SUMMARY OF DATA FOR CHEMICAL SELECTION

2-Methyltetrahydrofuran
96-47-9

BASIS OF NOMINATION TO THE CSWG

2-Methyltetrahydrofuran is brought to the attention of the CSWG because a new, cost-competitive manufacturing process that uses biomass is expected to greatly increase its use. For example, 2-methyltetrahydrofuran is a component of P-series fuels. These blends of ethanol, methyltetrahydrofurans, and pentanes have recently been classified as an alternative fuel by the US Department of Energy. Analysts do not expect P-series fuels to replace gasoline, but they expect sales to grow rapidly in the next 10 years.

Although the market for 2-methyltetrahydrofuran is posed for future expansion, the potential toxicity of methyltetrahydrofuran has not been characterized. Development of the biomass technology and the P-series fuels has been conducted at universities and small start-up firms not in an immediate position to conduct such testing. Thus, Federal intervention appears warranted.

INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

Dr. John Walker, Executive Director of the TSCA Interagency Testing Committee (ITC), Environmental Protection Agency (EPA), provided information on the annual production range methyltetrahydrofuran and levulinic acid, its precursor chemical.

SELECTION STATUS

ACTION BY CSWG: 9/28/00

Studies requested:

Subchronic (90-day) tests
Carcingoenicity using the Tg.AC mouse model

Ames *Salmonella* and micronucleus assays

Mechanistic studies using the International Agency for Research in Cancer (IARC) criteria for chemicals that induce alpha-2u-globulin

Priority: High

Rationale/Remarks:

Although methyl tetrahydrofuran is presently produced in low volumes, a new manufacturing process will reduce the cost of producing methyl tetrahydrofuran, thus greatly increasing its use.

New use in P-series fuels is increasing market demand

Virtually no information on toxicity; concerns about possibility that methyl tetrahydrofuran might form peroxides

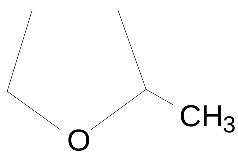
Testing recommendations take into consideration the structural similarity to tetrahydrofuran, a non-genotoxic carcinogen that induced renal tubule tumors in male rats.

NCI will conduct Ames and mouse lymphoma assays.

CHEMICAL IDENTIFICATION

CAS Registry Number:	96-47-9
Chemical Abstracts Service Name:	Furan, tetrahydro-2-methyl- (8CI, 9CI)
Synonyms and Trade Names:	2-Methyloxolane; methyltetrahydrofuran; tetrahydrosylvan
Structural Class:	Furan

Structure, Molecular Formula and Molecular Weight:



$C_5H_{10}O$ Mol. wt.: 86.13

Chemical and Physical Properties:

Description:	Clear, colorless to yellow, mobile liquid; mildly irritating, ether-like odor (Lewis, 1993; Penn Specialty Chemicals, 1999)
Boiling Point:	78 °C (Lide, 1997)
Melting Point:	-136 °C (Penn Specialty Chemicals, 1999)
Density:	0.8600 (Fisher, 1999a)
Solubility:	Soluble in water, solubility in water increases with decrease in temperature; very soluble in ethanol, acetone, and ethyl ether (Lewis, 1993; Lide, 1997)
Vapor Density	2.9 (air=1) (Penn Specialty Chemicals, 1999)
Flash Point:	-11.1 °C (TOC) (Lewis, 1993)
Reactivity:	Stable under normal temperature and pressure; incompatible with oxidizing agents, strong acids, strong bases; extremely flammable (Fisher, 1999b)

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Technical Products and Impurities: 2-Methyltetrahydrofuran (MTHF), stabilized with 1% butylated hydroxytoluene, is available in research quantities at a purity of >99% from Fisher Scientific and Sigma-Aldrich. Sigma-Aldrich also supplies 97% pure MTHF stabilized with 0.1% hydroquinone (Fisher Scientific, 1999a; Sigma-Aldrich, 1999). The following quality specifications have been cited for MTHF: 2-MTHF (min.), wt % 99.0; 2-methylfuran (max.), wt % 0.05; water (max.), wt % 0.10; and pentanols (max.), wt % 0.50 (McKillip *et al.*, 1989).

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EXPOSURE INFORMATION

Production and Producers: MTHF is produced in limited quantities from furfural by Great Lake Chemical Corporation, which has plans to leave the market (Hoffman, 1998).

Pure Energy Corporation (PEC), which has purchased MTHF from Great Lakes in the past, plans to use biotechnology to produce its own MTHF. PEC would then sell MTHF and its derivatives, as well as P-series and other fuels containing MTHF (Hoffman, 1998).

The changes in the MTHF market are occurring because of a new multistep, catalytic process to produce MTHF. This process was developed by the Department of Energy's Pacific Northwest National Laboratory. MTHF is prepared from levulinic acid which is produced from relatively low-grade waste cellulosic by-products using technology developed by Biofine, Inc. (Science Daily, 1998).

The MTHF process is conducted at elevated temperatures and pressures inside a catalytic, continuous flow reactor. Levulinic acid is warmed to about 40°C and mixed with hydrogen. In the presence of a catalyst the resultant chemical reactions include multiple hydrogenations and two dehydration steps to produce MTHF. On a weight basis, the yield is 63 pounds of MTHF for every 100 pounds of levulinic acid (Alternate Fuels Data Center, 2000; Hoffman, 1998; OTI, 2000; Science Daily, 1998).

Methyltetrahydrofuran (2- not specified) is listed as a chemical of commerce in the U.S. International Trade Commission (USITC) publication *Synthetic Organic Chemicals, US Production and Sales* for the years 1988, 1989, 1991, 1992, and 1993 (USITC, 1989, 1990, 1993, 1994a, 1994b). The reporting company was QO Chemicals Inc.; but no production or sales quantities were included. According to the USITC, separate statistics were not published to avoid disclosure of individual company operations; however, the USITC reporting guidelines specify that each company's report of a chemical represents production of 4,500 kg [10,000 lbs.] or sales $10,000. This source is no longer published.

MTHF is listed in the EPA's Toxic Substances Control Act Inventory (NLM, 2000). The annual production of MTHF was reported to be below 10,000 lbs. based on non-confidential data received by the EPA (Walker, 2000).

Use Pattern: MTHF is used as a specialty solvent and as a reactant for the production of chemicals including 2-methylpyrrolidine and *N*-substituted 2-methylpyrrolidines (McKillip *et al*.,1989). MTHF is a more convenient solvent than tetrahydrofuran for Grignard reagents; it is higher boiling and wet MTHF is more easily recovered and made anhydrous for recycle and reuse (Kottke, 1998). MTHF is also used as a solvent for other organometallic reagents as well as for electrolytic solutions in lithium batteries (Suzuki *et al*., 2000).

MTHF is a gasoline extender that has been successfully road-tested in fuel blends. It is a component of P-series fuels that were recently classified as alternative fuels by the US Department of Energy. The fuels, produced from cellulosic wastes, contain 45 to 50% ethanol, 15-20% MTHF, and 30-35% pentanes-plus. A spokesman for PEC, which plans to manufacture the P-series fuels, notes that although there were fewer than 100,000 flexible fuel vehicles in 1997, industry estimates that there will be approximately 3 million by 2005. Analysts do not expect P-series fuels to replace gasoline, but they feel sales could grow rapidly in the next decade. Success for the P-series fuels would mean a significant increase in MTHF use (Anon., 1998; Hoffman, 1998; OTI, 2000).

Human Exposure: No reports of occupational exposure to MTHF were found in the available literature. No listing was found for MTHF in the National Occupational Exposure Survey (NOES), which was conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983.

Human exposure to MTHF occurs primarily through its use as a solvent. However, MTHF use in the new P-series fuels could result in significant environmental and consumer exposure.

MTHF was identified in samples of mother's milk collected from persons in 5 U.S. cities; it was found in 1 of the 8 samples selected for qualitative analysis. The researchers noted that the furans identified appeared to be metabolites (Erickson *et al*., 1980).

Environmental Occurrence: No information on the environmental occurrence of MTHF was identified in the available literature.

Regulatory Status: No standards or guidelines have been set by NIOSH or OSHA for occupational exposure to or workplace allowable levels of MTHF. MTHF was not on the American Conference of Governmental Industrial Hygienists (ACGIH) list of compounds for which recommendations for a threshold limit value (TLV) or biological exposure index (BEI) are made.

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports investigating the exposure of MTHF and cancer risk in humans were identified in the available literature.

Animal Data: No 2-year carcinogenicity studies of MTHF in animals were identified in the available literature.

The acute LC_{50} dose of MTHF in rats was reported to be 6000 ppm for 4 hours (inhalation). The dermal LD_{50} dose in rabbits was 4500 mg/kg. MTHF at a dose of 500 mg for 24 hours was a mild eye irritant in rabbits (NLM, 2000).

Short-Term Tests: No *in vitro* or *in vivo* studies evaluating MTHF for mutagenic effects were identified in the available literature.

Metabolism:

No studies on the metabolism of MTHF were identified in the available literature.

Furan, the parent compound of MTHF, is metabolized to an electrophilic species. The subsequent reaction of electrophilic species with tissue nucleophiles takes place primarily at the site of necrosis. It has been suggested that furan rings are important in the toxicity of compounds, while tetrahydrofuranyl or other analogs are generally less toxic than the parent compound (NTP, 1998). Whether MTHF is metabolized to more toxic chemicals is not known.

Structure/Activity Relationships: Four compounds structurally similar to MTHF were screened for relevant information associating these chemicals with a mutagenic or carcinogenic effect. No pertinent information was found for 2,5-dimethyltetrahydrofuran [1003-38-9], 2-butyltetrahydrofuran [1004-29-1], or cis-2,5-dimethyltetrahydrofuran [2144-41-4].

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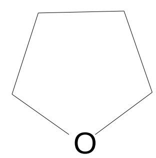
Information was identified on carcinogenicity and mutagenicity for tetrahydrofuran [109-99-9] (structure shown below).



Tetrahydrofuran

Carcinogenicity

Tetrahydrofuran induced tumors in male F344/N rats and female B6C3F_1 mice in 2-year inhalation studies. There was some evidence of carcinogenic activity in male rats based on increased incidences of renal tubule adenoma or carcinoma (combined) and clear evidence of carcinogenic activity in female mice based on increased incidences of hepatocellular neoplasms. Results in female rats and male mice were negative (NTP, 1998).

Mutagenicity

Tetrahydrofuran was negative in most tests of mutagenic or genotoxic activity including the following: mutation in *Salmonella typhimurium*; sister chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells *in vitro* or in mouse bone marrow cells *in vivo*; and sex-linked recessive lethal mutations in *Drosophila melanogaster*. Tetrahydrofuran produced an equivocal response in the micronucleus assay in male mice; results in female mice were negative (NTP, 1998).

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References

Alternate Fuels Data Center (2000) P-series General Information. *Alternative Fuels.* [http://www.afdc.doc.gov/pse-general.html]

Anon. (1998) Out of waste comes a clean, high-octane fuel. *Chem. Eng.,* Sept., p 25 [Abstract]

Erickson, M.D., Harris, B.S.H., Pellizzari, E.D., Tomer, K.B., Waddell, R.D. & Whitaker, D.A. (1980) *Acquisition and Chemical Analysis of Mother's Milk* (*US EPA/OTS* #40-8023083; US NTIS OTS0527479), US Environmental Protection Agency.

Fisher Scientific (1999a) Methyltetrahydrofuran. *Catalogs.* [http://www.fishersci.com/catalogs]

Fisher Scientific (1999b) *Material Safety Data Sheet: 2-Methyltetrahydrofuran 99+% Stabilized with 1% Butylated Hydroxytoluene.* [http://www.fishersci.com/catalogs]

Hoffman, J., (1998) Pure Energy plans new fuel based on chemicals and NGLs. *Chem. Market Rep.,* **253**(3), p13

Kottke, R.H. (1998) Furan derivatives. In: Kroschwitz, J.I. & Howe-Grant, M., eds., *Kirk-Othmer Encyclopedia of Chemical Technology,* 4th. ed., Supplement Vol., New York, John Wiley & Sons, pp176-177

Lewis, R.J., Sr. ed. (1993) *Hawley's Condensed Chemical Dictionary*, 12th ed., New York, Van Nostrand Reinhold Co., p 781

Lide, D.R., ed. (1997) *CRC Handbook of Chemistry and Physics,* 78th ed., New York, CRC Press, p **3-**171

McKillip, W.J., Collin, C. & Höke, H (1989) Furan and derivatives. In: Elvers, B., Hawkins, S., Ravenscroft, M., Rounsaville, J.F. & Schulz, G., eds., *Ullmann's Encyclopedia of Industrial Chemistry,* 5th ed., vol.12, New York, VCH Publishers, p 128

NLM (2000) *RTECS (Registry of Toxic Effects of Chemical Substances),* Bethesda, MD, National Library of Medicine, searched March 2000 [Record No. 59784]

NTP (1998) *Toxicology and Carcinogenesis Studies of Tetrahydrofuran (CAS NO. 109-99-9) in F344/N Rats and B6C3F1 Mice (Inhalation Studies) (Technical Report Series No. 475; NIH Publ. No. 98-3965),* Research Triangle Park, NC, National Toxicology Program, 244 pp

OTI (2000) Office of Industrial Technologies, US Department of Energy. Commercialization of the Biofine technology for levulinic acid production from paper sludge. *Forest Products, Product Fact Sheet.* [http://www.oit.doe.gov/forest/biofine.htm]

Penn Specialty Chemicals, Inc. (1999) *Material Safety Data Sheet: 2-Methyltetrahydrofuran,* Memphis, TN

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Science Daily (1998) *Chemical Process Provides New Source for Alternate Fuels*. [http://www.sciencedaily.com/releases/1998/1081030081400.htm]

Sigma-Aldrich (1999) *Product Search: 2-Methyltetrahydrofuran*. [http://vsearch.sial.com/]

Suzuki, H., Maruyama, S. & Ohe, K. (2000) *Polymeric Solid Electrolyte and Lithium Secondary Cell Using Same*. Assignee: TDK Corp. (US Patent 6,051,343), 17 pp

US International Trade Commission (1989) *Synthetic Organic Chemicals, US Production and Sales, 1988 (USITC Publication 2219),* Washington, DC, US Government Printing Office, p 15-11

US International Trade Commission (1990) *Synthetic Organic Chemicals, US Production and Sales, 1989 (USITC Publication 2338),* Washington, DC, US Government Printing Office, p 15-11

US International Trade Commission (1993) *Synthetic Organic Chemicals, US Production and Sales, 1991 (USITC Publication 2607),* Washington, DC, US Government Printing Office, p 15-14

US International Trade Commission (1994a) *Synthetic Organic Chemicals, US Production and Sales, 1992 (USITC Publication 2720),* Washington, DC, US Government Printing Office, p 3-170

US International Trade Commission (1994b) *Synthetic Organic Chemicals, US Production and Sales, 1993 (USITC Publication 2810),* Washington, DC, US Government Printing Office, p 3-170

Walker, J (2000) Personal Communication [electronic mail] from John Walker, Ph.D., M.P.H., Executive Director, TSCA Interagency Testing Committee, Environmental Protection Agency, Washington, to Imogene Sevin, Ph.D., Technical Resources International, Inc., 4/3/2000