2,6-DIMETHYLANILINE (2,6-XYLIDINE)

1. Exposure Data

1.1 Chemical and physical data

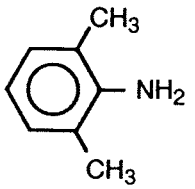
1.1.1 *Synonyms, structural and molecular data*

Chem. Abstr. Serv. Reg. No.: 87-62-7

Chem. Abstr. Name: 2,6-Dimethylbenzenamine

IUPAC Systematic Name: 2,6-Xylidine

Synonyms: 1-Amino-2,6-dimethylbenzene; 2-amino-1,3-dimethylbenzene; 2-amino-1,3-xylene; 2-amino-*meta*-xylene; 2,6-dimethylphenylamine; *ortho*-xylidine; 2,6-*meta*-xylidine; 2,6-xylylamine



$C_8H_{11}N$ Mol. wt: 121.18

1.1.2 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Clear liquid (Ethyl Corp., 1990); pungent odour (Ethyl Corp., 1991)

(*b*) *Boiling-point*: 214 °C at 739 mm Hg [98.5 kPa] (Lide, 1991)

(*c*) *Melting-point*: 11.2 °C (Lide, 1991)

(*d*) *Density*: 0.9842 at 20 °C (Lide, 1991)

(*e*) *Spectroscopy data*: Infrared, ultraviolet and nuclear magnetic resonance spectral data have been reported (Sadtler Research Laboratories, 1980; Pouchert, 1981, 1983; Sadtler Research Laboratories, 1991).

(*f*) *Solubility*: Slightly soluble in water (7.5 g/l at 20 °C); soluble in ethanol and diethyl ether (Hoechst Celanese Corp., 1989; Lide, 1991)

(*g*) *Volatility*: Vapour pressure, 0.125 mm Hg [17 Pa] at 25 °C; 1 mm Hg [133 Pa] at 44 °C (Chao *et al.*, 1983; Lide, 1991)

(*h*) *Stability*: Sensitive to air oxidation and light; inflammable (Hoechst Celanese Corp., 1989)

(*i*) *Conversion factor*: $mg/m^3 = 5.0 \times ppm$[1]

1.1.3 *Trade names, technical products and impurities*

2,6-Dimethylaniline is available commercially at purities ranging from 98 to 99.6%, with xylenol as a typical impurity (Hoechst Celanese Corp., 1989; Ethyl Corp., 1991). It is also available in research quantities at purities in the same order of magnitude (Janssen Chimica, 1990; Riedel-de Haen, 1990; Heraeus, 1991; Lancaster Synthesis, 1991; TCI America, 1991; Aldrich Chemical Co., 1992; Fluka Chemie AG, 1993).

1.1.4 *Analysis*

Amines can be liberated during the manufacture of rubber, especially by vulcanization and other other thermal degradations. A method was described for the determination of free aromatic amines, including 2,6-dimethylaniline, using high-temperature glass-capillary gas chromatography and nitrogen-selective detection (thermionic specific detector), with detection limits of 10–20 pg (Dalene & Skarping, 1985).

Combined gas chromatography–mass spectrometry and –Fourier transform–infrared spectrometry have been used for the identification of a large number of aromatic compounds, including 2,6-dimethylaniline. Use of infrared spectrometry often allowed unambiguous differentiation of isomers (Chiu *et al.*, 1984).

An isocratic on-line liquid chromatographic preconcentration system with ultraviolet absorbance detection at 230 nm has been developed for the determination in tap-water of polar pollutants, including 2,6-dimethylaniline, with widely varying characteristics. The detection limit for 2,6-dimethylaniline was 0.4 µg/l (Brouwer *et al.*, 1991).

A procedure has been described for the detection of 2,6-disubstituted anilines, including 2,6-dimethylaniline, in the low-nanogram range in blood. The aromatic anilines were extracted from blood with ethyl acetate, converted to the corresponding *N*-heptafluorobutyramides and analysed by gas chromatography with electron capture detection; identities were confirmed by gas chromatrography–mass spectrometry (DeLeon *et al.*, 1983).

1.2 Production and use

1.2.1 *Production*

2,6-Dimethylaninile is prepared by nitration of xylene and reduction, followed by removal of the 2,4-isomer by formation of the acetate salt, removal of the 2,5-isomer by formation of the hydrochloride salt, and recovery of the 2,6-isomer by sublimation (US National Library of Medicine, 1992a).

2,6-Dimethylaniline is produced by one company each in Japan, Switzerland and the USA and by three companies in Germany (Chemical Information Services, 1991).

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[1]Calculated from: mg/m^3 = (molecular weight/24.45) × ppm, assuming normal temperature (25 °C) and pressure (760 mm Hg [101.3 kPa])

1.2.2 *Use*

2,6-Dimethylaniline is used as a chemical intermediate in the manufacture of pesticides, dyestuffs, antioxidants, pharmaceuticals, synthetic resins, fragrances and other products (Ethyl Corp., 1990; Kuney, 1991).

1.3 Occurrence

1.3.1 *Natural occurrence*

2,6-Dimethylaniline is one of many amino compounds occurring naturally in Latakia tobacco leaves (Irvine & Saxby, 1969).

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 4354 workers, including 729 women, may have been exposed to 2,6-dimethylaniline in five occupations (US National Library of Medicine, 1992b).

1.3.3 *Water and sediments*

2,6-Dimethylaniline was identified in a sample from a shallow aquifer contaminated by coal-tar wastes. The site, in St Louis Park, MN, USA, had been used as a waste disposal site by a coal-tar distillation (see IARC, 1984, 1985, 1987a) and wood-preserving facility from 1918 through 1972 (Pereira *et al.*, 1983).

1.3.4 *Other*

Xylidine metabolites are released from drugs, and particularly the xylidine group of local anaesthetics. 2,6-Dimethylaniline was identified as a metabolite in the urine of rats, guinea-pigs, dogs and humans administered lidocaine orally (Keenaghan & Boyes, 1972). 2,6-Dimethylaniline may also enter the environment through the degradation of certain pesticides (US National Toxicology Program, 1990). It was detected in stack effluents from an incinerator burning hazardous wastes (James *et al.*, 1985) and has been detected in tobacco smoke (Irvine & Saxby, 1969; Patrianakos & Hoffman, 1979; Florin *et al.*, 1980; Pettersson *et al.*, 1980; Thelestam *et al.*, 1980; see IARC, 1986, 1987b).

1.4 Regulatory status and guidelines

Occupational exposure limits and guidelines for all isomers of xylidine, including 2,6-dimethylaniline, in some countries are presented in Table 1.

2. Studies of Cancer in Humans

No data were available to the Working Group.

Table 1. Occupational exposure limits and guidelines for xylidine (all isomers)

Country	Year	Concentration (mg/m^3)	Skin irritant notation	Interpretation
Australia		10	Yes	TWA
Austria		25	Yes	TWA
Belgium		10	Yes	TWA
ex-Czechoslovakia		5	No	TWA
Denmark	1988	10	Yes	TWA
Finland		25	Yes	TWA
		50	No	STEL
France		10	Yes	TWA
Germany	1992	25	Yes	TWA
Hungary		5	Yes	TWA
		10	No	STEL
Indonesia	1978	25	Yes	TWA
Italy	1978	10	Yes	TWA
Mexico	1983	25	Yes	TWA
Netherlands	1989	25	Yes	TWA
Poland	1984	5	No	TWA
Romania	1975	1	Yes	TWA
		2	Yes	STEL
Switzerland		10	Yes	TWA
United Kingdom	1990	10	Yes	TWA
		50	No	STEL
USA				
ACGIH	1992	2.5	Yes[a]	TWA
OSHA	1989	10	Yes	TWA
ex-USSR		3	Yes	STEL
Venezuela	1978	25	Yes	TWA
		25	Yes	Ceiling
ex-Yugoslavia	1971	3	No	TWA

From Cook (1987); ACGIH (1991); ILO (1991); Deutsche Forschungsgemeinschaft (1992); TWA, time-weighted average; STEL, short-term exposure limit

[a] A_2, suspected human carcinogen

3. Studies of Cancer in Experimental Animals

Pre- and postnatal administration in the diet

Rat

Groups of 28 male and 56 female Charles River CD rats, five weeks of age, were administered 0, 300, 1000 or 3000 ppm (mg/kg) of diet 2,6-dimethylaniline (99.06% pure). At 16 weeks of age, they were mated, and the pregnant females were allowed to deliver naturally over a two-week period (F_0 generation). F_0 females continued to receive treatment

or control diet during pregnancy and lactation. Progeny (F_1) were weaned at 21 days of age, and groups of 56 males and 56 females received the same diet as their parents for 102 weeks. Mean body weight gains relative to those of controls were reduced for high-dose male and mid-dose and high-dose female rats (by > 10%). Survival at 105 weeks was: males—control, 43/56; low-dose 40/56; mid-dose 33/56; high-dose, 14/56 ($p < 0.001$); females—control, 33/56; low-dose 25/56; mid-dose, 32/56; high-dose, 24/56. In males, papillary adenomas of the nasal cavity occurred in 0/56 control, 0/56 low-dose, 2/56 mid-dose and 10/56 high-dose rats ($p = 0.001$, incidental tumour test). Carcinomas [not otherwise specified] of the nasal cavity were observed only in high-dose males (26/56; $p < 0.001$, life table test); two adenocarcinomas were also observed in high-dose male rats. In females, nasal adenomas occurred in 0/56 control, 0/56 low-dose, 1/56 mid-dose and 6/56 high-dose rats ($p = 0.02$, incidental tumour test). Carcinomas of the nasal cavity occurred in 0/56 control, 0/56 low-dose, 1/56 mid-dose and 24/56 high-dose females ($p < 0.001$, life table test). Unusual tumours of the nasal cavity also occurred among high-dose males and females: one undifferentiated sarcoma was present in a female, rhabomyosarcomas occurred in two males and two females, and malignant mixed tumours (features of adenocarcinomas and rhabdomyosarcomas) were observed in one male and one female rat. Subcutaneous fibromas and fibrosarcomas combined occurred in 0/56 control, 2/56 low-dose, 2/56 mid-dose and 5/56 high-dose male rats ($p = 0.001$, life table test; $p < 0.001$ life table trend test); and in 1/56 control, 2/56 low-dose, 2/56 mid-dose and 6/56 high-dose female rats ($p = 0.01$, life table trend test). Neoplastic nodules of the liver occurred in female rats with a significant positive trend: control, 0/56; low-dose, 1/56; mid-dose, 2/56; high-dose, 4/55 ($p = 0.03$, incidental test; $p = 0.012$, incidental trend test). Hepatocellular carcinomas occurred in 1/56 control, 0/56 low-dose, 1/56 mid-dose and 1/55 high-dose female rats (US National Toxicology Program, 1990). [The Working Group noted that no data were provided on the parent generation.]

4. Other Relevant Data

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

Evidence for the metabolism of 2,6-dimethylaniline in humans is derived from studies on cigarette smokers and nonsmokers and on patients receiving the anaesthetic and cardiac drug, lidocaine, which is known to be metabolized principally to 2,6-dimethylaniline. Using capillary gas chromatography–mass spectrometry, haemoglobin adducts of 2,6-dimethylaniline were found to be present at high levels in nonsmokers with no known exposure to this compound; moreover, adduct levels were appreciably lower in cigarette smokers. In contrast, 2,6-dimethylaniline–haemoglobin adduct levels were elevated substantially in patients receiving lidocaine treatment. These results are indicative of environmental and iatrogenic exposure to 2,6-dimethylaniline, and of its biotransformation to a circulating *N*-hydroxy-2,6-dimethylaniline metabolite in humans, which enters erythrocytes, is oxidized to 2,6-dimethylnitrosobenzene and forms a sulfinamide adduct with haemoglobin (Bryant *et al.*, 1988, 1992 (abstract)).

On the basis of the haemoglobin binding index determined in rats, the levels of 2,6-dimethylaniline–haemoglobin adducts found in nonsmokers correspond to an estimated daily exposure of 23 μg (Sabbioni, 1992). 2,6-Dimethylaniline has also been found as a human urinary metabolite of two other drugs, etidocaine and lidamidine hydrochloride (US National Toxicology Program, 1990).

4.1.2 *Experimental systems*

Since free 2,6-dimethylaniline may be formed by intestinal metabolism of 2,6-dimethylaniline-based azo dyes, its absorption into the circulation from the small intestine was studied. Male Wistar rats were instilled with 10 mg 2,6-dimethylaniline ('pure') in 10 ml phosphate-buffered saline pH 6 into the intestine. Since the absorption half-time was rapid (14.4 min), metabolism of azo dyes by intestinal microflora would be expected to result in complete absorption of the resulting 2,6-dimethylaniline by the body (Plá-Delfina *et al.*, 1972).

The metabolism of 2,6-dimethylaniline was examined qualitatively in male Osborne-Mendel rats given the hydrochloride salt [purity unspecified] by gavage in water at 200 mg/kg bw. 4-Hydroxy-2,6-dimethylaniline and 3-methyl-2-aminobenzoic acid were identified as major and minor urinary metabolites, respectively. The unchanged amine could be detected chromatographically, but only after acidic urine hydrolysis, suggesting the presence of urinary *N*-conjugates (Lindstrom *et al.*, 1963). These data were confirmed by enzymatic hydrolysis in male Fischer 344 rats given 2,6-dimethylaniline (> 99% pure) by gavage in corn oil at a daily dose of 262.5 mg/kg bw for 10 days. Levels of the 4-hydroxy metabolite were further increased by pretreatment with 3-methylcholanthrene, but not by pretreatment with phenobarbital. Oral administration to male beagle dogs (25 mg/kg bw per day for 10 days) resulted in the same major metabolite; 3-methyl-2-aminobenzoic acid and its glycine conjugate were minor components in the urine. Evidence was also provided for the presence of two potentially reactive metabolites, 2,6-dimethyl-4-nitrosobenzene, which may arise from *N*-hydroxy-2,6-dimethylaniline, and 2,6- or 3,5-dimethyl-4-iminoquinone, neither of which was detectable in rats (Short *et al.*, 1989a).

Haemoglobin adduct levels were determined in female Wistar rats given 0.5 mmol [61 mg]/kg bw 2,6-dimethylaniline (purity, > 98%) by gavage in propylene glycol and found to be significant but relatively low [haemoglobin binding index = 1.1 mmol compound/mol haemoglobin per (mmol compound/kg bw)], in comparison with levels of adducts of other aromatic amines (Sabbioni, 1992).

4.2 Toxic effects

4.2.1 *Humans*

Methaemoglobinaemia has been reported following lidocaine treatment of human subjects (Burne & Doughty, 1964; Weiss *et al.*, 1987). Like haemoglobin adduct formation, it can be attributed to a circulating *N*-hydroxy metabolite.

4.2.2 *Experimental systems*

Methaemoglobinaemia has been reported in cats but not dogs following an intravenous dose of 30 mg/kg bw 2,6-dimethylaniline [purity unspecified] in a pH 5.5 saline vehicle. Lido-

caine also caused methaemoglobinaemia in cats after intravenous treatment at 47 mg/kg bw (McLean *et al.*, 1967, 1969).

LD_{50} values have been determined in several rodent strains. In male Osborne-Mendel rats given the hydrochloride [purity unspecified] in water by gavage, the LD_{50} was 2042 mg/kg bw (Lindstrom *et al.*, 1969). The LD_{50} of 2,6-dimethylaniline [purity and vehicle unspecified] administered by gavage was estimated as 840 mg/kg bw (Jacobson, 1972) and 1230 mg/kg for male Sprague-Dawley rats and 710 mg/kg for male CF_1 mice (Vernot *et al.*, 1977). An LD_{50} of 630 mg/kg was reported (Short *et al.*, 1983) for male Fischer 344 rats administered 2,6-dimethylaniline [purity unspecified] by gavage without a vehicle. The LD_{50} for female Fischer 344 rats given the compound (> 99% pure) by gavage in corn oil was calculated to be 1160 mg/kg; and LD_{50} values of 1270–1310 mg/kg were estimated for male and female Charles River CD rats after a single gavage dose (purity, > 99%) in corn oil (US National Toxicology Program, 1990).

In rats, only splenic haemosiderosis was observed in male Fischer 344 animals administered 2,6-dimethylaniline [purity unspecified] by gavage without a vehicle at daily doses of 157.5 mg/kg bw for 5–20 days (Short *et al.*, 1983). In male and female Sprague-Dawley rats given 400–700 mg/kg by gavage [purity not specified] daily for four weeks, however, decreased weight gain, lowered haemoglobin values and liver enlargement were observed, with increases in the levels of microsomal glucuronyltransferase in males and females and of aniline hydroxylase in females (Magnusson *et al.*, 1971, 1979). Similarly, in male and female Fischer 344 rats given the compound (> 99% pure) by gavage in corn oil at doses up to 310 mg/kg for five days a week for 13 weeks, increased liver weight, decreased body weight and decreases in erythrocyte, haemoglobin and haematocrit levels were observed (US National Toxicology Program, 1990). In male Osborne-Mendel rats given up to 10 000 ppm 2,6-dimethylaniline in the diet for three to six months, 25% weight retardation, anaemia, liver enlargement (no microscopic change), splenic congestion and kidney damage that included depressed scar formation, tubular atrophy, interstitial fibrosis, chronic inflammation, papillary oedema and necrosis, and cystic dilation of tubular segments were observed, predominantly at the high dose (Lindstrom *et al.*, 1963). In the 104-week carcinogenicity study described on pp. 326–327, male and female Charles River CD rats developed non-neoplastic changes including dose-related decreases in body weight gain and inflammation, hyperplasia and squamous metaplasia of the nasal mucosa (US National Toxicology Program, 1990).

Chronic dosing of male and female beagle dogs with oral doses (in capsules) of 50 mg/kg bw 2,6-dimethylaniline for four weeks resulted in decreased body weight, hyperbilirubinaemia, hypoproteinaemia and, in contrast to rats, marked fatty degenerative changes in the liver (Magnusson *et al.*, 1971).

4.3 Reproductive and prenatal effects

No data were available to the Working Group.

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 2 and Appendices 1 and 2)

Reports on the mutagenicity of 2,6-dimethylaniline in *Salmonella typhimurium* are conflicting. In the most detailed report, two of three participating laboratories reproducibly demonstrated weak activity in the presence of an exogenous metabolic system from hamster, but not rat, liver. 2,6-Dimethylaniline was reported to induce mutation in mouse lymphoma cells at the *tk* locus (abstract), and it induced both sister chromatid exchange and chromosomal aberrations in Chinese hamster ovary cells.

It did not induce micronuclei in the bone marrow of mice treated *in vivo* by oral administration. Unlabelled 2,6-dimethylaniline bound covalently to the DNA of the ethmoid turbinates and liver of rats after oral pretreatment.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

2,6-Dimethylaniline is used as a chemical intermediate in the manufacture of pesticides, dyestuffs, antioxidants, pharmaceuticals and other products. It is a metabolite of the xylidine group of anaesthetics, including, for example, lidocaine, and is produced by the reduction of certain azo dyes by intestinal microflora. It may also enter the environment through degradation of certain pesticides.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

2,6-Dimethylaniline was tested for carcinogenicity in one study in rats by pre- and postnatal administration in the diet. It induced adenomas and carcinomas as well as several sarcomas in the nasal cavity. It also produced subcutaneous fibromas and fibrosarcomas in both males and females and increased the incidence of neoplastic nodules in the livers of female rats.

5.4 Other relevant data

Methaemoglobinaemia has been observed in humans and animals exposed to 2,6-dimethylaniline. The metabolism of 2,6-dimethylaniline in humans and rats appears to be similar and gives rise to a characteristic haemoglobin adduct in both species.

Table 2. Genetic and related effects of 2,6-dimethylaniline

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	-[b]	-[b]	363.0000	Florin *et al.* (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	0	-	0.0000	Zimmer *et al.* (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	(+)[c]	167.0000	Zeiger *et al.* (1988)
SA0, *Salmonella typhimurium* TA100, reverse mutation	0	-	2000.0000	Kugler-Steigmeier *et al.* (1989)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	-	-	1815.0000	Florin *et al.* (1980)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	-	-	1667.0000	Zeiger *et al.* (1988)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	-	-	1815.0000	Florin *et al.* (1980)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	-	-	1667.0000	Zeiger *et al.* (1988)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	0	-	0.0000	Zimmer *et al.* (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-[b]	-[b]	363.0000	Florin *et al.* (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	-	1667.0000	Zeiger *et al.* (1988)
SA9, *Salmonella typhimurium* TA98, reverse mutation	0	-	0.0000	Zimmer *et al.* (1980)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus	+	+	0.0000	Rudd *et al.* (1983); abstr.
SIC, Sister chromatid exchange, Chinese hamster ovary (CHO) cells *in vitro*	+	+	301.0000	Galloway *et al.* (1987)
CIC, Chromosomal aberrations, Chinese hamster ovary (CHO) cells *in vitro*	+	+	1200.0000	Galloway *et al.* (1987)
MVM, Micronucleus test, ICR mouse bone marrow *in vivo*	-		350 mg/kg po × 1	Parton *et al.* (1988)
MVM, Micronucleus test, ICR mouse bone marrow *in vivo*	-		375 mg/kg po × 3	Parton *et al.* (1990)
BVD, Binding (covalent) to DNA, rats *in vivo*	+		4 mg/kg ip[d] × 1	Short *et al.* (1989b)

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

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

[b]Spot tests only

[c]Weakly positive in two of three laboratories, negative in the other one

[d]Pretreatment with unlabelled 262.5 mg/kg 2,6-dimethylaniline daily for nine days

2,6-Dimethylaniline gave conflicting results for gene mutation in bacteria. Sister chromatid exchange and chromosomal aberrations were induced in cultured mammalian cells. The compound bound covalently to DNA in rat tissues but did not induce micronuclei in the bone marrow of mice treated *in vivo*.

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of 2,6-dimethylaniline.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 2,6-dimethylaniline.

Overall evaluation

2,6-Dimethylaniline is *possibly carcinogenic to humans (Group 2B).*

6. References

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

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