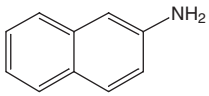
2-Naphthylamine
CAS No. 91-59-8

Known to be a human carcinogen
First Listed in the *First Annual Report on Carcinogens* (1980)



Carcinogenicity

2-Naphthylamine is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity in humans. Epidemiological studies have shown that occupational exposure to 2-naphthylamine, either alone or present as an impurity in other compounds, causes bladder cancer. Studies of dyestuff workers and of chemical workers exposed mainly to 2-naphthylamine found increased risks of bladder cancer. At one of the dyestuff plants, the risk increased with increasing exposure to 2-naphthylamine. In these studies, the increased risk of bladder cancer could not be explained by workers' smoking habits. Case reports also support the conclusion that 2-naphthylamine causes bladder cancer in humans. The International Agency for Research on Cancer (IARC) concluded that there was sufficient evidence for the carcinogenicity of 2-naphthylamine in humans (IARC 1974, 1987).

There is sufficient evidence for the carcinogenicity of 2-naphthylamine in experimental animals. When administered orally, 2-naphthylamine caused malignant bladder tumors in hamsters, dogs, and rhesus monkeys and liver tumors in mice; bladder tumors also were observed in rats at a low incidence (IARC 1987).

Additional Information Relevant to Carcinogenicity

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 (changes in chromosome structure or number), micronucleus formation (a sign of chromosome damage or loss), aneuploidy (extra or missing chromosomes), sister chromatid exchange, and cell transformation (a step in tumor formation) (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 can be either activated via *N*-hydroxylation (by cytochrome P-450 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 arylamine with a molecular weight of 143.2. It occurs as faintly aromatic, colorless crystals that turn purple-red when exposed to air. 2-Naphthylamine melts at 111°C to 113°C, boils at 306°C, and has a specific gravity of 1.061 at 98°C/4°C. It is soluble in hot water, alcohol, ether, and many organic solvents, and its log octanol-water partition coefficient was calculated as 2.07 to 2.28. 2-Naphthylamine is a weak base with the same general characteristics as primary aromatic amines. Its vapor pressure is 1 mm Hg at 108°C, and the vapor is heavier than air, with a density of 4.95. 2-Naphthylamine is stable at low temperatures in the absence of air and oxidizes in the presence of air (IARC 1974, HSDB 2003).

Use

2-Naphthylamine now is used only in laboratory research. It formerly was used commercially as an intermediate in the manufacture of dyes, as an antioxidant in the rubber industry, and to produce 2-chloronaphthylamine (IARC 1974, HSDB 2003).

Production

2-Naphthylamine was commercially produced in the United States from at least the early 1920s to the early 1970s. In 1955 (the latest year for which production data were found), 581,000 kg (1.3 million pounds) were 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. Six U.S. suppliers of 2-naphthylamine were identified in 2003 (ChemSources 2003). The last year in which it was imported in significant amounts was 1967, when 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 2003). 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). In 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 (1972–1974) estimated that 420 workers potentially were exposed to 2-naphthylamine in the workplace (NIOSH 1976), and the National Occupational Exposure Survey (1981–1983) estimated that 275 workers, including 265 women, potentially were exposed (NIOSH 1984).

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 (4 kg) in 1999, 15 lb (7 kg) in 2000, and 265 lb (120 kg) in 2001. No records of earlier releases were found (TRI01 2003).

Regulations

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 as a Hazardous Constituent of Waste
- Listed Hazardous Waste: Waste codes in which listing is based wholly or partly on substance - U168

OSHA

Potential occupational carcinogen: Engineering controls, work practices, and personal protective equipment required

Guidelines

ACGIH

Threshold Limit Value - Time-Weighted Average Limit (TLV-TWA) = as low as possible

NIOSH

Listed as a potential occupational carcinogen

References

ChemSources. 2003. Chemical Sources International, Inc. http://www.chemsources.com.

Gene-Tox. 1998. 2-Naphthylamine. National Library of Medicine. Last updated: 4/8/98. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?GENETOX and search by CAS number. Last accessed: 2/4/04.

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

HSDB. 2003. Hazardous Substances Database. 2-Naphthylamine. National Library of Medicine. Last updated: 8/29/03. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB and search CAS number. Last accessed: 2/4/04.

IARC. 1974. 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. 286 pp.

IARC. 1987. Overall Evaluations of Carcinogenicity. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, Supplement 7. Lyon, France: International Agency for Research on Cancer. 440 pp.

NIOSH. 1976. National Occupational Hazard Survey (1972-74). Cincinnati, OH: Department of Health, Education and Welfare.

NIOSH. 1984. National Occupational Exposure Survey (1981-83). Cincinnati, OH: U. S. Department of Health and Human Services. http://www.cdc.gov/noes/noes3/empl0003.html.

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

Stabbert, R., K. H. Schafer, C. Biefel and K. Rustemeier. 2003. Analysis of aromatic amines in cigarette smoke. Rapid Commun Mass Spectrom 17(18): 2125-32.

TRI01. 2003. Toxic Chemical Release Inventory 2001. Data contained in the Toxic Chemical Release Inventory (TRI). U. S. Environmental Protection Agency Office of Environmental Information. http://www.epa.gov/triexplorer/.

Yu, M. C., P. L. Skipper, S. R. Tannenbaum, K. K. Chan and R. K. Ross. 2002. Arylamine exposures and bladder cancer risk. Mutat Res 506-507: 21-8.