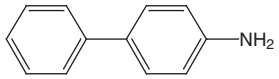
4-Aminobiphenyl
CAS No. 92-67-1

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



Carcinogenicity

4-Aminobiphenyl is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity in humans. Bladder cancer was first reported to be associated with occupational exposure to 4-aminobiphenyl in a descriptive epidemiological study (published in the mid 1950s), in which 11% (19 of 171) of workers in a plant manufacturing 4-aminobiphenyl developed bladder cancer. These workers had been exposed to 4-aminobiphenyl for 1.5 to 19 years between 1935 and 1955. Publication of this study led to an effort to discontinue production and use of 4-aminobiphenyl. Starting in 1955, 541 workers who had been exposed to 4-aminobiphenyl were followed for an additional 14 years; 43 men (7.9%) developed histologically confirmed bladder cancer. In a survey among workers at a plant producing a variety of chemicals, the risk of mortality from urinary bladder cancer was elevated tenfold, and all of the men who died of bladder cancer had worked at the plant during the period when 4-aminobiphenyl was used (1941 through 1952) (IARC 1972, 1987). The International Agency for Research on Cancer (IARC) concluded that there was sufficient evidence for the carcinogenicity of 4-aminobiphenyl in humans (IARC 1987).

Since 4-aminobiphenyl was reviewed for listing in the *First Annual Report on Carcinogens*, most research on its carcinogenicity has focused on exposure from cigarette smoking. Epidemiological studies have reported the incidence of bladder cancer to be 2 to 10 times as high among cigarette smokers as among nonsmokers. Higher levels of 4-aminobiphenyl adducts (4-aminobiphenyl metabolites bound to DNA or protein) were detected in bladder tumors (DNA adducts) and red blood cells (hemoglobin adducts) from smokers than from nonsmokers (as reviewed by Feng *et al.* 2002). In a case-control study, levels of 4-aminobiphenyl hemoglobin adducts were higher in smokers with bladder cancer than in a control group of similarly exposed smokers (Del Santo *et al.* 1991). A Taiwanese study reported that 4-aminobiphenyl hemoglobin adducts were associated with increased risk of liver cancer (Wang *et al.* 1998).

There is sufficient evidence for the carcinogenicity of 4-aminobiphenyl in experimental animals as demonstrated by studies showing that 4-aminobiphenyl causes cancer in rats, mice, rabbits, and dogs. When administered orally, 4-aminobiphenyl caused bladder tumors in rabbits and dogs and dose-related incidences of angiosarcoma (blood-vessel tumors), liver tumors, and bladder tumors in mice. When administered to rats by subcutaneous injection, 4-aminobiphenyl caused mammary-gland and intestinal tumors (IARC 1987).

Additional Information Relevant to Carcinogenicity

4-Aminobiphenyl caused genetic damage in various test systems, including mutations in bacteria and in cultured human and other mammalian cells. Other types of genetic damage included mitotic gene conversion (in yeast), transformation of cultured mammalian cells (a step in tumor formation), and inhibition of DNA repair in bacteria and cultured mammalian cells. Genetic damage detected in experimental animals exposed *in vivo* to 4-aminobiphenyl included micronucleus formation (a sign of chromosome damage or loss), chromosomal aberrations (changes in chromosome structure or number), and sister chromatid exchange (IARC 1987, Shelby *et al.* 1989, Gene-Tox 1998, HSDB 2003).

The mechanism by which 4-aminobiphenyl causes cancer is thought to require its metabolism to a reactive form. When arylamines, such as 4-aminobiphenyl, 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 or albumin), which circulate freely, or they can undergo further transformation to form reactive compounds that can be transported to the bladder and can bind to DNA (Yu *et al.* 2002). 4-Aminobiphenyl DNA adducts have been found in cells from the lining (epithelium) of the bladder in exposed dogs and humans, and protein adducts have been found in serum albumin from exposed rats and in hemoglobin from humans exposed via cigarette smoking (IARC 1987, Feng *et al.* 2002). Moreover, cigarette smokers who were slow acetylators (with inefficient versions of the enzyme *N*-acetyltransferase) had higher levels of 4-aminobiphenyl hemoglobin adducts than did smokers who were rapid acetylators (who could more efficiently detoxify arylamines via *N*-acetylation) (Vineis 1994).

Properties

4-Aminobiphenyl is an arylamine with a molecular weight of 169.2. It has a floral odor and occurs as a colorless, crystalline solid that turns purple when exposed to air. 4-Aminobiphenyl melts at 53°C, boils at 302°C, and has a specific gravity of 1.16 at 20°C. It is soluble in alcohol, ether, and chloroform and slightly soluble in water, with a log octanol-water partition coefficient of 2.8. It has a very low vapor pressure (6×10^{-5} torr) and a vapor density of 5.8 at its boiling point. 4-Aminobiphenyl oxidizes in the presence of air, poses a low-to-moderate fire hazard, and emits toxic fumes when heated (IARC 1972, HSDB 2003).

Use

In the United States, 4-aminobiphenyl now is used only in laboratory research. It formerly was used commercially as a rubber antioxidant, as a dye intermediate, and in the detection of sulfates (HSDB 2003).

Production

Because of its carcinogenic effects, 4-aminobiphenyl has not been produced commercially in the United States since the mid 1950s (Koss *et al.* 1969). It was present in the drug and cosmetic color additive D&C yellow no. 1; however, use of this color additive was discontinued in the late 1970s (HSDB 2003). Nine U.S. suppliers of 4-aminobiphenyl (for use in research) were identified in 2003 (ChemSources 2003). 4-Aminobiphenyl also has been reported as a contaminant in diphenylamine (HSDB 2003).

Exposure

The potential for exposure to 4-aminobiphenyl is low, because it has no commercial uses. Mainstream cigarette smoke was reported to contain 4-aminobiphenyl at levels of 2.4 to 4.6 ng per cigarette (unfiltered) and 0.2 to 23 ng per cigarette (filtered), and sidestream smoke to contain up to 140 ng per cigarette (Patrianakos and Hoffmann 1979, Hoffman *et al.* 1997). At greatest risk of occupational exposure are laboratory technicians and scientists who use 4-aminobiphenyl in research. The U.S. Environmental Protection Agency's Toxics Release Inventory listed only one industrial facility reporting releases of 4-aminobiphenyl, which ranged from 2 to 48 lb (0.9 to 22 kg) per year from 1988 to 2001, except in 1997 and 1998, when no releases were reported. Most of the 4-aminobiphenyl was disposed of in underground injection wells, and small amounts were released to the air in 1988, 1989, and 2000 (TRI01 2003).

Regulations

EPA

Clean Air Act

NESHAP: Listed as a Hazardous Air Pollutant (HAP)

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable Quantity (RQ) = 1 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

FDA

The color additives, FD&C yellow no. 5 and yellow no. 6, and D&C red no. 33 may contain 4-aminobiphenyl at maximum levels that range from 5-275 ppb

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

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