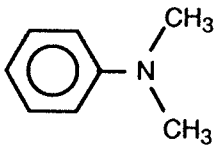
N,N-DIMETHYLANILINE

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Synonyms, structural and molecular data*

Chem. Abstr. Serv. Reg. No.: 121-69-7
Chem. Abstr. Name: *N,N*-Dimethylbenzenamine
IUPAC Systematic Name: *N,N*-Dimethylaniline
Synonyms: (Dimethylamino)benzene; *N,N*-dimethylaminobenzene; dimethylaniline; dimethylphenylamine; *N,N*-dimethylphenylamine



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

1.1.2 *Chemical and physical properties*

(*a*) *Description*: Yellowish to brownish oily liquid (Sax & Lewis, 1987)
(*b*) *Boiling-point*: 192–194 °C (Eller, 1985; Lide, 1991)
(*c*) *Melting-point*: 2–2.45 °C (Eller, 1985; Lide, 1991)
(*d*) *Density*: 0.956 g/ml at 20 °C (Eller, 1985)
(*e*) *Spectroscopy data*: Infrared, ultraviolet and nuclear magnetic resonance spectral data have been reported (Sadtler Research Laboratories, 1980; Pouchert, 1981, 1983; US National Toxicology Program, 1989; Sadtler Research Laboratories, 1991).
(*f*) *Solubility*: Insoluble in water (2–14 g/l at 25 °C). Since *N,N*-dimethylaniline is a basic compound, its solubility is dependent on the pH of the aqueous medium: its solubility in water at pH > 7 is lower than that in water of pH < 5. The data on aqueous solubility reported in the literature thus vary widely (US Environmental Protection Agency, 1986). Soluble in acetone, benzene, chloroform, diethyl ether and ethanol (Amoore & Hautala, 1983; Dragun & Helling, 1985; Sax & Lewis, 1987; Lide, 1991)
(*g*) *Volatility*: Vapour pressure, 1 mm Hg [133 Pa] at 29.5 °C (Lide, 1991)

(*h*) *Stability*: Slowly oxidizes and darkens in air; can react with nitrous acid to form ring-substituted nitroso compounds (US Environmental Protection Agency, 1986)
(*i*) *Octanol/water partition coefficient (P)*: 2.31 (Hansch & Leo, 1979)
(*j*) *Conversion factor*: $mg/m^3 = 4.95 \times ppm$[1]

1.1.3 *Trade names, technical products and impurities*

N,N-Dimethylaniline is available commercially at a minimum purity of 99.7%, with aniline (see IARC, 1982a, 1987a) (0.05% max.) and *N*-methylaniline (0.3% max.) as impurities (Buffalo Color Corp., 1987, 1992). 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; Aldrich Chemical Co., 1992; Fluka Chemie AG, 1993).

1.1.4 *Analysis*

N,N-Dimethylaniline can be detected in air by adsorption on silica gel, desorption with ethanol and analysis by gas chromatography and flame ionization detection. The limit of detection is 10 μg/sample (Campbell *et al.*, 1981; Eller, 1985).

Amines can be liberated during the manufacture of rubber, especially by vulcanization and by other thermal degradations. A method was described for the determination of free aromatic amines, including *N,N*-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).

A gas chromatographic procedure for the determination of residual *N,N*-dimethylaniline as a contaminant in commercial antibiotics has been described, which involves dissolution of the sample in aqueous alkali, extraction of *N,N*-dimethylaniline with cyclohexane and analysis by gas chromatrography–flame ionization detection (Margosis, 1977).

1.2 Production and use

1.2.1 *Production*

N,N-Dimethylaniline is produced commercially by heating aniline at 300 °C with methanol in the presence of a catalyst at high pressure; sulfuric acid, phosphoric acid or alumina can be used as the catalyst (Northcott, 1978; Rosenwald, 1978; Budavari, 1989).

N,N-Dimethylaniline is produced by one company each in France, Germany, Hungary, Mexico, Poland, the Republic of Korea, Spain and the USA, by two companies in Japan and the United Kingdom and by four companies in India (Chemical Information Services, 1991).

US production was estimated to be 6000 tonnes in 1976 (US Environmental Protection Agency, 1986) and between 1000 and 10 000 tonnes in 1988 (US National Toxicology Program, 1989). In 1987, approximately 500 tonnes were imported into the USA (US International Trade Commission, 1988).

---

[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*

N,N-Dimethylaniline is used as an intermediate in the manufacture of dyes, Michler's ketone and vanillin. It is also used as a specialty industrial solvent, a rubber vulcanizing agent (see IARC, 1982b, 1987b), a stabilizer and an acid scavenger (Northcott, 1978; Sax & Lewis, 1987; Budavari, 1989; US National Toxicology Program, 1989).

1.3 Occurrence

1.3.1 *Natural occurrence*

N,N-Dimethylaniline is not known to occur as a natural product.

1.3.2 *Occupational exposure*

N,N-Dimethylaniline was reported in the air of coal liquefaction plants (Harris *et al.*, 1980) and in the air of a plant for the manufacture of fibre glass-reinforced plastic pipes (Markel & Wilcox, 1981), at levels below the standard of the US Occupational Safety and Health Administration (see below) (US Environmental Protection Agency, 1986). Concentrations of *N,N*-dimethylaniline in 23 workplace air samples from two pilot coal liquefaction plants in Canada were consistently below the analytical detection limit of 0.05 mg/m^3 (Leach *et al.*, 1987).

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 30 480 workers, including 7448 women, were potentially exposed to *N,N*-dimethylaniline in 15 industries at 1428 sites (US National Library of Medicine, 1992).

1.3.3 *Water and soils*

N,N-Dimethylaniline has been detected in Lake Ontario (US Environmental Protection Agency, 1986) and in river water in Spain (Rivera *et al.*, 1987). River water near effluent sources of industrial dyestuff wastes in the Netherlands showed concentrations of up to 3.6 µg/l (Meijers & van der Leer, 1976; Zoeteman *et al.*, 1980). *N,N*-Dimethylaniline was found in soil samples near a dye manufacturing plant in the USA at a concentration of up to 40 mg/kg (Nelson & Hites, 1980).

1.3.4 *Other*

N,N-Dimethylaniline is used as an acid scavenger in the synthesis of penicillins and cephalosporins and has been reported as a contaminant of commercial preparations of those antibiotics at levels of up to 1500 ppm (Margosis, 1977; Quercia *et al.*, 1980).

1.4 Regulations and guidelines

Occupational exposure limits and guidelines for *N,N*-dimethylaniline in some countries are presented in Table 1.

Table 1. Occupational exposure limits and guidelines for *N,N*-dimethylaniline

Country	Year	Concentration (mg/m^3)	Interpretation
Australia		25	TWA
		50	STEL
Austria	1982	25	TWA
Belgium		25	TWA
		50	STEL
China	1979	5	TWA
Denmark	1988	25	TWA
Finland		25	TWA
		50	STEL
France		25	TWA
Germany	1992	25	TWA
Hungary		5	TWA
		10	STEL
Indonesia	1978	25	TWA
Mexico	1983	25	TWA
Netherlands	1989	25	TWA
Norway	1984	25	TWA
Poland		5	TWA
Romania	1975	10	TWA
		20	STEL
Switzerland		25	TWA
		50	STEL
United Kingdom	1990	25	TWA
		50	STEL
USA			
ACGIH	1992	25	TWA
		50	STEL
NIOSH	1990	10	TWA
		50	STEL
OSHA	1989	25	TWA
		50	STEL
Venezuela	1978	25	TWA
		60	STEL

From Cook (1987); US Occupational Safety and Health Administration (OSHA) (1989); American Conference of Governmental Industrial Hygienists (ACGIH) (1990, 1992); ILO (1991); Deutsche Forschungsgemeinschaft (1992); TWA, time-weighted average; STEL, short-term exposure limit

All countries have a notation that the compound may be a skin irritant.

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, eight weeks old, were administered 0 (controls), 15 or 30 mg/kg bw *N,N*-dimethylaniline (> 98% pure) in 10 ml/kg bw corn oil by gavage on five days a week for 103 weeks. Survival at week 104 was: males—controls, 34/50; low-dose, 30/50; high-dose, 34/50; females—controls, 35/50; low-dose, 39/50; high-dose, 33/50. In females, epithelial hyperplasia of forestomach occurred in 8/50 controls, 11/19 low-dose and 13/50 high-dose; and squamous-cell papillomas of the forestomach were found in 2/50 controls, 2/19 low-dose and 8/50 high-dose animals ($p = 0.042$, incidental tumour test) (US National Toxicology Program, 1989). [The Working Group noted that only 19 forestomachs from females in the low-dose group were examined microscopically and that the high dose used may not have reached the maximal tolerable dose].

3.1.2 *Rat*

Groups of 50 male and 50 female Fischer 344 rats, seven weeks old, were administered 0 (controls), 3 or 30 mg/kg bw *N,N*-dimethylaniline (> 98% pure) in 5 ml/kg bw corn oil by gavage on five days a week for 103 weeks. Survival at 104 weeks was: males—controls, 29/50; low-dose, 32/50; high-dose, 28/50; females—controls, 21/50; low-dose, 32/50; high-dose, 36/50. Sarcomas of the spleen occurred in 0/49 controls, 0/49 low-dose and 3/50 high-dose male rats; one osteosarcoma of the spleen was observed in a high-dose male. Although the proportion of high-dose male rats with splenic sarcomas or osteosarcomas (4/50, 8%) was not significantly greater than that in controls (0/50), it exceeded the historical control incidence (study laboratory, 1/148 (0.7 ± 1%); all National Toxicology Program laboratories, 3/2081 (0.1 ± 0.5%)). The severity of haematopoiesis and haemosiderosis of the spleen was increased in high-dose rats of each sex, and an increased incidence of fibrosis and fatty metamorphosis of the spleen occurred in high-dose males. The incidence of mononuclear cell leukaemias was significantly decreased in high-dose rats: males—controls, 13/50; low-dose, 4/50; high-dose, 3/50 ($p = 0.017$, incidental tumour test); females—controls, 11/50; low-dose, 7/50; high-dose, 0/50 ($p = 0.005$, incidental tumour test) (Abdo *et al.*, 1989 (abstract); US National Toxicology Program, 1989).

4. Other Relevant Data

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

The metabolism of *N,N*-dimethylaniline has been studied in adult and fetal human tissues *in vitro*. In adult liver microsomes, both *N*-oxidation and oxidative *N*-demethylation were shown to occur, resulting in the formation of *N,N*-dimethylaniline *N*-oxide and of *N*-methylaniline and formaldehyde, respectively. The *N*-oxide was found to be metabolized further to formaldehyde and *N*-methylaniline (Kitada *et al.*, 1974). *N*-Oxidation has also been demonstrated in fetal liver microsomes, adult kidney microsomes and adult liver homogenates (Ziegler & Gold, 1971; Rane, 1974; Lemoine *et al.*, 1990). In experiments with enzyme inhibitors, antibodies and enzyme thermal stability, it was concluded that the flavin-containing mono-oxygenases are primarily responsible for *N*-oxidation (McManus *et al.*, 1987), while cytochrome(s) P450 appears to catalyse the *N*-demethylation reactions (Lemoine *et al.*, 1990).

The metabolism of *N,N*-dimethylaniline was studied in mongrel dogs given a dose of 40 mg/kg [purity unspecified] by intravenous injection; blood samples were collected over 4 h and urine samples over 48 h. Aniline was detected in blood but not in urine, while *N*-methylaniline, 2- and 4-aminophenol, *N*-methyl-4-aminophenol, *N,N*-dimethyl-2-aminophenol and *N,N*-dimethyl-4-aminophenol were isolated from urine after enzymatic deconjugation with glucuronidase/sulfatase and were characterized by spectral and chromatographic criteria; *N,N*-dimethylaniline *N*-oxide was not detected. *N,N*-Dimethyl-4-aminophenol and *N*-methyl-4-aminophenol were recovered as urinary metabolites in rabbits; and rats were found to excrete *N,N*-dimethyl-4-aminophenyl sulfate and 4-aminophenyl sulfate (reviewed by Kiese & Renner, 1974). Incubation of isolated rat hepatocytes with *N,N*-dimethylaniline resulted in the formation of *N*-methylaniline, aniline, *N,N*-dimethylaniline *N*-oxide and *N*-methylaniline *N*-glucuronide (Sherratt & Damani, 1989).

The metabolism of N,N-dimethylaniline has been studied in a wide variety of tissues and species *in vitro*, including the livers of rats, mice, hamsters, rabbits, guinea-pigs, cats, cows, pigs, squirrels, bats, armadillos, opossums, raccoons and several avian, fish, amphibian and reptile species; extrahepatic tissues (notably lung, kidney, nasal mucosa, adrenals and intestine) of rats, pigs and rabbits; and even in a protozoan (Machinist *et al.*, 1968; Pan *et al.*, 1975; Hlavica & Kehl, 1976; Gorrod & Gooderham, 1981; McNulty *et al.*, 1983; Ohmiya & Mehendale, 1983; Agosin & Ankley, 1987). The major reactions are *N*-oxidation of *N,N*-dimethylaniline to form *N,N*-dimethylaniline *N*-oxide and oxidative *N*-demethylation of *N,N*-dimethylaniline and its *N*-oxide to form *N*-methylaniline and formaldehyde. Aryl ring-hydroxylation is a minor reaction and results in the formation of *N,N*-dimethyl-4-aminophenol and its non-enzymatic decomposition product, *N*-methyl-4-aminophenol. The latter reaction is of interest as it appears to proceed through a reactive quinoneimine intermediate (Gooderham & Gorrod, 1981). Further *N*-demethylation of *N*-methylaniline to aniline and ring- and *N*-hydroxylation to 4-aminophenol and phenylhydroxylamine (Holzer & Kiese, 1960) have also been reported *in vitro*. On the basis of several studies using inhibitors, antibodies, inducers and purified enzymes, *N,N*-dimethylaniline *N*-oxidation has been shown to be catalysed selectively by the flavin-containing mono-oxygenases, while *N*-demethylation and ring-hydroxylation are catalysed primarily by cytochromes P450 (principally the PB, BNF and ISF families) (Devereux & Fouts, 1974; Ziegler & Pettit, 1964; Hlavica &

Hülsmann, 1979; Gorrod & Gooderham, 1981; Akhrem *et al.*, 1982; Hamill & Cooper, 1984; MacDonald *et al.*, 1989; Pandey *et al.*, 1989). The demethylation of *N,N*-dimethylaniline can also be catalysed by peroxidative mechanisms involving ram seminal vesicle prostaglandin synthase (Sivarajah *et al.*, 1982) and fungal chloroperoxidase (Kedderis & Hollenberg, 1984).

4.2 Toxic effects

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

The LD_{50} values for *N,N*-dimethylaniline [purity and vehicle unspecified] were estimated to be 1350 mg/kg bw after single gavage doses to male Carworth-Wistar rats and 1690 mg/kg bw after dermal administration to male New Zealand rabbits (Smyth *et al.*, 1962).

Exposure of rats to *N,N*-dimethylaniline by inhalation (0.0055 and 0.3 mg/m^3 continuously for 100 days) resulted in methaemoglobinaemia, lowered erythrocyte haemoglobin, leukopenia and reticulocytosis, and reduced muscle chronaxy. Exposure to *N*-methylaniline (0.03 and 0.04 mg/m^3 only) under the same conditions resulted in lesser toxicity but included methaemoglobinaemia (Markosyan, 1969). Intravenous injection of 25 mg/kg bw *N,N*-dimethylaniline to cats increased the levels of haemoglobulin (Holzer & Kiese, (1960).

In chronic studies in which male and female Fischer 344 rats and B6C3F$_1$ mice were given the compound (98.2% pure) by gavage in corn oil at doses of up to 500 mg/kg for five days per week for 13 weeks, dose-related decreases in body weight gain were observed in male rats and cyanosis and decreased motor activity in both species of each sex, as well as splenomegaly and haemosiderosis in the spleen, liver, kidney and testes. Bone marrow hyperplasia was seen in rats and increased haematopoiesis in the liver in mice and in the spleen in mice and rats (Abdo *et al.*, 1990). Rats were generally more sensitive than mice to these toxic effects, all of which could be attributed to chronic methaemoglobinaemia, erythrocyte destruction and erythrophagocytosis.

In the 103-week carcinogenicity study described on p. 341, dose-related, non-neoplastic changes observed in rats involved fibrosis, haemosiderosis, fatty metamorphosis of the spleen and chronic focal inflammation of the liver (US National Toxicology Program, 1989).

After oral dosing of female Wistar rats with *N,N*-dimethylaniline [purity unspecified] in propylene glycol at 73 mg/kg bw, 11.4 mmol [1.4 g] compound/kg bw was bound to haemoglobin (Birner & Neumann, 1988).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Pregnant CD-1 mice were administered *N,N*-dimethylaniline in corn oil at 365 mg/kg bw per day by gavage on gestation days 6–13 and allowed to deliver litters (Hardin *et al.*,

1987). Live pups were counted and weighed within one-half day after birth and again on the third day after birth. The dose killed 6% of treated females but did not significantly affect maternal body weight gain, number of viable litters (at least one live pup) produced, body weight or number of liveborn pups per litter, or body weight gain or survival of pups up to three days of age.

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)

N,N-Dimethylaniline did not induce mutation in *Salmonella typhimurium* but was mutagenic at the *tk* locus of mouse lymphoma L5178Y cells. It induced both sister chromatid exchange and chromosomal aberrations in Chinese hamster ovary cells but did not induce unscheduled DNA synthesis in rat primary hepatocyte cultures.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

N,N-Dimethylaniline is used as an intermediate in the manufacture of dyes and other products and as a solvent for special purposes, a rubber vulcanizing agent and a stabilizer. It has been detected in ambient water and soil in the vicinity of industrial facilities.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

N,N-Dimethylaniline was tested for carcinogenicity in one study in mice and in one study in rats by gavage. It increased the incidence of forestomach papillomas in female mice. A few splenic sarcomas were observed in treated male rats.

5.4 Other relevant data

The metabolism of *N,N*-dimethylaniline has been studied in many species and in human tissues. It involves enzymatic *N*-demethylation, *N*-oxidation and ring hydroxylation. Aniline is a major metabolite. Chronic methaemoglobinaemia and erythrocyte haemolysis, with concomitant splenomegaly and other pathological lesions characteristic of aniline, were observed in mice and rats treated with *N,N*-dimethylaniline.

Table 2. Genetic and related effects of *N,N*-dimethylaniline

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	60.0000	Mori *et al.* (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	167.0000	Mortelmans *et al.* (1986)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	167.0000	Mortelmans *et al.* (1986)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	167.0000	Mortelmans *et al.* (1986)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	60.0000	Mori *et al.* (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	0	–	25.0000	Ho *et al.* (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	167.0000	Mortelmans *et al.* (1986)
URP, Unscheduled DNA synthesis, rat primary hepatocytes	–	0	121.2000	Yoshimi *et al.* (1988)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus	+	+	19.0000	US National Toxicology Program (1989)
SIC, Sister chromatid exchange, Chinese hamster (CHO) ovary cells *in vitro*	–	+	30.0000	Loveday *et al.* (1989)
CIC, Chromosomal aberrations, Chinese hamster (CHO) ovary cells *in vitro*	(+)	+	83.0000	Loveday *et al.* (1989)

+, positive; (+), weakly positive; –, negative; 0, not tested
[a]In-vitro tests, μg/ml; in-vivo tests, mg/kg bw

N,N-Dimethylaniline did not induce gene mutation in bacteria or DNA damage in cultured mammalian cells. It induced gene mutation, sister chromatid exchange and chromosomal aberrations in cultured mammalian cells.

5.5 Evaluation[1]

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

There is *limited evidence* in experimental animals for the carcinogenicity of *N,N*-dimethylaniline.

Overall evaluation

N,N-Dimethylaniline *is not classifiable as to its carcinogenicity to humans (Group 3).*

6. References

Abdo, K.M., Bucher, J., Haseman, J.K., Eustis, S.L. & Huff, J.E. (1989) Induction of splenic sarcomas in F344/N rats given *N,N*-dimethylaniline (Abstract No. 703). *Proc. Am. Assoc. Cancer Res.*, **30**, 177

Abdo, K.M., Jokinen, M.P. & Hiles, R. (1990) Subchronic (13-week) toxicity studies of *N,N*-dimethylaniline administered to Fischer 344 rats and B6C3F$_1$ mice. *J. Toxicol. environ. Health*, **29**, 77–88

Agosin, M. & Ankley, G.T. (1987) Conversion of *N,N*-dimethylaniline to *N,N*-dimethylaniline-*N*-oxide by a cytosolic flavin-containing enzyme from *Trypanosoma cruzi*. *Drug Metab. Disposition*, **15**, 200–203

Akhrem, A.A., Khatyleva, S.Y., Shkumatov, V.M., Chashchin, V.L. & Kiselev, P.A. (1982) Cumene hydroperoxide supported demethylation of *N,N*-dimethylaniline by cytochrome P-450 from adrenal cortex mitochondria. *Acta biol. med. germ.*, **11**, 1019–1028

Aldrich Chemical Co. (1992) *Aldrich Catalog/Handbook of Fine Chemicals 1992–1993*, Milwaukee, WI, p. 490

American Conference of Governmental Industrial Hygienists (1990) *Guide to Occupational Exposure Values—1990*, Cincinnati, OH, p. 42

American Conference of Governmental Industrial Hygienists (1992) *1992–1993 Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices*, Cincinnati, OH, p. 19

Amoore, J.E. & Hautala, E. (1983) Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J. appl. Toxicol.*, **3**, 272–290

Birner, G. & Neumann, H.-G. (1988) Biomonitoring of aromatic amines. II. Hemoglobin binding of some monocyclic aromatic amines. *Arch. Toxicol.*, **62**, 110–115

Budavari, S., ed. (1989) *The Merck Index*, 11th ed., Rahway, NJ, Merck & Co., p. 510

Buffalo Color Corp. (1987) *Specification Sheet:* N,N-*dimethylaniline*, Parsippany, NJ

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

Buffalo Color Corp. (1992) *Material Safety Data Sheet: Dimethylaniline*, Parsippany, NJ

Campbell, E.E., Wood, G.O. & Anderson, R.G. (1981) Method 1—Gas chromatographic analysis of aromatic amines in air. In: Egan, H., Fishbein, L., Castegnaro, M., O'Neill, I.K. & Bartsch, H., eds, *Environmental Carcinogens: Selected Methods of Analysis*, Vol. 4, *Some Aromatic Amines and Azo Dyes in the General and Industrial Environment* (IARC Scientific Publications No. 40), Lyon, IARC, pp. 109–118

Chemical Information Services Ltd (1991) *Directory of World Chemical Producers 1992/93 Edition*, Dallas, TX, p. 234

Cook, W.A. (1987) *Occupational Exposure Limits—Worldwide*, Akron, OH, American Industrial Hygiene Association, pp. 120, 137, 183

Dalene, M. & Skarping, G. (1985) Trace analysis of amines and isocyanates using glass capillary gas chromatography and selective detection. IV. Determination of free aromatic amines using nitrogen-selective detection. *J. Chromatogr.*, **331**, 321–330

Deutsche Forschungsgemeinschaft (1992) *MAK- and BAT-Values List 1992. Maximum Concentrations at the Workplace (MAK) and Biological Tolerance Values (BAT) for Working Materials* (Report No. 28), Weinheim, VCH Verlagsgesellschaft, p. 36

Devereux, T.R. & Fouts, J.R. (1974) *N*-Oxidation and demethylation of *N,N*-dimethylaniline by rabbit liver and lung microsomes. Effects of age and metals. *Chem.-biol. Interactions*, **8**, 91–105

Dragun, J. & Helling, C.S. (1985) Physicochemical and structural relationships of organic chemicals undergoing soil- and clay-catalyzed free-radical oxidation. *Soil Sci.*, **139**, 100–111

Eller, P.M., ed. (1985) *NIOSH Manual of Analytical Methods*, 3rd ed., Suppl. 1, (DHHS (NIOSH) Publ. No. 84-100), Washington DC, US Government Printing Office, pp. 2002-1—2002-6

Fluka Chemie AG (1993) *Fluka Chemika-BioChemika*, Buchs, p. 513

Gooderham, N.J. & Gorrod, J.W. (1981) Routes to the formation of *N*-methyl-4-aminophenol, a metabolite of *N,N*-dimethylaniline. *Adv. exp. Med. Biol.*, **136B**, 1109–1120

Gorrod, J.W. & Gooderham, N.J. (1981) The in vitro metabolism of *N,N*-dimethylaniline by guinea pig and rabbit tissue preparations. *Eur. J. Drug Metab. Pharmacol.*, **6**, 195–206

Hamill, S. & Cooper, D.Y. (1984) The role of cytochrome P-450 in the dual pathways of *N*-demethylation of *N,N*-dimethylaniline by hepatic microsomes. *Xenobiotica*, **14**, 139–149

Hansch, C. & Leo, A. (1979) *Substituent Constants for Correlation Analysis in Chemistry and Biology*, New York, John Wiley & Sons, p. 235

Hardin, B.D., Schuler, R.L., Burg, J.R., Booth, G.M., Hazelden, K.P., MacKenzie, K.M., Piccirillo, V.J. & Smith, K.N. (1987) Evaluation of 60 chemicals in a preliminary developmental toxicity test. *Teratog. Carcinog. Mutag.*, **7**, 29–48

Harris, L.R., Gideon, J.A., Berardinelli, S., Reed, L.D. & Dobbin, R.D. (1980) *Coal Liquefaction: Recent Findings in Occupational Safety and Health* (NIOSH-80-122/US NTIS PB81-223422), Cincinnati, OH, National Institute for Occupational Safety and Health

Heraeus (1991) *Feinchemikalien und Forschungsbedarf*, Karlsruhe, p. 280

Hlavica, P. & Hülsmann, S. (1979) Studies on the mechanism of hepatic microsomal *N*-oxide formation. *Biochem. J.*, **182**, 109–116

Hlavica, P. & Kehl, M. (1976) Comparative studies on the *N*-oxidation of aniline and *N,N*-dimethylaniline by rabbit liver microsomes. *Xenobiotica*, **11**, 679–689

Ho, C.-H., Clark, B.R., Guerin, M.R., Barkenbus, F.D., Rao, T.K. & Epler, J.L. (1981) Analytical and biological analyses of test materials from the synthetic fuel technologies. IV. Studies of chemical structure–mutagenic activity relationships of aromatic nitrogen compounds relevant to synfuels. *Mutat. Res.*, **85**, 335–345

Holzer, N. & Kiese, M. (1960) Formation of nitrosobenzene, aniline and haemoglobin in cats and dogs after intravenous injection of *N*-alkylanilines (Ger.). *Naunyn-Schmiedeberg's Arch. exp. Pathol. Pharmakol.*, **238**, 546–556

IARC (1982a) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 27, *Some Aromatic Amines, Anthraquinones, and Nitroso Compounds, and Inorganic Fluorides Used in Drinking-water and Dental Preparations*, Lyon, pp. 39–61

IARC (1982b) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 28, *The Rubber Industry*, Lyon

IARC (1987a) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of* IARC Monographs *Volumes 1 to 42*, Lyon, pp. 99–100

IARC (1987b) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of* IARC Monographs *Volumes 1 to 42*, Lyon, pp. 332–334

ILO (1991) *Occupational Exposure Limits for Airborne Toxic Substances*, 3rd ed. (Occupational Safety and Health Series No. 37), Geneva, International Labour Office, pp. 164–167

Janssen Chimica (1990) *1991 Catalog Handbook of Fine Chemicals*, Beerse, p. 477

Kedderis, G.L. & Hollenberg, P.F. (1984) pH Kinetic studies of the *N*-demethylation of *N,N*-dimethylaniline catalyzed by chloroperoxidase. *Arch. Biochem. Biophys.*, **233**, 315–321

Kiese, M. & Renner, G. (1974) Urinary metabolites of *N,N*-dimethylaniline produced by dogs. *Arch. Pharmacol.*, **283**, 143–150

Kitada, M., Kamataki, T. & Kitagawa, H. (1974) Comparison of *N*-oxidation and *N*-demethylation of dimethylamine in human liver. *Jpn. J. Pharmacol.*, **24**, 644–647

Lancaster Synthesis (1991) *MTM Research Chemicals/Lancaster Catalogue 1991/92*, Windham, NH, MTM Plc, pp. 534–535

Leach, J.M., Otson, R. & Armstrong, V. (1987) Airborne contaminants in two small Canadian coal liquefaction pilot plants. *Am. ind. Hyg. Assoc. J.*, **48**, 693–697

Lemoine, A., Johann, M. & Cresteil, T. (1990) Evidence for the presence of distinct flavin-containing monooxygenases in human tissues. *Arch. Biochem. Biophys.*, **276**, 336–342

Lide, D.R., ed. (1991) *CRC Handbook of Chemistry and Physics*, 72nd ed., Boca Raton, FL, CRC Press, pp. 3–40, 6–76

Loveday, K.S., Lugo, M.H., Resnick, M.A., Anderson, B.E. & Zeiger, E. (1989) Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells *in vitro*: II. Results with 20 chemicals. *Environ. mol. Mutag.*, **13**, 60–94

MacDonald, T.L., Gutheim, W.G., Martin, R.B. & Guengerich, F.P. (1989) Oxidation of substituted *N,N*-dimethylanilines by cytochrome P-450: estimation of the effective oxidation–reduction potential of cytochrome P-450. *Biochemistry*, **28**, 2071–2077

Machinist, J.M., Dehner, E.W. & Ziegler, D.M. (1968) Microsomal oxidases. III. Comparison of species and organ distribution of dialkylarylamine *N*-oxide and dealkylase and dialkylarylamine *N*-oxidase. *Arch. Biochem. Biophys.*, **125**, 858–864

Markel, H., Jr & Wilcox, T. (1981) *Health Hazard Evaluation Report No. HHE- 79-104-838. A.O. Smith-Inland, Inc., Little Rock, AR* (US NTIS PB82-182429), Cincinnati, OH, National Institute for Occupational Safety and Health

Margosis, M. (1977) GLC determination of *N,N*-dimethylaniline in penicillins. *J. pharmacol. Sci.*, **66**, 1634–1636

Markosyan, T.M. (1969) Comparative toxicity of monomethylaniline and dimethylaniline in chronic test (Russ.). *Gig. Sanit.*, **34**, 7–11

McManus, M.E., Stupans, I., Burgess, W., Koenig, J.A., Hall, P.delaM. & Birkett, D.J. (1987) Flavin-containing monooxygenase activity in human liver microsomes. *Drug Metab. Disposition*, **15**, 256–261

McNulty, M.J., Casanova-Schmitz, M. & Heck, H.d'A. (1983) Metabolism of dimethylamine in the nasal mucosa of the Fischer 344 rat. *Drug Metab. Disposition*, **11**, 421–425

Meijers, A.P. & van der Leer, R.C. (1976) The occurrence of organic micropollutants in the River Rhine and the River Maas in 1974. *Water Res.*, **10**, 597–604

Mori, Y., Niwa, T., Hori, T. & Toyoshi, K. (1980) Mutagenicity of 3′-methyl-N,N-dimethyl-4-amino azobenzene metabolites and related compounds. *Carcinogenesis*, **1**, 121–127

Mortelmans, K., Haworth, S., Lawlor, T., Speck, W., Tainer, B. & Zeiger, E. (1986) *Salmonella* mutagenicity tests: II. Results from the testing of 270 chemicals. *Environ. mol. Mutag.*, **8** (Suppl. 7), 1–119

Nelson, C.R. & Hites, R.A. (1980) Aromatic amines in and near Buffalo River. *Environ. Sci. Technol.*, **14**, 1147–1149

Northcott, J. (1978) Aniline and its derivatives. In: Mark, H.F., Othmer, D.F., Overberger, C.G., Seaborg, G.T. & Grayson, N., eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd ed., Vol. 2, New York, John Wiley & Sons, pp. 309–321

Ohmiya, Y. & Mehendale, H.M. (1983) *N*-Oxidation of *N,N*-dimethylaniline in the rabbit and rat lung. *Biochem. Pharmacol.*, **32**, 1281–1285

Pan, H.P., Fouts, J.R. & Devereux, T.R. (1975) Hepatic microsomal *N*-oxidation and *N*-demethylation of *N,N*-dimethylaniline in red-winged blackbird compared with rat and other birds. *Life Sci.*, **17**, 819–826

Pandey, R.N., Armstrong, A.P. & Hollenberg, P.F. (1989) Oxidative *N*-demethylation of N,N-dimethylaniline by purified isozymes of cytochrome P-450. *Biochem. Pharmacol.*, **38**, 2181–2185

Pouchert, C.J. (1981) *The Aldrich Library of Infrared Spectra*, 3rd ed., Milwaukee, WI, Aldrich Chemical Co., p. 715

Pouchert, C.J. (1983) *The Aldrich Library of NMR Spectra*, 2nd ed., Vol. 1, Milwaukee, WI, Aldrich Chemical Co., p. 990

Quercia, V., De Sena, C., Iela, G., Pagnozzi, G. & Pierini, N. (1980) Determination of the content of *N,N*-dimethylaniline in some antibiotics (Ital.). *Boll. chim. farm.*, **119**, 619–622

Rane, A. (1974) *N*-Oxidation of a tertiary amine (*N,N*-dimethylaniline) by human fetal liver microsomes. *Clin. Pharmacol. Ther.*, **15**, 32–38

Riedel-de Haen (1990) *Laboratory Chemicals 1990*, Seelze, p. 493

Rivera, J., Ventura, F., Caixach, J., De Torres, M. & Figueras, A. (1987) GC/MS, HPLC and FAB mass spectrometric analysis of organic micropollutants in Barcelona's water supply. *Int. J. environ. anal. Chem.*, **29**, 15–35

Rosenwald, R.H. (1978) Alkylation. In: Mark, H.F., Othmer, D.F., Overberger, C.G., Seaborg, G.T. & Grayson, N., eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd ed., Vol. 2, New York, John Wiley & Sons, p. 67

Sadtler Research Laboratories (1980) *Sadtler Standard Spectra. 1980 Cumulative Index*, Philadelphia, PA

Sadtler Research Laboratories (1991) *Sadtler Standard Spectra. 1981–1991 Supplementary Index*, Philadelphia, PA

Sax, N.I. & Lewis, R.J. (1987) *Hawley's Condensed Chemical Dictionary*, 11th ed., New York, Van Nostrand Reinhold Co., p. 411

Sherratt, A.J. & Damani, L.A. (1989) The metabolism of *N,N*-dimethylaniline by isolated rat hepatocytes: identification of a novel *N*-conjugate. *Xenobiotica*, **19**, 379–388

Sivarajah, K., Lasker, J.M., Eling, T.E. & Abou-Donia, M.B. (1982) Metabolism of *N*-alkyl compounds during the biosynthesis of prostaglandins. *N*-Dealkylation during prostaglandin biosynthesis. *Mol. Pharmacol.*, **21**, 133–141

Smyth, H.F., Jr, Carpenter, C.P., Weil, C.S., Pozzani, U.C. & Striegel, J.A. (1962) Range-finding toxicity data: list VI. *Am. ind. Hyg. Assoc. J.*, **23**, 95–107

US Environmental Protection Agency (1986) *Health and Environmental Effects Profile for* N,N-*Dimethylaniline* (Report No. EPA-600/X-87-052/US NTIS PB89-123038), Cincinnati, OH, Environmental Criteria and Assessment Office

US International Trade Commission (1988) *US Imports for Consumption and General Imports* (FT 246/Annual 1987), Washington DC, US Department of Commerce

US National Library of Medicine (1992) *Registry of Toxic Effects of Chemical Substances* (RTECS No. BX4725000), Bethesda, MD

US National Toxicology Program (1989) *Toxicology and Carcinogenesis Studies of* N,N-*Dimethylaniline (CAS No. 121-69-7) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies)* (NTP TR 360; NIH Publ. No. 90-2815), Research Triangle Park, NC, US Department of Health and Human Services

US Occupational Safety and Health Administration (1989) Air contaminants—permissible exposure limits. *US Code fed. Regul.*, Part 1910.1000, **Title 29**, p. 602

Yoshimi, N., Sugie, S., Iwata, H., Niwa, K., Mori, H., Hashida, C. & Shimizu, H. (1988) The genotoxicity of a variety of aniline derivatives in a DNA repair test with primary cultured rat hepatocytes. *Mutat. Res.*, **206**, 183–191

Ziegler, D.M. & Gold, M.S. (1971) Oxidative metabolism of tertiary amine drugs by human liver tissue. *Xenobiotica*, **1**, 325–326

Ziegler, D.M. & Pettit, F.H. (1964) Formation of an intermediate *N*-oxide in the oxidative demethylation of *N,N*-dimethylaniline catalyzed by liver microsomes. *Biochem. biophys. Res. Commun.*, **15**, 188–193

Zoeteman, B.C.J., Harmsen, K., Linders, J.B.H.J., Morra, C.F.H. & Slooff, W. (1980) Persistent organic pollutants in river water and groundwater of the Netherlands. *Chemosphere*, **9**, 231–249