a CSPG meeting (5/7/85). The nomination was based on the extensive production of the compound, its increasing use as a blending component in high octane gasoline, its recent application in the dissolving of gallstones, and the lack of carcinogenicity testing information.

SELECTION STATUS

ACTION BY CSWG: (9/19/85)

Priority: Moderate

Studies Requested: Carcinogenicity

Comments:

Methyl tertiary-butyl ether (MTBE) was submitted to the CSWG for review on the basis of the extensive production of the compound, its increasing use as a blending component in high octane gasoline, its recent application in the dissolving of gallstones, and the lack of carcinogenicity testing information. It was noted that MTBE is used as an additive in unleaded gasoline in amounts up to 11%. Although the major human exposure was considered as occurring in people working in gas stations, it was recognized that the possibility of general population exposure is very high. It was noted that in rats, MTBE is exhaled mostly intact with small amounts of formic acid and methanol being excreted in the feces and urine. [API has also reported the identification of t-butyl alcohol and formaldehyde as metabolites of MTBE.] In addition, the CSWG considered that the compound has not been tested for carcinogenicity and that the mutagenicity data available is limited and does not permit meaningful assessment of the mutagenicity potentials of MTBE. The Group unanimously recommended that MTBE be tested for carcinogenicity.

EXPOSURE INFORMATION

Commercial Availability

Production and Producers: Methyl t-butyl ether (MTBE) was introduced into the US market by Phillips chemi- cal in 1979 (5). Since that time, there has been a dramatic increase in MTBE production, as represented by eight major US manufacturers (6).

MTBE Producer	Production Capacity*
Arco	855
Champlin	150
Charter International	135
Exxon	230
Petro-Tex	620
Phillips	265[a]
Texaco	600
Texas Petrochemical	55
	2910

* Capacity in millions of lbs., as of July 1985 (6)
[a]No longer available as of May 1985 (7)

U.S. Production of MTBE (8)
(millions of lbs)

1980	1981	1982	1983	1984
705.7	760.0	824.0	838.7	1,469.5

The Arco chemical company plans to expand its MTBE capacity to a total of 950 million lbs. (6). Amoco is preparing to place on-stream two MTBE plants with a combined capacity of 3078 million lbs. In addition, Cosden plans to open a facility in 1986 with a 66 million lb capacity, and Exxon will add to its MTBE production capability in 1987 (9). The total US production capacity of MTBE in 1986 is projected to be 3.38 billion lbs. Recent correspondence with the Phillips Chemical Company indicates that MTBE is no longer commercially available

from that firm (7).

The US International Trade Commission (8) reported the production of 1.47 bil- lion lbs. of MTBE by US producers in 1984. This represents 42% increase over the previous year's total, and ranked MTBE production among the top 50 industrial chemicals manufactured in the US (10). Consumption of MTBE in 1984 was estimated at between 1.49 and 1.52 billion lbs., with demand expected to increase by 10% in 1985 (6). Import/export figures for this compound are not available (11).

MTBE is produced commercially by reacting methanol with isobutylene contained in mixed C_4 stream and passing the mixture over a fixed bed ctalyst (1,6,12). Differing technologies for this process have been utilized by Neochem, Arco, Phillips, and Texaco in the US, Huels in Germany, and Snamprogetti in Italy (13).

A Saudi Arabian plant will begin making MTBE by 1988 by reacting isobutylene with field butenes (14).

Use Pattern:

The primary use for MTBE is as a high-octane blending component for gasoline. The increased demand for MTBE in this application is in response to EPA's restriction on the use of lead in gasolines. EPA first allowed the use of MTBE as a gasoline additive in February 1979 at 7% (v/v) or less. This ruling was amended in October 1980 to permit 11% (v/v) MTBE in the finished gasoline (15).

Industry sources suggest that the availability of high purity MTBE will promote new chemical and solvent applications for this substance (1). MTBE has been used as a chromatographic eluent for liquid and thin-layer chromatographic procedures, as a replacement for diethyl or diisopropyl ether.

Approximately 10% of the MTBE produced in the US in 1981 was used for the production of high-purity isobutylene (5). In this process, MTBE is cracked to isobutylene and methanol by passing the ether over a fixed-bed catalyst. Schenectady Chemicals, which no longer makes MTBE, had a 110 million pound production capacity for the compound in 1982, all of which was channeled into the production of t-butyl phenol via isobutylene (5).

Several recent papers have reported the results of investigational studies in which MTBE is utilized as a gallstone solvent to produce cholelitholysis in dogs (17,18) and humans (19). In all cases, the MTBE is introduced directly into the gallbladder by means of a biliary catheter. This treatment was found to dissolve the cholesterol gallstones in approximately 4 hours, as opposed to the 3-21 days necessary for the currently preferred agent, mono-octanoin, to accomplish the same task.

Human Exposure: MTBE is not included in NIOSH's National Occupational Hazard Survey. Also, NIOSH has not published a criteria document for occupational exposure to MTBE, nor has the American Conference of Governmental Industrial Hygienists recommended a threshold limit value (TLV) for this compound. The greatest potential for human exposure to MTBE is through contact with unleaded gasoline (20).

Environmental Occurrence: No information on the occurrence or fate of methyl tert-butyl ether in the environment was found in the literature (11,20).

Regulatory Status: The Environmental Protection Agency first allowed the use of MTBE as a gasoline additive in February 1979 at 7% (v/v) or less. This ruling was amended in October 1980 to permit 11% (v/v) MTBE in the finished gasoline (15).

The use of MTBE as a therapeutic agent for cholelitholysis in humans is approved by the Food and Drug Administration only for feasibility studies (19).

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies relating human cancer incidences and exposure to MTBE have been cited (11,20,21).

Animal Data: MTBE is neither currently being tested nor scheduled for testing in a standard NCI bioassay (11,20,21).

No animal carcinogenicity studies were cited in the recent literature (20). Recent studies of acute exposure to treated air (6 hr/day) in rats revealed no treatment-related tissue abnormalities in male and female rats exposed to 101-2970 ppm for nine days (22) and female rats and their fetuses exposed to 250- 2500 ppm for 10 days of gestation (23). Treatment-related tissue abnormalities were not apparent in gonads of male rats similarly treated pre- and post-mating at 250-2500 ppm for 25 weeks, in gonads of female rats treated at the same concentrations during the pre-mating, gestation and lactating periods (20 weeks), and in the gross morphology of their progeny, which were exposed to the same concentrations for three weeks (24).

An LD_{50} of 4000 mg/kg has been reported for mice (16). A dermal LD_{50} of approximately 10,000 mg/kg and an oral LD_{50} of 3,865 mg/kg have been reported for rats. An LD_{50} of 33,427 ppm has also been determined for rats (1).

In Vitro Tests: Limited and inconclusive data are available on the in vitro mutagenicity of MTBE. Tests utilizing the Salmonella assay showed that exhaust emissions from an automobile fueled with 7% MTBE in gasoline resulted in a significantly higher number of revertants per mg extract than emissions resulting from the use of similar but untreated gasoline. However, in two other makes of automobiles, addition of MTBE resulted in the same mutagenicity or in a significantly lowered mutagenicity rate than straight gasoline (25).

Metabolism: MTBE, given intraperitoneally to rats at sub-lethal doses was almost completely eliminated intact through expired air within 48 hours post-treatment. Small amounts of formic acid were determined in urine and feces at the same time interval, and evidence of the presence of formic acid and methanol in tissue and plasma was reported (26). Additional reports have also indicated that approximately 90% or more of an administered dose is exhaled and that the remainder is converted to methanol and formic acid (18,19). Metabolism studies with diethyl ether have similarly shown this compound to be eliminated quickly and unchanged through expired air (27).

Structure/Activity Relationships: Limited information is available on the carcinogenicity and mutagenicity of low-molecular weight allyl ethers (20). Exposure of hamster ovary cell cultures to diethyl ether (mol. wt. 74.12) for one hour did not increase sister chromatid exchanges (28).

REFERENCES

1. Arco Chemical Corporation (1982) Technical Bulletin: MTBE Gasoline Blending Component, Philadelphia, PA

2. Weast, R.C., ed. (1984) CRC Handbook of Chemistry and Physics, 65th Ed., Boca Raton, FL, CRC Press, Inc., p. C-200

3. Windholz, M., ed. (1983) The Merck Index, 10th Ed., Rahway, NJ, Merck & Co., Inc.

4. Texas Petrochemicals Corp. (1985) Methyl-tert-butyl-ether (MTBE). Shipping Specification Technical Data, Houston, TX

5. Anon. (1981) Chemical Briefs: MTBE. Chemical Purchasing, 17(2), 55-78

6. Verbanic, C. (1985) The Octane Scramble. Chem. Business, July, 1985, pp. 9-13

7. Personal communication (1985). Letter from Lora White, Phillips Chemical Co., dated May 3, 1985

8. US International Trade Commission (1984) Synthetic Organic Chemicals, United States Production and Sales, 1983, USITC Publication 1588

9. Anon. (1985) MTBE growth seen booming as phaseout gives extra push; latest expansion slated by Arco. Chem. Marketing Reporter, April 29, 1985

10. Webber, D. (1985) Basic chemical production grew strongly in 1984. Chem. and Eng. News, 63(18), 11-14

11. DIALOG (Lockheed) Information System Data Bases: Occupational Safety and Health; Chemical Exposure; Chemical Industry Notes; Federal register; Federal Index; National Technical Information Service; PTS Promt; Chemical Abstract; Biosis

12. Chemical Engineering (1979) Sources and Production Economics of Chemical Products. New York, McGraw-Hill Publication Co., p. 209

13. Anon. (1984) Dravo's strong bid to build MTBE plants. Chemical Week, 135(10), 15-18

14. Anon. (1985) MTBE production technology. Chemical Week, 136(20), 14

15. Federal Register, Vol. 45 (October 10, 1980), pp. 67443-67448

16. Little, C.J., Dale, A.D., Whatley, J.A. & Wickings, J.A. (1979) Methyl tert-butyl ether: a new chromatographic eluent. J. Chromatography, 169, 381-385

17. Allen, M.J. Borody, T.J., Bugliosi, T.F., May, G.R., LaRusso, N.F. & Thistle, J.L. (1985) Cholelitholysis using methyl tertiary butyl ether. Gastroenterology, 88, 122-125

18. Bugliosi, T.F., Borody, T.J., Allen, M.J., Rach, G.J., LaRusso, N.F. & Thistle, J.L. (1984) Methyl tertiary butyl ether (MTBE) in expired and methanol in blood does not reach potentially harmful levels after gallbladder and duodenal instillation of therapeutic doses of MTBE in dogs. Gastroenterology, 86, 1313 (abstract)

19. Allen, M.J., Borody, T.J., Bugliosi, T.F., May, G.F. , LaRusso, N.F. & Thistle, J.L. (1985) Rapid dissolution of gallstones by methyl tert-butyl ether. New Engl. J. Med., 312(4), 217-220

20. National Library of Medicine Data Bases: MEDLINE, TOXLINE, CANCERLIT, April, 1985

21. Not listed in PHS-149, Survey of Compounds Which Have Been Tested for Carcinogenic Activity

22. American Petroleum Institute (1984) A nine day inhalation toxicity study of methyl t-butyl ether in the rat, Biodynamics Project No. 80-7452, Washington, D.C.

23. American Petroleum Institute (1984) An inhalation teratology study in rats with methyl t-butyl ether (MTBE), Biodynamics Project No. 80-2515, Washington, D.C.

24. American Petroleum Institute (1984) Methyl t-butyl ether (MTBE) composite report, Biodynamics Projects 80-7453 and 80-089. Washington, D.C.

25. MacFarland, H.N., Holdsworth, C.E., MacGregor, J.A., Call, R.W. & Lane, M.L. (eds.) (1984) Applied Toxicology of Petroleum Hydrocarbons, Volume VI, Princeton Scientific Publ., Inc., pp. 109-122

26. American Petroleum Institute (1984) The metabolic fate of methyl-t-butyl ether (MTBE) following an acute intraperitoneal injection, Biodynamics Project No. 80-089, Washington, D.C.

27. Browning, E. (1965) Toxicity and Metabolism of Industrial Solvents. Elsevier Publ. Co., New York, p. 10

28. White, A.E., Takehisa, S., Eger, E.I., Wolff, S. & Stevens, W.C. (1979) Sister chromatid exchanges induced by inhaled anesthetics. Anesthesiology, 50, 426-430