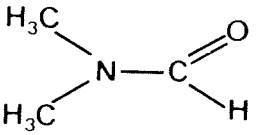
DIMETHYLFORMAMIDE

1. Chemical and Physical Data

1.1 Synonyms

Chem. Abstr. Services Reg. No.: 68-12-2
Chem. Abstr. Name: *N,N*-Dimethylformamide
Synonyms: *N,N*-Dimethylmethanamide; DMF; DMFA; DMF (amide); *N*-formyldimethylamine

1.2 Structural and molecular formulae and molecular weight



C_3H_7NO Mol. wt: 73.1

1.3 Chemical and physical properties of the pure substance

From E.I. duPont de Nemours & Co. (1986) unless otherwise specified.

(*a*) *Description*: Clear, colourless hygroscopic liquid (Eberling, 1980) with slight amine odour (Windholz, 1983)

(*b*) *Boiling-point*: 153.0°C

(*c*) *Freezing-point*: -61.0°C

(*d*) *Flash-point*: 67°C (open-cup); 58°C (closed-cup)

(*e*) *Density*: 0.949 g/ml at 20°C

(*f*) *Viscosity*: 0.802 cp at 25°C

(*g*) *Spectroscopy data*: Nuclear magnetic resonance and infrared spectral data have been reported (Sadtler Research Laboratories, 1980; Pouchert, 1981, 1983, 1985)

(*h*) *Solubility*: Soluble in water, acetone, alcohols, benzene, chloroform, diethyl ether, esters and chlorinated and aromatic hydrocarbons; limited solubility in aliphatic hydrocarbons

(*i*) *Refractive index*: 1.428 at 25°C

(*j*) *Volatility*: Vapour pressure, 3.7 mm Hg at 25°C

(*k*) *Stability*: Photodegrades when exposed to ultraviolet radiation (or strong sunlight), with formation of dimethylamine and formaldehyde (see IARC, 1987)

(*l*) *Reactivity*: Reacts violently when mixed with oxidizing agents, such as perchlorates, nitrates, permanganates, chromates, nitric acid, chromic acid, halogens and some cleaning solutions; may cause fire or explosion when reacted with any halogenated hydrocarbon in the presence of metal; generates carbon monoxide vapours when heated to decomposition (E.I. DuPont de Nemours & Co., 1988a); can attack copper, brass and other copper alloys (Eberling, 1980)

(*m*) *Octanol/water partition coefficient*: log P = -1.01 (Hansch & Leo, 1979)

(*n*) *Conversion factor*: $mg/m^3 = 2.99 \times ppm$[1]

1.4 Technical products and impurities

Dimethylformamide is available commercially with the following specifications: purity, approximately 99.9%; water, 0.03–0.05% (max), typically, 0.01%; *N*-methylformamide, 100 ppm (max); dimethylamine, 15–20 ppm (max), typically, 6 ppm; iron, 0.05 ppm (max), typically 0.01 ppm; methanol, 100 ppm (max); formic acid, 20 ppm (max), typically, 7 ppm (Eberling, 1980; Air Products and Chemicals, Inc., 1985; E.I. duPont de Nemours & Co., 1986).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

Dimethylformamide was first synthesized in 1893. In a one-stage process, a solution of dimethylamine in methanol reacts with carbon monoxide in the presence of sodium methylate or with metal carbonyls at 110–150°C and pressures of 1.5–2.5 MPa (15–25 atm). In the two-stage process, methyl formate is first produced from carbon monoxide and methanol under high pressure at 60–100°C in the presence of sodium methylate. The methyl formate is distilled and then reacts with dimethylamine at 80–100°C and low pressure. The product is purified by distillation (Eberling, 1980).

Worldwide production capacity was estimated to be about 225 000 tonnes in 1979, approximately half of which was located in Europe (Eberling, 1980). By 1983, estimated world-

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

wide capacity had dropped to 181 600 tonnes and worldwide production was only about 100 000 tonnes. These decreases were a result of a decline in consumer demand for 'wet-look' fabrics. In 1983, production capacity in North America was 54 400 tonnes. US consumption was about 18 100 tonnes in 1977–78 and decreased to 13 600 tonnes in 1983. US production of dimethylformamide was estimated to be 23 000–27 000 tonnes in 1987 (E.I. DuPont de Nemours & Co., 1988b).

Mexico, Taiwan, Brazil and the Republic of Korea were estimated to have a combined capacity for dimethylformamide production of 29 500–31 800 tonnes in 1983 (Anon., 1983). Total production capacity for dimethylformamide in Japan was estimated in 1985 to be 41 000 tonnes per year; 60% was used for the production of polyurethane artificial leather, 30% for export to North America and south-east Asia and the rest used as solvents for fabric materials and resins (Anon., 1985).

(*b*) *Use*

(i) *Polymer and resin solvent*

Dimethylformamide is used as a solvent for many vinyl-based polymers in the manufacture of films, fibres and coatings, and as a booster or cosolvent for both high molecular-weight polyvinyl chlorides and vinyl chloride–vinyl acetate copolymers in the manufacture of protective coatings, films, printing inks and adhesive formulations. Since it is a highly polar solvent capable of hydrogen bonding, it is effective as a solvent for polar polymers with strong intermolecular forces. Dimethylformamide is used as a solvent for making polyurethane lacquers for clothing and accessories made of synthetic leather, and its use in leather tanneries has been reported (Levin *et al.*, 1987). Dimethylformamide has been used as a solvent for certain epoxy resin curing agents, such as dicyandiamide and *meta*-phenylenediamine, and acts as a catalyst in accelerating cure at elevated temperatures. It has been widely used as a solvent in the production of fibres and films based on polyacrylonitrile (E.I. duPont de Nemours & Co., 1986).

(ii) *Separations*

Dimethylformamide is used commercially as a selective solvent to recover high purity acetylene from hydrocarbon feed streams. It is also used as a scrubbing solvent for the purification of ethylene and propylene, and has become a major solvent for extracting and separating butadiene from hydrocarbon streams (E.I. duPont de Nemours & Co., 1986).

(iii) *Selective solvent extractions*

Dimethylformamide is used in petroleum processing for the separation of non-paraffinic from paraffinic hydrocarbons and is the preferred solvent for extraction of condensed-ring polycyclic aromatic compounds from wax. Aqueous dimethylformamide has been used as a selective solvent for the separation of polycarboxylic acids, such as isophthalic from terephthalic acid, brassylic from azelaic acid and sebacic from adipic acid and fatty acid oxidation products (E.I. duPont de Nemours & Co., 1986).

(iv) *Miscellaneous*

Dimethylformamide has been used as a reactant in many organic synthetic preparations, as a component in cold formulation industrial paint strippers and as a solvent for elec-

trolytes, particularly in high-voltage capacitors. Dimethylformamide is also used as a combination quench and solvent cleaner for hot-dipped tinned articles (E.I. duPont de Nemours & Co., 1986).

(c) *Regulatory status and guidelines*

The US Food and Drug Administration (1988) permits the use of dimethylformamide as a component of adhesives used in articles intended for use in packaging, transporting or holding food.

Occupational exposure limits for dimethylformamide in 29 countries or regions are presented in Table 1.

Table 1. Occupational exposure limits for dimethylformamide[a]

Country	Year	Concentration[b] (mg/m^3)	Interpretation[c]
Australia	1984	S 30	TWA
Austria	1985	S 60	TWA
Belgium	1985	S 30	TWA
Brazil	1985	24	TWA
Bulgaria	1985	S 10	TWA
China	1985	S 10	TWA
Czechoslovakia	1985	30	Average
		60	Maximum
Denmark	1988	S 30	TWA
Finland	1987	S 30	TWA
		S 60	STEL (15 min)
France	1986	S 30	TWA
German Democratic Republic	1985	S 10	TWA
Germany, Federal Republic of	1988	S 60	TWA
Hungary	1985	S 10	TWA
		S 20	STEL
Indonesia	1985	S 30	TWA
Italy	1985	S 30	TWA
Japan	1988	S 30	TWA
Mexico	1985	60	TWA
Netherlands	1986	S 30	TWA
Norway	1981	S 30	TWA
Poland	1985	10	TWA
Rumania	1985	S 20	Average
		S 50	Maximum
Sweden	1987	S 30	TWA
		S 45	STEL (15 min)
Switzerland	1985	S 30	TWA
Taiwan	1985	S 30	TWA
UK	1987	S 30	TWA
		S 60	STEL (10 min)

Table 1 (contd)

Country	Year	Concentration[b] (mg/m^3)	Interpretation[c]
USA[d]			
OSHA	1987	30	TWA
ACGIH	1988	S 30	TWA
USSR	1986	10	Ceiling
Venezuela	1985	S 30	TWA
		S 60	Ceiling
Yugoslavia	1985	S 10	TWA

[a]From Direktoratet for Arbeidstilsynet (1981); International Labour Office (1984); Arbeidsinspectie (1986); Institut National de Recherche et de Sécurité (1986); Cook (1987); Health and Safety Executive (1987); National Swedish Board of Occupational Safety and Health (1987); Työsuojeluhallitus (1987); US Occupational Safety and Health Administration (1987); American Conference of Governmental Industrial Hygienists (1988); Arbejdstilsynet (1988); Deutsche Forschungsgemeinschaft (1988)
[b]S, skin notation
[c]TWA, 8-h time-weighted average; STEL, short-term exposure limit
[d]OSHA, Occupational Safety and Health Administration; ACGIH, American Conference of Governmental Industrial Hygienists

2.2 Occurrence

(*a*) *Natural occurrence*

Dimethylformamide is not known to occur as a natural product.

(*b*) *Occupational exposure*

On the basis of a US National Occupational Exposure Survey, the National Institute for Occupational Safety and Health (1983) estimated that 94 000 workers were potentially exposed to dimethylformamide in the USA in 1981–83. Levels of exposure to dimethylformamide are given in Table 2.

(*c*) *Environmental occurrence*

No data were available to the Working Group on the environmental occurrence of dimethylformamide.

2.3 Analysis

Methods have been reported for the analysis of dimethylformamide in air and water, and as its metabolite, methylformamide in biological media. Dimethylformamide has been determined in air by drawing air samples through charcoal or silica gel adsorption tubes, desorption with an appropriate solvent and analysis by gas chromatography with flame-ionization detection or high-pressure liquid chromatography. Lower limits of detection for these

Table 2. Occupational exposure to dimethylformamide

Environment	Biological monitoring[a] (no. of samples)	Concentration in air[b] and monitoring method	Reference
Solvent extraction in a chemical plant	Analysed as MF in urine < 10 µl/l (288) > 20 µl/l (15) 54 µl/l (1) 62 µl/l (1) 77 µl/l (1)	ND–200 ppm (600 mg/m^3); area samples by detector tube	Lyle *et al.* (1979)
Polyurethane surface-treatment of synthetic leather	0.4–19.6 mg MF in urine/day	ND–5.13 ppm (15 mg/m^3); 8-h TWA personal samples	Yonemoto & Suzuki (1980)
Artificial leather factory	0.4–7.1 mg/m^3; mean, 1.5 mg/m^3 DMF in alveolar air	1.1–20.9 mg/m^3; mean, 5.3 mg/m^3; 8-h TWA personal samples	Brugnone *et al.* (1980)
Polyurethane lacquering for textile substrate	12 mg/l MF in urine	Mean, 28.4 mg/m^3; 8-h TWA personal samples	Pozzoli *et al.* (1981)
Polyurethane production plant		Mean, 1.3–1.8 mg/m^3; 8-h TWA personal samples 1.3 mg/m^3; area samples	Rimatori & Carelli (1982)
Textile dye manufacturing plant		0.83 mg/m^3; 8-h TWA 15.6 mg/m^3; area sample	Zey *et al.* (1987)
Synthetic fibre plant	8.9–13.2 µg/l MF in urine (geometric mean)	3.4–3.6 mg/m^3; 8-h TWA (geometric mean)	Dixon *et al.* (1983)
Acrylic fibre plant	10.3–63 mg MF/g creatine, daily means	Mean, 1.0–46.6 mg/m^3; 8-h TWA area samples	Lauwerys *et al.* (1980)
Amine processing plant		mean, 12.3 mg/m^3	Berger *et al.* (1985)

[a]MF, methylformamide; DMF, dimethylformamide
[b]ND, not detected

methods are in the range of 0.5–1.0 mg/m^3 (Lipski, 1982; Rimatori & Carelli, 1982; Eller, 1985; Guenier *et al.*, 1986; Stránsky, 1986). Colorimetric detection systems have been developed for dimethylformamide in air (Matheson Gas Products, undated; Roxan, Inc., undated; The Foxboro Co., 1983; Sensidyne, 1985; National Draeger, Inc., 1987; SKC, 1988).

Gas chromatography with flame-ionization or mass spectrometric detection has been used for the analysis of aqueous solutions of dimethylformamide by direct injection (Kubelka *et al.*, 1976).

A method has been reported for the direct analysis of dimethylformamide in breath samples using a modified portable quadrupole mass spectrometer. The lower limit of detection was 0.5 mg/m^3 (Wilson & Ottley, 1981). Personal exposures to dimethylformamide have also been monitored by gas chromatographic analysis of urine for *N*-methylformamide

(Barnes & Henry, 1974). This compound has been shown, however, to originate mainly from thermal degradation during the analysis of *N*-hydroxymethyl-*N*-methylformamide, which is the main metabolite present in urine (Scailteur & Lauwerys, 1984).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals[1]

(*a*) *Oral administration*

Rat: One group of 15 and one group of five BD rats [sex and age unspecified] were given 75 or 150 mg/kg bw dimethylformamide [purity unspecified] per day in the drinking-water until a total dose of 38 g/kg bw had been given to both groups. The total experimental period was 107 weeks (mean survival time, 76 weeks). No tumour was observed (Druckrey *et al.*, 1967). [The Working Group noted the small number of animals used and the incomplete reporting of the results.]

(*b*) *Subcutaneous administration*

Rat: Two groups of 12 BD rats [sex and age unspecified] received weekly subcutaneous injections of 200 or 400 mg/kg bw dimethylformamide [purity unspecified] until total doses of 8 and 20 g/kg bw had been given, which was at 104 weeks for the low-dose group and 109 weeks for the high-dose group. No tumour was observed (Druckrey *et al.*, 1967). [The Working Group noted the small number of animals used and the incomplete reporting of the results.]

(*c*) *Intraperitoneal administration*

Rat: Groups of 20 male and 20 female MRC rats, 13–14 weeks of age, received weekly intraperitoneal injections of 0.1 ml dimethylformamide (distilled, gas chromatography grade) for ten weeks (total dose, 1 ml [949 mg]). A group of 15 male and 15 female rats served as untreated controls. Median survival times were 87 weeks for treated males and 96 weeks for treated females, 92 weeks for control males and 100 weeks for control females. The experiment was terminated at 115 weeks. In the treated groups, 9/18 males and 11/19 females had tumours at different sites; in the control groups, 4/14 males and 5/14 females had tumours. A total of 13 tumours (three malignant) occurred in treated males and 17 (nine malignant) in females; untreated males had four (benign) tumours and untreated females, eight

[1]The Working Group was aware of a study in progress in mice and rats by inhalation (IARC, 1988)

(two malignant). A few uncommon tumours were reported in treated animals: an embryonal-cell carcinoma of the testis in one male, and two colon adenocarcinomas and a squamous-cell carcinoma of the rectum in females (Kommineni, 1972). [The Working Group noted the small number of animals, the unequal group sizes, the short duration of treatment and the incomplete description of some of the pathological results.]

3.2 Other relevant data

The toxicology of dimethylformamide has been reviewed (Kennedy, 1986; Lauwerys, 1986).

(*a*) *Experimental systems*

(i) *Absorption, distribution, excretion and metabolism*

Dimethylformamide is readily absorbed by mammals following its oral administration, dermal contact or inhalation exposure (Massmann, 1956; Kimmerle & Eben, 1975a; Kennedy, 1986). After rats were exposed for 4 h by inhalation, dimethylformamide and its main metabolite were distributed uniformly throughout the tissues; almost all was removed within two days (Lundberg *et al.*, 1983).

The main metabolic pathway of dimethylformamide in rodents involves hydroxylation of the methyl group to form *N*-hydroxymethyl-*N*-methylformamide (Brindley *et al.*, 1983; Scailteur & Lauwerys, 1984; Scailteur *et al.*, 1984). Liver is the main organ in which metabolism occurs (Scailteur *et al.*, 1984). Other metabolites excreted in rodent urine include *N*-methylformamide (Scailteur & Lauwerys, 1984), monomethylamine and dimethylamine, each of which constituted less than 5% of the administered dose (Kestell *et al.*, 1987). Some unmetabolized dimethylformamide is also excreted, to a greater extent in female rats than males (Scailteur *et al.*, 1984). When ^{14}C-dimethylformamide (labelled in the formyl group) was administered to mice, 83% of the dose was recovered in urine within 24 h. Of this amount, 56% was excreted as *N*-hydroxymethyl-*N*-methylformamide and 5% as unmetabolized dimethylformamide; 3% of the dose administered was excreted as *N*-(hydroxymethyl)formamide or formamide and 18% as unidentified metabolites (Brindley *et al.*, 1983). [The Working Group noted that, until recently, *N*-methylformamide was considered to be the main metabolite; however, *N*-hydroxymethyl-*N*-methylformamide is broken down to *N*-methylformamide during gas chromatographic analysis.]

Dimethylformamide has been shown to cross the placenta after exposure of rats by inhalation (Sheveleva *et al.*, 1977).

(ii) *Toxic effects*

The oral LD_{50} for dimethylformamide has been reported to be 3.8–6.8 g/kg bw in mice, 2.0–7.6 g/kg bw in rats, 3.4 g/kg bw in guinea-pigs and 3–4 g/kg bw in gerbils. The intraperitoneal LD_{50} has been reported to be 1.1–6.2 g/kg bw in mice, 1.4–4.8 g/kg bw in rats, 4 g/kg bw in guinea-pigs, 3–4 g/kg bw in gerbils, 1 g/kg bw in rabbits and 0.3–0.5 g/kg bw in cats. The intravenous LD_{50} was 2.5–4.1 g/kg bw in mice, 2–3.0 g/kg bw in rats, 1.0 g/kg bw in guinea-pigs, 1–1.8 g/kg bw in rabbits and 0.5 g/kg bw in dogs. The subcutaneous LD_{50} was 3.5–6.5 g/kg bw in mice, 3.5–5 g/kg bw in rats, 2 g/kg bw in rabbits and 3–4 g/kg bw in gerbils. An intramuscu-

lar LD_{50} of 3.8–6.5 g/kg bw has been reported in mice, and dermal LD_{50}s of 11 and 1.5 g/kg bw have been reported for rats and rabbits, respectively (Massmann, 1956; Davis & Jenner, 1959; Thiersch, 1962; Kutzche, 1965; Druckrey *et al.*, 1967; Spinazzola *et al.*, 1969; Kimura *et al.*, 1971; Llewellyn *et al.*, 1974; Bartsch *et al.*, 1976; Stula & Krauss, 1977; Kennedy, 1986). A 2-h inhalational LD_{50} of 9400 mg/m^3 was reported in mice and a 4-h inhalation LD_{50} of >2500 ppm (7500 mg/m^3) in rats (Clayton *et al.*, 1963). Dimethylformamide was more toxic in younger than in older rats, with oral LD_{50}s of <1 g/kg bw in newborn, 1.4 g/kg bw in 14-day-old, 4.0 g/kg bw in young adult and 6.8 g/kg bw in adult animals (Kimura *et al.*, 1971).

Rats survived a single 4-h exposure to saturated vapours of dimethylformamide [dose unspecified] (Smyth & Carpenter, 1948); no mortality was observed when rats were exposed to 2500 ppm saturated vapours of dimethylformamide for 4 h, but deaths occurred when the period was extended to 6 h (Clayton *et al.*, 1963).

Slight skin irritation was observed after skin applications of 2.5 g/kg bw dimethylformamide to mice; no such irritation was found in rabbits similarly treated with 0.5 g/kg (Wiles & Narcisse, 1971). Moderate corneal injury and moderate to severe conjunctivitis were observed after application of 0.01 ml dimethylformamide on the corneal surface or of 50% in the conjunctival sac of rabbits (Massmann, 1956; Williams *et al.*, 1982).

Feeding of dimethylformamide to mice (160, 540, 1850 mg/kg) and to rats (215, 750, 2500 mg/kg) in the diet for more than 100 days resulted in a slight increase in liver weights in both species but no evidence of histopathological damage in the liver or other tissues (Becci *et al.*, 1983). When dimethylformamide was given to gerbils at concentrations of 10 000, 17 000, 34 000 and 66 000 mg/l in the drinking-water, mortality and severe liver toxicity (necrotic foci) were observed in a dose-dependent fashion at the three higher dose levels (Llewellyn *et al.*, 1974).

In several experiments, rats were exposed by inhalation to 100–1200 ppm dimethylformamide, for up to about 120 days. Liver toxicity (as evaluated by clinical chemistry and/or gross pathological and histopathological examination) was seen after prolonged exposure and at higher concentrations (Massman, 1956; Clayton *et al.*, 1963; Tanaka, 1971; Craig *et al.*, 1984). Liver necrosis was also seen in mice given 150–1200 ppm (450–3600 mg/m^3) dimethylformamide (Craig *et al.*, 1984); and toxicity was observed in guinea-pigs after several daily intragastric administrations of 10 ml of the undiluted compound (Martelli, 1960). In one study, however, inhalation exposure of rats and cats to 1000 ppm (3000 mg/m^3) for 6 h per day for two months induced no toxic effect in liver (Hofmann, 1960), and no macroscopic effect was seen in the liver of rats exposed to 600 ppm (1800 mg/m^3) dimethylformamide (Schottek, 1970). After mice, rats, rabbits, guinea-pigs and dogs were exposed to 58 aerosolized doses of 23 ppm (69 mg/m^3) dimethylformamide for 5.5 h and 426 ppm (1300 mg/m^3) for a further 30 min, no adverse clinical sign was seen in rodents. One of four dogs had decreased systolic blood pressure, and all four had degenerative changes in heart muscle. Liver weights were elevated in all species, except guinea-pigs, and liver fat content was increased in rats. No other toxic change, as evaluated by haematology or tissue histopathology, was detected (Clayton *et al.*, 1963).

Kidney toxicity was seen in gerbils given dimethylformamide in the drinking-water (17 000, 34 000 and 66 000 mg/l) for up to 80 days (Llewellyn *et al.*, 1974) and in guinea-pigs

given several daily oral administrations of 10 ml of the undiluted compound (Martelli, 1960). Exposure of rats and cats to 1000 ppm (3000 mg/m^3) dimethylformamide by inhalation for 6 h per day for two months did not induce kidney toxicity (Hofmann, 1960).

(iii) *Effects on reproduction and prenatal toxicity*

As reported in an abstract, intraperitoneal administration of 1.24 ml (1.2 g)/kg bw dimethylformamide to NMRI mice on days 6–15 of gestation had no teratogenic effect, although monomethylformamide at a dose of 0.1 ml/kg induced a high incidence of fetal death and malformation (Gleich, 1974).

Groups of 12–30 AB Jena–Halle or C57Bl mice were given intraperitoneal injections of 170–2100 mg/kg bw dimethylformamide on either one or several days of gestation, and the fetuses were examined for growth, morphology and viability. Single injections of 2100 mg/kg bw into Jena–Halle strain mice on day 3, 7 or 9 of gestation were reported to be embryotoxic. [The Working Group noted that no statistical analysis was included in the table of experimental results and that it is not clear what the effect was.] Treatment of AB Jena Halle mice with 600 or 1080 mg/kg bw and of C57Bl mice with 1080 mg/kg bw on days 1–14 of gestation induced a high incidence of malformations in both strains. Defects included deficient ossification of the occipital and parietal bones, and open eyes (Scheufler & Freye, 1975).

Rats were exposed by inhalation to 0, 0.05 or 0.6 mg/m^3 dimethylformamide for 4 h per day on days 1–19 of gestation. No maternal effect was observed, but fetal growth was reduced at the lower dose and growth retardation and postimplantation embryonic death were seen at the higher dose. The number of postnatal deaths was increased in the higher dose group (Sheveleva & Osina, 1973).

Groups of 22–23 Long–Evans rats were exposed by inhalation to 0, 18 or 172 ppm (54 or 515 mg/m^3) dimethylformamide for 6 h per day on days 6–15 of gestation, and the fetuses were examined by routine teratological techniques. No clinical sign of systemic toxicity was reported in the exposed females, and no effect on fetal viability or morphology was observed. The growth of fetuses in the high–dose group was retarded, but they showed normal skeletal development (Kimmerle & Machemer, 1975).

As reported in an abstract, Sprague–Dawley rats were exposed to 0, 32 or 301 ppm (96 or 900 mg/m^3) dimethylformamide vapours for 6 h per day on days 6–15 of gestation. Slight maternal toxicity and fetal growth retardation were reported at the highest dose level (Keller & Lewis, 1981).

Dimethylformamide was one of several acetamides and formamides administered in a teratology study by oral gavage to rabbits on days 6–18 of gestation. Doses were 0 (24 rabbits), 46.4 µl (44 mg)/kg bw (12 rabbits), 68.1 µl/kg (65 mg/kg) (18 rabbits) and 200 µl/kg (190 mg/kg) (11 rabbits). A dose–related increase in the incidence of internal hydrocephalus was noted in fetuses. In the high–dose group, maternal toxicity, abortion, retardation of fetal growth and additional malformations (umbilical hernia, eventratio simplex, exophthalmus, cleft palate and abnormal positioning of limbs) were also observed (Merkle & Zeller, 1980).

Groups of three to nine Sprague–Dawley rats and four to five New Zealand white rabbits received dermal application of dimethylformamide (commercial grade with less that 2% impurities). Rats were treated for several 1–3–day periods during the middle of gestation

while rabbits were exposed on days 8–16. The administered dose was 200 mg/kg bw to rabbits and 600–2400 mg/kg bw to rats. It was reported that the test agent caused an increase in the rate of embryonic death in rats at a dose that also resulted in maternal mortality. Subcutaneous haemorrhages were observed in fetuses exposed during days 12 and 13 or 11–13, but the authors did not consider these to be toxicologically significant. No adverse effect was noted in the few rabbits that were studied (Stula & Krauss, 1977).

(iv) *Genetic and related effects*

Dimethylformamide was one of 42 chemicals selected for study in the International Collaborative Program for the Evaluation of Short-term Tests for Carcinogens (de Serres & Ashby, 1981), in which 30 assay systems were included and more than 50 laboratories contributed data. Dimethylformamide gave negative results in five studies for DNA repair in prokaryotes, 16 studies for mutation in bacteria, five studies for mutation or mitotic recombination in yeast, three studies for DNA repair in cultured human cells, three studies for sister chromatid exchange in cultured animal cells, one study for mutation in cultured animal cells, one study for mutation in cultured human cells, two studies for chromosomal aberrations in cultured animal cells, one study for sex-linked recessive lethal mutation in *Drosophila*, one study for sister chromatid exchange in bone marrow and liver of mice, three studies for micronuclei in mice, and one sperm morphology assay. In most of the in-vitro studies, dimethylformamide was tested both in the presence and absence of an exogenous metabolic system. Dimethylformamide gave inconclusive results in one study of lambda induction. It gave positive results in one study of differential toxicity in yeast. It induced mutation in *Salmonella typhimurium* TA1538 and TA98 in one test with metabolic activation. It induced DNA damage in *Saccharomyces cerevisiae* in one study and aneuploidy in *S. cerevisiae* D6 both in the presence and absence of an exogenous metabolic system in a single study. Dimethylformamide gave positive results in one study for mitotic recombination in yeast.

In many other studies, dimethylformamide did not induce mutation in *S. typhimurium* TA1530, TA1531, TA1532, TA1535, TA1537, TA1538, TA98, TA100 or TA1964 either in the presence or absence of an exogenous metabolic system (Green & Savage, 1978 [solvent control]; Purchase *et al.*, 1978; Antoine *et al.*, 1983; Falck *et al.*, 1985; Mortelmans *et al.*, 1986). Negative results were also obtained with *Escherichia coli* WP2*uvrA* in the presence of an exogenous metabolic system (Falck *et al.*, 1985). Dimethylformamide enhanced the mutagenicity of tryptophan-pyrolysate in *S. typhimurium* TA98 in the presence of an exogenous metabolic system (Arimoto *et al.*, 1982).

Dimethylformamide induced a slight increase in unscheduled DNA synthesis in primary rat hepatocyte cultures in one study (Williams, 1977) but not in two others (Williams & Laspia, 1979; Ito, 1982). It gave negative responses in the hepatocyte primary culture/DNA repair assay using mouse or hamster hepatocytes (McQueen *et al.*, 1983; Klaunig *et al.*, 1984).

Dimethylformamide had no effect on the frequency of recessive chlorophyll and embryonic lethal mutations in *Arabidopsis thaliana* (Gichner & Velemínský, 1987). In the same system, dimethylformamide altered the mutagenic activity of known mutagens (Gichner & Velemínský, 1986, 1987). It did not induce sex-linked recessive lethal mutations or somatic

mutation in *Drosophila* (Fahmy & Fahmy, 1972, 1983). [The Working Group noted that dimethylformamide was used as a solvent control in these experiments.]

Dimethylformamide was reported to induce a marginal mutagenic response in L5178Y $TK^{+/-}$ mouse lymphoma cells in the absence but not in the presence of an exogenous metabolic system (McGregor *et al.*, 1988); in similar studies, negative results were obtained (Mitchell *et al.*, 1988; Myhr & Caspary, 1988).

In one study, dimethylformamide did not increase the incidence of chromosomal aberrations or of sister chromatid exchange in human peripheral blood lymphocytes *in vitro* (highest no-effect dose, 80 000 μg/ml; Antoine *et al.*, 1983). In another study, chromosomal aberrations were reported in human peripheral lymphocyte cultures treated with dimethylformamide (lowest effective dose, 0.007 μg/ml; Koudela & Spazier, 1979).

In Balb/c mice injected intraperitoneally with 0.2, 20 or 2000 mg/kg bw dimethylformamide, no increase in the frequency of micronuclei in bone-marrow cells was observed (Antoine *et al.*, 1983), and no increase was seen in the frequency of sperm abnormalities after five doses of 0.1–1.5 ml/kg bw (Topham, 1980) or after 0.2–2000 mg/kg bw (Antoine *et al.*, 1983). It induced micronuclei in the bone marrow of Kunming mice after single (1 mg/kg) or multiple (3×1 mg/kg) intraperitoneal injections (Ye, 1987).

As reported in an abstract, no dominant lethal effect was observed in groups of ten Sprague–Dawley rats exposed by inhalation to dimethylformamide for 6 h per day for five consecutive days (Lewis, 1979).

Dimethylformamide did not induce morphological transformation in Syrian hamster embryo cells (Pienta *et al.*, 1977), nor did it induce transformation of hamster embryo cells after transplacental exposure by intraperitoneal injection (Quarles *et al.*, 1979). [The Working Group noted that since dimethylformamide was being used as a solvent control in these experiments, no other control was available and only one dose was tested.]

Dimethylformamide inhibited intercellular communication (as measured by metabolic cooperation) between Chinese hamster V79 *hprt*$^{+/-}$ cells (Chen *et al.*, 1984).

(*b*) *Humans*

(i) *Absorption, distribution, excretion and metabolism*

Dimethylformamide in liquid or vapour form is readily absorbed through the skin, by inhalation or after oral exposure (Maxfield *et al.*, 1975). It is rapidly metabolized and excreted in the urine in the form of *N*-hydroxymethyl-*N*-methylformamide and, to a small extent, *N*-methylformamide, *N*-hydroxymethylformamide and unmetabolized dimethylformamide (Scailteur & Lauwerys, 1984, 1987). In volunteers exposed by inhalation, *N*-hydroxymethyl-*N*-methylformamide (measured as *N*-methylformamide) was detected in urine 4 h after onset of exposure; almost complete elimination had taken place by 24 h (Kimmerle & Eben, 1975b). *N*-methylformamide, formed from *N*-hydroxymethyl-*N*-methylformamide during gas chromatographic analysis, has been measured in the urine of exposed workers. Urinary measurements showed a dose-relationship to airborne levels of dimethylformamide after exposure by inhalation (Lauwerys *et al.*, 1980); however, extensive skin contact may markedly influence the dose absorbed. Other methods for assessing exposure can include measurements of dimethylformamide in blood or exhaled air (Lauwerys, 1986).

(ii) *Toxic effects*

Accidental dermal and inhalation exposure has been reported to cause liver injury, with symptoms of abdominal pain, vomiting, hypertension and elevated levels of urinary bilirubin and serum transaminases. Some dermal irritation and hyperaemia were seen. After the disappearance of clinical signs, 11 days after exposure, a liver biopsy revealed septal fibrosis and accumulation of mononuclear cells (Potter, 1973, 1974). In other cases of chronic exposure in work place settings (to 14–60 mg/m^3), irritation of the eyes, upper respiratory tract and digestive tract were observed (Tomasini *et al.*, 1983).

High exposures at various work places have been reported to cause nausea, vomiting, colic (Reinl & Urban, 1965), gastrointestinal abnormalities, hepatopathy (Aldyreva *et al.*, 1980; Paoletti *et al.*, 1982; Redlich *et al.*, 1987), cardiovascular abnormalities and nervous system disorders (Aldyreva *et al.*, 1980). Of five persons exposed occupationally [concentration unspecified], four had increased levels of serum amylase, suggesting pancreatitis (Chary, 1974).

Exposure to dimethylformamide through the skin in an acrylic fibre production plant led to five cases of intoxication, with gastritis, gastroesophagitis and hepatic dysfunction. These effects were reversible on removal from exposure (Guirguis, 1981).

In a study of 100 workers exposed to dimethylformamide (determined as 22 mg/m^3 by 8-h TWA personal sampling) in two factories producing artificial polyurethane leather (mean period of exposure, five years), headache, dyspepsia and hepatic-type digestive impairment could be specifically associated with chronic exposure. Increased levels of γ-glutamyl transpeptidase demonstrated minimal hepatocellular damage (Cirla *et al.*, 1984). No sign of liver function change was reported in other studies of persons exposed to up to 60 ppm (180 mg/m^3) dimethylformamide (Kennedy, 1986).

Polyacrylonitrile fibre production workers exposed to 30–60 ppm dimethylformamide for three to five years complained of fatigue, weakness, numbness of the extremities and eye and throat irritation (Kennedy, 1986). Skin sensitivity, allergic dermatitis, eczema and vitiligo have also been reported (Bainova, 1975; Kennedy, 1986).

Occupational exposure to dimethylformamide followed by consumption of alcohol has resulted in alcohol intolerance, dermal flushing (especially of the face), severe headache and dizziness (Reinl & Urban, 1965; Lyle *et al.*, 1979; Tomasini *et al.*, 1983).

(iii) *Effects on fertility and pregnancy outcome*

No data were available to the Working Group.

(iv) *Genetic and related effects*

In a study of 20 workers exposed to mono-, di- and trimethylamines as well as dimethylformamide in the German Democratic Republic, the mean workplace concentrations during one year before blood sampling were: 12.3 mg/m^3 (range, 5.6–26.4) dimethylformamide, 5.3 mg/m^3 (range, 1.2–10.1) monomethylformamide and 0.63 mg/m^3 (range, 0.01–3.3) dimethylamine, which were within the maximal admissible range in the country. Eighteen unexposed employees from the same factory were used as controls. Increases in the frequency of chromosomal gaps and breaks were observed in 1.4% of the exposed group compared to 0.4% of controls (Berger *et al.*, 1985). [The Working Group noted the low number of chromosomal

breaks observed in the controls, and that the possible effect of smoking was not accounted for.]

Chromosomal aberrations in peripheral lymphocytes were also reported in another study of workers who had been exposed occupationally to dimethylformamide with trace quantities of methylethylketone, butyl acetate, toluene, cyclohexanone and xylene. Sampling at two four-month intervals, when exposure was to an average of 180 and 150 mg/m^3 dimethylformamide, respectively, showed an increase in the frequency of chromosomal aberrations; but subsequent sampling at three six-month intervals, when average exposures were to 50, 40 and 35 mg/m^3, showed no increase (Koudela & Spazier, 1981).

It was reported in an abstract that there was no evidence for an increased frequency of chromosomal aberrations in peripheral lymphocytes of a group of workers exposed to dimethylformamide [details not given] (Šrám *et al.*, 1985).

3.3 Epidemiological studies of carcinogenicity to humans

Ducatman *et al.* (1986) reported three cases of testicular germ-cell tumour in 1981–83 among 153 white men who repaired the exterior surfaces and electrical components of F4 Phantom jet aircraft in the USA. This finding led to surveys of two other repair shops at different geographical locations, in one of which the same type of aircraft was repaired and in another at which different types of aircraft were repaired. Four among 680 white male workers in the same type of repair shop had a history of testicular germ-cell cancers (0.95 expected) occurring in 1970–83. No case of testicular germ-cell cancer was found among the 446 white men employed at the facility where different types of aircraft were repaired. Of the seven cases, five were seminomas and two were embryonal-cell carcinomas. All seven men had long work histories in aircraft repair. There were many common exposures to solvents in the three facilities, but the only exposure identified as unique to the F4 Phantom jet aircraft repair facilities where the cases occurred was to a solvent mixture containing 80% dimethylformamide [20% unspecified]. Three of the cases had been exposed to this mixture with certainty and three cases had probably been exposed. Other cases of cancer were not searched for, and cases were found through foremen and from filed death certificates. The authors suggested that underreporting was possible.

Levin *et al.* (1987), in a letter to the Editor, described three cases of embryonal-cell carcinoma of the testis in workers at one leather tannery in the USA, all of whom had worked as swabbers on the spray lines in leather finishing. According to the authors, all the tanneries they had surveyed used dimethylformamide, as well as a wide range of dyes and solvents. [The Working Group noted that the number of workers from which these three cases arose was not given and that other cancers were not looked for.]

Chen *et al.* (1988a) studied cancer incidence among 2530 actively employed workers with potential exposure to dimethylformamide in 1950–70 and 1329 employees with exposure to dimethylformamide and acrylonitrile at an acrylic fibre manufacturing plant in South Carolina, USA (O'Berg *et al.*, 1985). Cancer incidence rates for the company (1956–84) and US national rates (1973–77) were used to calculate expected numbers of cases. For all workers exposed to dimethylformamide (alone or with acrylonitrile), the standardized incidence ratio

(SIR) based on company rates for all cancers combined was 110 ([95% confidence interval (CI), 88–136]; 88 cases); the SIR based on national rates was 92. The SIR for cancer of the buccal cavity and pharynx was 344 ([172–615]; 11 cases) based on company rates and 167 based on US rates. More cancer cases than expected from company rates (34 cases: SIR, 134; [98–195]) were found among wage employees exposed to dimethylformamide alone, due mainly to eight carcinomas of the buccal cavity or pharynx *versus* 1.0 expected (SIR, 800; [345–1580]). An additional case occurred in salaried employees exposed to dimethylformamide alone (SIR, 167); four of these tumours were cancers of the lip. No such excess was found among the workers exposed to both dimethylformamide and acrylonitrile (two observed; SIR, 125, based on company rates). The authors reported no association with intensity or duration of exposure: low and moderate exposure, SIR, 420 (five cases); high exposure, SIR, 300 (six cases). 'Low' exposure was defined as no direct contact with liquids containing any dimethylformamide, even with protective equipment, and workplace levels consistently below 10 ppm (30 mg/m^3) in air (no odour of dimethylformamide evident). 'Moderate' exposure was defined as intermittent contact with liquids containing > 5% dimethylformamide, and workplace levels sometimes > 10 ppm (more than once per week); dimethylformamide-laden materials handled but fumes contained the levels described above. 'High' exposure was defined as frequent contact with liquids containing > 5% dimethylformamide, and workplace levels often > 10 ppm, use of breathing protection often required for 15 min to 1 h; dimethylformamide vapour frequently > 10 ppm when handling pure dimethylformamide or dimethylformamide-containing materials. [The Working Group noted that the exposure categories do not seem to be mutually exclusive.] One case of testicular cancer was found among the 3859 workers exposed to dimethylformamide (alone or with acrylonitrile), with 1.7 expected based on company rates; no case of liver cancer was seen. [The Working Group noted that the company rates may be more relevant for comparison, as there were only actively employed persons among the exposed and because the US rates are based on a limited time period, 1973–77. No data on tobacco use, alcohol consumption or other occupational exposures were given.]

Chen *et al.* (1988b) analysed mortality in 1950–82 in the same cohort among both active and pensioned employees. Expected numbers (adjusted for age and time period) were based on company rates. For all workers exposed to dimethylformamide (alone or with acrylonitrile), the standardized mortality ratio (SMR) for lung cancer was 124 (33 cases; [95% CI, 85–174]). An increased risk for lung cancer was found in the cohort exposed only to dimethylformamide (19 cases; SMR, 141; [84–219]) but not in that exposed to dimethylformamide and acrylonitrile. There were three deaths from cancer of the buccal cavity and pharynx (SIR, 188) in all persons exposed to dimethylformamide (alone or with acrylonitrile). No other excess cancer risk was reported. [The Working Group noted that no information on loss to follow-up or on death certificates is given in this report or whether these deaths were included in the incidence study reported above.]

4. Summary of Data Reported and Evaluation

4.1 Exposures

Dimethylformamide is a synthetic organic liquid used mainly as an industrial solvent in the manufacture of films, fibres, coatings and adhesives, in the purification of hydrocarbons in petroleum refining and in other chemical processes. Exposure to dimethylformamide may occur through inhalation and dermal absorption. Occupational exposure has been reported during manufacturing processes and during use of products in which dimethylformamide is a solvent.

4.2 Experimental carcinogenicity data

Dimethylformamide was tested for carcinogenicity by oral administration and subcutaneous injection in one strain of rats. In a study in which dimethylformamide was administered by intraperitoneal injection in another strain of rats, a small number of uncommon tumours was observed in treated rats. All of these studies were inadequate for evaluation.

4.3 Human carcinogenicity data

An excess risk for testicular germ-cell tumours was identified among workers involved in aircraft repair who had been exposed to a solvent mixture containing 80% dimethylformamide. An excess risk for cancer of the buccal cavity or pharynx and a nonsignificant excess of lung cancer, but no excess risk for testicular cancer, were observed in workers exposed to dimethylformamide at a plant manufacturing acrylic fibres. No adjustment was made for possible confounding variables in either study.

4.4 Other relevant data

Liver toxicity and dermatitis have been observed in persons occupationally exposed to dimethylformamide. Dimethylformamide also induces liver toxicity in experimental animals.

Dimethylformamide induced malformations in mice following intraperitoneal administration and in rabbits following oral (but not dermal) exposure. Fetal growth retardation but no malformation was seen following exposure of rats by inhalation.

An increased frequency of chromosomal aberrations was observed in peripheral lymphocytes of industrial workers exposed to dimethylformamide in one study. Another study showed an increased frequency but was inconclusive because the workers were also exposed to other industrial chemicals.

Dimethylformamide did not induce sister chromatid exchange or micronuclei in mice. It did not induce DNA damage, mutation or sister chromatid exchange in cultured human cells but gave equivocal results for chromosomal aberrations. It did not induce chromosomal aberrations, sister chromatid exchange, mutation or DNA damage in cultured animal cells. It inhibited intercellular communication in cultured animal cells. It did not induce mutation in *Drosophila*, plants or yeast nor mitotic recombination in yeast. It induced DNA damage and aneuploidy in yeast. Dimethylformamide did not induce mutation or DNA damage in bacteria. (See Appendix 1.)

4.5 Evaluation[1]

There is *limited evidence* for the carcinogenicity of dimethylformamide in humans.

There is *inadequate evidence* for the carcinogenicity of dimethylformamide in experimental animals.

Overall evaluation

Dimethylformamide *is possibly carcinogenic to humans (Group 2B).*

5. References

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[1]For definitions of the italicized terms, see Preamble, pp. 27–30.

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