

# 2-NAPHTHYLAMINE

2-Naphthylamine was considered by previous IARC Working Groups in 1973, 1987, and 2008 ([IARC, 1974, 1987, 2010](#)). Since that time new data have become available, which have been incorporated in this *Monograph*, and taken into consideration in the present evaluation.

## 1. Exposure Data

### 1.1 Identification of the agent

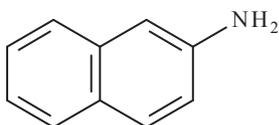
From [IARC \(2010\)](#)

*Chem. Abstr. Serv. Reg. No.:* 91-59-8

*Chem. Abstr. Serv. Name:*

2-Naphthalenamine

*Synonym:* this compound is also known as  $\beta$ -naphthylamine



$C_{10}H_9N$

Relative molecular mass: 143.18

*Description:* White to reddish crystals ([O'Neil, 2006](#))

*Solubility:* Soluble in water, diethyl ether, and ethanol ([O'Neil, 2006](#); [Lide, 2008](#))

### 1.2 Uses

2-Naphthylamine formerly was used commercially as an intermediate in the manufacture of dyes, as an antioxidant in the rubber industry, and to produce 2-chloronaphthalene

([IARC, 2010](#)). Because of its carcinogenicity, the manufacture and use of 2-naphthylamine have been prohibited in the European Union (EU) since 1998, in Italy since 1960, in the United Kingdom since 1952, and in Switzerland since 1938. Production and use of dyestuffs containing 2-naphthylamine have been banned in Japan since 1972 ([Olfert et al., 2006](#)). In the United States of America (USA), 2-naphthylamine is a carcinogen regulated by the Occupational Safety and Health Administration (OSHA). As such, exposure must be strictly controlled through mandatory use of engineering controls, safe work practices, and personal protective equipment ([OSHA, 2011](#)).

Small quantities of 2-naphthylamine are used in laboratory research ([IARC, 2010](#)). The substance has been found as a contaminant in other chemicals and industries ([Olfert et al., 2006](#)). Phenyl- $\beta$ -naphthylamine (PBNA) has been used as a substitute; however, it partially metabolizes in the body to 2-naphthylamine ([Olfert et al., 2006](#)).

## 1.3 Human exposure

### 1.3.1 Occupational exposure

In the past, occupational exposure to 2-naphthylamine mainly occurred during its production and when it was used in the manufacture of azo dyes. Exposure may still occur in laboratories where it is used as a model compound in cancer research, when workers are exposed to pyrolysis fumes containing 2-naphthylamine (e.g. foundry fumes, second-hand tobacco smoke, heated cooking-oils), to 2-nitronaphthalene (e.g. foundry workers), a nitro-PAH that can be metabolized to 2-naphthylamine, or to products containing 2-naphthylamine as a contaminant, such as certain rubber chemicals ([IARC, 2010](#)). Countries in which exposure was reported include: Italy, Japan, the Russian Federation, the United Kingdom, and the USA ([IARC, 2010](#)).

CAREX (CARcinogen EXposure) is an international information system on occupational exposure to known and suspected carcinogens, based on data collected in the European Union (EU) from 1990 to 1993. The CAREX database provides selected exposure data and documented estimates of the number of exposed workers by country, carcinogen, and industry ([Kauppinen et al., 2000](#)). [Table 1.1](#) presents the results for 2-naphthylamine by industry in the EU ([CAREX, 1999](#)).

From the US National Occupational Exposure Survey (1981–83) it was estimated that 275 workers, including 265 women, were potentially exposed to 2-naphthylamine ([NIOSH, 1990](#)). Exposure data were reported for a 2-naphthylamine/benzidine dye factory in Moscow ([Bulbulyan et al., 1995](#)). 2-Naphthylamine concentrations in indoor air samples taken in the factory during the period 1939–1948 ranged from < 1 µg/L to > 3 µg/L. Factory-wall wipes sampled in 1948 contained 60.0–115 mg/m<sup>2</sup> wall surface. Dermal wipes sampled in 1940 and 1947 from workers after a shower at work contained between 0.018 and 37.5 mg 2-naphthylamine (data on the surface area sampled were not available).

In a German study of workers primarily exposed to aniline and 4-chloroaniline, urinary 2-naphthylamine concentrations were 0–9.8 µg/L (mean, 3.9 ± 2.2) in 22 smokers and 0–11.6 µg/L (mean, 2.1 ± 2.8) in 21 non-smokers, both significantly higher than the concentrations measured in non-smoking, non-exposed workers (0.0–1.6 µg/L; mean, 0.5 ± 0.7) ([Riffelmann et al., 1995](#)).

In a study of two Danish iron foundries, airborne PAH concentrations were measured in relation to 2-naphthylamine (as a possible marker of 2-nitronaphthalene) in the urine of PAH-exposed workers ([Hansen et al., 1994](#)). The concentration of 2-naphthylamine in urine was significantly higher in PAH-exposed workers than in controls (matched for smoking habits). Hand moulders, finishing workers and truck drivers tended to have the highest levels. These results may be explained by the presence of 2-nitronaphthalene (which can be metabolized to 2-naphthylamine), the presence of aromatic amines, e.g. in moulding sand, or the presence of nitrogen oxides, e.g. in diesel exhaust. It has been estimated that a maximum of 1% of total *N*-phenyl-2-naphthylamine uptake can be transformed into 2-naphthylamine ([Weiss et al., 2007](#)).

### 1.3.2 Non-occupational exposure

The general population can be exposed to 2-naphthylamine through tobacco smoke and other fumes containing 2-naphthylamine, or reportedly when in contact with dyes and hair dyes contaminated with 2-naphthylamine [The Working Group could not find evidence of current contamination of these consumer products]. Exposure to 2-nitronaphthalene, which is formed by incomplete combustion of organic material and generally found in the environment in a mixture with other nitro-PAH and non-nitro-PAH, can also become an indirect source of contact with 2-naphthylamine ([IARC, 2010](#)).

**Table 1.1 Estimated numbers of workers exposed to 2-naphthylamine in the European Union**

Industry, occupational activity	
Education services	1260
Research and scientific institutes	450
Medical, dental, other health and veterinary services	340
TOTAL	2050

From [CAREX \(1999\)](#)

Mainstream cigarette smoke from eight different conventional market cigarettes in the USA contained 2-naphthylamine at concentrations of 1.47 to 14.06 ng/cigarette ([Stabbert et al., 2003](#)). A review of similar studies in the IARC Monograph on tobacco indicated that amounts of 2-naphthylamine in mainstream cigarette smoke range from 1–22 ng/cigarette; those in sidestream cigarette smoke range from 113.5–171.6 ng/cigarette ([IARC, 2004](#)).

In a German study ([Grimmer et al., 2000](#)), 2-naphthylamine was found in urine in comparable levels for non-smokers ( $n = 14$ ; mean, 120.8 ng/24 hours), smokers ( $n = 12$ ; mean, 84.5 ng/24 hours) and persons exposed to second-hand tobacco smoke ( $n = 22$ ; mean, 94.9 ng/24 hours). In a study by [Riedel et al. \(2006\)](#), smokers ( $n = 10$ ) excreted significantly higher amounts of 2-naphthylamine compared with non-smokers ( $n = 10$ ) (20.8 vs 10.7 ng/24 hours).

2-Naphthylamine has been detected in fumes of heated cooking-oils ([Chiang et al., 1999](#)) in a study in Taiwan (China) looking at three different commercial cooking oils. Concentrations of 2-naphthylamine in oil fumes were 31.5  $\mu\text{g}/\text{m}^3$  for sunflower oil, 31.9  $\mu\text{g}/\text{m}^3$  for vegetable oil, and 48.3  $\mu\text{g}/\text{m}^3$  for refined lard oil.

## 2. Cancer in Humans

Studies of cancer in humans exposed to 2-naphthylamine were most recently reviewed by a Working Group in 2008 ([IARC, 2010](#)): it was concluded that there was *sufficient evidence*

in humans for the carcinogenicity of 2-naphthylamine in the human urinary bladder. Numerous case series reported bladder cancer in workers exposed to 2-naphthylamine; in coal-tar dye workers exposed to 2-naphthylamine, and not to other aromatic amines, the cumulative incidence of bladder cancer was 25% ([Goldwater et al., 1965](#)). Eleven cohort studies (four in the USA, two in the United Kingdom, two in Japan, and one each in Poland, the Russian Federation and Italy) are available concerning bladder-cancer risks in workers engaged in the manufacture and use of 2-naphthylamine (see Table 2.1 available at <http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-05-Table2.1.pdf>). All these studies indicate markedly elevated bladder cancer risks associated with the manufacture and use of 2-naphthylamine. In most of the studies, it was not possible to quantify the relative contributions of exposures to benzidine and 2-naphthylamine to the overall excess risks. However, [Case et al. \(1954\)](#) had reported 26 bladder-cancer deaths, with 0.3 expected [SMR 86.7, 95%CI: 56.6–127.0], in British dyestuff-industry workers exposed to 2-naphthylamine. Also, in a study of bladder-cancer risks in the British rubber industry, [Veys \(2004\)](#) showed excesses of bladder cancer in workers employed between 1946 and 1949 when 2-naphthylamine-contaminated antioxidants were still used (58 cases, SIR 1.71; 95%CI: 1.3–2.21) and no excess in workers employed after this exposure was removed (39 cases, SIR 1.02 95%CI: 0.72–1.39).

### 3. Cancer in Experimental Animals

Studies on the carcinogenicity of 2-naphthylamine in the mouse, rat, hamster, rabbit, dog, and monkey after oral administration, after subcutaneous or intraperitoneal injection, after intravesicular implantation, or after dermal application have been reviewed in previous *IARC Monographs* ([IARC, 1974, 1987, 2010](#)). There have been no additional carcinogenicity studies in animals reported since the most recent evaluation ([IARC, 2010](#)).

2-Naphthylamine was tested for carcinogenicity by oral administration (in the feed, by gavage or in a gelatin capsule) in five experiments in mice, three experiments in rats, ten experiments in dogs, and one experiment each in hamsters, rabbits and monkeys; by subcutaneous administration in five experiments in mice; by intraperitoneal injection in two experiments in mice and one in rats; and by one intravesicular implantation and one skin-painting study in mice and one bladder instillation study in dogs. Results of adequately conducted carcinogenicity studies are summarized in [Table 3.1](#).

Oral administration of 2-naphthylamine to mice caused a significant increase in the incidence of cholangiomas, hepatomas and liver adenomas ([Bonser et al., 1952](#); [Yoshida et al., 1979](#)) and induced ‘malignant’ hepatomas ([Bonser et al., 1952](#)). 2-Naphthylamine caused a significant increase in urinary bladder tumours (including carcinomas) following its oral administration to rats ([Hicks et al., 1982](#); [Hicks & Chowanec, 1977](#)), hamsters ([Saffiotti et al., 1967](#)), dogs ([Hueper et al., 1938](#); [Bonser et al., 1956](#); [Harrison et al., 1969](#); [Conzelman & Moulton, 1972](#); [Romanenko & Martynenko, 1972](#); [Rigotti et al., 1977](#); [Purchase et al., 1981](#)) and monkeys ([Conzelman et al., 1969](#)). Intraperitoneal injection of 2-naphthylamine ([Theiss et al., 1981](#)) or its administration by gavage ([Stoner et al., 1986](#)) increased the

multiplicity of benign lung tumours in strain A mice.

The results of the oral study in rabbits, the intraperitoneal injection study in rats, the subcutaneous injection study, the intravesicular implant study and the skin-painting study in mice, and the bladder-instillation study in dogs were found to be inadequate for the evaluation of the carcinogenicity of 2-naphthylamine.

### 4. Other Relevant Data

A general Section on “Aromatic amines: metabolism, genotoxicity, and cancer susceptibility” appears as Section 4.1 in the *Monograph* on 4-aminobiphenyl in this volume.

2-Naphthylamine is a constituent of tobacco smoke, and the amounts of 2-naphthylamine-haemoglobin adducts are higher in cigarette smokers than in non-smokers ([Bryant et al., 1988](#)). Similarly to other aromatic amines, 2-naphthylamine may undergo *N*-hydroxylation by CYP1A2 ([Butler et al., 1989](#)) followed by conjugation of the hydroxyl group with sulfate or glucuronide, or conjugation of the amino group with acetate (*N*-acetylation), sulfate, or glucuronide. In addition, 2-naphthylamine may undergo *N*-oxidation and ring oxidation by peroxidative enzymes such as prostaglandin H synthase in the bladder ([Wise et al., 1984](#); [Yamazoe et al., 1985](#)) to form an arene oxide. The *N*-hydroxylated intermediate may re-arrange to form 2-amino-1-naphthol and conjugates with sulfate or glucuronide, or form DNA adducts such as *N*-(deoxyguanosin-8-yl)-2-NA, 1-(deoxyguanosin-*N*<sup>2</sup>-yl)-2-naphthylamine, and 1-(deoxyadenosin-*N*<sup>6</sup>-yl)-2-naphthylamine ([Beland et al., 1983](#)). These adducts are also formed by prostaglandin H synthase ([Yamazoe et al., 1985](#)), or from the 2-imino-1-naphthoquinone intermediate (e.g. *N*<sup>4</sup>-deoxyguanosin-*N*<sup>2</sup>-yl)-2-amino-1,4-naphthoquinone-imine).

Table 3.1 Carcinogenicity studies of exposure to 2-naphthylamine in experimental animals

Species, strain (sex) Duration Reference	Route Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, IF (M, F) up to 72 wk <a href="#">Bonser et al. (1952)</a>	Gavage A group of 13 M and 12 F mice received 2-naphthylamine suspended in arachis oil, twice weekly at a dose of 400 mg/kg bw per wk. A group of 6 M and 5 F served as arachis-oil controls.	Liver cholangiomas: M-0/6 (controls), 5/13 F-0/5 (controls), 5/12 M+F-0/11 (controls), 10/25	NR, [NS] [ <i>P</i> < 0.02]	Age NR Small number of animals studied, especially controls
Mouse, CBA (M, F) up to 89 wk <a href="#">Bonser et al. (1952)</a>	Gavage A group of 9 M and 14 F mice received 2-naphthylamine suspended in arachis oil twice/wk at a dose of 240 mg/kg bw per wk. A group of 7 M and 7 F served as arachis-oil controls	Hepatomas: M-0/7 (controls), 6/9 (67%) F-0/7 (controls), 7/14 (50%)	NR [ <i>P</i> < 0.05] [ <i>P</i> < 0.05]	Age NR Small number of animals studied, especially controls. Authors reported the incidence of hepatomas in the control breeding mice of the laboratory to be 8%
Mouse, CBA (M, F) up to 89 wk <a href="#">Bonser et al. (1952)</a>	Feed Groups of 14-15 M and 12-15 F mice were given four different synthetic diets containing 2-naphthylamine at a dose of 160 mg/kg bw per wk	Hepatomas: M-24/57 F-25/54 Hepatomas (malignant): M+F-16/111	-	Age NR No controls
Mouse, BALB/c (F) 55 wk <a href="#">Yoshida et al. (1979)</a>	Feed Groups of 20 F mice were fed a diet containing 0 or 2000 ppm 2-naphthylamine for 40 wk	Liver tumours: Adenoma-0/17, 10/16 Hepatoma-0/17, 3/16 Urinary bladder-epithelium hyperplasia: 0/17, 6/16	NR [ <i>P</i> < 0.0001] [NS] [ <i>P</i> < 0.01]	Purity NR
Mouse, A/J (M, F) 24 wk <a href="#">Stoner et al. (1986)</a>	Gavage A group of 16 M and 16 F mice received 2-naphthylamine in tricaprilyn by gavage 3 × /wk for 8 wk, resulting in a total dose per animal of 600 mg/kg bw. A group of 16 M and 16 F mice served as tricaprilyn controls.	Lung tumours: M-3/15 (controls), 8/14 F-2/14 (controls), 4/13 Lung tumour multiplicity: M-0.93 ± 1.00 vs 0.27 ± 0.59 (controls)	[NS] [NS] <i>P</i> < 0.05	
Rat, Albino (strain NR) (M, F) over 90 wk <a href="#">Bonser et al. (1952)</a>	Feed Three groups of 18, 15 and 17 M and F rats were fed low-, mid- and high-protein diets containing 2-naphthylamine at a dose of 310 mg/kg bw per wk for life. Three groups of 15, 17 M and 17 F rats served as controls.	Urinary bladder papillomas: 0/49 (controls), 4/50	NR, [NS]	Age NR

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Wistar (F) up to 104 wk <a href="#">Hicks &amp; Chowaniec (1977)</a>	Gavage A group of 25 F rats were given 2-naphthylamine in arachis oil by gavage, at a dose of 300 mg/kg bw per wk for one yr, and were then left untreated until symptoms of bladder disease were seen. A group of 50 F served as untreated controls.	Urinary bladder tumours: 0/50, 5/17	NR; [P < 0.001]	Purity NR Bladder tumours not further specified
Rat, Wistar (F) 100 wk <a href="#">Hicks et al. (1982)</a>	Gavage A group of 20 F rats received 2-naphthylamine suspended in arachis oil by gavage at a dose of 300 mg/kg bw per wk for 57 wk. A group of 20 F served as vehicle controls.	Urinary bladder: Carcinomas–0/20, 4/18 Urothelial hyperplasias–0/20, 8/18	NR [P < 0.05] [P < 0.001]	Purity NR
Hamster, Random-bred Syrian golden (M, F) Lifetime <a href="#">Saffiotti et al. (1967)</a>	Feed Groups of 30 M and 30 F hamsters were fed diets containing 0, 0.1 or 1.0% (w/w) 2-naphthylamine.	Urinary bladder carcinomas: M–0/30, 0/30, 10/23* F–0/30, 0/30, 8/16*	NR *[P < 0.0001]	Purity NR Hepatoma was found in one high-dose male and one high-dose female.
Dog, Mongrel (F) 89 wk <a href="#">Hueper et al. (1938)</a>	Oral and subcutaneous injection A group of 16 F mongrel dogs received subcutaneous injections of 4 mg/d (for dogs ≤ 12 kg) or 5 mg/d (for dogs > 12 kg) 2-naphthylamine, daily for 14 wk followed by doubling of the dose for 12 wk and a tripling for the subsequent 63 wk. During the last 54 wk of the study, dogs started to receive a daily oral dose of 2-naphthylamine by capsule that started at 100 mg/dog and increased to 300 mg/dog by the end of the treatment. A group of four F dogs served as controls.	Urinary bladder tumours (papillomas and carcinomas combined): 0/4, 13/16	NR; [P < 0.01]	Purity NR Bladder-tumour incidence based partly on autopsy and partly on cystoscopy and biopsy. Dosing poorly described.
Dog, Mongrel (F) up to 3 yr <a href="#">Bonser et al. (1956)</a>	Oral A group of 4 F dogs were given 2-naphthylamine by mouth in a capsule at a dose of 200 mg/d, on six d/wk during 6 mo and then 600 mg/d for up to 2 yr.	Urinary bladder carcinomas: 2/4	-	Age NR, purity NR One dog died after 14.5 mo of treatment. No controls
Dog, Mongrel (F) 79 mo <a href="#">Harrison et al. (1969)</a>	Oral A group of 4 F dogs were fed 2-naphthylamine at a dose of 400 mg/d for 2 yr	Urinary bladder carcinomas: 4/4	-	Age NR, purity NR No controls Experimental details poorly described

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Dog, Beagle (M, F) up to 30 mo <a href="#">Conzelman &amp; Moulton (1972)</a>	Oral Groups of 2–7 M and 2–5 F 8–10-mo-old dogs were given 2-naphthylamine by mouth in a capsule at doses of 0, 6.25, 12.5, 25, or 50 mg/kg bw per d on 6 d/wk for 2–26 mo. Total dose/dog ranged from 12 g to 204 g	Urinary bladder carcinomas: M–0/2, 4/6, 2/5, 6/7, 1/2 F–0/2, 0/3, 2/5, 2/3, 3/3 M+F–0/4 (controls), 20/34* (treated)	NR *[ $P < 0.05$ ]	Purity NR
Dog, Breed NR (F) 55 mo <a href="#">Romanenko &amp; Martynenko (1972)</a>	Oral A group of eight F dogs were given 2-naphthylamine at a dose of 5–30 mg/kg bw, 4–6 d/wk, for 7.5 mo and then 30 mg/kg bw, 4–6 d/wk, for 8.5 mo	Urinary bladder carcinomas: 7/8	-	Age NR, purity NR No controls. Route of administration poorly described.
Dog, Breed NR (F) 26 mo <a href="#">Rigotti et al. (1977)</a>	Oral A group of 20 F dogs were given 2-naphthylamine in a capsule, daily at a dose of 500–600 mg for 20–26 mo.	Urinary bladder carcinomas: 20/20	-	Age NR, purity NR No controls.
Dog, Beagle (M, F) up to 47 mo <a href="#">Purchase et al. (1981)</a>	Oral 3 M and 2 F dogs (age, 9 mo) were given capsules containing 400 mg 2-naphthylamine 5 × /wk for 34 mo. A group of 4 M and 4 F control dogs received capsules with lactose.	Urinary bladder transitional-cell carcinomas: 0/8, 5/5	NR, [ $P < 0.001$ ]	
Monkey, Rhesus <i>Macaca mulatta</i> (M, F) up to 60 mo <a href="#">Conzelman et al. (1969)</a>	Gavage A group of 8 M and 19 female monkeys (weighing 2–3 kg) were given 2-naphthylamine in a capsule by gavage at a dose of 0 (control, three females) or 6.25–400 mg/kg bw per d, on 6 d/wk for 33–60 mo.	Urinary bladder carcinomas: 0/3 (controls), 9/24	NR	Age NR Some animals received a fixed dose during the entire experiment, others received different doses over the course of five yr. The majority of tumours occurred in animals given high doses.
Mouse, Inbred A/St mice (M, F) 24 wk <a href="#">Theiss et al. (1981)</a>	Intraperitoneal injection A group of 10 M and 10 F mice were given 2-naphthylamine in tricapylin by injection at doses of 0, 62.5, 125 or 250 mg/kg bw, 3 × /wk for 8 wk.	Lung adenomas/mouse: 0.19, 0.40, 0.50, 1.38*	* $P < 0.01$	Purity NR

bw, body weight; d, day or days; F, female; M, male; mo, month or months; NR, not reported; NS, not significant; vs, versus; wk, week or weeks; yr, year or years

2-Naphthylamine was mutagenic in *S. typhimurium* strains TA98 and TA100 in the presence of bovine bladder cells ([Hix et al., 1983](#)). 2-Naphthylamine-induced DNA damage was triggered by an NAT1-overexpressing *S. typhimurium* strain, but not by an O-acetyltransferase-deficient strain, in the presence of human CYP1A2 (*umu* response) ([Oda, 2004](#)). In another *umu* gene-expression assay, DNA damage in *S. typhimurium* strain NM2009 exposed to 2-naphthylamine was induced by the CYP4B1 isoenzyme from rat-bladder epithelium ([Imaoka et al., 1997](#)). 2-Naphthylamine was mutagenic in Chinese hamster ovary cells in the presence or absence of an exogenous activating system ([Gupta & Singh, 1982](#)).

## 5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of 2-naphthylamine. 2-Naphthylamine causes cancer of the urinary bladder.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 2-naphthylamine.

There is strong mechanistic evidence indicating that the carcinogenicity of 2-naphthylamine operates by a genotoxic mechanism of action 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.

2-Naphthylamine is *carcinogenic to humans* (Group 1).

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