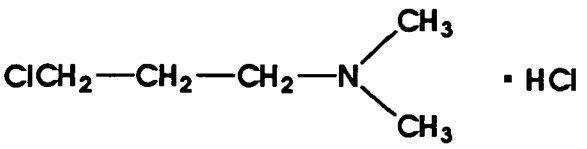
DIMETHYLAMINOPROPYL CHLORIDE, HYDROCHLORIDE
CAS NO. 5407-04-5

Structure, Molecular Formula and Molecular Weight:



$C_5H_{12}ClN \cdot HCl$ Mol. wt.: 158.1

BASIS OF NOMINATION TO THE CSWG

The nomination of DMPC to the CSWG is based on potential for human exposure and suspicion of carcinogenicity.

DMPC is one of 41 industrial chemicals of diverse structures and applications tested for genotoxicity activity in several *in vitro* test systems by researchers at a Shell Research Laboratory. DMPC is a representative and commercially important member of the class of nitrogen mustard-type compounds. DMPC is listed in the recent USITC *Synthetic Organic Chemicals* publications (1990-1993) but no specific information on annual production volumes was provided. Supporting information on the production, supply, and use of DMPC is found in other chemical industry directories. DMPC is an alkylating agent and is used mainly as an industrial and research organic chemical reagent

DMPC was mutagenic in *Salmonella* strains TA1535 and 1537 both with and without metabolic activation and in TA100 with activation.

Alkylating abilities of varying strengths have been described for a number of nitrogen mustard-type compounds. Because of the genetic toxicity and DNA-damaging effects associated with this group of chemicals, there is reason to suspect they may be carcinogenic; and, in fact, two analogs of DMPC have been reported to be tumorigenic.

Prepared for NCI by Technical Resources International, Inc. under Contract No. NO1-CP-56019 (5/94; rev. 6/95)

SELECTION STATUS

ACTION BY CSWG: 12/16/94

Studies Requested: Genetox assays

Priority: Low-to-moderate.

Rationale/Remarks:

- Potential for human exposure
- Widely used chemical
- Member of the nitrogen mustard-type chemical class, which is associated with genetic toxicity and DNA damaging effects
- Need to resolve question of the mutagenicity of DMPC
- It might be interesting to compare test results of propyl mustards versus ethyl mustards
- It was suggested that the alkylating activity of DMPC be studied using 4-nitrobenzene pyridine.

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SUMMARY OF DATA FOR CHEMICAL SELECTION

CHEMICAL IDENTIFICATION

CAS Registry No.: 5407-04-5

Chemical Abstracts Name: 1-Propanamine, 3-chloro-N,N-dimethyl, hydrochloride (9CI)

Synonyms: 1-Propylamine, 3-chloro-N,N-dimethyl-, hydrochloride; (3-chloropropyl)dimethylamine, hydrochloride; 3-dimethylamino-1-propyl chloride hydrochloride; 3-chloropropyldimethyl-ammonium chloride; N-(3-chloropropyl)-N,N-dimethylammonium chloride; 3-dimethylaminopropyl chloride hydrochloride; DMPC

Free base

CAS Registry No.: 109-54-6

Chemical Abstracts Name: 1-Propanamine, 3-chloro-N,N-dimethyl (9CI)

Chemical and Physical Properties:

Description: Hygroscopic, white to off-white crystalline solid (Anon., 1992a; Anon., 1994b).

Melting Point: 141-144°C (Anon., 1992a)

Solubility: Soluble in water (400 mg in 4 ml H_2O giving a colorless to faintly yellowish clear solution) (Anon., 1994b).

Technical Products and Impurities: DMPC is available at purities ranging from 96 to 99%: Aldrich Chemical Co., 96%; Sigma Chemical Co., ≥98%; and Janssen Chimica, 99% (Anon., 1992b; Anon., 1994a; Anon., 1994b).

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EXPOSURE INFORMATION

Commercial Availability

Production and Producers: Chloroalkylamine hydrochlorides, including DMPC, can be prepared by chlorination of the corresponding aminoalkyl ether hydrochloride with HCl with the removal of H_2O, according to a patent assigned to Daicel Chemical Industries in 1983 (STN, 1994). Calgon Corp. reported purifying this chemical in both batch and continuous processes by treating aqueous solutions with activated carbon (Woodrum & Barnett, 1975).

Although no specific production volumes were found in the literature searched, DMPC has been listed by the U.S. International Trade Commission publications, *Synthetic Organic Chemicals, United States Production and Sales,* which is an indication of its commercial significance (USITC, 1990-1993). The USITC reporting guidelines specify that each company's report of a chemical represents manufacture of a quantity ≥4,500 kg [~10,000 lbs] or sales of $10,000. In addition, Dean *et al.* (1985) of Shell Research, Ltd., included DMPC in genetic toxicity testing as one of "41 representative industrial chemicals of diverse structure and application;" and Thompson *et al.* (1981) of Lilly Research Laboratories described the generic class of dialkylaminoalkyl chlorides, including DMPC, as important monofunctional alkylating agents used as chemical manufacturing intermediates. This group of related chemicals are usually employed as hydrochloride salts.

The 31 companies listed in Table 1 were identified in a search of recent chemical industry directories and databases for producers and suppliers of DMPC. In addition, companies with recently patented processes using DMPC as a reagent in pharmaceutical synthesis include: American Home Products Corp.; Hoechst-Roussel Pharmaceuticals, Inc. USA; Procter and Gamble Co.; A.H. Robins Co., Inc.; Upjohn Corp.; and Zeneca Ltd. (STN, 1994). And some research institutions recently reporting use of DMPC in patented processes include: Department of Chemistry, Columbia University; Department of Pharmacology, Mayo Medical School; and the Cancer Center of the University of Kansas.

DMPC is listed on the EPA TSCA Inventory. Aceto Chemical Co, Inc. and Rhone-Poulenc, Inc. were listed in EPA's TSCA Plant and Productions (TSCAPP) database as importers of this substance (CIS, 1994).

Table 1. Producers/suppliers of DMPC identified in chemical publications and database sources (see search resource list)

Company Name	Bulk Production Noted	TSCAPP Listing	USITC 1990-93 Listing	Industry Directories 1993-94 Listing	DIALOG Fine Chemicals Database (FCDB) Listing
Aceto Corp., Pfaltz & Bauer Division		X		X	X
Aldrich Chemical Co.				X	X
American Biorganics, Inc.				X	
Austin Chemical Co., Inc.				X	
Chem Service, Inc.				X	X
Crescent Chemical Co. Inc.				X	X
Chicagai Boyeki (America) Corp.				X	
D&O Chemicals, Inc.				X	
Davos Chemical Corp.				X	
Eastern Chemical Co.				X	
Fairfield Chemical Co.				X	
Fluka chemical Corp.				X	
R.W. Greef & Co., Div. Howard Hall				X	
ICN Biomedicals Inc.				X	
Interchem Corp.				X	
Isochem				X	X
Janssen Chimica, Spectrum Mfg. Co.				X	
K&K Rare & Fine Chemicals				X	X
Lancaster Synthesis, Inc.				X	
Lonza, Inc.	X			X	
Maypro Industries, Inc.				X	
Narchem Corp.				X	
Polysciences, Inc.				X	
Richman Chemical, Inc.				X	
Schwertzerhall, Inc.				X	
Sigma Chemical Co.				X	X
SmithKline Beecham Chemicals	X		X	X	
St.-Jean Photo Chemicals, Inc.				X	
S.S.T. Corp.				X	
TCI America, Inc.	X			X	X
Velsicol Chemical Corp.		X		X	
Wilshire Chemical Co., Inc.				X	

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Use Pattern: DMPC is primarily used as an industrial and research organic chemical intermediate which acts as an aklylating reagent in Grignard and other types of reactions. For example, DMPC as the starting material is neutralized to the free base intermediate in the preparation of the corresponding Grignard reagent for use in many syntheses; and DMPC as starting material undergoes alkaline hydrolysis in the preparation of N,N-dimethyl-N-(3-hydroxypropyl)amine (Clennan *et al.*, 1989).

DMPC is widely used as a pharmaceutical intermediate, and nitrogen mustards were among the groups of compounds investigated in early efforts to find chemotherapeutic compounds (Williams & Weisburger, 1991). Some of the many types of drugs synthesized using DMPC as a reagent include analgesics, antiarrythmics, antibiotics, anticholesteremics, antidepressants (anxiolytics, tranquilizers), antiischemics, antineoplastics, etc. (STN, 1994). DMPC is also used as an agricultural chemical intermediate, a photographic chemical intermediate, and a biochemical reagent for enzyme and other studies. For example, Fuji Photo Film Co., Ltd., of Japan holds several patents for the preparation and use of DMPC as a nucleation-promoting agent in direct-positive color photographic emulsions (STN, 1994), and Syntex (USA) Inc. was issued a patent in 1986 for the use of DMPC as a starting material to prepare the free base for further reaction in an immunoassay method for determination of nortryptiline (Hu & Singh, 1986).

Human Exposure: Human occupational or other accidental exposure could occur by inhalation, ingestion, or skin absorption. According to Soper *et al.* (1979) DMPC and its analogs are stable compounds and, when used as pharmaceutical intermediates, may persist through drug syntheses and remain as trace contaminants in the final products.

Environmental Occurrence: DMPC has not been reported to occur naturally. No information was found in the available literature on the occurrence of DMPC in environmental media. However, the Ministry of Defence in Great Britain reported an accident involving free base DMPC as a reactant in a preparation of lithiodimethylaminopropane (Service, 1987). Kamienskis (1987) speculated that the cause of the resulting fire was an exothermic build up of unreacted DMPC in the reaction mixture at the low temperature used. No information was reported on possible contamination of the work environment.

Regulatory Status: No standards or guidelines have been set for occupational exposure to or workplace maximum allowable levels of DMPC. The American Conference of Governmental Industrial

Hygienists (ACGIH) has not adopted a Threshold Limit Value (TLV) or Biological Exposure Index (BEI) for this compound.

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports investigating the association of exposures to DMPC and a cancer risk in humans were identified in the available literature. DMPC is an irritant to skin, eyes and mucous membranes (Anon. 1992a). According to the SmithKline Beecham Material Safety Data Sheet (MSDS) no determination of carcinogen status has been made by the company or has been reported by the NTP, IARC or OSHA (Anon., 1992a). Thompson *et al.* (1981) postulated that, based on results in a battery of short-term tests, some dialkylaminoalkyl chlorides are likely to be carcinogenic but that the carcinogenic potential of the dialkylaminopropyl chlorides, including DMPC, is probably lower than that of the dialkylaminoethyl chloride analogs.

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

Short-Term Test: Thompson *et al.* (1981) reported the results of testing DMPC in a battery of short-term tests, including the concentration gradient bacterial mutagen assay, the Ames test, and the hepatocyte primary culture-DNA repair test. They reported the following results:

- positive in the gradient plate test for bacterial mutagenicity in *Salmonella typhimurium* strains TA100 and TA1535 at mutagenic concentration ranges of 10-1,000 and 200-1,000 µg/ml respectively but negative in strain G46 and negative, as well, in *Escherichia coli* strains, WP_2 and WP_2 *uvrA*$^-$.
- weakly mutagenic in *Salmonella* strains TA100 and TA1535 without metabolic activation.
- inactive for induction of unscheduled DNA synthesis (UDS) in a hepatocyte primary culture-DNA repair tests.

Dean *et al.* (1985). reported DMPC was positive for mutagenicity in an Ames/*Salmonella* assay in strains TA1535 and 1537 both with and without S9 and TA100 with S9. The same authors reported that this compound tested negative in *E. coli* WP_2 and WP_2 *uvrA* assays both with and without S9, negative in *Saccharomyces cerevisiae*, both with and without S9, and negative in a rat liver (RL) chromosome assay.

Metabolism: No information on the metabolism of DMPC was found in the available literature. According to Williams and Weisburger (1991) nitrogen mustards are biotransformed to reactive electrophilic aziridinium ions. However, while dialkylaminoethyl chlorides probably exist in equilibrium with cyclic

aziridinium ion intermediates at near neutral pH, dialkylaminopropyl chlorides do not, according to Thompson *et al.* (1981).

Other Biological Effects: DMPC, a monofunctional nitrogen mustard-type chemical, has been shown to be a DNA alkylating agent, but weaker than bifunctional nitrogen mustards and without DNA-interstrand crosslinking ability (Bodell, 1990). Wheeler *et al.* (1970) postulated that, while higher concentrations of monofunctional nitrogen mustard-type compounds are required for DNA cross-linking than related polyfunctional alkylating agents, exposure of cells to these compounds produces toxicity to cell mitosis, namely interference with the progression of cells from S to metaphase apart from the DNA effect.

According to Boudikova-Girard *et al.* (1993) DMPC is one of a group of aliphatic and aromatic amine compounds which act as competitive inhibitors of human kidney histamine N-methyltransferase (HNMT). DMPC, as the free base, inhibited the enzyme with a reported IC_{50} value of 0.32 mM, the IC_{50} being the concentration which caused 50% inhibition.

Deves and Krupka (1990) studied DMPC as one of a group of tertiary amine analogs of choline useful as substrates for investigations of mechanisms of membrane transport. They reported that this compound migrated rapidly across the cell membrane of human erythrocytes (characteristic of lipid-soluble molecules) and, in the protonated form, was a strong inhibitor of choline uptake at the transport carrier site (61% inhibition). An observed decrease in flux ratio (the ratio of infinite-trans to zero-trans flux) indicated a preferential binding by DMPC at the inner carrier site. In another study on rat liver mitochondria, Porter *et al.* (1992) reported that DMPC demonstrated high affinity as an inhibitor of choline uptake (55% inhibition).

Structure/Activity Relationships: Mixed results in a variety of short-term tests have been reported for various structural analogs of DMPC. According to Bodell (1990), close monofunctional analogs demonstrate DNA alkylating ability and induction of SCEs in a rat 9L cell line, but to a lesser extent than similar bifunctional nitrogen mustards. A literature search was carried out for information relevant to mutagenicity and carcinogenicity on the eleven analogs shown in Appendix A. For five of them [B,D,E,H,K] no information was found; while only general toxicity information was found for one other [G]. Pertinent information was identified for the other five all ethyl mustard-type analogs

[A,C,F,I,J]. In each case, at least one citation with positive results was reported from mutagenicity or carcinogenicity testing. The relevant information found is summarized as follows.

- 2-Chloro-N-(2-chloroethyl)-N-methylethanamine hydrochloride (mechlorethamine hydrochloride; nitrogen mustard hydrochloride) [A] was tested by the NTP for genetic toxicity only and was reported to be an Ames positive mutagen (NTP, 1994). IARC placed this chemical in Group 2A (probably carcinogenic to humans) on the basis of limited evidence for carcinogenicity to humans and sufficient evidence for carcinogenicity to animals (IARC, 1975; IARC, 1987). This chemical has also been reported to have given positive results in a battery of short-term tests, including the following test systems: Ames/*Salmonella*, mammalian somatic cell, unscheduled DNA synthesis (UDS), cytogenetics and *Drosophila* assays (Soderman, 1982). Schiestl *et al.* (1989) reported, in addition, that this chemical induced intrachromosomal recombinations in the yeast deletion assay with *S. cerevisiae*. Manson (1991) listed nitrogen mustard as one of the known causal agents of malformations in mammalian species, raising the possibility that DMPC might also have a teratogenic effect.

- An ethyl mustard, 2-dimethylaminopropyl chloride hydrochloride [J], has also been tested by the NTP for mutagenicity only in an Ames/*Salmonella* assay with a positive result reported. No other testing for this chemical was reported in the NTP results report (NTP, 1994).

- Analog [I], 2-chloro-N,N-dimethylethylamine hydrochloride (dimethyl mustard), was the only analog for which information was found in PHS-149. In the one citation identified, Theiss *et al.* (1979) reported that this chemical was carcinogenic to the lungs of strain A mice following *i.p.* administration in saline for 24 weeks. Doses of 0.21 mmol/kg, 0.52 mmol/kg, and 1.04 mmol/kg (the MTD) administered in 0.9% saline solution 3 times per week (total doses of 5.0, 12.5 and 25.0 mmol/kg) all produced tumors. In addition, Tokuda and Bodell (1987) reported that this chemical, at a concentration of 0.1 mM, induced sister chromatid exchanges (SCEs) in 9L rat brain tumor cells with a linear dose response relationship.

- The closely related free base of compound [I], dimethylaminoethyl chloride [C] was reported to have given positive results in three mutagenicity assays summarized as follows (NLM, 1994):

  - positive in an Ames/*Salmonella* assay in strains TA100 and TA1535 both with and without S9 activation
  - positive in an *E. coli* assay both with and without S9 activation
  - positive in a yeast assay, *S. cerevisiae*

  Quillardet and Hofnung (1993) also reported that this chemical was genotoxic to *E. coli* when tested in an SOS chromotest.

- Analog [F], diethylaminoethyl chloride hydrochloride (diethyl mustard), was reported by Probst *et al.* (1981) to have given a positive response in both a modified Ames test and a hepatocyte UDS test. Soper *et al.* (1979) reported that this chemical induced base substitution mutations in *E. coli* strains WP2 and WP2*uvr*A$^-$ when tested at a concentration of 0.1 μmol/L. This analog was also reported in the EPA GENETOX Program of 1988 to have given a positive response in a yeast reversion assay with *Saccharomyces pombe* (NLM, 1994).

Although Thompson *et al.* (1981) found that the alkylating abilities and mechanisms of action differ among the chemicals of the nitrogen mustard-type class, they concluded that there is a reasonable chance alkylaminoalkyl chlorides will be found to be carcinogenic in long-term studies in rodents.

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Summary Sheet Checklist for Dimethylaminopropyl chloride hydrochloride (5407-04-5)

NLM	STN INTERNATIONAL	DIALOG
CCRIS	CA PREVIEWS	Enviroline (40)
DART	CHEMLIST	Pollution Abstracts (41)
EMICBACK	CSCHEM	NIOSH/OSHA (161)
GENETOX	CSCORP	Chapman & Hall Chemical Database (303)
HSDB	HODOC	
IRIS	REGISTRY	Chemical Safety NewsBase (317)
RTECS	NUMERIGUIDE	Fine Chemicals Database (360)
	CIS	Beilstein Online (390)
	TSCAPP	Piers Imports (573,574)

Prepared for NCI by Technical Resources International, Inc. under Contract No. NO1-CP-56019 (5/94; rev. 6/95)

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