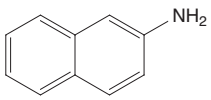
2-Naphthylamine

CAS No. 91-59-8

Known to be a human carcinogen

First listed in the *First Annual Report on Carcinogens* (1980)

Also known as β-naphthylamine



Carcinogenicity

2-Naphthylamine is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Epidemiological studies have shown that occupational exposure to 2-naphthylamine, either alone or present as an impurity in other compounds, causes cancer of the urinary bladder. Studies of dyestuff workers and of chemical workers exposed mainly to 2-naphthylamine found increased risks of urinary-bladder cancer that could not be explained by workers' smoking habits. At one dyestuff plant, the cancer risk increased with increasing exposure to 2-naphthylamine. In addition, many case reports have linked 2-naphthylamine exposure with urinary-bladder cancer in workers who manufactured or used 2-naphthylamine. The International Agency for Research on Cancer concluded that there was sufficient evidence for the carcinogenicity of 2-naphthylamine in humans (IARC 1974, 1987).

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of 2-naphthylamine from studies in experimental animals. Oral exposure to 2-naphthylamine caused urinary-bladder cancer (carcinoma) in hamsters, dogs, and rhesus monkeys and benign liver tumors (hepatocellular adenoma) in mice (IARC 1974). Since 2-naphthylamine was listed in the *First Annual Report on Carcinogens*, additional studies in rodents have been identified. Oral administration of 2-naphthylamine to rats caused a low incidence of urinary-bladder cancer (carcinoma), and administration to mice by intraperitoneal injection caused benign lung tumors (adenoma) (IARC 1987).

Studies on Mechanisms of Carcinogenesis

2-Naphthylamine caused genetic damage in various test systems, including mutations in bacteria, yeast, insects, plants, cultured human and other mammalian cells, and experimental animals exposed *in vivo*. Other types of genetic damage observed in some of these systems included DNA strand breaks, chromosomal aberrations, micronucleus formation, aneuploidy, sister chromatid exchange, and cell transformation (IARC 1987, Gene-Tox 1998).

The mechanism by which 2-naphthylamine causes cancer is thought to require its metabolism to a reactive form. When arylamines, such as 2-naphthylamine, are metabolized, they are either activated via N-hydroxylation (by cytochrome P450 liver enzymes) or detoxified via pathways such as N-acetylation. The *N*-hydroxylamine metabolites can form adducts with blood-serum proteins (such as hemoglobin), which circulate freely, or they can undergo further metabolism (conjugation) to form reactive compounds that can be transported to the bladder and can bind to DNA (Yu *et al.* 2002). 2-Naphthylamine DNA adducts have been found in bladder and liver cells from exposed dogs (IARC 1987).

Properties

2-Naphthylamine is an aromatic amine (arylamine) that exists at room temperature as colorless crystals with a faint aromatic odor. It is soluble in hot water, alcohol, ether, and many organic solvents. 2-Naphthylamine oxidizes in the presence of air, and the vapors can be explosive (IARC 1974, Akron 2009). Physical and chemical properties of 2-naphthylamine are listed in the following table.

Property	Information
Molecular weight	143.2
Specific gravity	1.061 at 98°C/4°C
Melting point	111°C to 113°C
Boiling point	306°C
Log K_{ow}	2.28
Water solubility	0.00640 g/L at 18°C
Vapor pressure	2.56×10^{-4} mm Hg at 25°C
Vapor density relative to air	4.95
Dissociation constant (pK_a)	4.16

Source: HSDB 2009.

Use

2-Naphthylamine now is used only in laboratory research. It formerly was used as an intermediate in the manufacture of dyes, as an antioxidant in the rubber industry, and to produce 2-chloronaphthylamine (IARC 1974, HSDB 2009).

Production

2-Naphthylamine was commercially produced in the United States from at least the early 1920s to the early 1970s. In 1955 (the last year for which production data were found), 581,000 kg (1.3 million pounds) was produced by four manufacturers (IARC 1974). Since its commercial manufacture and use were banned in the early 1970s, 2-naphthylamine has been available only in small quantities for laboratory research. In 2009, it was available from 10 U.S. suppliers (ChemSources 2009). 2-Naphthylamine has not been imported in significant amounts since 1967, when U.S. imports totaled 17,400 kg (38,400 lb) (IARC 1974).

Exposure

Because commercial production and use of 2-naphthylamine are banned, the potential for exposure is low. The general population may be exposed through inhalation of emissions from sources where nitrogen-containing organic matter is burned, such as coal furnaces and cigarettes (HSDB 2009). The U.S. Environmental Protection Agency's Toxics Release Inventory listed one industrial facility reporting releases of 2-naphthylamine for 1998 through 2001; none was released in 1998, and releases were 8 lb in 1999, 15 lb in 2000, and 265 lb in 2001. No records of earlier releases were found (TRI 2009). Mainstream cigarette smoke from eight different U.S. conventional market cigarettes contained 2-naphthylamine at concentrations of 1.5 to 14.1 ng per cigarette (Stabbert *et al.* 2003); other investigators reported levels as high as 35 ng per cigarette (Hoffman *et al.* 1997). For sidestream smoke, a concentration of 67 ng per cigarette was reported (Patrianakos and Hoffmann 1979). 2-Naphthylamine also occurs as an impurity (0.5% or less) in commercially produced 1-naphthylamine.

At greatest risk of occupational exposure to 2-naphthylamine are laboratory technicians and scientists who use it in research. Before U.S. commercial production of 2-naphthylamine and its use in the dye and rubber industries were banned, workers in these industries potentially were exposed. The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 420 workers potentially were exposed to 2-naphthylamine (NIOSH 1976), and the

National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 275 workers, including 265 women, potentially were exposed (NIOSH 1990).

Regulations

Department of Transportation (DOT)

2-Naphthylamine is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of 2-naphthylamine = U168.

Listed as a hazardous constituent of waste.

Mine Safety and Health Administration (MSHA, Dept. of Labor)

To control airborne exposure, 2-naphthylamine shall not be used or stored except by competent persons under laboratory conditions approved by a nationally recognized agency acceptable to the Secretary.

Occupational Safety and Health Administration (OSHA, Dept. of Labor)

Potential occupational carcinogen.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = exposure by all routes should be as low as possible.

National Institute for Occupational Safety and Health (NIOSH, CDC, HHS)

Listed as a potential occupational carcinogen.

References

Akron. 2009. *The Chemical Database.* The Department of Chemistry at the University of Akron. http://ull.chemistry.uakron.edu/erd and search on CAS number. Last accessed: 11/18/09.

ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. http://www.chemsources.com/chemonline.html and search on naphthylamine. Last accessed: 10/22/09.

Gene-Tox. 1998. *Genetic Toxicology Data Bank*. National Library of Medicine. Last updated: 4/8/98. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?GENETOX and search on CAS number.

Hoffman D, Djordjevic M, Hoffman I. 1997. The changing cigarette. *Prev Med* 26: 427-434.

HSDB. 2009. *Hazardous Substances Data Bank.* National Library of Medicine. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB and search on CAS number. Last accessed: 10/22/09.

IARC. 1974. 2-Naphthylamine. In *Some Aromatic Amines, Hydrazine and Related Substances, N-Nitroso Compounds and Miscellaneous Alkylating Agents*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 4. Lyon, France: International Agency for Research on Cancer. pp. 97-111.

IARC. 1987. 2-Naphthylamine. In *Overall Evaluations of Carcinogenicity.* IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, suppl. 7. Lyon, France: International Agency for Research on Cancer. pp. 261-263.

NIOSH. 1976. *National Occupational Hazard Survey (1972-74)*. DHEW (NIOSH) Publication No. 78-114. Cincinnati, OH: National Institute for Occupational Safety and Health.

NIOSH. 1990. *National Occupational Exposure Survey (1981-83)*. National Institute for Occupational Safety and Health. Last updated 7/1/90. http://www.cdc.gov/noes/noes1/50065sic.html.

Patrianakos C, Hoffmann D. 1979. Chemical studies in tobacco smoke LXIV. On the analysis of aromatic amines in cigarette smoke. *J Anal Toxicol* 3: 150-154.

Stabbert R, Schafer KH, Biefel C, Rustemeier K. 2003. Analysis of aromatic amines in cigarette smoke. *Rapid Commun Mass Spectrom* 17(18): 2125-2132.

TRI. 2009. *TRI Explorer Chemical Report.* U.S. Environmental Protection Agency. Last updated: 3/19/09. http://www.epa.gov/triexplorer and select Beta-Naphthylamine.

Yu MC, Skipper PL, Tannenbaum SR, Chan KK, Ross RK. 2002. Arylamine exposures and bladder cancer risk. *Mutat Res* 506-507: 21-28.