3-Dimethylaminopropylamine

109-55-7

OVERVIEW

This material was prepared for the National Cancer Institute (NCI) for consideration by the Chemical Selection Working Group (CSWG) by Technical Resources International, Inc. under Contract no. N02-07007.

3-Dimethylaminopropylamine (DMAPA) came to the attention of the National Cancer Institute (NCI) Division of Cancer Biology as the result of a review of chemical industry information suggesting an increased production or use of this chemical.

DMAPA appears to have a significant and increasing demand for its use in personal care products. This chemical also has applications in the leather processing, paper, and rubber industries and is an intermediate in the production of fabric softeners, polymers, agrochemicals, flocculating agents, liquid soaps, and dye intermediates.

There is a lack of information on the chronic toxicity of DMAPA and other chemicals structurally related to DMAPA. In a SIDS screen, DMAPA produced deaths in high dose animals exposed for 28 days, but this chemical lacked reproductive or developmental effects and produced a negative mutagenicity profile. Workers occupationally exposed to DMAPA at concentrations of 0.55-1.38 mg/m^3 experienced impaired respiration that may not have been completely reversible even when concentrations of DMAPA were reduced. Given the lack of chronic toxicity data for DMAPA, its high production volume, and its widespread use, additional toxicity testing appears warranted.

NOMINATION OF 3-DIMETHYLAMINOPROPYLAMINE TO THE NTP

Based on a review of available relevant literature and the recommendations of the Chemical Selection Working Group (CSWG) held on December 17, 2003, NCI nominates this chemical

for testing by the National Toxicology Program (NTP) and forwards the following information:

- The attached Summary of Data for Chemical Selection
- Copies of references cited in the Summary of Data for Chemical Selection
- CSWG recommendations to:

  (1) Evaluate the chemical in combination with a nitrosating agent for genetic toxicology in *Salmonella typhimurium* strains TA100 and TA1535

  (2) Evaluate the disposition of the chemical in rodents, specifically dermal absorption, to determine nitrosamines and other metabolites.

PRIORITY

The CSWG suggested that the recommended testing be conducted with high priority.

COMMENTS

A concern of the CSWG is the possible formation of nitrosamines if the chemical is absorbed via common routes of exposure, e.g., dermal and inhalation

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SUMMARY OF DATA FOR CHEMICAL SELECTION

CHEMICAL IDENTIFICATION

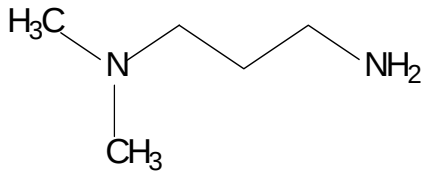
CAS Registry Number: 109-55-7

Chemical Abstract Service Name: 1,3-Propanediamine, N, N-dimethyl (9CI)

Synonyms: 1-Amino-3-dimethylaminopropane; 3-amino-1-dimethylaminopropane; 3-aminopropyldimethylamine; 1-dimethylamino-3-aminopropane; 3-(dimethylamino)-1-propanamine; dimethylaminopropylamine; γ-dimethylaminopropylamine; *N*,*N*-dimethyl-1,3-diaminopropane; *N*,*N*-dimethylpropylenediamine; *N*,*N*-dimethyltrimethylenediamine; DMAPA; EINECS 203-680-9 (ChemFinder, 2004; ChemID, 2004; Eller *et al*., 2003)

Structural Class: Diamine

Structure, Molecular Formula and Molecular Weight:



$C_5H_{14}N_2$ Mol. wt. 102.2

Chemical and Physical Properties:

Description: Colorless liquid; strong base (pK_1 = 9.9; pK_2 = 7.7) (Lewis, 2002; OECD, 2004)

Boiling Point: 135 ^oC (Verschueren, 2001)

Melting Point: -60 ^oC (Verschueren, 2001)

Flash Point: 32 ^oC (Fisher Scientific, 2004)

Solubility: Miscible in water; soluble in organic solvents (Lewis, 2002; OECD, 2004)

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Log Po/w: -0.353 at 25 ^{o}C for neutral DMAPA (Celanese Chemicals Europe GmbH, 2001; OECD, 2004)

Reactivity: Incompatible with strong oxidizing agents, acid chlorides, carbon dioxide, aliphatic amines, and acid anhydrides (Fisher Scientific, 2004)

Technical Products and Impurities: 3-Dimethylaminopropylamine, 99%, is available from Fisher Scientific and Sigma-Aldrich (Fisher Scientific, 2004; Sigma-Aldrich, 2004a).

EXPOSURE INFORMATION

Production and Producers:

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Manufacturing Process. DMAPA is produced in a two-stage process from acrylonitrile and dimethyl amine. In the first stage, the reaction of the starting materials leads to raw reaction products containing approximately 99 percent 3-dimethyl aminopropionitrile. This addition product is then hydrogenated to DMAPA and a number of byproducts in the second stage. The byproducts are then removed from the DMAPA through multiple-stage distillation. The remaining pure product has a DMAPA content of >99.5% (OECD, 2004).

Producers and Importers. DMAPA for industrial uses is available in tank trucks, tank wagons, and 55-gallon steel drums. With facilities in Europe and Geismar, Louisiana, BASF is the world's largest supplier of DMAPA (BASF Corporation 1999; Huntsman, 1995).

According to Chemical Sources International, there are 10 United States (U.S.) suppliers of DMAPA (Chemical Sources International, 2004).

According to recent issues of chemical directories, DMAPA is manufactured or distributed by A Johnson Matthey Company; Air Products and Chemicals, Inc.; Alfa Aesar; ARC; BASF Corporation; Benco International LLC; Brook-Chem Inc.; Brown Chemical Co. Inc.; Celanese Chemicals; ICN; Lancaster; Mytech; Performance Chemicals Group; Pharmco, and TCI (ChemACX, 2004; Chemcyclopedia, 2003; Chem Week Associates, 2003; Tilton, 2003).

Production/Import Level:

DMAPA is listed in the EPA's Toxic Substances Control Act (TSCA) Inventory, and it is a high production volume (HPV) chemical with U.S. production in 1998 between 10 and 50

million pounds**.** It is not sponsored by industry in the HPV Challenge Program but has been tested by OECD in the SIDS screen (ChemID, 2004; EPA, 2004).

The Port Import/Export Reporting Service (PIERS) database reported DMAPA exports with a cargo weight of 1,658,129 pounds and imports with a cargo weight of 221 pounds over

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the 38-month period between December 2000 to February 2004 (Dialog Information Service, 2004).

Use Pattern:

DMAPA has nondispersive or closed system uses, uses resulting in inclusion into or onto a matrix, and wide dispersive uses (European Chemicals Bureau, 2000).

According to the Cosmetic, Toiletry, and Fragrance Association's *CTFA Cosmetic Ingredient Handbook*, DMAPA is an aliphatic amine that functions as a pH adjuster in cosmetic products (Nikitakis, 1988).

DMAPA is also used for the synthesis of betaines, which are widely employed in personal care products, shampoos, washing and dishwashing detergents. According to BASF, the launch of liquid soaps and rising demand for skin-friendly surfactants has boosted demand for DMAPA. Most BASF production of this specialty amine is processed to amphoteric surfactants for use in personal care products (BASF Corporation, 2004; Huntsman, 1995; Turcotte & Johnson, 1992).

Because DMAPA contains one primary and one tertiary amine group, it has numerous uses in the production of other chemicals. Final products include agricultural chemicals, anti-static agents, binding agents, carburetor detergents, fabric softeners, flocculants, fungicides, ion exchange resins, phthalocyanine dyes, and water-resistant textile fibers. Derivatives based on DMAPA can be used in fuels as cloud point reducers, dispersants, and stabilizers for prevention of deposits or icing and reduction of octane number requirements. Derivatives are also used as dispersants, anti-oxidants, and corrosion inhibitors for lubricants. Water soluble cationic polyelectrolytes based on DMAPA act as flocculants in removing floating solids and oil from waste water and are used as drilling fluid in the mining industry (Alkyl Amines Chemicals Limited, 2001; BASF Corporation, 2004; Huntsman, 1995; OECD, 2004; Speight *et al.*, 1993).

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DMAPA also has direct uses in consumer and industrial markets:

- As an unleaded gasoline additive that improves properties to the gasoline and provides bactericidal activity (Huntsman, 1995)
- In synthetic dyes and paints for cotton, silk, synthetics, leather, paper, hair, and special printing inks (Huntsman, 1995)
- As a crosslinking and bonding agent for epoxy and novolak resins (Huntsman, 1995).
- To treat polyester films and fibers, thereby reducing static electricity and improving receptivity to dyes (Huntsman, 1995)
- To stabilize polystyrene to outdoor weathering (Huntsman, 1995; OECD, 2004)
- As an anti-shrinking agent for leather (OECD, 2004)
- As a crosslinking agent for cellulose fibers in the paper industry (OECD, 2004).

As of May 2004, 537 patents describing the use of DMAPA were filed with the US Patent and Trademark Office (USPTO) since 1976 (US Patent and Trademark Office, 2004).

Human Exposure:

Consumer Exposure. DMAPA has been identified as an impurity in many shampoos, cosmetics, and detergents, so that consumer exposure to low levels of DMAPA from these uses would be expected. Exposure may also occur from the use of DMAPA in products such as carburetor cleaners or gasoline additives**.**

Occupational Exposure. Exposure to DMAPA has been confirmed in persons whose occupations required repeated contact with shampoos and other personal care products containing technical grade cocamidopropyl betaine (Kanerva *et al.*, 1996). DMAPA may be an important sensitizing allergen in cosmetic products containing cocamidopropyl betaine (Uter, 1999).

Exposure to DMAPA may also occur during manufacturing processes that use this product.

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In 1974, DMAPA concentrations between 1.74 mg/m^3 and 5.86 mg/m^3 were measured in the mold room of a ski production facility in Connecticut. Because of worker complaints, these concentrations were reduced, and a followup study in 1977 showed average concentrations of 0.55 mg/m^3 in the workers' breathing zone air. DMAPA has also been detected in the workplace air at a polyurethane foam production facility (Brubaker *et al.*, 1979; Celanese Chemicals Europe GmbH, 2001; European Chemicals Bureau, 2000; Speight *et al.*, 1993).

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 6,127 employees, including 119 females, were potentially exposed to DMAPA in the workplace (CDC, 2004). The NOES data does not reflect recent changes and the growing use of DMAPA by the cosmetics industry.

Environmental Exposure. Releases into the environment may be possible during production and processing, from use as a hardener, and during the use of subsequent products due to possible residues of DMAPA (OECD, 2004). The Russian literature reported that DMAPA was present in wastewaters near petrochemical plants and oil refineries (HSDB, 2004).

Once released into the water, DMAPA may be toxic to aquatic species. Acute toxicity values reported for DMAPA in *Leuciscus idus* (fresh water fish) exposed to DMAPA for 96 hours under static conditions showed an LC_0 of 100 mg/l, an LC_{50} of 122 mg/l, and an LC_{100} of 140 mg/l. The EC_{50} for the crustacean, *Daphnia magna* was 68.3 mg/l; with an EC_0 of 50 mg/l and an EC_{100} of 100 mg/l (Celanese Chemicals Europe GmbH, 2001). Similar information for terrestrial species was not identified in the available literature.

Environmental Occurrence:

The environmental occurrence of DMAPA would be influenced by its properties as a base. In aquatic systems, the conjugated acid can also be present depending on pH. The calculated half-life due to photochemical-oxidative degradation in the atmosphere by OH

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radicals is 3.2 hours (OECD, 2004). This chemical is readily biodegradable in tests of activated sludge complying with OECD Guideline 301D (Celanese Chemicals Europe GmbH, 2001).

Regulatory Status:

No standards or guidelines have been set by the National Institute for Occupational Safety and Health (NIOSH) or the Occupational Safety and Health Administration (OSHA) for occupational exposure or allowable workplace levels of DMAPA. This chemical 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.

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TOXICOLOGICAL INFORMATION

Human Data:

DMAPA is considered corrosive to the skin and eyes, and this chemical may also cause sensitization by skin contact (BASF Corporation, 1997; European Chemicals Bureau, 2000).

In a study of 1,200 Italian patients with eczema, 46 (3.8%) responded when tested with 1% cocamidopropyl betaine. Thirty of the 46 patients participated in follow-up studies. All 30 subjects demonstrated positive responses to 1% DMAPA while 53% responded to 1% cocamidopropyl betaine of a purer grade. The results of this study and follow-up studies by the same authors suggested that contact allergy to commercial cocamidopropyl betaine is caused by DMAPA (Angelini *et al.*, 1995, 1996, 1997; Foti *et al.*, 2003).

Case reports from England and Finland also discuss the possibility that allergic reactions to cocamidopropyl betaine are from the presence of DMAPA as an impurity in the amphoteric surfactant. In the Finnish case, an assistant nurse who repeatedly washed patients' hair, often without gloves, developed hand dermatitis. In patch testing, she demonstrated sensitivity to DMAPA but not to cocamidopropyl betaine. In the English study, the authors concluded that DMAPA is unlikely to be an important contact allergen in cocamidopropyl betaine of suitable purity (Kanerva *et al.*, 1996; MacFadden *et al.*, 2001).

In 1974, a study was undertaken to assess the symptoms and pulmonary function of 25 mold room workers exposed to DMAPA in an epoxy resin used at a ski manufacturing plant. Ten of the workers reported upper respiratory symptoms with 11 reporting lower respiratory complaints including cough, increased phlegm, wheezing, and chest tightness. None of the nine control subjects experienced any complaints. Assemblers, the group with the highest breathing zone exposure to DMAPA, 0.9 ppm, had the highest prevalence of symptoms and a significant decrease in lung function over the workshift (Brubaker *et al.*, 1979; Sargent *et al.*, 1976).

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In followup to ventilation improvements in the mold room, a cross-sectional study was conducted in 1977. A total of 34 subjects participated in the study (6 non-exposed controls, 8 assemblers, six gluers, eight pressmen, and six other mold room workers). Only four participants in the 1974 study participated in the 1977 study. In the respiratory disease questionnaire, none of the control group reported respiratory complaints, although 5 of 28 mold room workers reported nasal irritation and 2 reported increased phlegm. The assemblers' lung function no longer decreased significantly over the workshift. DMAPA concentrations in the breathing zone air of assemblers had decreased to an average of 0.13 ppm (Brubaker *et al.*, 1979).

To determine the effects of cumulative exposure, in 1978, 17 employees who had worked in the mold room for 1 year, eight who had worked two to four years, and five who had worked five to seven years were examined. Compared with predicted values, the decrease in FEV_1 /FVC for the combined group with two to seven years of exposure was significantly decreased; this decrease could not be accounted for wholly by smoking (Brubaker *et al.*, 1979).

Animal Data:

No 2-year carcinogenicity studies of DMAPA were identified in the available literature.

Acute Studies. Reported acute toxicity values for DMAPA are presented in Table 1 below.

Table 1. LD_{50} (mg/kg)/LC_{50} (mg/l) Values for DMAPA

Species	Route	LD_{50} (mg/kg)/ /LC_{50} (mg/l)
female rat	oral	1,037
male rat	oral	1,870
mouse	oral	1,500 and 1,640
rat	inhalation	> 4.31

Source: OECD, 2004

Depending on its concentration, DMAPA is strongly irritating or corrosive to the skin and

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mucous membranes upon application. DMAPA was classified as sensitizing (OECD, 2004).

In a rabbit skin corrosivity test, DMAPA caused necrosis in two out of two rabbits exposed to the agent for four hours (American Cyanamid Co., 1983).

In the guinea pig maximization test performed using female Hartley guinea pigs, DMAPA (5% v/v) was reported to cause extreme contact dermal sensitization based on observation at 48 hours (Allied Signal, Inc., 1987).

SIDS Screen. A 28-day oral toxicity study was performed on Wistar rats exposed to DMAPA at 0, 10, 50, and 250 mg/kg/day. One of five high dose males showed impaired respiration. In contrast, 4 of 10 high dose females died during the 28-day treatment. Decreased spontaneous activity, stilted gait, swollen abdomen, and impaired respiration were observed between days 11 and 24, mainly in the females that died. All other observations were similar to controls. In the four high-dose females that died, macroscopically visible changes such as discoloration of lungs with multiple red spots on its surfaces and foamy content were observed. Histopathological examinations revealed lesions which included congestion of organs, pulmonary hemorrhage, and edema, consistent with cardiorespiratory failure as cause of death. In addition, one of the females exhibited marked loss of lymphatic follicles of the spleen with massive marginal zone and periarteriolar lymphoid sheath atrophy. The one high-dose male rat that exhibited clinical signs had focal ballooning degeneration of the squamous epithelium of the forestomach found at necropsy (OECD, 2004).

Short-Term Tests:

Several studies related to the mutagenic potential of DMAPA were found in the available literature.

- DMAPA was not mutagenic in *Salmonella typhimurium* strains TA100, TA1535, and TA1537 at 33-3333 μg/plate. The mutagenicity of this compound was not enhanced

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by rodent liver S-9 activation (Takahashi *et al.*, 1993 and Zeiger *et al.*, 1987, cited in CCRIS, 1995a).

- DMAPA was not mutagenic in *S. typhimurium* strains TA98 and TA1537 in the presence of rodent liver S-9 at 100-10,000 μg/plate (Takahashi *et al.*, 1993 and Zeiger *et al.*, 1987, cited in CCRIS, 1995a).
- DMAPA was not mutagenic in *S. typhimurium* strains TA1538, TA1950 and his G46 in the presence of rodent liver S-9 (OECD, 2004).
- DMAPA did not induce micronuclei in normochromatic erythrocytes from mouse bone marrow cells (OECD, 2004).

These studies suggest that DMAPA is not a mutagen.

Metabolism:

No studies on the metabolism of DMAPA were identified in the available literature. In general, lower primary aliphatic amines are metabolized to the corresponding carboxylic acid and urea. The tertiary site would be expected to be more resistant to metabolism (Williams, 1959).

Other Biological Effects:

Reproductive/Developmental Toxicity. Reproductive and developmental toxicity studies were performed following oral administration of DMAPA (10, 50, and 200 mg/kg/day by gavage) to Wistar rats. Males, 10 per dose, received daily doses of compound two weeks before mating and two weeks during mating; females, 10 per dose, were treated throughout the 8-week study. No adverse effects on reproductive performance or fertility were found among the treated F_0 parental animals. Decreased food consumption and body weight gain were observed in males treated with 200 mg/kg/day, with piloerection and respiratory sounds also noted in two. No compound related adverse effects were observed in female rats at any dose. No signs of developmental toxicity were observed in the progeny of the F_0 parents up to 200 mg/kg/day. A no-observed-adverse-effect level (NOAEL) of 200

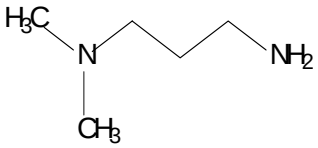
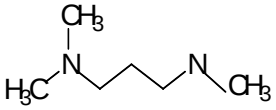
mg/kg/day was suggested to prevent reproductive and developmental toxicity (Celanese Chemicals Europe GmbH, 2001).

No other information on biological activity of DMAPA was identified in the available literature.

Structure Activity Relationships:

Three compounds structurally related to DMAPA were selected for review. These chemicals were *N,N,N´*-trimethyl-1,3-propanediamine, diethylaminopropylamine, and dimethylaminopropanol. No information on carcinogenic activity was found for any of these chemicals in a search of the National Library of Medicine TOXNET databases, including TOXLINE. No information on any of these chemicals was located in *Survey of Compound Which Have Been Tested for Carcinogenic Activity* (CancerChem). Toxicological information found in the available literature is presented below in Table 2.

Table 2. Toxicity Data of Chemicals Structurally Related to DMAPA

Name/CAS No.	Structure	Toxicological Information
3-Dimethylaminopropylamine (109-55-7)		Not mutagenic in *S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538, TA1950, and his G46 with and without rat liver S-9 (CCRIS, 1995a, OECD, 2004) Did not induce micronuclei in mouse bone marrow cells (OECD, 2004)
N,N,N´-Trimethyl-1,3-propanediamine (4543-96-8)		No information found in the available literature.

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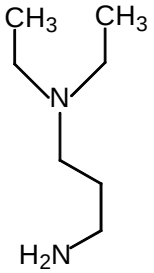
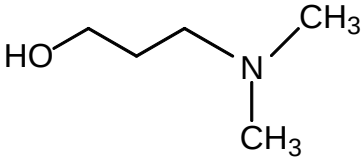
Diethylaminopropylamine (104-78-9)		Not mutagenic in *S. typhimurium* TA98 and TA100 with and without S-9 activation (CCRIS, 1995b).
Dimethylaminopropanol (3179-63-3)		No information found in the available literature.

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