2,6-Diaminopyridine

141-86-6

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.

2,6-Diaminopyridine came to the attention of the NCI Division of Cancer Biology (DCB) as the result of information collected for Summary Sheets on monoaminopyridines. 2,6-Diaminopyridine is a medium-production-volume chemical used as a pharmaceutical intermediate and a hair dye coupler in oxidation/permanent formulations.

Although mutagenic activity has been reported, no 2-year carcinogenicity studies or subchronic toxicity studies of 2,6-diaminopyridine were found in the available literature. Because of the information on mutagenicity, additional studies of the toxicity of 2,6-diaminopyridine appear warranted.

INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

Dr. John Walker, Executive Director of the TSCA Interagency Testing Committee (ITC), EPA, provided information on structure-related differences of 2,6-diaminopyridine with other diaminopyridines.

NOMINATION OF 2,6-DIAMINOPYRIDINE 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 for genetic toxicology in an *in vitro* mammalian assay,
  (2) Evaluate the disposition of the chemical in rodents, specifically dermal absorption.

PRIORITY

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

COMMENTS

The CSWG noted that extensive analysis of the genetic toxicity of this chemical has already been conducted, including the mouse lymphoma assay.

The CSWG noted that absorption via the dermal route duplicates human exposure potential

SUMMARY OF DATA FOR CHEMICAL SELECTION

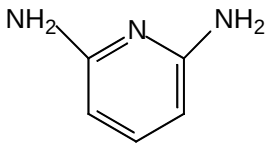
CHEMICAL IDENTIFICATION

CAS Registry No.: 141-86-6

Chemical Abstract Service Name: 2,6-Pyridinediamine (9CI)

Synonyms and Trade Name: 2,6-Diaminopyridine; 2,6-Pyridinediamine; 2,6-DAP;, DAP (amine); DAP; pyridine, 2,6-diamino- (ChemID, 2003; Properties of Organic Compounds, 2001)

Structure, Molecular Formula, and Molecular Weight



$C_5H_7N_3$ Mol. wt: 109.130

Structural Class: Heterocyclic aromatic tertiary amine derivative

Chemical and Physical Properties:

Description: Crystals (Lewis, 2002)

Boiling Point: 285 °C (Properties of Organic Compounds, 2001)

Melting Point: 121.5 °C (Properties of Organic Compounds, 2001)

Solubility: Soluble in water, acetone, ethanol, methanol, isopropanol, ethyl acetate (AerChem, Inc., 2003; Properties of Organic Compounds, 2001; Seal Sands Chemicals Ltd., 1998; Sigma-Aldrich, 2002a)

Reactivity: Combustible (Lewis, 2002)

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Technical Products and Impurities: 2,6-Diaminopyridine (98%) is available from Sigma-Aldrich (Sigma-Aldrich, 2002b).

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EXPOSURE INFORMATION

Production:

Manufacturing Processes: 2,6-Diaminopyridine is prepared through amination of pyridine or 2-aminopyridine under severe conditions (Shimizu *et al*., 1996).

Production/Import Level:

2,6-Diaminopyridine is listed in the U.S. Environmental Protection Agency's (EPA's) Toxic Substances Control Act (TSCA) Inventory (ChemID, 2003).

The annual production of 2,6-diaminopyridine in 1998 was reported to be 10,000-500,000 pounds based on non-confidential data received by EPA (EPA, 2003).

Producers:

According to Chemical Sources International, there are 21 United States (U.S) suppliers of 2,6-diaminopyridine and 1 supplier of 2,6-diaminopyridine hydrochloride (Chemical Sources International, 2003).

According to recent issues of chemical directories, 2,6-diaminopyridine is manufactured and/or distributed by Alfa Aesar; CBC (America) Corp.; Davos Chemical Corp.; Seal Sands Chemicals Ltd.; and Xishan city organic chemical factory (Hunter, 2002; Moynihan, 2002; Tilton, 2002).

Use Pattern:

2,6-Diaminopyridine has the following uses:

- Coupler in oxidation hair dye formulations (Health Canada, 2003; INCI, 2003; Nikitakis, 1988; Pepe *et al*., 2002; Rieger, 1993; Saninforma, 2003)

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- Epoxy curing agent and intermediate in the production of polyamides (Berenberg, 2003; Shimizu *et al*., 1993)

- Intermediate in the manufacturing of the analgesic phenazopyridine hydrochloride (Scriven *et al*., 1996).

The International Cosmetic Ingredient Dictionary and Handbook also lists 2,6-diaminopyridine sulfate [CAS No. 7280-83-3] as a hair dye ingredient (Pepe *et al*., 2002).

As of September 2003, 834 patents using 2,6-diaminopyridine were filed with the US Patent and Trademark Office (USPTO) since 1976 (U.S. Patent and Trademark Office, 2003).

Human Exposure:

Consumer Exposure: The principal source of human exposure to 2,6-diaminopyridine occurs through the use of permanent hair dyes (Health Canada, 2003; INCI, 2003; Nikitakis, 1988; Pepe *et al*., 2002; Rieger, 1993; Saninforma, 2003). The concentration of 2,6-diaminopyridine in a commercial hair dye was reported to be 0.31% w/w (Tokuda *et al*., 1986).

The Cosmetic, Toiletry, and Fragrance Association (CTFA) has estimated that two of five American women and a smaller number of men dye their hair. According to a survey by Clairol, approximately 55% of women and 11% of men color their hair; the largest group of women who have their hair colored choose a brown shade (Adams, 2003; FDA, 1993).

No information on the number of people using hair dyes containing 2,6-diaminopyridine was found in available literature.

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Occupational Exposure: The principal source of occupational exposure to 2,6-diaminopyridine is the application of hair dyes. According to the Bureau of Labor Statistics national employment data, 329,930 persons were employed as hairdressers, hairstylists, and cosmetologists as of 2001 (BLS, 2001).

Environmental Occurrence:

No information was found on the release of 2,6-diaminopyridine in the environment. Acute toxicity values for 2,6-diaminopyridine in aquatic species are summarized in Table 1.

Table 1. Ecotoxicity Values for 2,6-diaminopyridine

Organism	Study Time	Toxicity Endpoint	Toxic Dose (µg/L)
Oncorhynchus kisutch (Silver salmon)	24 hr (static conditions)	mortality (with observed behavioral effects)	10,000
Oncorhynchus tshawytscha (Chinook salmon)	24 hr (static conditions)	mortality (with observed behavioral effects)	10,000
Ptychocheilus oregonensis (Northern Squawfish)	24 hr (static conditions)	mortality (with observed behavioral effects)	10,000

Source: ECOTOX, 2003

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 to or workplace allowable levels of 2,6-diaminopyridine. 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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TOXICOLOGY INFORMATION

Human Data:

No epidemiological studies or case reports investigating the specific association of exposure to 2,6-diaminopyridine and cancer risk in humans were identified in the available literature.

Hair Dyes and Cancer: Since the early 20th century, hairdressers have made use of a wide variety of products, including hair colorants. In 1993, the International Agency for Research on Cancer (IARC) concluded that there was inadequate evidence that personal use of hair colorants entailed exposures that were carcinogenic (IARC, 1993).

The same IARC Working Group noted that there was consistent evidence from five of six cohort studies of an excess risk for cancer of the urinary bladder in male hairdressers and barbers (IARC, 1993).

Some more recent epidemiological studies have continued to show an association between the use of hair dyes and cancer in hairdressers. In a population-based case-control study of bladder cancer, occupational exposure to hair dyes was associated with a 5-fold increased risk in males and females who worked more than ten years as hairdressers or barbers (Gago-Domínguez *et al*., 2001). In another study, the association between the use of permanent hair dyes and the development of lymphomas and multiple myelomas was not clear (Correa *et al*., 2000).

In a Swedish study, an increased risk was observed in female hairdressers for cancers of the pancreas, lung, cervix, and *in situ* cancer of the skin affecting the scalp and neck. In male hairdressers, an increased risk was found for lung and colorectal adenocarcinoma but not for bladder cancer (Czene *et al*., 2003).

In 2003, the Cosmetic Ingredient Review (CIR) Expert Panel stated that hair dye

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epidemiology studies do not address the safety of individual hair dyes. The Panel expressed its concerns due to the association of the use of oxidative/permanent hair dyes and some cancer endpoints. The Panel, therefore, supported the need to replicate these studies and further examine the possibility of susceptible subpopulations (Cosmetic Ingredient Review Expert Panel, 2003).

Animal Data:

No 2-year carcinogenicity or subchronic studies of 2,6-diaminopyridine were identified in the available literature.

Short-Term Tests:

Several studies related to the mutagenic potential of 2,6-diaminopyridine were found in the available literature.

- 2,6-Diaminopyridine was not mutagenic in *Salmonella typhimurium* strain TA98 in the presence or absence of nonharman at 200 µg/plate. The mutagenicity of this compound was not enhanced by rodent liver S-9 (Sugimura *et al*., 1982).
- In another study, 2,6-diaminopyridine was not mutagenic in *S. typhimurium* strain TA98 without rodent liver S-9. However, it was mutagenic in the presence of rodent liver S-9 (Takahashi & Ono, 1993).
- 2,6-Diaminopyridine was not mutagenic in *S. typhimurium* strains TA98, TA100, and TA1535 in the presence or absence of rodent liver S-9 (JETOC, 1997; Takahashi & Ono, 1993)
- 2,6-Diaminopyridine was mutagenic in *S. typhimurium* strain TA1537 in the presence or absence of rodent liver S-9 (JETOC, 1997).
- 2,6-Diaminopyridine was not mutagenic in *Escherichia coli* strain WP2 *uvrA* in the presence or absence of rodent liver S-9 (JETOC, 1997).

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Metabolism:

No information was found on the metabolism of 2,6-diaminopyridine in the available literature.

Other Biological Effects:

A worker in the pharmaceutical industry developed contact dermatitis to 2,6-diaminopyridine after working eight years in this job. The symptoms disappeared after cessation of exposure to 2,6-diaminopyridine (Meier *et al*., 1999).

Structure-Activity Relationships:

Three compounds structurally related to 2,6-diaminopyridine were selected for review. These chemicals were 2,4-diaminopyridine; 3,4-diaminopyridine; and 2,3,6-triaminopyridine. 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 the *Survey of Compounds Which Have Been Tested for Carcinogenic Activity* (CancerChem). Toxicological information found in the available literature is presented below in Table 2.

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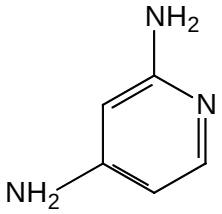
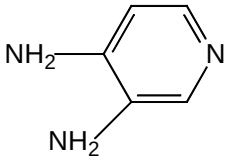
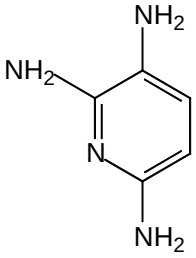
Table 2. Toxicity Data of Compounds Structurally Related to 2,6-diaminopyridine

Name/CAS No.	Structure	Toxicological Information
2,4-Diaminopyridine 461-88-1 (ChemID, 2003)		Increased release of acetylcholine after intrastriatal administration in rats. Did not induce acetylcholine release after intraperitoneal injection (Damsma *et al*., 1988)
3,4-Diaminopyidine 54-96-6 (ChemID, 2003)		Not mutagenic in *S. typhimurium* TA98 or TA100, w/wo S-9 and/or norharman (Wakabayashi *et al*., 1982) Blocks K+ channels *in vitro* (Muñoz-Caro & Nino, 2002) Experimental drug for treatment of Lambert-Eaton myasthenic syndrome (Sanders *et al*., 2000)
2,3,6-Triaminopyridine 4318-79-0 (ChemID, 2003)		Metabolite of analgesic phenazopyridine (Munday & Manns, 1998) Caused skeletal muscle necrosis and damage of renal distal tubules (Munday & Manns, 1998) Induced *in vitro* oxidative damage in erythrocytes (Munday & Fowke, 1994)

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The toxicological properties of 2,6-diaminopyridine may differ from 2,4-diaminopyridine or 3,4-diaminopyridine because the amino groups in 2,6-diaminopyridine would sterically hinder the pyridine nitrogen (Walker, 2003).

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References

Adams, P. (2003) For many aging people, gray hair is something to dye for. *Jewish Bulletin News*. [http://www.jewishsf.com/bk020517/supp09.shtml]. Searched November 17, 2003

AerChem, Inc. (2003) 2,6-Diaminopyridine. *Material Safety Data Sheet*. [http://www.aerchem.com/ html/products/msds.html] Searched September 11, 2003

Berenberg, B. (2003) 2,6-Diaminopyridine. *Composites/Plastics*. About, Inc. [http://plastics.about.com/library/glossary/d/bldef-d1581.htm] Searched September 9, 2003

BLS (2001) *Table 1. National Employment and Wage Data from the Occupational Employment Statistics Survey by Occupation, 2001*. Bureau of Labor Statistics. [http://www.bls.gov/ news.release/ocwage.t01.htm] Searched November 17, 2001

Chemical Sources International (2003) *Search ALL Chemical Suppliers for: 2,6-Diaminopyridine.* [http://db.chemsources.com/] Searched September 9, 2003

ChemID (2003) *Chemical Identification plus*. [Record nos. 000141866, 000461881, 004318790, 007280833]. National Library of Medicine, Bethesda, MD. [http://chem.sis.nlm.nih.gov/ chemidplus] Searched September 11 and October 2, 2003

Correa, A., Jackson, L., Mohan, A., Perry, H. & Helzlsouer, K. (2000) Use of hair dyes, hematopoietic neoplasms, and lymphomas: a literature review. II. Lymphomas and multiple myeloma. *Cancer Invest.*, **18**(5), 467-479

Cosmetic Ingredient Review Expert Panel (2003) *Announcements*. Cosmetic Ingredient Review. September 9, 2003. [http://www.cir-safety.org/staff_files/ results.pdf] Searched November 13, 2003

Czene, K., Tiikkaja, S. & Hemminki, K. (2003) Cancer risks in hairdressers: assessment of carcinogenicity of hair dyes and gels. *Int. J. Cancer*, **105**, 108-112

Damsma, G., Biessels, P.T., Westerink, B.H., De Vries, J.B. & Horn, A.S. (1988) Differential effects of 2,4-aminopyrdine on the *in vivo* release of acetylcholine and dopamine in freely moving rats measured by intrastriatal dialysis. *Eur. J. Pharmacol.*, **145**(1), 15-20 [abstract]

ECOTOX (2003) Aquatic records found: *6. ECOTOX:Ecotoxicology Database*. U.S. Environmental Protection Agency. [http://www.epa.gov/cgi-bin/ecotox_quick_search] Searched November 18, 2003

EPA (2003) Search results. *1998 Inventory Update Rule*. U.S. Environmental Protection Agency. [http://www.epa.gov/] Searched November 18, 2003

FDA (1993) *Hair Dye Dilemmas*. US Food and Drug Administration. [http://www.cfsan.fda.gov /~dms/cos-818.html] Searched November 17, 2003

Gago-Domínguez, M., Castelao, J.E., Yuan, J.M., Yu, M.C. & Ross, R.K. (2001) Use of permanent hair dyes and bladder-cancer risk. *Intl. J. Cancer*, **91**(4), 575-579

Health Canada (2003) *Substances in Cosmetics and Personal Care Products Regulated Under the Food and Drugs Act (F&DA) that were in Commerce between January 1, 1987 and September 13, 2001*. [http://www.hc-sc.gc.ca/ear-ree/87_01_w_cas_nymbers_ehtml] Searched September 9, 2003

Hunter, D., ed. (2002) 2-Aminopyridine, 3-aminopyridine, 4-aminopyridine. *Chemical Week 2003 Buyers' Guide and Industry Almanac*, New York, Chemical Week Associates, p 219

IARC (1993) *Occupational Exposures of Hairdressers and Barbers and Personal Use of Hair Colourants*. International Agency for Research on Cancer. [http://www-cie.iarc.fr/htdocs/ monographs/vol157/01-occh.htm] Searched November 17, 2003

INCI (2003) *INCI Inventory of Cosmetics Ingredients with the function: hair dyes*. European Commission. [http://pharmacos.eudra.org/F3/inci/incif26.htm] Searched September 10, 2003

JETOC (1997) *Mutagenicity Test Data of Existing Chemical Substances*. Supplement. Japan Chemical Industry Ecology-Toxicology & Information Center, Japan, p 119-120

Lewis, R.J., ed. (2002) 2,6-Diaminopyridine. *Hawley's Condensed Chemical Dictionary*, 14th ed., (On CD-Rom), NY, John Wiley & Sons, Inc.

Meier, H., Elsner, P. & Wuthrich, B. (1999) Occupationally-induced contact dermatitis and bronchial asthma in unusual delayed reaction to hydroxychloroquine. *Der Hautarzt*, **50**(9), 665-669 [abstract]

Moynihan, J. ed. (2002) 2-Aminopyridine, 3-aminopyridine, 4-aminopyridine. *Chemcyclopedia 2003*, Washington, DC, American Chemical Society, p 105

Munday, R. & Fowke, E.A. (1994) Generation of superoxide radical and hydrogen peroxide by 2,3,6-triaminopyridine, a metabolite of the urinary tract analgesic phenazopyridine. *Free Radical Res.*, **21**(2), 67-73 [abstract]

Munday, R. & Manns, E. (1998) 2,3,6-Triaminopyridine, a metabolite of the urinary tract analgesic phenazopyrdine, causes muscle necrosis and renal damage in rats. *J. Appl. Toxicol.*, **18**(2), 161-165 [abstract]

Muñoz-Caro, C. & Nino, A. (2002) The nature of the receptor site for reversible K^+ channel blocking by aminopyrdines. *Biophys. Chem.*, **96**(1), 1-14 [abstract]

Nikitakis, J.M., ed. (1988) *CTFA Cosmetic Ingredient Handbook*, 1st ed., The Cosmetic, Toiletry, and Fragrance Association, Washington, DC, p 21

Pepe, R.C., Wenninger, J.A. & McEwen, Jr., eds. (2002) *International Cosmetic Ingredient Dictionary and Handbook*, 9th ed., Vol. 1, The Cosmetic, Toiletry, and Fragrance Association, Washington, DC, p 481

Properties of Organic Compounds (2001) 2,6-Pyridineamine. *Properties of Organic Compounds*, Version 6:0 (On CD-ROM). Boca Raton, FL, Chapman & Hall/CRC

Rieger, M.M. (1993) Cosmetics. In Kroschwitz, J.I. & Howe-Grant, M., eds., *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th ed., Vol. 7, New York, John Wiley & Sons, Inc., p 612

Sanders, D.B., Massey, J.M., Sanders, L.L. & Edwards, L.J. (2000) A randomized trial of 3,4-diaminopyridine in Lambert-Eaton myasthenic syndrome. *Neurology*, **54**(3), 603-607 [abstract]

Saninforma (2003) *HennErbe Nativa Nero*. [http://www.saninforma.it/] Searched September 9, 2003

Scriven, E.F.V., Toomey, J.E. & Murugan, R. (1996) Pyridine and pyridine derivatives. In Kroschwitz, J.I. & Howe-Grant, M., eds., *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th ed., Vol. 20, New York, John Wiley & Sons, Inc., p 669

Seal Sands Chemicals Ltd. (1998) 2,6-Diaminopyridine. *Technical Data Sheet*. [http://www.rutherfordchemicals.com/images/data_sheets/26DAP.pdf] Searched October 6, 2003

Shimizu, S., Watanabe, N., Kataoka, T., Shoji, T., Abe, N., Morishita, S. & Ichimura, H. (1993) Pyridine and pyridine derivatives. In: Elvers, B., Hawkins, S., Ravenscroft, M. & Schulz, G., eds., *Ullmann's Encyclopedia of Industrial Chemistry*, 5th ed., Vol. A22, VCH Publishers, Würzburg, Germany, p 399, 417, 418

Sigma-Aldrich (2002a) *2,6-Diaminopyridine Material Safety Data Sheet.* [http://www.sigma-aldrich.com] Searched September 9, 2003

Sigma-Aldrich (2002b) Product name: 2,6-Diaminopyridine. *Product Info.* [http://www.sigma-aldrich.com] Searched September 9, 2003

Sugimura, T., Nagao, M. & Wakabayashi, K. (1982) Metabolic aspects of the comutagenic action of norharman. *Adv. Exp. Med. Biol.*, **136B**, 1011-1025

Takahashi, A. & Ono, H. (1993) Mutagenicity assessment in 44 epoxy resin hardeners in *Salmonella typhimurium* tester strains. *Chem. Express*, **8**(9), 785-788

Tilton, H., ed. (2002) 2,6-Diaminopyridine. *OPD 2003 Chemical Buyers Directory*, New York, Schnell Publishing Co., p 207

Tokuda, H., Kimura, Y. & Takano, S. (1986) Determination of dye intermediates in oxidative hair dyes by fused-silica capillary gas chromatography. *J. Chromatog.*, **367**, 345-356

U.S. Patent & Trademark Office (2003) *Results of search in ALL Years database* for "2,6-diaminopyridine": 831 patents and for "2,6-pyridinediamine": 3 patents, [http://www.uspto.gov/paaft/index.html] Searched September 11, 2003

Wakabayashi, K., Yahagi, T., Nagao, M. & Sugimura, T. (1982) Comutagenic effect of norharman with aminopyridine derivatives. *Mut. Res.*, **105**, 205-210

Walker, J.D. (2003) Personal communication [e-mail] from John Walker, Ph.D., P.P.H., Director, TSCA Interagency Testing Committee, Environmental Protection Agency, Washington, D.C., to Marta De Santis, Ph.D., Technical Resources International, Inc., October, 2003