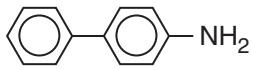
Overview information for

4-Aminobiphenyl

4-Aminodiphenyl

Synonyms	p-Aminodiphenyl
Formula	
Molecular weight	169.23
Melting point	53 – 54 °C
Boiling point	302 °C
MAK [last established: 1970]	Carcinogenic substance: category IIIA1 of the List of MAK and BAT Values

Until 1954 4-aminodiphenyl (4-ADP) was used, particularly in the American rubber industry, as a stabilising agent (44). Occupational medical investigations in 1954 showed among 171 exposed persons 19 tumours of the efferent urinary passages and in 1960 53 tumours among 315 exposed persons (13, 25, 43). Today 4-ADP only occurs in small amounts as a by-product, for example in the production and processing of certain amino and nitro aromatics (26). It is contained in traces in tobacco smoke (7, 46, 52, 54, 61). Furthermore, the products of technical combustion processes (diesel soot) include 4-nitrodiphenyl (4-NDP) (10, 18, 41, 62, 63, 65). 4-ADP is listed in the List of MAK and BAT Values in category IIIA1 (11). The most significant effect of exposure to 4-ADP is the formation of tumours of the efferent urinary passages with latency periods of up to 30 years (8, 9, 12, 12a, 14, 44, 58). Acute toxic effects of 4-ADP are not known in humans, neither after inhalation nor after oral or cutaneous exposure (2). In animal experiments (with dogs) formation of methaemoglobin can be induced with 4-ADP (55, 56).

1 Metabolism and Kinetics

4-Aminodiphenyl is absorbed rapidly via the skin and inhalation and excreted within 24 to 48 hours in the form of conjugates of the metabolites, predominantly via the kidneys (7, 17, 54). Low doses of 4-ADP are in general acetylated immediately and thus can be eliminated renally (26, 64). With increasing 4-ADP uptake the action of mixed function oxidases leads to significant increases in particular in hydroxylated metabolites (1, 17, 23, 40). The clinically important *N*-oxidation is more pronounced in "slow acetylators" than in "fast acetylators"; it leads to the formation of *N*-hydroxy-4-ADP (7, 19, 32, 45, 56). The *N*-hydroxy-4-ADP formed in the endoplasmatic reticulum of the liver is

stabilised by conjugation with *N*-glucuronide; the conjugate can be cleaved to yield *N*-hydroxy-4-ADP in the target organ (bladder) by β-glucuronidases (21, 27, 53).

In the erythrocytes *N*-hydroxy-4-ADP is oxidised to 4-nitrosodiphenyl. Part of the 4-nitrosodiphenyl formed in the erythrocytes binds covalently to the SH group of haemoglobin or of glutathione forming sulphinic acid amides (6, 7, 17, 20).

The electrophilic activation of the inert *N*-hydroxy-4-acetaminodiphenyl (*N*-hydroxy-4-AADP) takes place in several metabolic steps, for example by conjugation with sulphuric acid, deacetylation to *N*-hydroxy-4-ADP or intramolecular N,O-acyl transfer to*N*-acetoxy-4-ADP (3). In the acidic urine of the bladder (pH: 5–6) the *N*-acetoxy-4-ADP or the *N*-hydroxy-4-ADP which is instable in free form can decompose into the electrophilic diphenylnitrcnium ion or into other electrophilic derivatives (27, 28, 53). These bind either directly to macromolecules of the bladder epithelium or are detoxified by conjugation and excreted (7, 27, 37, 42, 51, 53). The individual reaction steps are represented in figure 1 (7, 27, 29).

The relatively long biological half-life of the erythrocytic 4-ADP adducts leads to accumulation, which makes a correlation with the 4-ADP adduct dose in other compartments difficult (20). For this reason the determination of the haemoglobin adducts can only provide general monitoring of the internal dose of 4-ADP, not specific monitoring of the target organ (7).

Variability of the Effect of 4-ADP

Adduct formation with proteins such as, e.g., haemoglobin (Hb) (34) and thus probably also with nucleic acids is largely avoided if the incorporated 4-aminodiphenyl is completely acetylated and thus eliminated quickly (via the kidneys) (33). Therefore the acetylator status has an important influence on the level of adduct formation which in general is particularly pronounced in “slow acetylators” (34, 48).

In 1979 attention was drawn for the first time to the association between the acetylator status and the development of bladder carcinomas (34, 36, 38, 47). In epidemiological studies it was discovered that fast acetylators were represented to a markedly lesser extent among patients with tumours of the efferent urinary passages than were slow acetylators despite comparable exposures to carcinogenic amino aromatics (19, 22, 36, 38, 47, 48). Hansen et al. found that of 105 persons with a bladder tumour 61.9 % were slow acetylators compared to only 42.9 % of patients without bladder carcinomas (22). With occupationally-induced bladder tumours the ratio was even higher 70: 30 (22). Observations by Lewalter in collectives with complete occupational anamneses show a still more significant ratio (100:0) (32). Not only the amount of the 4-ADP taken up but also the interindividual variance of the metabolic pathways is decisive for the kind and extent of the 4-ADP protein adducts and 4-ADP-DNA adducts (39) and thus for possible genotoxic effects formed in the individual (3, 16, 49, 60).

In general detectable or conspicuously elevated 4-ADP haemoglobin adduct levels are only observed in slow acetylators (32).

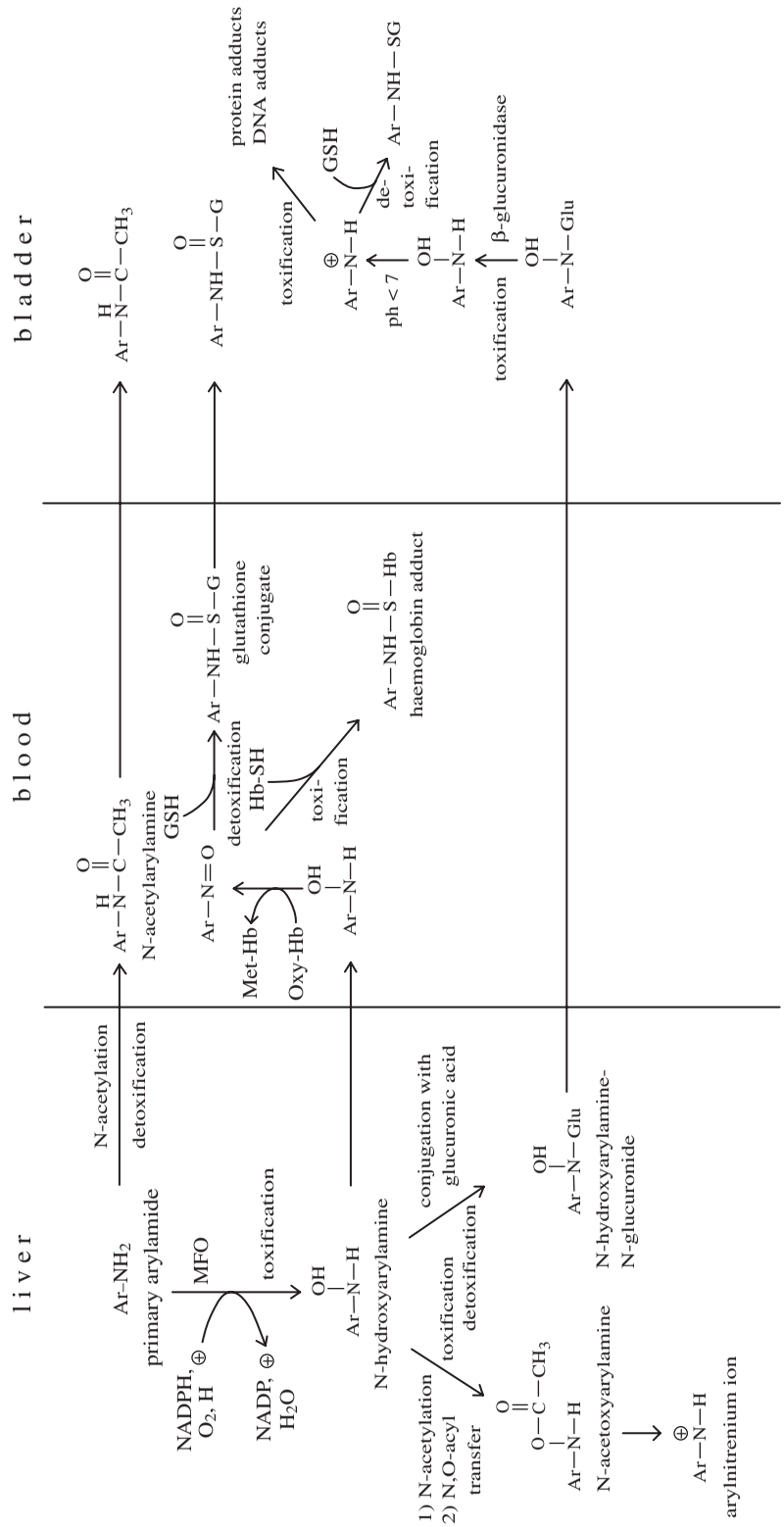


Fig. 1: Metabolism of primary amino aromatics (Ar-NH_2): formation and distribution of the metabolites (7, 27, 29); MFO = mixed function oxygenases, GSH = glutathione

2 Critical Toxicity

Presently available data have proved the carcinogenic effect of 4-ADP in humans.
Unlike the biological monitoring of aniline for which the BAT value is oriented on the Met-Hb level (24), the biological monitoring of persons exposed to 4-ADP must be focused on the minimising or avoidance of the macromolecular binding of 4-ADP.

3 Exposure and Effects

With 4-ADP every exposure which can lead to inhalation or dermal absorption is to be regarded as external exposure. The internal exposure is the biologically relevant concentration of the reactive intermediate in the target organ for which the carcinogenic effect is known, above all in the bladder.

A parameter of internal exposure is the 4-ADP concentration in body fluids such as blood, plasma and urine.

The 4-ADP adducts in the erythrocytes (Hb adducts) or leucocytes (DNA adducts) are understood as parameters of the internal effect of 4-ADP.

With the monitoring of the incidence of DNA strand breaks in leucocytes of persons exposed to 4-ADP a further parameter of effect is available, albeit unspecific and mainly suitable for the evaluation of acute 4-ADP intoxications.

4 Selection of the Indicators

4.1 4-Aminodiphenyl in Urine

It has been possible for some time now to measure the 4-ADP excretion (as conjugates) in the urine of persons exposed occupationally to 4-ADP (35, 50). Nevertheless, a measured correlation between the inhaled 4-ADP concentrations and the urinary excretion of the 4-ADP conjugates is still not available. The reasons for this include the frequently predominantly dermal 4-ADP exposures which cannot be evaluated quantitatively.

In practice, therefore, the excretion of 4-ADP in the urine of persons exposed to 4-ADP is assessed on the basis of occupational medical experience (31).

4.2 4-Aminodiphenyl Protein Adducts

According to the investigations of various research groups, glutathione conjugates are formed in the reaction of the metabolite 4-nitrosodiphenyl with the thiol group of glutathione (15) and corresponding adducts with the thiol groups of proteins (7). In particular the 4-ADP adducts with serum albumin (HSA) can be used for biological monitoring (7).

In order to restrict the amount of work required to detect these 4-ADP adducts it is recommended to test for 4-ADP adduct formation by HSA screening and only when these results are conspicuous or positive to quantify the Hb adducts. For the reasons already mentioned in section 4.1, there are no investigations on the correlation between defined Hb and HSA adducts and the level of the external exposure to 4-ADP.

4.3 DNA Adducts

Within the DNA the position C8 in guanine is the preferred target for the binding of active metabolites of 4-ADP. The reaction with *N*-hydroxy-4-ADP yields *N*-(deoxyguanosine-8-yl)-4-ADP (30). Biological monitoring of 4-ADP-DNA adducts in leucocytes is possible in principle. To what extent the detection of DNA adducts can be correlated with an effect on the DNA requires, however, further investigation (16, 49, 60). A genotoxic effect can also be detected by determining the incidence of DNA strand breaks (5).

5 Methodology

The analysis of 4-ADP takes place by high pressure liquid chromatography or (after derivatisation) capillary gas chromatography with an ECD detector or by GC/MS. HSA adducts are determined by isoelectric focusing. DNA adducts in the leucocytes are analysed with the GC/MS technique. The methods of analysis are described in the literature (7, 27, 59).

Determination of the incidence of DNA strand breaks in the leucocytes makes use of the method of alkaline elution (57).

Evaluation of the 4-ADP Content of Haemoglobin (Hb) Adducts and DNA Adducts

The 4-ADP content of the Hb adducts (µg 4-ADP$_{Hb}$) and the DNA adducts in the leucocytes (µg 4-ADP$_{DNA}$) are calculated, taking into account possible losses during preparation by use of the corresponding packed cell volumes (PCV) expressing the PCV of the erythrocytes or leucocytes in terms of the PCV of whole blood according to:

$$c_{Hb/DNA}\left(\frac{\mu g\ 4\text{-ADP}}{1\ blood}\right) = \frac{PCV_{blood}}{PCV_{suspension}} \cdot c_{suspension}\left(\frac{\mu g\ 4\text{-ADP}}{1\ suspension}\right)$$

$c_{Hb/DNA}$ = amount of 4-aminodiphenyl bound to haemoglobin (erythrocytes) or to DNA (leucocytes) per volume of blood
$c_{suspension}$ = amount of 4-aminodiphenyl measured in the erythrocyte or leucocyte suspension
PCV_{blood} = packed cell volume of whole blood
$PCV_{suspension}$ = packed cell volume of the erythrocyte or leucocyte suspension

6 Evaluation of the Biological Exposure Equivalents for Carcinogenic Substances (EKA)

6.1 4-Aminodiphenyl in Urine

Despite the monitoring of 4-ADP excretion in the urine of persons exposed to amino aromatics in industry, there are no published investigations of its dependence upon inhaled 4-ADP concentrations. Urinary excretion of 4-ADP detectable after contact with amino aromatics can be most probably explained by dermal absorption. Interindividual differences in the 4-ADP excretion rate are due to individual differences in the capability to acetylate 4-ADP (48).

In practice, for the occupational medical monitoring of exposure to 4-ADP "4-ADP monitoring values" of the order of magnitude of 100 ng 4-ADP per g creatinine have been named, however without scientific justification (4, 31).

6.2 4-Aminodiphenyl in Blood Cells

In an investigation of 29 smokers (on average 20 cigarettes/day) the 4-ADP content of the 4-ADP-Hb adducts was found to be 24.4 ng per 1 blood (7). The 4-ADP dose taken up daily amounted to approx. 100 ng in the main stream smoke and approx. 3000 ng 4-ADP in the side stream smoke.

The information available to the Commission at present indicates that 4-ADP exposures which cause urinary excretion levels below 100 ng per g creatinine and 4-ADP-Hb adduct levels below 100 ng per 1 blood do not produce detectable levels of DNA adducts in the leucocytes. In practice, the biological monitoring of persons exposed to 4-ADP can be based on these values. The establishing of correlations with the exposure is, with the database available at present, not possible for the reasons mentioned above.

7 Interpretation of the Data

For purposes of prevention, the 4-ADP concentrations measured in urine are not equal in value with the effect values measured in blood cells.

As a routine procedure, the investigation of the erythrocytic 4-ADP-Hb adducts is to be recommended as it determines not only current exposures but also any exposure from one week to two months previously (7).

Investigations in erythrocytes are not bound to any particular sampling time (31). On the other hand, urine investigations only provide reliable results if the sampling is carried out immediately after exposure (31).

8 References

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4-Aminobiphenyl

92-67-1

Hazard Summary

Limited exposure to 4-aminobiphenyl occurs since it is no longer produced commercially. Acute (short-term) inhalation exposure to 4-aminobiphenyl produces headaches, lethargy, cyanosis, urinary burning, and hematuria (the presence of blood in urine) in humans. 4-Aminobiphenyl is a known human bladder carcinogen and animal studies have reported an increase in bladder and liver tumors from oral exposure. EPA has not classified 4-aminobiphenyl for potential carcinogenicity; however, the International Agency for Research on Cancer (IARC) has classified 4-aminobiphenyl as a Group 1 carcinogen, the agent is carcinogenic to humans.

Please Note: The main sources of information for this fact sheet are the IARC monographs on chemicals carcinogenic to humans (2,4) and the Hazardous Substances Data Bank (HSDB) (1), a database of summaries of peer-reviewed literature. Other secondary sources include the Registry of Toxic Effects of Chemical Substances (RTECS) (7), a database of toxic effects that are not peer reviewed and The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals (6).

Uses

- 4-Aminobiphenyl is no longer manufactured commercially; it was used as a rubber antioxidant and a dye intermediate in the past. (3,5,6)

Sources and Potential Exposure

- Currently, individuals are unlikely to be exposed to 4-aminobiphenyl in the workplace because it is no longer manufactured commercially. However, past exposure may have occurred in the workplace. (1,2)
- 4-Aminobiphenyl is found in tobacco smoke; smokers have been found to have higher levels of the breakdown products of 4-aminobiphenyl in their blood than nonsmokers. (1)

Assessing Personal Exposure

- A method exists to measure the breakdown products of 4-aminobiphenyl in the blood. However, this is a newly developed research method that is not currently available for routine use. (1)

Health Hazard Information

Acute Effects:

- Acute inhalation exposure to 4-aminobiphenyl produces headaches, lethargy, cyanosis, urinary burning, and hematuria (the presence of blood in urine) in humans. (3)
- Tests involving acute exposure of rats, mice, and rabbits have demonstrated 4-aminobiphenyl to have moderate to high acute toxicity from ingestion. (7)

Chronic Effects (Noncancer):

- No information is available on the chronic (long-term) effects of 4-aminobiphenyl in humans or animals.
- EPA has not established a Reference Concentration (RfC) or a Reference Dose (RfD) for 4-aminobiphenyl.

Reproductive/Developmental Effects:

- 4-Aminobiphenyl has been shown to cross the placenta in humans and has been detected in fetal blood. No other information is available on the reproductive or developmental effects of 4-aminobiphenyl in humans or animals. (1)

Cancer Risk:

- 4-Aminobiphenyl is a known human bladder carcinogen, based on epidemiological studies of occupationally exposed workers who reported a high incidence of bladder cancer. (1,2-5)
- 4-Aminobiphenyl is carcinogenic in mice, rats, rabbits, and dogs. Bladder and liver tumors have been observed in mice, and bladder tumors have also been observed in rabbits and dogs following oral administration. Mammary gland and intestinal tumors have been reported in rats exposed by subcutaneous injection. (1,2,4,5)
- EPA has not classified 4-aminobiphenyl for potential carcinogenicity.
- IARC has classified 4-aminobiphenyl as a Group 1 carcinogen; i.e., there is sufficient evidence from epidemiological studies to support a causal association between the exposure and cancer. (4)

Physical Properties

- The chemical formula for 4-aminobiphenyl is $C_{12}H_{11}N$, and its molecular weight is 169.22 g/mol. (2,6)
- 4-Aminobiphenyl is a yellowish-brown crystalline solid and is slightly soluble in cold water and very soluble in hot water. (3,6)
- The odor threshold for 4-aminobiphenyl has not been established.
- The log octanol/water partition coefficient (log K_{ow}) for 4-aminobiphenyl is 2.80. (1)

Note: There are very few health numbers or regulatory/advisory numbers for 4-aminobiphenyl; thus a graph has not been prepared for this compound. The health values cited in this factsheet were obtained in December 1999.

Conversion Factors:
To convert concentrations in air (at 25°C) from ppm to mg/m^3: mg/m^3 = (ppm) × (molecular weight of the compound)/(24.45). For 4-aminobiphenyl: 1 ppm = 6.92 mg/m^3.

Summary created in April 1992, updated in January 2000.

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4-AMINOBIPHENYL
(Group 1)

For definition of Groups, see Preamble Evaluation.

Supplement 7: (1987) (p. 91)

CAS No.: 92-67-1
Chem. Abstr. Name: 4-Biphenylamine

A. Evidence for carcinogenicity to humans (*sufficient*)

The extent of bladder cancer risk associated with exposure to 4-aminobiphenyl was first documented by a descriptive study in the mid 1950s: of 171 men exposed to 4-aminobiphenyl between 1935 and 1955, 19 developed bladder tumours [ref: 1]. This observation appears to have been sufficient to prompt discontinuation of production and to prevent widespread use of the chemical. In 1955, a surveillance programme was initiated on workers reported to have been exposed to the chemical: during the following 14 years, 541 men were kept under surveillance by clinical and laboratory examinations; 86 had positive or suspicious cytology of the urinary sediment some time during the observation period, and 43 developed histologically confirmed carcinoma of the urinary bladder [ref: 2].

The hypothesis that another potential carcinogen, 4-nitrobiphenyl, was actually associated with the increased bladder cancer risk among these workers was raised but was dismissed by careful reconsideration of the processes involved and the possible exposures of the workers under surveillance [ref: 3].

In a survey of cancer mortality among workers at a chemical plant producing a variety of chemicals, a ten-fold increase in mortality from bladder cancer was reported. All of the nine cases on which the excess was based had started work in the plant before 1949, and 4-aminobiphenyl was known to have been used from 1941 until 1952 [ref: 4].

B. Evidence for carcinogenicity to animals (*sufficient*)

4-Aminobiphenyl was tested for carcinogenicity by oral administration in rabbits, dogs and mice and by subcutaneous administration in rats. Following its oral administration, it induced bladder papillomas and carcinomas in rabbits [ref: 1] and dogs [ref: 1,5], and neoplasms at various sites in mice, including dose-related increases in the incidences of angiosarcomas [ref: 6], hepatocellular tumours [ref: 1,6] and bladder carcinomas [ref: 1,6]. Following its subcutaneous administration to rats, it induced tumours of the mammary gland and intestine [ref: 1].

C. Other relevant data

No data were available on the genetic and related effects of 4-aminobiphenyl in humans. It formed DNA adducts in the bladder epithelium of dogs and protein adducts in serum albumin of rats treated *in vivo*. It induced mutation in human fibroblasts and mutation, DNA strand breaks and unscheduled DNA synthesis in cultured rodent cells. 4-Aminobiphenyl was mutagenic to bacteria and induced prophage [ref: 7].

Overall evaluation

4-Aminobiphenyl is *carcinogenic to humans (Group 1).*

For definition of the italicized terms, see Preamble Evaluation.

Also see previous evaluation: Vol. 1 (1972)

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Synonyms

- *para*-Aminobiphenyl
- *para*-Aminodiphenyl
- 4-Aminodiphenyl
- *para*-Biphenylamine
- *para*-Phenylaniline
- Xenylamine

Last updated: 6 February 1998

5. Evaluation – 4-Aminobiphenyl

There is ***sufficient evidence*** in humans for the carcinogenicity of 4-aminobiphenyl. 4-Aminobiphenyl causes cancer of the urinary bladder.

There is ***sufficient evidence*** in experimental animals for the carcinogenicity of 4-aminobiphenyl. 4-Aminobiphenyl causes a significant increase in the incidence of malignant bladder tumours in dogs and mice, and of angiosarcomas (all sites) and liver tumours in mice.

There is strong mechanistic evidence indicating that the carcinogenicity of 4-aminobiphenyl in humans operates by a genotoxic mechanism that involves metabolic activation, formation of DNA adducts, and induction of mutagenic and clastogenic effects. Metabolic activation to DNA-reactive intermediates occurs by multiple pathways including *N*-oxidation in the liver, *O*-acetylation in the bladder, and peroxidative activation in the mammary gland and other organs.

Overall Evaluation

4-Aminobiphenyl is *carcinogenic to humans (Group 1).*

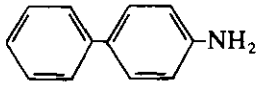
OCCUPATIONAL SAFETY AND HEALTH GUIDELINE FOR 4-AMINODIPHENYL POTENTIAL HUMAN CARCINOGEN

INTRODUCTION

This guideline summarizes pertinent information about 4-aminodiphenyl for workers, employers, and occupational safety and health professionals who may need such information to conduct effective occupational safety and health programs. Recommendations may be superseded by new developments in these fields; therefore, readers are advised to regard these recommendations as general guidelines.

SUBSTANCE IDENTIFICATION

- **Formula:** $C_{12}H_{11}N$
- **Structure:**



- **Synonyms:** 4-ADP; p-aminodiphenyl; 4-aminobiphenyl; 4-biphenylamine; (1,1' -biphenyl)-4-amine; diphenylamine; p-phenylaniline; xenylamine
- **Identifiers:** CAS 92-67-1; RTECS DU8925000; DOT not assigned
- **Appearance and odor:** Colorless crystals with a floral odor which turn purple on contact with air

CHEMICAL AND PHYSICAL PROPERTIES

- **Physical data**

1. Molecular weight: 169.24
2. Boiling point (at 760 mmHg): 302 °C (575.6 °F)
3. Specific gravity (water = 1): 1.160
4. Vapor density (air = 1 at boiling point of 4-aminodiphenyl): 5.8
5. Melting point: 53 °C (177 °F)
6. Solubility in water, g/100 g water at 25 °C (77 °F): 0.18

- **Reactivity**

Hazardous decomposition products: Toxic vapors and gases (e.g., carbon monoxide and oxides of nitrogen) may be released in a fire involving 4-aminodiphenyl.

- **Flammability**

1. Flash point: 152.7 °C (307 °F) (closed cup)
2. Autoignition temperature: 635 °C (1,175 °F)
3. Extinguishant: Dry chemical, alcohol foam, or carbon dioxide
4. Combustible solid, Flammability Rating 1 (NFPA)

- **Warning properties**

Evaluation of warning properties for respirator selection: Warning properties are not considered in recommending respirators for use with carcinogens.

EXPOSURE LIMITS

The Occupational Safety and Health Administration (OSHA) does not have a specific permissible exposure limit (PEL) for 4-aminodiphenyl; however, the OSHA standard requires implementation of stringent controls wherever 4-aminodiphenyl or solid or liquid mixtures containing at least 0.1% by weight or volume of 4-aminodiphenyl are manufactured, processed, repackaged, released, handled, or stored (see "General Control Procedures"). Details of this standard can be found in the Code of Federal Regulations, 29 CFR 1910.1011, 4-Aminodiphenyl. The National Institute for Occupational Safety and Health (NIOSH) concurs with the OSHA standard. The American Conference of Governmental Industrial Hygienists (ACGIH) has designated 4-aminodiphenyl as an A1 carcinogen (confirmed human carcinogen) (Skin). The "Skin" refers to the potential contribution to overall exposure by the cutaneous route including the mucous membranes and eyes. ACGIH recommends that virtually no exposure or contact by any route (i.e., respiratory, skin, or oral, as detected by the most sensitive methods) be permitted.

HEALTH HAZARD INFORMATION

- **Routes of exposure**

4-Aminodiphenyl may cause adverse health effects following exposure via inhalation, ingestion, or dermal contact.

- **Summary of toxicology**

1. *Effects on animals:* In mice, subchronic or chronic subcutaneous injection or oral administration of 4-aminodiphenyl produced cancers of the liver, bladder, or mammary glands. Chronic oral administration of 4-aminodiphenyl to dogs caused salivation, loss of body weight, blood in the urine, and bladder cancer.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service Centers for Disease Control
National Institute for Occupational Safety and Health
Division of Standards Development and Technology Transfer

2. *Effects on humans:* Chronic exposure of workers to 4-aminodiphenyl has been associated with an increased incidence of bladder cancer.

• **Signs and symptoms of exposure**

1. *Short-term (acute):* Exposure to 4-aminodiphenyl can cause headache, lethargy, urinary tract burning, blood in the urine, and bluish discoloration of the skin and mucous membranes (due to methemoglobinemia).

2. *Long-term (chronic):* Exposure to 4-aminodiphenyl can cause blood and pus in urine and frequent, painful urination.

RECOMMENDED MEDICAL PRACTICES

• **Medical surveillance program**

Workers with potential exposures to chemical hazards should be monitored in a systematic program of medical surveillance intended to prevent or control occupational injury and disease. The program should include education of employers and workers about work-related hazards, placement of workers in jobs that do not jeopardize their safety and health, earliest possible detection of adverse health effects, and referral of workers for diagnostic confirmation and treatment. The occurrence of disease (a "sentinel health event," SHE) or other work-related adverse health effects should prompt immediate evaluation of primary preventive measures (e.g., industrial hygiene monitoring, engineering controls, and personal protective equipment). A medical surveillance program is intended to supplement, not replace, such measures.

A medical surveillance program should include systematic collection and epidemiologic analysis of relevant environmental and biologic monitoring, medical screening, morbidity, and mortality data. This analysis may provide information about the relatedness of adverse health effects and occupational exposure that cannot be discerned from results in individual workers. Sensitivity, specificity, and predictive values of biologic monitoring and medical screening tests should be evaluated on an industry-wide basis prior to application in any given worker group. Intrinsic to a surveillance program is the dissemination of summary data to those who need to know, including employers, occupational health professionals, potentially exposed workers, and regulatory and public health agencies.

• **Preplacement medical evaluation**

Prior to placing a worker in a job with a potential for exposure to 4-aminodiphenyl, the physician should evaluate and document the worker's baseline health status with thorough medical, environmental, and occupational histories, a physical examination, and physiologic and laboratory tests appropriate for the anticipated occupational risks. These should concentrate on the function and integrity of the liver and urinary tract.

A preplacement medical evaluation is recommended in order to detect and assess preexisting or concurrent conditions which may be aggravated or result in increased risk when a worker is exposed to 4-aminodiphenyl. The examining physician should consider the probable frequency, intensity, and duration of exposure, as well as the nature and degree of the condition, in placing such a worker. Such conditions, which should not be regarded as absolute contraindications to job placement, include chronic diseases of the liver. The physician should obtain baseline values for liver function tests.

• **Periodic medical screening and/or biologic monitoring**

Occupational health interviews and physical examinations should be performed at regular intervals. Additional examinations may be necessary should a worker develop symptoms that may be attributed to exposure to 4-aminodiphenyl. The interviews, examinations, and appropriate medical screening and/or biologic monitoring tests should be directed at identifying an excessive decrease or adverse trend in the physiologic function of the liver and urinary tract as compared to the baseline status of the individual worker or to expected values for a suitable reference population. The physician should consider use of a test which characterizes internal exposure (e.g., benzidine in urine). However, this test should be used and interpreted according to standardized epidemiologic procedures and evaluation criteria.

• **Medical practices recommended at the time of job transfer or termination**

The medical, environmental, and occupational history interviews, the physical examination, and selected physiologic and laboratory tests which were conducted at the time of placement should be repeated at the time of job transfer or termination. Any changes in the worker's health status should be compared to those expected for a suitable reference population. Because occupational exposure to 4-aminodiphenyl may cause diseases of prolonged induction-latency, the need for medical surveillance may extend well beyond termination of employment.

• **Sentinel health events**

Delayed-onset SHE's include bladder cancer.

MONITORING AND MEASUREMENT PROCEDURES

• **Method**

Sampling and analysis may be performed by collecting 4-aminodiphenyl dust with glass fiber filters and silica gel tubes followed by elution with 2-propanol and analysis by gas chromatography. Direct-reading devices calibrated to measure 4-aminodiphenyl may also be used if available. A detailed sampling and analytical method for 4-aminodiphenyl may be found in the *NIOSH Manual of Analytical Methods* (method number 269).

PERSONAL PROTECTIVE EQUIPMENT

Chemical protective clothing (CPC) should be selected after utilizing available performance data, consulting with the manufacturer, and then evaluating the clothing under actual use conditions.

In operations involving "laboratory-type hoods" or in locations where 4-aminodiphenyl is contained in an otherwise "closed system" but is transferred, charged, or discharged into other normally closed containers, OSHA requires that workers: (1) be provided with and required to use clean, full-body CPC (smocks, coveralls, or long-sleeved shirts and long pants), shoe

covers, and gloves prior to entering a regulated area; (2) be provided with and required to use approved respirators (a respirator affording higher levels of protection may be substituted); and (3) remove the protective clothing and equipment prior to exiting from a regulated area, and at the last exit of the day, place used clothing and equipment in impervious containers for decontamination or disposal.

SANITATION

For closed system operations or in locations where 4-aminodiphenyl is contained in an otherwise "closed system" but is transferred, charged, or discharged into other normally closed containers, OSHA requires that workers: (1) wash their hands, forearms, faces, and necks prior to exiting from the regulated area and before engaging in other activities, and (2) shower in designated facilities after the last exit of the day.

In isolated systems, such as a "glove box," OSHA requires that workers wash their hands and arms with soap and water upon completion of the assigned task and before engaging in other activities not associated with the isolated system.

If it is necessary for workers to wear protective clothing, OSHA requires that a clean change room be provided and equipped with showers and washing facilities. NIOSH recommends that lockers that permit separation of street and work clothes be provided for the worker.

Clothing which is contaminated with 4-aminodiphenyl should be removed immediately and placed in sealed containers for storage until it can be discarded or until provision is made for the removal of 4-aminodiphenyl from the clothing. If the clothing is to be laundered or cleaned, the person performing the operation should be informed of 4-aminodiphenyl's hazardous properties. Reusable clothing and equipment should be checked for residual contamination before reuse or storage.

Decontamination and disposal procedures should be established and implemented to remove 4-aminodiphenyl from materials and equipment. Contaminated material should be removed from regulated areas without further contamination of the facility.

OSHA requires that workers wash their faces, necks, hands, and forearms thoroughly with soap and water before eating, smoking, or using toilet facilities.

In regulated areas, OSHA prohibits the storage or consumption of food or beverages, the storage or application of cosmetics, the storage or smoking of tobacco or other smoking materials, or the storage or use of products for chewing.

OSHA prohibits the location of drinking fountains in regulated areas.

GENERAL CONTROL PROCEDURES

The following control procedures are derived from OSHA requirements as stated in 29 CFR 1910.1011:

Areas where 4-aminodiphenyl is manufactured, processed, used, repackaged, released, handled, or stored shall be designated as regulated areas, and entry into and exit from these areas shall be restricted and controlled. Only authorized workers shall be permitted access to regulated areas.

Workers authorized to enter regulated areas shall receive a training and indoctrination program including but not limited to the nature of the carcinogenic hazards of 4-aminodiphenyl, including local and systemic toxicity, the specific nature of the operation which could result in exposure, and the purpose for and the significance of decontamination and emergency practices and procedures.

Entrances to regulated areas shall be posted with signs indicating that a cancer-suspect agent is present and that only authorized workers wearing appropriate protective clothing and equipment shall be admitted.

Appropriate signs and instructions shall be posted at the entrance to and exit from regulated areas to inform workers of the procedures that must be followed when entering or leaving a regulated area.

Open vessel system operations involving 4-aminodiphenyl which are not in an isolated system, laboratory-type hood, or other system affording equivalent protection against the entry of 4-aminodiphenyl into regulated areas, nonregulated areas, or the external environment are prohibited.

In operations involving "laboratory-type hoods" or in locations where 4-aminodiphenyl is contained in an otherwise "closed system" but is transferred, charged, or discharged into other normally closed containers, each operation shall be provided with continuous local exhaust ventilation so that air movement is always from ordinary work areas to the operation. Exhaust air shall not be discharged to regulated areas, nonregulated areas, or the external environment unless decontaminated. Clean makeup air shall be introduced in sufficient volume to maintain the correct operation of the local exhaust system.

Containers of 4-aminodiphenyl shall be identified as to contents and shall contain a hazard warning.

Regulated areas (with the exception of outdoor operations) shall be operated under negative pressure with respect to nonregulated areas. Local exhaust ventilation may be used to satisfy this requirement. Clean makeup air in equal volume shall replace air that is removed.

The introduction or removal of any equipment, materials, or other items to or from a regulated area shall be done in a manner that does not cause contamination of nonregulated areas or the external environment.

Decontamination procedures shall be established and implemented to remove 4-aminodiphenyl from the materials, equipment, and decontamination facility.

COMMON OPERATIONS AND CONTROLS

Common operations in which exposure to 4-aminodiphenyl may occur and control methods which may be effective in each case are listed in Table 1.

Table 1.—Operations and methods of control for 4-aminodiphenyl

Operations	Controls
During use in research and laboratory facilities	Process enclosure, restricted access, local exhaust ventilation, personal protective equipment, good housekeeping and personal hygiene practices, substitution with less toxic substances

EMERGENCY FIRST AID PROCEDURES

In the event of an emergency, remove the victim from further exposure, send for medical assistance, and initiate emergency procedures. If a worker has contact with 4-aminodiphenyl, OSHA requires that the worker shower as soon as possible, unless contraindicated by physical injuries.

• **Eye exposure**

Where there is any possibility of a worker's eyes being exposed to 4-aminodiphenyl, an eye-wash fountain should be provided within the immediate work area for emergency use.

If 4-aminodiphenyl gets into the eyes, flush them immediately with large amounts of water for 15 minutes, lifting the lower and upper lids occasionally. Get medical attention as soon as possible. Contact lenses should not be worn when working with this chemical.

• **Skin exposure**

Where there is any possibility of a worker's body being exposed to 4-aminodiphenyl, facilities for quick drenching of the body should be provided within the immediate work area for emergency use.

If 4-aminodiphenyl gets on the skin, wash it immediately with soap and water. If 4-aminodiphenyl penetrates the clothing, remove the clothing immediately and wash the skin with soap and water. Get medical attention promptly.

• **Rescue**

If a worker has been incapacitated, move the affected worker from the hazardous exposure. Put into effect the established emergency rescue procedures. Do not become a casualty. Understand the facility's emergency rescue procedures and know the locations of rescue equipment before the need arises.

SPILLS AND LEAKS

OSHA requires that hazardous conditions created by spills or leaks be eliminated and that potentially affected areas be decontaminated prior to the resumption of normal operations.

OSHA requires that affected areas of spills or leaks be evacuated as soon as an emergency has been determined.

OSHA requires that only authorized workers provided with and wearing clean, impervious garments (including gloves, boots, and continuous air-supplied hoods) enter areas of spills or leaks.

OSHA requires that workers authorized to enter areas of spills or leaks be decontaminated before removing the protective garments and hoods and showering.

If 4-aminodiphenyl is spilled or leaked, the following steps should be taken:

1. Remove all ignition sources.
2. Ventilate area of spill or leak.
3. If in solid form, 4-aminodiphenyl may be collected and placed in an appropriate container.
4. For small quantities of liquids containing 4-aminodiphenyl, absorb on paper towels and place in an appropriate container. Place towels in a safe place such as a fume hood for evaporation.
5. Large quantities of liquids containing 4-aminodiphenyl may be absorbed in vermiculite, dry sand, earth, or a similar material and placed in an appropriate container.
6. 4-Aminodiphenyl dust may be collected by vacuuming with an appropriate high-efficiency filtration system or by using wet methods; it may then be placed in an appropriate container. Dry sweeping and dry mopping of 4-aminodiphenyl are prohibited by OSHA. If a vacuum system is used, there should be no sources of ignition in the vicinity of the spill, and flashback prevention devices should be provided.

WASTE REMOVAL AND DISPOSAL

U.S. Environmental Protection Agency, Department of Transportation, and/or state and local regulations shall be followed to assure that removal, transport, and disposal are in accordance with existing regulations.

RESPIRATORY PROTECTION

It must be stressed that the use of respirators is the least preferred method of controlling worker exposure and should not normally be used as the only means of preventing or minimizing exposure during routine operations. However, there are some exceptions for which respirators may be used to control exposure: when engineering and work practice controls are not technically feasible, when engineering controls are in the process of being installed, or during emergencies and certain maintenance operations including those requiring confined-space entry (Table 2).

In addition to respirator selection, a complete respiratory protection program should be instituted which as a minimum complies with the requirements found in the OSHA Safety and Health Standards 29 CFR 1910.134. A respiratory protection program should include as a minimum an evaluation of the worker's ability to perform the work while wearing a respirator, the regular training of personnel, fit testing, periodic environmental monitoring, maintenance, inspection, and cleaning. The implementation of an adequate respiratory protection program, including selection of the correct respirators, requires that a knowledgeable person be in charge of the program and that the program be evaluated regularly.

Only respirators that have been approved by the Mine Safety and Health Administration (MSHA, formerly Mining Enforcement and Safety Administration) and by NIOSH should be used. **Remember! Air-purifying respirators will not protect from oxygen-deficient atmospheres.**

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Table 2.—Respiratory protection for 4-aminodiphenyl

Condition	Minimum respiratory protection*
Any detectable concentration	Any self-contained breathing apparatus with a full facepiece and operated in a pressure-demand or other positive pressure mode
	Any supplied-air respirator with a full facepiece and operated in a pressure-demand or other positive pressure mode in combination with an auxiliary self-contained breathing apparatus operated in a pressure-demand or other positive pressure mode
Planned or emergency entry into environments containing unknown or any detectable concentration	Any self-contained breathing apparatus with a full facepiece and operated in a pressure-demand or other positive pressure mode
	Any supplied-air respirator with a full facepiece and operated in a pressure-demand or other positive pressure mode in combination with an auxiliary self-contained breathing apparatus operated in a pressure-demand or other positive pressure mode
Firefighting	Any self-contained breathing apparatus with a full facepiece and operated in a pressure-demand or other positive pressure mode
Escape only	Any air-purifying full facepiece respirator with a high-efficiency particulate filter
	Any appropriate escape-type self-contained breathing apparatus

* Only NIOSH/MSHA-approved equipment should be used.

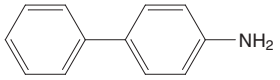
4-Aminobiphenyl

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, GeneTox 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	5.79×10^{-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 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.

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