Naphthylamine, 2-

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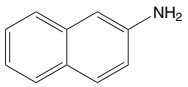
- Chemical Name: 2-Naphthylamine
- CAS Number: 91-59-8
- Synonyms: 2-Aminonaphthalene, β-Naphthylamine, 2NA, BNA, Fast Scarlet Base B
- Chemical Class: Aromatic amine
- Molecular Formula: $C_{10}H_7NH_2$
- Molecular Weight: 143.2
- Chemical Structure:



β-Naphthylamine

Background (Significance/History)

In the British rubber industry, the use of β-naphthylamine ended in 1949 and was mainly replaced by *N*-phenyl-2-naphthylamine (PBNA), which contained 2NA (1–2%) as impurities up to the early 1960s until further purification steps were introduced (Weiss et al., 2007). The production of PBNA in the United States was terminated at the beginning of the 1980s but was still a key component in rubber mixtures from other parts of the world. In addition, antioxidants in the rubber industry such as PBNA and *N*,*N*′-di-2-naphthyl-*p*-phenylenediamine have been shown to be metabolized to 2NA following absorption. However, the observed quantities of urinary 2NA in workers exceeded the exposure to 2NA impurity by factors between 50 and 400 and have yet to be explained. 2NA and other aromatic amines such as 4-aminobiphenyl are also produced during the burning of tobacco, especially low-temperature burning, and when cooking fats and oils are heated. Trace amounts of 2NA have been found in dye containing products such as children's finger paints.

Uses

2-Naphthylamine (2NA) was used as an intermediate in the dye industry and as an antioxidant in the rubber industry (e.g., the last company to manufacture it in the United States supposedly ceased production in 1972). However, it probably still presents an exposure hazard for at least some time afterward as a contaminant of dye stocks such as Broenner's acid and replacement antioxidants that retain the 2NA nucleus, for example, Nonox S (which contains 2.5% 2NA).

2NA has been found in emissions from industries where nitrogen-containing organic matter is pyrolyzed, in cigarette smoke, in coal tar, and as impurity in commercial 1-naphthylamine.

Environmental Fate and Behavior

2NA will exist solely as a vapor in the ambient atmosphere based on a vapor pressure of 2.56×10^{-4} mm Hg at 25 °C. Vapor-phase 2NA will be degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 1.9 h.

2NA is expected to have low mobility in soil based upon a K_{oc} of 1000. Volatilization from moist soil surfaces is not expected to be an important fate process based upon a Henry's law constant of 8.10×10^{-8} atm m^3 mol^{-1}. 2NA will partially exist in cation form in the environment (pK_a is 4.16) and hence adsorb to organic carbon and clay. 2NA is not expected to volatilize from dry soil surfaces based upon its vapor pressure. 2NA biodegradation in soil will be slow (no primary biodegradation after 90 days in chernozem soil and initial mineralization rate in soil/water suspension was 0.12 μg g^{-1} day^{-1}).

2NA is expected to adsorb to suspended solids and sediment in water based upon the K_{oc} and to biodegrade slowly in water (based on the primary soil biodegradation and mineralization studies). Volatilization from water surfaces is not expected to be an important fate process based upon 2NA's Henry's law constant. Hydrolysis is not expected to be an important environmental fate process since 2NA lacks functional groups that hydrolyze under environmental conditions.

Exposure and Exposure Monitoring

2NA is well absorbed through the skin, as well as via the gastrointestinal and respiratory tracts. With this and other aromatic amines, the skin appears to be a significant, if not the major occupational exposure pathway. This is not true for PBNA, which appear to penetrate skin poorly (Wellner et al., 2008). Workers tolerate skin contamination since the acute effects of exposure are minimal. Inhalation is the major route of exposure for tobacco smokers. There have been reports that passive burning of tobacco (environmental tobacco smoke) produces larger amounts of 2NA and other aromatic amines on a per cigarette basis than is seen with active smoking. Thus, there is some concern that passive smoke exposure may contribute to the burden of urinary bladder cancer in the nonsmoking population.

Occupational exposure to compounds containing a 2NA nucleus can result in 2NA exposure if metabolic enzymes can degrade the material. For example, workers inhaling approximately 30 mg in 1 day PBNA excreted 3–4 μg 2NA in their urine over the next 24 h. This is the 2NA exposure equivalent of smoking approximately five packs of cigarettes.

Toxicokinetics

Aromatic amines are well absorbed from the skin, the gut, and the respiratory tract. Aromatic amines like 2NA are metabolized rapidly and several systems compete for these agents as substrate. For example, the majority of 2NA is excreted in the urine as the glucuronide that is deconjugated prior to analysis. Ring oxidation and *N*-acetylation are considered the detoxification reactions and this is evidenced by the finding that person with the slow *N*-acetyltransferase 2 phenotype and exposed to many aromatic amines are at elevated risk of urinary bladder cancer in comparison to their fast acetylating cohorts. *N*-oxidation by cytochrome P450 (CYP450) enzymes is considered activating for bladder carcinogenesis. Polymorphisms of CYP4B1, involved in the metabolism of 2NA, may modify bladder cancer risk; e.g., subjects carrying the CYP4B1*1/*2 or *2/*2 genotypes had a 1.75-fold increased risk of bladder cancer compared with subjects carrying the CYP4B1*1/*1 genotype (Sasaki et al., 2008).

Also, 2NA has enhanced (*in vitro*) the impact of benzo(*a*) pyrene on Ah receptor-dependent genes (Borza et al., 2008).

Mechanisms of Toxicity

The acute toxicity of 2NA is low and due to the formation of methemoglobin. However, this is greatly overshadowed by the urinary bladder carcinogenicity of this compound. The proposed mechanism for this affect includes *N*-oxidation and excretion of the amine into the blood in an unconjugated form. Then, the *N*-hydroxy-2-naphthylamine is co-oxidized to the corresponding nitroso form while hemoglobin is oxidized to methemoglobin. 2-Nitrosonaphthalene is then capable of covalent binding with sulfhydral groups on hemoglobin, forming stable hemoglobin adducts.

The mechanism of chronic toxicity is related but not identical. 2NA and other aromatic amines including benzidine and 4-aminobiphenyl are potent human urinary bladder carcinogens. Apparently *N*-hydroxy-2-naphthylamine is *N*-glucuronidated and the product is transported from the liver to the urinary bladder, where the glucuronide can be hydrolyzed liberating *N*-hydroxy aromatic amine. This material is capable of binding with DNA in the urothelium of the exposed persons. While this pathway has not been shown specifically using 2NA as a substrate in humans, it is consistent with the animal data.

The low acute toxicity of 2NA masks its extreme carcinogenicity as exposed persons experience no or very slight ill effects and assume that the material is not toxic. The latency period for 2 NA urinary bladder cancer is estimated from 16 to 30 years after initial exposure.

Acute or Short-term Toxicity

Animal

Dogs and cats have been shown to be sensitive to methemoglobinemia following exposure to 2NA. A dose of 200 mg kg^{-1} was found to produce this effect 'reliably'.

Human

Methemoglobin formation was considered the most serious health outcome following exposure to 2NA until the increased rate of urinary bladder tumors was confirmed in the workers. Methemoglobinemia is symptom less until acutely toxic. In one report, workers exposed to 2NA were required to pass through the medical department following their shift so that any cyanosis could be ascertained.

Chronic Toxicity

Human

Chronic exposures to 2NA have been associated with bladder cancer (IARC group 1) and it can cause hematuria, dysuria, and hemorrhagic cystitis. Epidemiologic studies examining nonurological cancer risks among workers exposed to aromatic amines are few and inconsistent. Functional human NAT are present in different lung epithelial cells indicating that inhaled aromatic amines may undergo NAT-dependent metabolism in lung epithelium, and genetic and nongenetic impairment of this enzyme may compromise the detoxification pathway of aromatic amine *N*-acetylation in the lung (Dairou et al., 2009).

Immunotoxicity

In workers exposed to benzidine and β-naphthylamine, a decrease of CD4+ T lymphocytes was found (Araki et al., 1993). This decrease might be compensated by the increase in CD57+ CD16− cells, i.e., circulating peripheral lymphocytes with poor NK cell activity (Tanigawa et al., 1996).

Genotoxicity

Mutagenicity testing was positive in the *Salmonella* test (8.5 revertant colonies per nmol; 590 revertant colonies at 10 μg per plate) (Verschueren, 1983), in a series of wild-type and repair-deficient strains of *Drosophila melanogaster* (Vogel et al., 193), in several genetic loci in Chinese hamster ovary cells without microsomal activation (weakly mutagenic) (Gupta and Singh, 1982), induced crossing over in *Saccromyces cerevisiae* in the presence of hydroxylation medium (De Serres and Hollaender, 1978), in a test with a co-oxidizer (prostaglandin endoperoxide synthetase) (Robertson et al., 1983). Overall, 2NA exhibits weak mutagenicity in the microbial assays and in some mammalian systems *in vitro*.

Carcinogenicity

Humans exposed to 2NA during the production of this compound are at dramatically increased risk of urinary bladder cancer. According to one report, all 15 workers involved with distilling the product fell victim to the disease. In other rubber plants, clustering of relatively uncommon urothelial tract cancer were found in the early stages in

processing such as mixing and milling where dust and fume exposures were greatest (Veys, 2004). Bladder cancer risk ceased in one rubber plant when the use of the 2NA product ended. In other studies, the relative risk of urinary bladder cancer ranged from 30 to 60 times higher than expected with it not being uncommon that 50% of the exposed workforce were prevalent cases. As noted above, the estimates of the so-called 'latency' (time between first exposure and disease) period ranged from 16 to 30+ years for 2NA-exposed workers.

Clinical Management

Fortunately, urinary bladder cancer is amendable to effective treatment if detected early. A full spectrum of biomarkers and early diagnostic screens are available to alert the health professional when exposure to 2NA has occurred and when changes consistent with early neoplasia are occurring.

The (US) Occupational Safety and Health Administration (OSHA) standard for 2NA, 29 CFR 1910.1009, contains regulations covering periodic medical surveillance, examinations, and medical records for current employees who may have been exposed to 2NA. However, it should be noted that these regulations do not apply to former employees and that medical surveillance or treatment of former employees is not regulated or required by OSHA.

Ecotoxicology

None reported (checked: algae growth inhibition test, *Daphnia* sp. reproduction test, fish, early life stage test, activated sludge, respiration inhibition test).

Other Hazards

Other symptoms of exposure include methemoglobinemia, dyspnea, ataxia, and dermatitis.

Exposure Standards and Guidelines

As indicated above, 2NA is one of the carcinogens covered under a specific OSHA regulation, 29 CFR 1910.1009. The American Conference of Governmental Industrial Hygienists (ACGIH) indicates that exposure by all routes to 2NA should be controlled to levels as low as possible. IARC (IARC, 2010) concluded that there was sufficient evidence in humans for the carcinogenicity of 2NA. 2NA causes cancer in the human urinary bladder.

Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), commonly known as Superfund, requires that the National Response Center (NRC) is notified immediately, when there is a release of this designated hazardous substance, in an amount equal to or greater than its reportable quantity of 1 lb or 0.454 kg 2NA is regarded as hazardous waste, hence it must be managed according to federal and/or state hazardous waste regulations, which includes not only the substance itself or mixtures but also any residue, contaminated soil, water, or other debris (40 CFR 261.5).

Miscellaneous

The molecular weight of BNA is 143.2. It has a negligible vapor pressure ($2.56 \times 10{-}4$ mm Hg at 25 °C) until heated; at 108 °C (226.4 °F), the vapor pressure is 1 mm Hg. The concentration of 2NA in the air can be determined using NIOSH method 5518 and it oxidizes in air. Biological monitoring has been done for this material using urinary analysis of metabolites by high-performance liquid chromatography, hemoglobin adducts using gas chromatography–mass spectroscopy, and DNA adducts in lymphocytes and exfoliated urothelial cells using ^{32}P-postlabelling.

See also: Aminobiphenyl, 4-; Acetylaminofluorene; Benzidine; Cytochrome P450; National Center for Toxicological Research, US; Carcinogenesis; Polycyclic Aromatic Amines; Tobacco.

Further Reading

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Relevant Websites

http://www.osha.gov/dts/sltc/methods/organic/org093/org093.html OSHA website for analytical method #93, 4-aminobiphenyl, 1-naphthylamine and 2-naphthylamine