SUMMARY OF DATA FOR CHEMICAL SELECTION

_N,N_-Dimethyl-_p_-toluidine
99-97-8

BASIS OF NOMINATION TO THE CSWG

_N,N_-Dimethyl-_p_-toluidine (DMPT) is presented to the CSWG for review because it is a high-production-volume chemical that has the potential for widespread human exposure from its use in dental materials and bone cements.

Exposure to DMPT is of concern because it belongs to a class of chemicals suspected of having carcinogenic activity. Like other members of this class which have produced cancer in experimental animals, DMPT is mutagenic and genotoxic in several test systems. Like its parent compound, _p_-toluidine, DMPT produces methemoglobinemia and is a dermal irritant and sensitizer. _p_-Toluidine is listed as a confirmed animal carcinogen with unknown relevance to humans by the American Conference of Governmental Hygienists.

DMPT is the accelerator in the redox initiator-accelerator system used commercially to cure methyl methacrylate monomers. Polymerization is rarely complete; DMPT retained in bone cements and dental materials is sufficient to cause exposure to surgical staff, dental prosthetic device manufacturers, and denture wearers, among others. DMPT is thought to be the causative agent in "burning mouth" observed in denture wearers and it may be responsible for aseptic loosening of hip replacements.

INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

Dr. John Walker, Executive Director of the TSCA Interagency Testing Committee, US Environmental Protection Agency, provided information on annual production of DMPT for 1994.

SELECTION STATUS

ACTION BY CSWG: 12/16/99

Studies requested:

Subchronic study (90-day)

Refer to the Interagency Testing Committee for collection of data on use

Priority: High (see remarks)

Rationale/Remarks:

High production volume chemical (annual production >1 million lbs.) sponsored for testing by industry under EPA's HPV Challenge Program since the December CSWG meeting

NTP to coordinate efforts with EPA HPV Challenge Program to avoid any duplication of work

Accelerator used commercially to cure methyl methacrylate monomers

Significant human exposure by inhalation and dermal contact from use in dental materials and bone cements

Genotoxic in several test systems; information on chronic toxicity & carcinogenicity extremely limited

CHEMICAL IDENTIFICATION

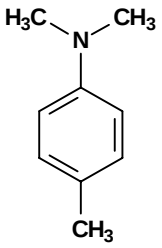
CAS Registry Number: 99-97-8

Chemical Abstracts Service Name: Benzenamine, *N*,*N*,4-trimethyl- (9CI); *p*-toluidine, *N*,*N*-dimethyl- (8CI)

Synonyms and Trade Names: *p*-(Dimethylamino)toluene; *N*,*N*-dimethyl-4-methyl-aniline; *p*,*N*,*N*-trimethylaniline; *N*,*N*,4-trimethyl-aniline

Structural Class: Tertiary arylamine

Structure, Molecular Formula and Molecular Weight:



$C_9H_{13}N$ Mol. wt.: 135.21

Chemical and Physical Properties:

Description: Colorless to brown oil, sweet odor (Mallinckrodt Baker, 1996; Verschueren, 1996)

Boiling Point: 211°C (Verschueren, 1996)

Density: 0.93 (Verschueren, 1996)

Solubility: Insoluble in water; miscible in ether and ethanol; soluble in carbon tetrachloride (Lide, 1996)

Log *P*: 2.99 (Verschueren, 1996)

Flash Point: 83°C (closed cup) (Mallinckrodt Baker, 1996)

Reactivity: Stable under ordinary conditions of use and storage; incompatible with strong oxidizing agents (Mallinckrodt Baker, 1996)

Technical Products and Impurities: *N*,*N*-Dimethyl-*p*-toluidine (DMPT) is available in research quantities at a purity of 99% from Aldrich Chemical Co. (Aldrich Chemical Co., Inc. 1999).

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EXPOSURE INFORMATION

Production and Producers: *N*-Alkyltoluidines can be prepared from unalkylated toluidines with common alkylating agents such as alkyl halides, sulfates, and carbonates. However large-scale manufacture of *N*-alkyltoluidines usually involves one of two methods; acid-catalyzed alkylation with lower unbranched alcohols or ethers, or reductive alkylation with lower aldehydes or ketones over active metal catalysts and under hydrogen pressure. Toluidines can also be alkylated with reactive three-membered-ring compounds such as ethylene oxide and aziridine (Bowers, 1996).

According to recent chemical catalogs and directories, DMPT is manufactured and/or distributed by Aceto Corp., Alfa Aesar, Fallek Chemical Co., First Chemical Corp., Kessler Chemical, Inc., Mafatial Industries, Ltd., Monomer-Polymer & Dajac Labs, Inc., and R.S.A Corp. (Tilton, 1998; Hunter, 1999).

DMPT is listed as a chemical of commerce in the US International Trade Commission (USITC) publication *Synthetic Organic Chemicals, US Production and Sales, 1984-1993* (USITC, 1985-1994a,b). The reporting companies were First Chemical Corp., Hexcel Corp., and R.S.A Corp.; 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 ≥ 4500 kg [10,000 lbs.] or sales ≥ $10,000. This source is no longer published.

DMPT is listed in the EPA's Toxic Substance Control Act Inventory (NLM, 1999a). US production of DMPT in 1994 was reported to be in the range of >1 million to <1 billion pounds based on non-confidential data received by the EPA. DMPT is on the EPA's high production volume (HPV) Challenge Program Chemical List (Walker, 1999).

Increased DMPT production volume and the potential for increased exposure were cited

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by ChemFirst, Inc. (1997) as reasons for submitting an acute inhalation toxicology study of DMPT to the EPA in accordance with TSCA Section 8(e).

Use Pattern: DMPT is used as a polymerization accelerator for the manufacture of bone cements and dental materials. It is found in industrial glues and artificial fingernail preparations and it is also used as an intermediate in dye and pesticide synthesis (Potter *et al.*, 1988; Taningher *et al*., 1993; Haddad *et al*. 1996).

The curing of bone cement involves the induction of polymerization at room temperature of a mixture of methylmethacrylate monomer and polymethylmethacrylate powder using benzoyl peroxide as an initiator, hydroquinone as a stabilizer and DMPT as an accelerator. DMPT is present in all the commonly used bone cements at concentrations ranging from 0.7 to 2.6% (Linder, 1976; Haddad *et al*., 1996; Stea *et al*., 1997).

Acrylic resins which are widely used for prosthetics in dentistry, are also produced by polymerization of a mixture of methyl methacrylate monomer and polymethylmethacrylate powder with benzoyl peroxide and an accelerator. DMPT is the most commonly used accelerator for dental materials (Tosti *et al*., 1990; Tesk *et al*., 1993).

The current use of DMPT in both bone cements and dental materials was confirmed by a representative of Esstech, a manufacturer of bulk polymers for dental materials (Johnston, 1999).

Human Exposure: There is potential for widespread human exposure to DMPT in occupational settings related to its use in bone cements, dental prostheses, industrial glues, and artificial fingernails. Surgeons, surgical staffs, dentists, dental technicians, nail salon operators, and users of industrial glues may receive significant exposure to DMPT. Exposure to DMPT is also of concern to prosthesis users because of a possible release of unreacted chemicals from polymeric composites (Kronoveter *et al*., 1977; Taningher *et al*., 1993; Haddad *et al*.,

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1996). In addition to the potential for inhalation exposures, DMPT can be absorbed through the intact skin (ChemFirst, 1997).

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 62,720 workers, including 27,118 female workers, were potentially exposed to DMPT 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 (NLM, 1999a).

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

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

Under the Food and Drug Administration (FDA) guidelines and regulations, bone cements are classified as drugs (Brauer *et al*., 1986).

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EVIDENCE OF POSSIBLE CARCINOGENIC ACTIVITY

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

Methemoglobinemia due to ingestion of DMPT has been reported. A 16-month-old girl and a 5 month-old boy developed methemoglobinemia following ingestion of 15 mL and 30 mL, respectively of artificial fingernail solutions containing DMPT (DMPT doses of 6 mg/kg bw and unknown, respectively); both children recovered. *In vitro* studies suggested that the activity of DMPT was probably due to its biochemical transformation to *p*-methylphenylhdroxylamine (Potter *et al*., 1988; Kao *et al*., 1997).

Allergic responses to DMPT may contribute to early aseptic loosening of total hip replacements as well as to contact stomatitis and "denture sore mouth" or "burning mouth" syndrome (Haddad *et al*., 1995).

Haddad and coworkers (1996) studied 70 patients, 15 with aseptic loosening less than two years after total hip replacement, 25 with satisfactory long-term cemented fixation, 5 with infected loosening, and 25 awaiting hip arthroplasty. Skin patch tests showed 7 positive reactions to DMPT, all of them in patients with early aseptic loosening.

A 60-year old patient who had experienced rapid onset loosening after total hip replacement was found to be hypersensitive to DMPT. Although he had given no history of contact dermatitis, the patient was a joiner who handled many glues in the course of his work. The investigators speculated that he may unknowingly have been sensitized to DMPT (Haddad *et al*., 1995).

The role of contact hypersensitivity was investigated in 22 patients with "burning mouth" syndrome. Twenty of these patients wore a complete or partial denture. Positive patch test reactions to DMPT were seen in three cases; all were denture wearers (Dutrée-

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Meulenberg *et al*., 1992). Fifty-three denture wearers with symptoms of "burning mouth" syndrome were studied by Kaaber and coworkers (1979); a positive skin reaction to DMPT was seen in one patient. Verschueren and Bruynzeel (1991) and Tosti and coworkers (1990) also cite DMPT allergy in relation to "burning mouth" syndrome seen in a patient.

In the production of bone cements and dental prostheses, polymerization is rarely complete and small amounts of DMPT present in the final compounds may be responsible for sensitization. DMPT has been identified in bone cements after storage in air or after long-term implantation in patients (Brauer *et al*., 1986; Tosti *et al*., 1990). Bösch and coworkers (1982) detected an average of 0.41% w/w DMPT in bone cements which had been implanted in patients for up to 10.25 years.

Animal Data: *Acute Studies*. LD_{50} values of DMPT in the rat are: oral, 1650 mg/kg (methemoglobinemia noted); dermal, >2000 mg/kg; and 4-hour inhalation (LC_{50}), 1.4 mg/L. The intraperitoneal LD_{50} in the mouse is 212 mg/kg and both the 24-hour and 96-hour LC_{50} values in fish are 52 mg/L (Verschueren, 1996; ChemFirst, Inc., 1997; NLM, 1999a).

The acute 4-hour inhalation toxicity of DMPT was assessed in male and female Sprague-Dawley rats following doses of 5.27, 1.73, 0.99, and 0.30 mg/L. Clinical signs in rats exposed to 1.73 mg/L included hypoactivity, a comatose/prostrate condition, dyspnea or rapid respiration and salivation. Nasal discharge and red material around the nose were the most frequently observed signs in the 0.99 and 0.30 mg/L dose groups. Mottled lungs, red ovaries, and gas-filled gastrointestinal organs were the most frequent gross lesions in rats exposed to 5.27 or 1.73 mg/L. No gross lesions were observed in rats exposed to lower concentrations (ChemFirst, Inc., 1997).

DMPT is moderately irritating and both positive and negative results have been found in

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guinea pig sensitization studies (ChemFirst, Inc., 1997).

Chronic Studies. DMPT did not induce tumors in a 1954 life-time study in male and female rats. BDI, BDII, and white rats (28 animals per strain) were given 7 mg/day of DMPT in the diet for a total dose of 5 g (Druckrey *et al*., 1954).

Short-Term Test: The genotoxicity of DMPT has been assessed in several assays. DMPT was mutagenic in mouse lymphoma cells and in one of five strains of *Salmonella typhimurium*. It was also positive for DNA damage in rodent liver cells and for the induction of chromosomal aberrations and micronuclei in Chinese hamster V-79 cells. Details of these tests are shown in Table 1.

Metabolism: Potter and coworkers (1988) suggested that the methemoglobinemia produced by DMPT ingestion was probably due to the metabolite *p*-methylphenylhydroxylamine. No further information on the metabolism of DMPT was identified in the literature.

The *para*, *meta*, and *ortho*-toluidines are all metabolized by rats to the corresponding phenols and undergo conjugation to acid-hydrolyzable polar metabolites. After oral administration of 500 mg/kg bw of *p*-toluidine in corn oil to male rats, only 2.5 percent of the dose was excreted unchanged; the major urinary metabolite was 2-amino-5-methylphenol (ACGIH, 1992).

Structure/Activity Relationships: A number of toluidines have been tested under NTP and NCI programs. Twelve of these compounds structurally similar to DMPT were screened for relevant information on carcinogenicity and genotoxicity. Of the seven toluidines tested for carcinogenicity, six were positive in at least one species. Ten of the twelve compounds were positive in at least one genotoxicity assay. Information on the carcinogenicity and genotoxicity of the selected toluidines is summarized in Table 2.

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Table 1. Genotoxicity of DMPT

Test system/cell line	Dose, route	Endpoint/results	Reference
		Mutation	
S. typhimurium			
TA 1535	10-100 μg/plate with S-9	+	NLM (1999b)
	33-3333 μg/plate without S-9	+	
TA97, TA98, TA100	1-100 μg/plate with or without S-9	-	Taningher *et al*. (1993)
TA97, TA98, TA100, TA104	50-5000 μg/plate with or without S-9	-	Miller *et al*. (1986)
Mouse Lymphoma			
L5178Y(TK^+/TK^-)	0.018-0.044 μl/ml with S-9	+	NLM (1999b)
	0.05-0.24 μl/ml without S-9	+	
		Chromosomal Aberrations	
Chinese Hamster			
V-79 cells	0.3-1.2 mM	+	Taningher *et al*. (1993)
		Micronuclei	
V-79 cells	0.3-1.2 mM	+	Taningher *et al*. (1993)
		DNA Damage	
Alkaline DNA Elution			
Mouse liver cells	1; 2 mmol/kg ip	+	Taningher *et al*. (1993)
Rat liver cells	8 mmol/kg oral	+	Taningher *et al*. (1993)
Rat liver cells	4; 8 mmol/kg ip	+	

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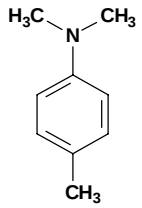
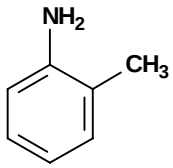
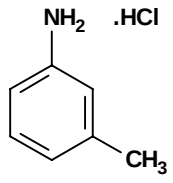
Table 2. Summary of information on DMPT and structurally related compounds

Chemical [CAS No.]	Carcinogenicity data	Genotoxicity data
DMPT [99-97-8] 	Not carcinogenic in male and female BDI, BDII, or white rats; lifetime feed study (Druckrey *et al.*, 1954)	(+) *S. typhimurium* TA1535 (NLM, 1999b); (-) *S. typhimurium* TA97, TA98, TA100, TA104 (Miller *et al.*, 1986; Taningher *et al.*, 1993); (+) Mouse lymphoma (NLM, 199b); (+) CA in V-97 cells (Taningher *et al.*, 1993); (+) SCE in V-97 cells (Taningher *et al.*, 1993); (+) DNA damage in mouse and rat liver cells (Taningher *et al.*, 1993)
o-Toluidine [95-53-4] *o*-Toluidine HCl [636-21-5] 	<u>Hydrochloride salt</u> Positive in male and female F344 rats; positive in male and female B6C3F1 mice, 2-year feed study (NCI, 1979a)	(+) *S. typhimurium*; (+) Mouse lymphoma; (+) CA *in vitro;* (+) SCE *in vitro;* (+) Micronucleus, male; (-) Micronucleus female (NTP, 1999) <u>Hydrochloride salt</u> (+) *S. typhimurium*; (-) *S. typhimurium;* (-) Sex-linked recessive lethal; (-) Reciprocal translocation; (?) CA *in vitro*; (+) SCE *in vitro*; (+) SCE *in vivo* (NTP, 1999)
m-Toluidine HCl [638-03-9] 	NDF	(-) *S. typhimurium* (NTP, 1999)

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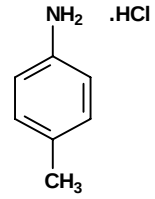
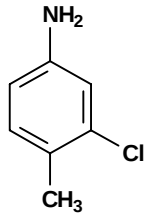
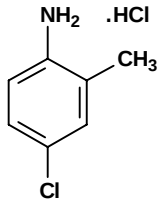
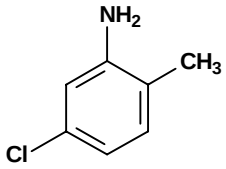
Chemical [CAS No.]	Carcinogenicity data	Genotoxicity data
p-Toluidine HCl [540-23-8] 	Not carcinogenic in male CD rats, 18-mo feed study; positive in male and female CD-1 mice, 21-mo feed study (Weisburger *et al.*, 1978); confirmed animal carcinogen with unknown relevance to humans (ACGIH, 1999)	(w+) *S. typhimurium* (NTP, 1999)
3-Chloro-*p*-toluidine [95-74-9] 	Not carcinogenic in male and female F344 rats and B6C3F1 mice; 2-year feed study (NCI, 1978a)	(-) *S. typhimurium*; (w+) *S. typhimurium*; (?) Mouse lymphoma; (?) CA *in vitro*; (+) SCE *in vitro* (NTP, 1999)
4-Chloro-*o*-toluidine HCl [3165-93-3] 	Not carcinogenic in male and female F344 rats, 2-year feed study; positive in male and female B6C3F1 mice, 2-year feed study (NCI, 1979b)	(?) *S. typhimurium*; (-) *S. typhimurium*; (+) Mouse lymphoma; (w+) CA *in vitro*; (+) SCE *in vitro* (NTP, 1999)
5-Chloro-*o*-toluidine [95-79-4] 	No conclusive evidence of carcinogenicity in male and female F344 rats, 2-year feed study; positive in male and female B6C3F1 mice, 2-year feed study (NCI, 1979c)	(-) *S. typhimurium*; (-) Mouse lymphoma; (-) CA *in vitro*; (-) SCE *in vitro* (NTP, 1999)

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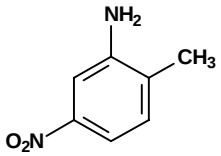
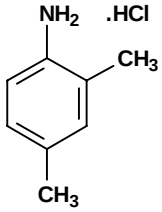
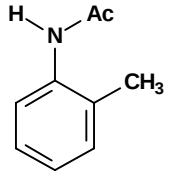
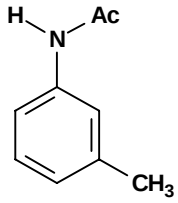
Chemical [CAS No.]	Carcinogenicity data	Genotoxicity data
5-Nitro-*o*-toluidine [99-55-8] 	Not carcinogenic in male and female F344 rats; 2-year feed study; positive in male and female B6C3F1 mice, 2-year feed study (NCI, 1978b)	(+) *S. typhimurium*; (+) CA *in vitro*; (+) SCE *in vitro* (NTP, 1999)
2-Methyl-*p*-toluidine HCl [21436-96-4] 	Not carcinogenic in male CD rats, 18-mo feed study; not carcinogenic in male CD-1 mice, positive in female CD-1 mice, 21-mo feed study (Weisburger *et al*., 1978)	(+) *S. typhimurium* (NLM, 1999a)
N-Acetyl-*o*-toluidine [120-66-1] 	NDF	(w+) *S. typhimurium* (NTP, 1999)
N-Acetyl-*m*-toluidine [537-92-8] 	NDF	(-) *S. typhimurium* (NTP, 1999)

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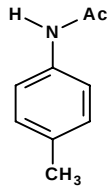
Chemical [CAS No.]	Carcinogenicity data	Genotoxicity data
N-Acetyl-*p*-toluidine [103-89-9] 	NDF	(w+) *S. typhimurium* (NTP, 1999)

(+) = positive; (-) = negative; (w+) = weakly positive; (?) = inconclusive; CA = chromosomal aberrations; SCE = sister chromatid exchanges; NDF = no data found

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