

SUMMARY OF DATA FOR CHEMICAL SELECTION

METHYLAL CAS NO. 109-87-5

BASIS OF NOMINATION TO THE CSWG

The nomination of methylal to the CSWG is based on high production volume and exposure potential. Dr. Elizabeth Weisburger, a member of the American Conference of Governmental Industrial Hygienists (ACGIH) TLV Committee as well as the Chemical Selection Working Group (CSWG), provided a list of 281 chemical substances with ACGIH recommended TLVs for which there were no long term studies cited in the supporting data and no designations with respect to carcinogenicity. She presented the list to the Chemical Selection Planning Group (CSPG) for evaluation as chemicals which may warrant chronic testing: it was affirmed at the CSPG meeting held on August 9, 1994, that the 281 "TLV Chemicals" be reviewed as a Class Study. As a result of the class study review, methylal is presented as a candidate for testing by the National Toxicology Program because of:

- potential for occupational exposures based on high production volume (1.2-64 million lbs) and estimate of worker exposure
- evidence of occupational exposures based on TLV and other literature documentation
- potential for general population exposures based on use as a solvent in consumer products and occurrence in environmental media
- suspicion of carcinogenicity based on potential for metabolic release of formaldehyde and positive mutagenicity data
- lack of chronic toxicity data.

SELECTION STATUS

ACTION BY CSWG: 9/25/96

Studies requested:

- Carcinogenicity

Priority: Moderate to High

Rationale/Remarks:

- Potential for human exposure
- Inhalation route recommended for testing
- Consider transgenic mouse model (p53 or TGAC)

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 total annual production level of methylal and the TSCA ITC status of this chemical (see Regulatory Status section).

CHEMICAL IDENTIFICATION

<u>CAS Registry Number:</u>	109-87-5
<u>Chemical Abstract Service Name:</u>	Methane, dimethoxy- (8CI,9CI)
<u>Synonyms and Trade Names:</u>	Dimethoxymethane; methylal; formal; methyl formal; formaldehyde dimethylacetal; methylene dimethyl ether; DMM
<u>Structural class:</u>	Aliphatic diether

Structure, Molecular Formula and Molecular Weight



$\text{C}_3\text{H}_8\text{O}_2$

Mol. Wt.: 76.10

Chemical and Physical Properties (from ACGIH, 1992, unless otherwise referenced)

<u>Description:</u>	Colorless, highly volatile, flammable liquid with an odor described as chloroform-like.
<u>Boiling Point:</u>	42.3°C
<u>Melting Point</u>	-104.8°C
<u>Flash Point:</u>	-17°C, closed cup; -32°C open cup
<u>Specific Gravity:</u>	0.8601 @ 20°C
<u>Vapor Pressure:</u>	330 torr @ 20°C
<u>Vapor Density:</u>	2.6 (Verschueren, 1983)
<u>Solubility:</u>	Soluble in water (>32%); miscible with alcohol, ether, and hydrocarbons
<u>Stability:</u>	Stable under ordinary conditions of use and storage; alkyl ethers have a tendency to form explosive peroxides (Plog, 1988; Mallinckrodt Specialty Chemicals Co., 1989)
<u>Reactivity:</u>	Incompatible with strong oxidizers and acids (Sittig, 1985)
<u>Log P:</u>	0.18 (Hansch <i>et al.</i> , 1995)

Technical Products and Impurities: Methylal is available in purities ranging from 97 to greater than 99% from numerous manufacturers or suppliers of research and bulk chemicals (Pfaltz & Bauer, Inc., undated; Janssen Chimica, 1992; Eastman Chemical Co., 1993; Fluka Chemical Corp., 1995; Lancaster Synthesis, Inc., 1995; Aldrich Chemical Co., Inc., 1996; Avocado Research Chemicals, Ltd., 1996). Mallinckrodt offers methylal in Analytical Reagent (AR) grade with a reported minimum purity of 99% and the following specifications regarding impurity levels: water, 0.05% maximum; acidity (as acetic acid), 0.01% (Mallinckrodt Specialty Chemicals Co., 1989).

Methylal is available in Europe from Rhone-Poulenc Rorer, marketed under the trade name, Hexomedine, in mouthwash, gel and transdermal formulations (Chemical Information Services, Inc., 1995).

EXPOSURE INFORMATION

Production and Producers:

Methylal can be prepared by the catalytic vapor phase oxidation of methanol in the presence of small amounts of hydrochloric acid; from methanol and paraformaldehyde in the presence of calcium chloride and hydrochloric acid; and from formaldehyde and methanol according to patents assigned to Dow Chemical Co. in the mid-1950s (Budavari, 1989). Methylal can be synthesized from methanol by an electrooxidation process described in a patent assigned to the E.I. duPont Co. (Fedkiw *et al.*, 1993). Methylal is one of a group of linear and cyclic acetals for which Hoechst A-G has recently been assigned a patent for a continuous industrial manufacturing process using a natural circulation reactor (Arnold *et al.*, 1996).

Methylal is listed in the EPA's TSCA Inventory (STN International, 1994, 1995). United States production of methylal in 1989 was reported to be in the range of 1.2 - 6.4 million pounds based on non-confidential data received by the EPA (Walker, 1995a). No other quantitative information on annual production was found in the available literature. Methylal is listed as a chemical in commerce in the U.S. International Trade Commission (USITC) publication, *Synthetic Organic Chemicals, US Production and Sales, 1993* (USITC, 1994). The reporting company was listed as Hoechst Celanese Corp., Chemical Group, 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 $\geq 4,500$ kg [10,000 lbs] or

sales \geq \$10,000. Based on a search of recent literature sources, including chemical industry catalogs, directories, and databases, the companies presented in Table 1 have been identified as producers/suppliers of methylal, recent patent assignees for its preparation and/or use, or companies providing toxicity study results to the EPA in response to a § TSCA 8(d) rule (Fisher Scientific, undated; Lewis, 1993; Chemical Information Services, Inc., 1994; Hunter, 1994; Kuney 1995; TCI America, 1994; Van, 1994; Chemical Information Services, Inc., 1995; CIS, 1995; STN International, 1994, 1995, 1996).

Use Pattern: Methylal has several use areas. They include: chemical intermediate; solvent; fuel, fuel additive; and polymer modifier (Budavari, 1989; ACGIH, 1992; Lewis, 1993; STN International, 1995, 1996). Some examples of these uses and some specialty uses are presented in Table 2. Methylal was formerly used as a surgical anaesthetic; it was found to be slower acting with a more transitory effect than diethyl ether (Proctor *et al.*, 1988).

Table 1. Companies producing or supplying methylal

	Producer/supplier listed in chemical industry catalog and/or directory	Company assigned patent for preparation and/or use	Company providing toxicity study data to EPA
Aceto Corp./Pfaltz & Bauer, Inc.	X		
Acros Organics/Fisher Scientific	X		
Aldrich Chemical Co.	X	X	
Alfa Aesar Organics	X		
Asahi Chem. Ind. Co., Ltd.	X		
BASF Corp.		X	X
Chemisphere	X		
Dow Chemical Co.		X	
Eastman Chemical Co.	X		
E.I. duPont de Nemours & E.	X		
Fluka Chemical Corp.	X	X	X
Harry Holland & Son, Inc.	X		
Hoechst Celanese/Hoechst A.G.	X		
Kururay Co., Ltd.	X		
Mallinckrodt Spec. Chems. Co.	X		
PCAS	X		X
Rhone-Poulenc Pharma/Rorer			
S.S.T. Corp.			
TCI America			
Union Carbide Corp.			

Human Exposure: There is potential for exposures to methylal in occupational, consumer and environmental settings by inhalation, ingestion, and skin and eye contact. Methylal's low boiling point and vapor characteristics, combined with its wide use as a solvent, constitute a vapor hazard, according to Plog (1988). Occupational exposures to methylal as an air contaminant may occur during its production and use. Its documented presence as an indoor air pollutant indicates a potential for general population exposures (Sexton *et al.*, 1985).

The National Occupational Exposure Survey (NOES), which was conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983, estimated that 156,795 workers, including 21,092 female employees, were potentially exposed to methylal in the workplace. The NOES database does not contain information on the frequency, level, or duration of exposure to workers of any chemical listed therein (NIOSH, 1990).

Table 2. Uses of methylal

<u>Use Areas</u>
<u>Chemical Intermediate</u>
<ul style="list-style-type: none">• starting material in industrial organic syntheses, including formaldehyde synthesis (for manufacture of polyacetal resins) and as formaldehyde replacement in methyl methacrylate synthesis (Nemec & Kirch, 1981; Masamoto <i>et al.</i>, 1992)• reagent/polymer modifier to promote crosslinking, end-capping and storage stability (Tanaka <i>et al.</i>, 1989)• reagent in numerous types of organic reactions, including Grignard and Reppe reactions (Budavari, 1989)
<u>Solvent</u>
<ul style="list-style-type: none">• solvent/entrainer in azeotropic distillations, supercritical extractions, and waste gas scrubbing (Schmidt & Ulrich, 1990)• component of electrolyte solutions for rechargeable lithium batteries (Abraham <i>et al.</i>, 1989)• cosolvent in many industrial binary solvent systems for cleaning, degreasing, and/or drying of metal, glass and plastic; e.g., in the electronics industry for cleaning/degreasing printed circuit boards (Kikuchi & Niiyama, 1990; Michaud & Desbiendras, 1994)• solvent component in many industrial and consumer product aerosol formulations, e.g., perfumes, cosmetics (hair sprays, antiperspirants, sunscreens, etc.), medicinals (skin coolant for pain relief), air fresheners, clothing and household fabric dry cleaning sprays, adhesives and coatings (Sittig, 1985; Anon., 1993; Berkhout, 1993; De Jager, 1993; Watling <i>et al.</i>, 1993; Russell, 1995)
<u>Fuel or Fuel Additive</u>
<ul style="list-style-type: none">• special purpose fuel (ACGIH, 1992)• fuel additive in gasohols (Kazama, 1989)• natural gas additive for anti-hydrate treatment (Minkkinen & Larue, 1993)

Environmental Occurrence: Methylal is not known to occur naturally. However, methylal has been identified as an air pollutant and water pollutant from waste water treatment (Verschueren, 1983).

Sexton *et al.* (1985) reported methylal as a common domestic indoor air pollutant. Wadden and coworkers (1994) also identified methylal as a volatile organic compound (VOC) emitted into the atmosphere.

Pollution of natural waters in Russia by methylal was attributed to its chemical use in the pharmaceutical industry (Korolev *et al.*, 1993). Gholson *et al.* (1991) measured

emissions of VOCs, including methylal, from quiescent liquid surfaces in hazardous waste treatment facilities.

Regulatory Status: The ACGIH-recommended threshold limit value-time weighted average (TLV-TWA) for methylal is 1000 ppm (3110 mg/m³) based on acute and subchronic animal data and clinical experience with methylal. No short term exposure limit (STEL) has been recommended to date (ACGIH, 1992, 1995). The Occupational Safety and Health Administration (OSHA) has established a permissible exposure limit-time weighted average (PEL-TWA) of 1000 ppm for methylal; and the National Institute for Occupational Safety and Health (NIOSH) has established a recommended exposure limit (REL) of 1,000 ppm (NIOSH, 1992).

The Environmental Protection Agency (EPA), in response to a request from the U.S. Consumer Product Safety Commission (CPSC), issued an 8(d) final rule in the Federal Register 52 #84:16022 (01 May 1987) requiring submission of unpublished health and safety studies by past, current, and prospective manufacturers, importers, and processors (STN International, 1994).

The following action has been taken by the TSCA Interagency Testing Committee (ITC) on methylal: scored for biological effects in 1977 with a notation of slight to moderate mutagenic and carcinogenic potential (Walker, 1995b).

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports investigating the association of exposure to methylal and cancer risk in humans were identified in the available literature. The physiological properties of the simple unsubstituted acetals are characterized by an ether-like anesthetic action and by a relatively low degree of primary irritation compared to the parent aldehyde (Brabec, 1993).

Animal Data: No 2-year carcinogenicity studies of methylal were identified in the available literature. Toxicity information identified was limited to acute and subacute studies. Acute toxicity values are shown in Table 3.

Table 3. Acute toxicity data for methylal

Route	Species	Toxicity value	Reference
Oral	Rat (male & female)	LD ₅₀ = 7.46 ml/kg	Bushy Run Research Center, 1982

Oral	Rabbit	LD ₅₀ = 5.7 g/kg	Brabec, 1993
Dermal	Rabbit	LD ₅₀ = >5000 mg/kg	Springborn Lab., Inc., 1989a
Subcutaneous	Guinea pig	LD ₅₀ = >5 g/kg	Brabec, 1993
Inhalation	Mouse	LC ₅₀ = 18,354 ppm (7 hr)	Weaver <i>et al.</i> , 1951

Mice and guinea pigs exposed to high levels of methylal by inhalation often developed severe fatty changes in the liver, kidney, and heart as well as inflammatory changes in the lungs. Low concentrations generally produced no significant pathological changes (Weaver *et al.*, 1951). Male and female rats exposed to 1000 ppm methylal for 7 hr/day 5 days/week for 22 days developed chronic pneumonia which was interpreted as spontaneous in origin. There were no abnormal pathological conditions observed in other organs (Dow Chemical Co., 1969).

Methylal was classified as a slight irritant when a dose of 0.5 ml was held in contact with rabbit skin for 4 hours. Exposure produced slight erythema which resolved in 72 hours post exposure (Springborn Lab., Inc., 1989b).

Applied to rabbit eyes at 0.1 ml per eye, methylal produced minor corneal injury, minor iritis, and moderate irritation of the conjunctivae (Bushy Run Research Center, 1982).

Short-Term Tests: Methylal was mutagenic when tested without activation at 667-10,000 ug/plate in the *Salmonella typhimurium* preincubation assay; methylal induced a 3.9 and 2.1 fold increase in revertants in strains TA98 and TA100, respectively. Results for strains TA1535, TA1537, and TA1538 were negative with or without activation (Microbiological Associates, 1989).

Negative results were obtained in the Chinese hamster ovary (CHO) assay for forward mutations at the HGPRT locus. Methylal was tested at concentrations of 0.5 to 5 mg/ml both with and without activation. Slight toxicity was seen above 1 mg/ml (Hazelton Laboratories America, 1990a).

Methylal did not induce a significant increase in micronuclei *in vivo* in the mouse bone marrow micronucleus assay. Male and female ICR mice were administered

intraperitoneal methylal doses of 400, 1333 or 4000 mg/kg and cells were harvested at 24, 48 or 72 hours after dosing (Hazelton Laboratories America, 1990b).

Metabolism: Methylal was metabolized by rats to methanol and dimethyl ether in equimolar ratio regardless of the route of administration. Inhalation experiments showed that the blood methanol concentration was proportional to the concentration of methylal in the air (Tomilina *et al.*, 1984).

In order to identify inhaled compounds which might be metabolized to formaldehyde in the nasal cavity, 32 potential substrates for cytochrome P-450-dependent monooxygenases were screened with rat nasal and, for comparison, liver microsomes. Methylal was metabolized to formaldehyde at a rate of 270 pmol/mg microsomal protein/minute following incubation of nasal microsomes with 2mM methylal for 30 minutes. Incubation with liver microsomes produced formaldehyde at a lower but detectable rate in the range of 70-200 pmol/mg microsomal protein/minute, reported by the authors as "trace". Methylal can release formaldehyde by hydrolysis or by oxidation of the terminal methyl groups. The authors noted that released formaldehyde may influence the irritancy of inhaled compounds, and this has been suggested to play a role in the tumorigenicity of some compounds (Dahl & Hadley, 1983). In their study of methylal toxicity, Weaver and coworkers (1951) found no indication of the presence of formaldehyde or formic acid in the urine or vitreous humor of test animals. In view of the stability of methylal in neutral or alkaline media, they suggested the possibility that it is not hydrolyzed at the pH of body tissue fluids.

Structure/Activity Relationships: Six compounds, structurally similar to methylal, were screened for relevant information associating these related chemicals with a mutagenic or carcinogenic effect. No information was found on carcinogenicity or mutagenicity for 2,2-dimethoxypropane [77-76-9] or methoxymethane [115-10-6]. Information on carcinogenicity was identified for only one of the compounds, methanol. Mutagenicity data were available for four of the structurally related compounds: diethoxymethane, 1,1-dimethoxyethane, 1,3-dioxane, and methanol.

Carcinogenicity

Lington and Bevan (1994) have reviewed summary reports of chronic methanol inhalation studies conducted by the Japan New Energy Development Organization. Groups of eight monkeys were exposed to 0, 10, 100, or 1000 ppm methanol for 22

hr/day for up to 2.5 years. Slight changes in the liver and kidney and some pathological changes in the nervous system were observed in the 1000 ppm group. The changes were considered transient in nature and probably reversible. Rats and mice were also exposed to 0, 10, 100, or 1000 ppm methanol for 20 hr/day for 18 months (mice) or 24 months (rats). There was no evidence of carcinogenicity at 1000 ppm. Lung papillary adenomas and adrenal pheochromocytomas were observed and reported as "biologically insignificant".

In another study reported by Lington and Bevan (1994), there were no gross or histopathological findings of note in dogs exposed to 450-500 ppm methanol 8 hr/day for 379 consecutive days.

Mutagenicity/Genotoxicity

A summary of the mutagenicity/genotoxicity data on methylal and four structurally related compounds is shown in Table 4. All of the structurally related compounds were tested in the *Salmonella typhimurium* assay; positive results were reported for two of these compounds. Two compounds were tested in the mouse lymphoma assay and were found positive. Two of the 3 compounds tested for induction of sister chromatid exchanges were positive. At least one of the 4 compounds was shown to induce DNA damage or micronuclei.

Table 4. Summary of information on methylal and structurally related compounds

Chemical [CAS No.]	Genotoxicity data	Reference
Methylal [109-87-5]	<p style="text-align: center;">Mutation</p> <p>positive in <i>S. typhimurium</i> strains TA98, TA100 without activation; negative in strains TA1535, TA1537, TA1538 with and without activation</p> <p>negative for forward mutations at HGPRT locus in CHO cells</p> <p style="text-align: center;">Micronuclei</p> <p>negative in a mouse in vivo micronucleus assay</p>	<p>Microbiological Associates, 1989</p> <p>Hazelton Labs America, 1990a</p> <p>Hazelton Labs America, 1990b</p>
Diethoxymethane	Mutation	

[462-95-3]	<p>negative in <i>S. typhimurium</i> strains TA98, TA100, TA1535, TA1537, TA1538 with and without activation</p> <p>positive in a mouse lymphoma L5178Y(TK+/-) assay with activation; negative without activation</p>	<p>NCI, 1995a</p> <p>NCI, 1995b</p>
1,1-Dimethoxyethane [110-71-4]	<p style="text-align: center;">Mutation</p> <p>positive in an NTP <i>S. typhimurium</i> assay</p> <p>negative in an in vitro CHO gene mutation assay</p> <p style="text-align: center;">Sister Chromatid Exchanges</p> <p>positive for induction of SCEs in CHO cells in vitro both with and without activation</p> <p style="text-align: center;">DNA Damage</p> <p>negative in an in vitro unscheduled DNA synthesis assay</p>	<p>NTP, 1995</p> <p>Gingell et al., 1994</p> <p>Gingell et al., 1994</p> <p>Gingell et al., 1994</p>
1,3-Dioxane [505-22-6]	<p style="text-align: center;">Mutation</p> <p>weakly positive in an NTP <i>S. typhimurium</i> assay; mixed results in strains TA98, TA1537 from weakly positive to negative; negative in strains TA100, TA1535</p> <p>negative in a <i>Drosophila melanogaster</i> sex-linked recessive lethal test</p> <p style="text-align: center;">Sister Chromatid Exchanges</p> <p>positive for the induction of SCEs in CHO cells in vitro with and without activation</p> <p style="text-align: center;">Chromosomal Aberrations</p> <p>positive for the induction of CAs in CHO cells in vitro with activation; negative without activation</p> <p style="text-align: center;">Micronuclei</p> <p>negative in an NTP in vivo micronucleus assay</p> <p style="text-align: center;">DNA Damage</p> <p>positive for the induction of umu gene expression in <i>S. typhimurium</i> strain TA1535/psk1002 without activation</p>	<p>NTP, 1995; Haworth et al., 1983</p> <p>NTP, 1995; Zimmering et al., 1985</p> <p>NTP, 1995; Galloway et al., 1987</p> <p>NTP, 1995; Galloway et al., 1987</p> <p>NTP, 1995</p> <p>Nakamura et al., 1987</p>
Methanol [67-56-1]	<p style="text-align: center;">Mutation</p> <p>negative in <i>S. typhimurium</i> strains TA1535, TA100, TA1538, TA98, TA1537 with and without activation</p> <p>negative in <i>Escherichia coli</i> strain WP2uvra with and without activation</p> <p>positive in a mouse lymphoma L5178Y assay with activation</p> <p style="text-align: center;">Sister Chromatid Exchanges</p> <p>negative for induction of SCEs in CHO cells in vitro without activation</p> <p style="text-align: center;">Chromosomal Aberrations</p>	<p>DeFlora et al., 1984; Shimizu et al., 1985</p> <p>Shimizu et al., 1985</p> <p>McGregor et al., 1985</p> <p>Latt et al., 1981</p>

	positive for the induction of CAs in a mouse in vivo assay	Pereira et al., 1982
	Micronuclei	
	positive in a mouse in vivo micronucleus assay	Pereira et al., 1982
	negative in a mouse in vivo micronucleus assay in either folate- deficient or folate-sufficient mice	O'Loughlin et al., 1992
	negative in an in vitro Syrian hamster embryo (SHE) cell micronucleus assay	Fritzenschaf et al., 1993
	DNA Damage	
	negative for DNA-repair in E. coli strains WP2, WP67, CM871	De Flora et al, 1984

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