

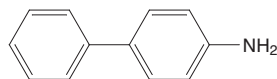
## 4-Aminobiphenyl

### CAS No. 92-67-1

Known to be a human carcinogen

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

Also known as *para*-aminodiphenyl



### Carcinogenicity

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

#### Cancer Studies in Humans

Cancer of the urinary bladder 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 urinary-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 urinary-bladder cancer. In a survey of 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 urinary-bladder cancer had worked at the plant during the period when 4-aminobiphenyl was used (1941 through 1952). The International Agency for Research on Cancer concluded that there was sufficient evidence of the carcinogenicity of 4-aminobiphenyl in humans (IARC 1972, 1987).

Since 4-aminobiphenyl was listed 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 urinary-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 (Feng *et al.* 2002). In a case-control study, levels of 4-aminobiphenyl-hemoglobin adducts were higher in smokers with urinary-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).

#### Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of 4-aminobiphenyl from studies in experimental animals. Oral exposure to 4-aminobiphenyl caused urinary-bladder cancer (carcinoma) in mice, rabbits, and dogs and blood-vessel cancer (angiosarcoma) and liver tumors in mice. 4-Aminobiphenyl administered to rats by subcutaneous injection caused mammary-gland and intestinal tumors (IARC 1987).

#### Studies on Mechanisms of Carcinogenesis

4-Aminobiphenyl caused genetic damage in several 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, and

inhibition of DNA repair in bacteria and cultured mammalian cells. Genetic damage in experimental animals exposed *in vivo* to 4-aminobiphenyl included micronucleus formation, chromosomal aberrations, and sister chromatid exchange (IARC 1987, Shelby *et al.* 1989, Gene-Tox 1998, HSDB 2009).

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 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 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 urinary-bladder epithelial cells from exposed dogs and humans, and 4-aminobiphenyl-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 (Vineis 1994).

### Properties

4-Aminobiphenyl is an aromatic amine (arylamine) that exists at room temperature as a colorless crystalline solid with a floral odor. It is slightly soluble in cold water, but readily soluble in hot water. It is soluble in ethanol, ether, acetone, chloroform, and lipids. It oxidizes in air and emits toxic fumes when heated to decomposition (Akron 2009). Physical and chemical properties of 4-aminobiphenyl are listed in the following table.

Property	Information
Molecular weight	169.2
Specific gravity	1.16
Melting point	53.5°C
Boiling point	302°C
Log $K_{ow}$	2.86 at pH 7.5
Water solubility	0.224 g/L at 25°C
Vapor pressure	$5.79 \times 10^{-4}$ mm Hg at 25°C
Vapor density relative to air	5.8
Dissociation constant ( $pK_a$ )	4.35 at 18°C

Source: HSDB 2009.

### 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 2009).

### 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 2009). 4-Aminobiphenyl has been reported to be formed by the decomposition of 1,3-diphenyltriazene produced by the reaction of diazoaniline and aniline during manufacture of the dye D&C red no. 33 (Bailey 1985). In 2009, 4-aminobiphenyl (for use in research) was available from 11 U.S. suppliers, including one company that supplied bulk quantities (ChemSources 2009). 4-Aminobiphenyl also has been reported as a contaminant in diphenylamine (HSDB 2009).

## 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 contained up to 140 ng per cigarette (Patrianakos and Hoffmann 1979, Hoffman *et al.* 1997). 4-Aminobiphenyl may be present in the color additives FD&C yellow no. 5 and yellow no. 6 and D&C red no. 33 at levels established by the FDA (see Regulations). The concentration of 4-aminobiphenyl in D&C red no. 33 was reported to range from 151 to 856 ppb (mean = 567 ppb) for 10 commercial samples of the dye certified by the FDA in 1983; an eleventh sample contained more than 6,500 ppb 4-aminobiphenyl and was reported to be withdrawn by the manufacturer (Bailey 1985). No data were identified on concentrations of 4-aminobiphenyl in foods prepared with any of the dyes in which 4-aminobiphenyl was permitted, but several studies have reported detectable levels of 4-aminobiphenyl adducts in pancreatic DNA (Ricicki *et al.* 2005) and in hemoglobin (Sarkar *et al.* 2006, Peluso *et al.* 2008) in both smokers and nonsmokers.

The U.S. Environmental Protection Agency's Toxics Release Inventory listed only one facility reporting environmental releases of 4-aminobiphenyl, which ranged from 2 to 48 lb per year from 1988 to 2001, except in 1997 and 1998, when no releases were reported. Most of the releases were to underground injection wells; small amounts were released to air in 1988, 1989, and 2000 (TRI 2009).

At greatest risk for occupational exposure are laboratory technicians and scientists who use 4-aminobiphenyl in research.

## Regulations

### Environmental Protection Agency (EPA)

#### Clean Air Act

*National Emission Standards for Hazardous Air Pollutants:* Listed as a hazardous air pollutant.

*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.

### Food and Drug Administration (FDA, an HHS Agency)

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 to 275 ppb.

The color additive Ext. D&C yellow no. 1 is banned because of contamination with 4-aminobiphenyl.

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

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

## 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: 10/19/09.
- Bailey JE Jr. 1985. Determination of unsulfonated aromatic amines in D&C red no. 33 by the diazotization and coupling procedure followed by reversed-phase liquid chromatographic analysis. *Anal Chem* 57: 189-196.
- ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. <http://www.chemsources.com/chemonline.html> and search on aminobiphenyl. Last accessed: 10/19/09.

- Del Santo P, Moneti G, Salvadori M, Saltutti C, Delle Rose A, Dolara P. 1991. Levels of the adducts of 4-aminobiphenyl to hemoglobin in control subjects and bladder carcinoma patients. *Cancer Lett* 60(3): 245-251.
- Feng Z, Hu W, Rom WN, Beland FA, Tang MS. 2002. 4-aminobiphenyl is a major etiological agent of human bladder cancer: evidence from its DNA binding spectrum in human p53 gene. *Carcinogenesis* 23(10): 1721-1727.
- 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. Last accessed: 2/4/04.
- 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: 10/19/09.
- IARC. 1972. 4-Aminobiphenyl. In *Some Inorganic Substances, Chlorinated Hydrocarbons, Aromatic Amines, N-Nitroso Compounds and Natural Products*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 1. Lyon, France: International Agency for Research on Cancer. pp. 74-79.
- IARC. 1987. 4-Aminobiphenyl. 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. 91-92.
- Koss LG, Melamed MR, Kelly E. 1969. Further cytologic and histologic studies of bladder lesions in workers exposed to para-aminodiphenyl: progress report. *J Natl Cancer Inst* 43(1): 233-243.
- Melick WF. 1972. Bladder carcinoma and xenylamine. *New Eng J Med*. 287:1103.
- 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.
- Peluso M, Airoidi L, Mannua A, Colombi A, Veglia F, Autrup H, *et al.* 2008. Bulky DNA adducts, 4-aminobiphenyl-haemoglobin adducts and diet in the European Prospective Investigation into Cancer and Nutrition (EPIC) prospective study. *Br J Nutr* 100:489-495.
- Ricicki EM, Soglia JR, Teitel C, Kane R, Kadybar F, Vouros P. 2005. Detection and quantification of N-(deoxyguanosin-8-yl)-4-aminobiphenyl adducts in human pancreas tissue using capillary liquid chromatography-microelectrospray mass spectrometry. *Chem Res Toxicol* 18: 692-699.
- Sarkar M, Stabbert R, Kinser RD, Oey J, Rustemeier K, von Holt K, Schepers G, Walk RA, Roethig HJ. 2006. CYP1A2 and NAT2 phenotyping and 3-aminobiphenyl and 4-aminobiphenyl hemoglobin adduct levels in smokers and non-smokers. *Toxicol Appl Pharmacol* 213: 198-206.
- Shelby MD, Gulati DK, Tice RR, Wojciechowski JP. 1989. Results of tests for micronuclei and chromosomal aberrations in mouse bone marrow cells with the human carcinogens 4-aminobiphenyl, treosulphan, and melphalan. *Environ Mol Mutagen* 13(4): 339-342.
- TRI. 2009. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. <http://www.epa.gov/triexplorer> and select 4-Aminobiphenyl. Last accessed: 10/19/09.
- Vineis P. 1994. Epidemiology of cancer from exposure to arylamines. *Environ Health Perspect* 102(Suppl 6): 7-10.
- Wang LY, Chen CJ, Zhang YJ, Tsai WY, Lee PH, Feitelson MA, Lee CS, Santella RM. 1998. 4-Aminobiphenyl DNA damage in liver tissue of hepatocellular carcinoma patients and controls. *Am J Epidemiol* 147(3): 315-323.
- Yu MC, Skipper PL, Tannenbaum SR, Chan KK, Ross RK. 2002. Arylamine exposures and bladder cancer risk. *Mutat Res* 506-507: 21-28.