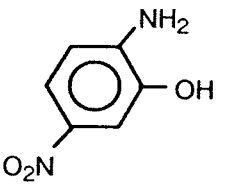
2-AMINO-5-NITROPHENOL

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Synonyms, structural and molecular data*

Chem. Abstr. Serv. Reg. No.: 121-88-0
Chem. Abstr. Name: 2-Amino-5-nitrophenol
Colour Index No.: 76535
Synonyms: 3-Hydroxy-4-aminonitrobenzene; 2-hydroxy-4-nitroaniline; 3-nitro-6-aminophenol; 5-nitro-2-aminophenol



$C_6H_6N_2O_3$ Mol. wt: 154.12

1.1.2 *Chemical and physical properties*

(*a*) *Description*: Olive-brown, brown to orange crystalline solid (US National Toxicology Program, 1988; Jos. H. Lowenstein & Sons, 1991)

(*b*) *Melting-point*: 200 °C (decomposes) (Aldrich Chemical Co., 1992); 207–208 °C (Lide, 1991); 198–202 °C (98% pure) (Jos. H. Lowenstein & Sons, 1991)

(*c*) *Spectroscopy data*: Infrared, ultraviolet and nuclear magnetic resonance spectral data have been reported (Sadtler Research Laboratories, 1980; Pouchert, 1981; US National Toxicology Program, 1988; Sadtler Research Laboratories, 1991).

(*d*) *Solubility*: Slightly soluble in water (US National Toxicology Program, 1988); soluble in ethanol, acetone and benzene (Lide, 1991)

1.1.3 *Trade names, technical products and impurities*

Trade names: Ursol Yellow Brown A; Rodol YBA

2-Amino-5-nitrophenol is available commercially with the following specifications: purity, 98% (min.); ash, 0.05% (max.); iron, 40 ppm (mg/kg) (max.); lead (see IARC, 1980a, 1987a), 5 ppm (mg/kg) (max.); and arsenic (see IARC, 1980b, 1987b), 2 ppm (mg/kg) (max.).

It is also available in research quantities, at purities ranging from 90 to 99% (Jos. H. Lowenstein & Sons, 1991; TCI America, 1991; Aldrich Chemical Co., 1992; Fluka Chemie AG, 1993).

1.1.4 *Analysis*

No data were available to the Working Group.

1.2 Production and use

1.2.1 *Production*

2-Amino-5-nitrophenol is produced from 2-aminophenol by reaction with acetic anhydride to form 2-methylbenzoxazole, which is nitrated and hydrolysed to form 2-amino-5-nitrophenol (Farris, 1978). It was first synthesized by Kaltwasser and Oehrn in 1920 (Society of Dyers and Colourists, 1971).

2-Amino-5-nitrophenol is produced by one company each in France and Germany and by three companies in Japan (Chemical Information Services, 1991). It is not produced in commercial quantities in the USA. Between 1973 and 1979, US imports averaged 13.4 tonnes per year (US National Toxicology Program, 1988).

1.2.2 *Use*

2-Amino-5-nitrophenol is used as an intermediate in the manufacture of several azo dyes, including CI Solvent Red 8, which is used for colouring synthetic resins, lacquers, inks and wood stains (US National Toxicology Program, 1988).

2-Amino-5-nitrophenol is also used in many countries as a dye in semi-permanent hair colouring products to produce red and gold-blond shades. These products are generally shampooed into the hair, lathered and then allowed to remain in contact with the hair and scalp for 30–45 min. For this application, 2-amino-5-nitrophenol is mixed (at levels up to 0.5%) with a blend of several other dyes in a shampoo base to produce the final colour or tint desired (Frenkel & Brody, 1973; US National Toxicology Program, 1988). It has been used (and still is to a limited extent) in permanent hair colouring products.

1.3 Occurrence

1.3.1 *Natural occurrence*

2-Amino-5-nitrophenol is not known to occur as a natural product.

1.3.2 *Occupational exposure*

No data were available to the Working Group.

On the basis of a survey conducted in the USA between 1981 and 1983, the US National Institute for Occupational Safety and Health estimated that a total of 14 512 workers, including 11 827 women, were potentially exposed to 2-amino-5-nitrophenol in 1339 beauty salons (US National Library of Medicine, 1992).

1.4 Regulations and guidelines

The use of 2-amino-5-nitrophenol in cosmetic products is prohibited in the European Economic Community (Commission of the European Communities, 1976, 1990, 1991).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

3.1.1 *Mouse*

Groups of 50 male and 50 female B6C3F$_1$ mice, seven to eight weeks of age, were administered 0, 400 or 800 mg/kg bw 2-amino-5-nitrophenol (98% pure) by gavage in corn oil (10 ml/kg) on five days a week for up to 103 weeks and were killed at 112 weeks of age. The mean body weights of high-dose males were 8–11% lower than those of vehicle controls from week 29 to week 74, whereas those of low-dose males were greater than those of vehicle controls throughout most of the study. The mean body weights of low-dose and high-dose female mice were 5–9 and 8–13% lower than those of vehicle controls from week 69 to the end of the study, respectively. Survival of high-dose males after week 20 and of females after week 22 was reduced compared with that of controls ($p < 0.001$, Cox and Tarone's test). Survival at termination of the study was: males—control, 31/50; low-dose, 36/50; and high-dose, 12/50; females—control, 37/50; low-dose, 36/50; and high-dose, 10/50. No significant increase in the incidence of tumours was observed in treated groups when compared with controls (US National Toxicology Program, 1988). [The Working Group noted the high mortality in the high-dose groups.]

3.1.2 *Rat*

Groups of 50 male and 50 female Fischer 344/N rats, six to seven weeks of age, were administered 0, 100 or 200 mg/kg bw 2-amino-5-nitrophenol (98% pure) by gavage in corn oil (5 ml/kg) on five days a week for up to 103 weeks and were killed at 111 weeks of age. Mean body weights of male and female high-dose rats were 5–10 and 4–5% lower than those of controls after weeks 33 and 93, respectively. Survival of high-dose males and females after week 75 and that of low-dose males and females after week 99 was significantly lower than that of vehicle controls ($p < 0.001$, Cox and Tarone's test). Survival at termination was: males—control, 33/50; low-dose, 16/50; and high-dose, 4/50; females—control, 30/50; low-dose, 32/50; and high-dose, 29/50. The incidence of pancreatic acinar-cell adenomas was significantly increased in low-dose (10/50; $p = 0.002$, incidental tumour test) but not in high-dose (3/49) males in comparison with controls (1/50). One acinar-cell carcinoma was also seen in a low-dose male (US National Toxicology Program, 1988). [The Working Group noted the poor survival of treated males.]

4. Other Relevant Data

4.1 Absorption, distribution, metabolism and excretion

No data were available to the Working Group.

4.2 Toxic effects

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

The LD_{50} of 2-amino-5-nitrophenol in rats has been reported to be greater than 4000 mg/kg bw by oral administration and greater than 800 mg/kg bw by intraperitoneal injection (Burnett *et al.*, 1977).

During 16-day studies, groups of five Fischer 344/N rats of each sex received 0, 156, 313, 625, 1250 or 2500 mg/kg bw 2-amino-5-nitrophenol (purity, 98%), and groups of five $B6C3F_1$ mice of each sex received 0, 313, 625, 1250, 2500 or 5000 mg/kg bw, by gavage in corn oil. A reduction in survival in relation to dose was observed in female mice (US National Toxicology Program, 1988).

In 13-week studies, groups of 10 Fischer 344/N rats and $B6C3F_1$ mice of each sex received 0, 100, 200, 400, 800 or 1600 mg/kg bw 2-amino-5-nitrophenol by gavage in corn oil. A dose-related reduction in survival was observed in rats. Rats receiving 400–1600 mg/kg and mice receiving 1600 mg/kg had acute or chronic perivasculitis of the vessels of the caecum and colon (US National Toxicology Program, 1988).

In the two-year studies described above, acute and chronic inflammation of the caecum and colon were observed in low- and high-dose male rats, high-dose female rats and high-dose male mice; the conditions were associated with the accumulation of an orange, granular pigment in the submucosa of the intestine. Focal ulceration of the intestinal mucosa was often present (US National Toxicology Program, 1988).

2-Amino-5-nitrophenol was present at low concentrations in an oxidative hair colouring formulation evaluated in a 13-week study of dermal toxicity in rabbits (Burnett *et al.*, 1976, 0.5%) and in a semi-permanent formulation evaluated in a 20-month study of dermal toxicity in mice (Jacobs *et al.*, 1984, 0.15%), described in detail on p. 97. No treatment-related adverse effect was detected. [The Working Group noted that the dose of each component of the formulations was very low and unlikely to have been toxic.]

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

No data were available to the Working Group on the reproductive and developmental effects of 2-amino-5-nitrophenol alone. The compound was present at low concentrations in

oxidative hair colouring formulations evaluated in a two-generation study of reproduction in rats (Burnett & Goldenthal, 1988, 2%) and in a study of teratogenesis in rats (Burnett *et al.*, 1976, 0.5%), described in detail on p. 100. No treatment-related adverse effect was detected. [The Working Group noted that the dose of each component of the formulations was very low and unlikely to have been toxic.]

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see also Table 1 and Appendices 1 and 2)

2-Amino-5-nitrophenol induced mutation in bacteriophage, *Salmonella typhimurium* and at the *tk* locus in mouse lymphoma L5178Y cells. It also induced sister chromatid exchange and chromosomal aberrations in cultured Chinese hamster ovary cells.

2-Amino-5-nitrophenol did not induce dominant lethal mutation in rats exposed *in vivo*.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

2-Amino-5-nitrophenol is used as an intermediate in the manufacture of certain azo dyes. It is also used in semi-permanent and permanent hair colouring products.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

2-Amino-5-nitrophenol was tested for carcinogenicity by gavage in one study in mice and one study in rats. In mice, no significant increase in tumour incidence was observed in the low-dose groups; data on the high-dose groups could not be evaluated owing to high mortality rates. An increased incidence of pancreatic acinar-cell tumours was observed in male rats.

5.4 Other relevant data

Oral treatment with 2-amino-5-nitrophenol was associated with inflammation of the lower intestinal tract in mice and rats.

2-Amino-5-nitrophenol induced gene mutation in bacteria and gene mutation, sister chromatid exchange and chromosomal aberrations in cultured mammalian cells. It did not induce dominant lethal mutation in rats.

Table 1. Genetic and related effects of 2-amino-5-nitrophenol

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
BPF, Bacteriophage T4D, forward mutation	+	0	256.4000	Kvelland (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	0	770.0000	Chiu *et al.* (1978)
SA0, *Salmonella typhimurium* TA100, reverse mutation	(+)	-	500.0000	Shahin *et al.* (1982)
SA0, *Salmonella typhimurium* TA100, reverse mutation	(+)	(+)	1667.0000	Zeiger *et al.* (1987)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	(+)	-	500.0000	Shahin *et al.* (1982)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	-	-	5000.0000	Zeiger *et al.* (1987)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	(+)	(+)	500.0000	Shahin *et al.* (1982)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	(+)	(+)	500.0000	Zeiger *et al.* (1987)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	+	0	5.0000	Ames *et al.* (1975)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	+	+	50.0000	Shahin *et al.* (1982)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	0	7.7000	Chiu *et al.* (1978)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	+	25.0000	Shahin *et al.* (1982)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	+	167.0000	Zeiger *et al.* (1987)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus	+	0	25.0000	US National Toxicology Program (1988)
SIC, Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	+	+	13.3000	US National Toxicology Program (1988)
CIC, Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	+	+	49.5000	US National Toxicology Program (1988)
DLR, Dominant lethal mutation, CD rats	-		20.0000 ip × 24	Burnett *et al.* (1977)

+, positive; (+), weakly positive; -, negative; 0, not tested

[a]In-vitro tests, μg/ml; in-vivo tests, mg/kg bw

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of 2-amino-5-nitrophenol.

There is *limited evidence* in experimental animals for the carcinogenicity of 2-amino-5-nitrophenol.

Overall evaluation

2-Amino-5-nitrophenol *is not classifiable as to its carcinogenicity to humans (Group 3).*

6. References

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[1]For definition of the italicized terms, see Preamble, pp. 26–30.

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