DIMETHYLFORMAMIDE

Data were last evaluated in IARC (1989).

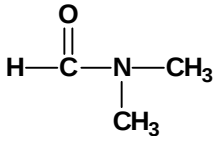
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 68-12-2
Chem. Abstr. Name: *N*,*N*-Dimethylformamide
IUPAC Systematic Name: *N*,*N*-Dimethylformamide
Synonym: DMF

1.1.2 *Structural and molecular formulae and relative molecular mass*



C_3H_7NO Relative molecular mass: 73.09

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless to very slightly yellow liquid with a faint amine odour (Budavari, 1996)
(*b*) *Boiling-point*: 153°C (Lide, 1997)
(*c*) *Melting-point*: –60.4°C (Lide, 1997)
(*d*) *Solubility*: Miscible with water and most common organic solvents (Budavari, 1996)
(*e*) *Vapour pressure*: 3 kPa at 20°C; relative vapour density (air = 1), 2.51 (Verschueren, 1996)
(*f*) *Flash-point*: 67°C, open cup (Budavari, 1996)
(*g*) *Explosive limits*: Upper, 15.2%; lower, 2.2%, by volume in air (American Conference of Governmental Industrial Hygienists, 1993)
(*h*) *Conversion factor*: $mg/m^3 = 3.0 \times ppm$

1.2 Production and use

World production of dimethylformamide is estimated to be 125 thousand tonnes (Marsella, 1995). Information available in 1995 indicated that it was produced in 19 countries (Chemical Information Services, 1995).

Dimethylformamide has been termed the universal solvent and is used commercially as a solvent, for example, for vinyl resins, adhesives and epoxy formulations (the latter for use in laminated printed circuit boards); for purification and/or separation of acetylene, 1,3-butadiene, acid gases and aliphatic hydrocarbons; in the production of polyacrylic or cellulose triacetate fibres and pharmaceuticals. It is also used as a catalyst in carboxylation reactions; in organic synthesis; as a quench and cleaner combination for hot-dipped tin parts (e.g., for high-voltage capacitors); as an industrial paint stripper; as a carrier for gases, and in inks and dyes in printing and fibre-dyeing applications (American Conference of Governmental Industrial Hygienists, 1991; Lewis, 1993; Marsella, 1994).

1.3 Occurrence

1.3.1 *Occupational exposure*

According to the 1981–83 United States National Occupational Exposure Survey (NOES, 1997), as many as 125 000 workers in the United States were potentially exposed to dimethylformamide (see General Remarks). Occupational exposures to dimethylformamide may occur in the production of the chemical, other organic chemicals, resins, fibres, coatings, inks and adhesives. Exposure also may occur during use of these coatings, inks, adhesives, in the synthetic leather industry, in the tanning industry and in the repair of aircraft (Ducatman *et al.*, 1986; IARC, 1989).

1.3.2 *Environmental occurrence*

Dimethylformamide has been measured in ambient air near a fibre plant and near waste facilities. It has rarely been found in water samples in the United States, other than at sewage treatment plants or in effluents of plants likely to have been using dimethylformamide. Levels measured were very low (WHO, 1991). It has been detected at low levels in drinking-water, surface water, wastewater and ambient air samples (United States National Library of Medicine, 1997).

Exposure through the use of dimethylformamide in food processing, food packaging and pesticides may occur, but no data are available (WHO, 1991).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has recommended 30 mg/m^3 as the 8-h time-weighted average threshold limit value, with a skin notation, for occupational exposures to dimethylformamide in workplace air. Values of 10–60 mg/m^3 have been used as standards or guidelines in other countries (International Labour Office, 1991).

No international guideline for dimethylformamide in drinking-water has been established (WHO, 1993).

2. Studies of Human Cancer

2.1 Case reports

Ducatman *et al.* (1986) reported three cases of testicular germ-cell tumour that occurred during 1981–83 among 153 white men who repaired the exterior surfaces and electrical components of F4 Phantom jet aircraft in the United States. This finding led to surveys of two other repair shops at different locations. One repaired F4 Phantom jets while the other repaired different types of aircraft. Four among 680 white male workers in the F4 Phantom shop had testicular germ-cell cancers (approximately one expected) diagnosed during 1970–83. No case of testicular germ-cell cancer was found among 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 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.

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 United States. According to the authors, all the tanneries they had surveyed used dimethylformamide, as well as a wide range of dyes and solvents. A screening effort to identify additional testicular cancers at the leather tannery with the three cases was undertaken in 1989 (Calvert *et al.*, 1990). Fifty-one of 83 workers employed at the plant between 1975 and 1989 participated. No additional case of testicular cancer was identified.

2.2 Industry-based studies

These case reports led to a cohort study of cancer among employees of the Du Pont company. Chen *et al.* (1988a) studied cancer incidence among 2530 actively employed workers with potential exposure to dimethylformamide during 1950–70 in Virginia and 1329 employees with exposure to dimethylformamide and acrylonitrile (see this volume) at an acrylic fibre manufacturing plant in South Carolina, United States. Cancer incidence rates for the company (1956–84) and national rates (1973–77) for the United States were used to calculate expected numbers of cases. [The tumour registry of the Du Pont company covers only active workers, but the Working Group noted this would be less of a limitation for testicular cancer than other tumours.] For all workers exposed to dimethylformamide (alone or with acrylonitrile), the standardized incidence ratio (SIR) based on company rates for all cancers combined was [1.1] [95% confidence interval (CI), 0.9–1.4] (88 cases). 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. The SIR for cancer of the buccal cavity and pharynx was [3.4] [95% CI, 1.7–6.2] (11 cases) among workers exposed to dimethylformamide, based on company rates. No such excess for any cancer was found among the 1329 workers exposed to both

dimethylformamide and acrylonitrile. There was no relationship between cancer of the buccal cavity and pharynx and intensity or duration of exposure: low exposure, SIR, 4.2 (five cases, 1.2 expected); moderate exposure, SIR, 3.0 (six cases, 2.0 expected). 'Low' exposure was defined as workplace levels consistently below 10 ppm (30 mg/m^3), while 'moderate' exposure was defined as workplace levels sometimes above 10 ppm.

Chen *et al.* (1988b) evaluated 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 only, the standardized mortality ratios (SMR) were [0.9] (38 obs./40.1 exp.) for all cancers combined, [2.5] (2 obs./0.8 exp.) for buccal cavity and pharynx and [1.4] (19 obs./13.5 exp.) for lung cancer. No other cancer excesses were reported.

Walrath *et al*. (1989) conducted case–control studies of cancers of the buccal cavity and pharynx (n = 39), liver (n = 6), prostate (n = 43), testis (n = 11) and malignant melanoma of the skin (n = 39) among workers from four DuPont plants. Two plants had been previously studied for exposure to acrylonitrile and dimethylformamide (Chen *et al*., 1988a,b) but two others had not. Cancers occurring during 1956 to 1985 were identified through the Du Pont Cancer Registry from a combined cohort composed of approximately 8700 workers per year. For each case, the first two eligible controls from the employment roster were selected matched on year of birth, sex, wage/salary class and plant. The plants studied included a dimethylformamide production plant, two acrylic fibre plants that used dimethylformamide as a spinning solvent and a plant using the chemical as a solvent for inks. Potential exposure to dimethylformamide was classified as low or moderate (no worker fell in the high category) from job title/work area combinations by a team of two industrial hygienists and an epidemiologist. Dimethylformamide measurements were available from all plants. Geometric means for air measurements of dimethylformamide ranged from less than 1.0 ppm [3.0 mg/m^3] to about 10 ppm [30 mg/m^3]. Relative risks were estimated by Mantel–Haenszel matched analyses and logistic regression (adjusted for plant, pay class, year of diagnosis and age at diagnosis), using all controls. Mantel–Haenszel odds ratios for ever exposed were 0.9 (n = 15) (90% CI, 0.4–2.3) for buccal cavity and pharynx cancers, 1.7 (n = 16) (90% CI, 0.5–5.5) for malignant melanoma, 1.5 (n = 17) (90% CI, 0.7–3.3) for prostate cancer and 1.0 (n = 3) (90% CI, 0.2–4.4) for testicular cancer. Two liver cancer cases and one control were exposed to dimethylformamide giving a logistic regression odds ratio of 6.1 (90% CI, 0.4–72.0). Odds ratios for malignant melanoma by level of exposure were 1.9 (90% CI, 0.5–7.3) for low and 3.1 (90% CI, 0.8–11.9) for moderate exposure. Odds ratios for testicular cancer by level of exposure were 0.9 (90% CI, 0.1–8.6) for low and 11.6 (2 exposed cases and 2 exposed controls) (90% CI, 0.5–286) for moderate exposure.

3. Studies of Cancer in Experimental Animals

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 (IARC, 1989).

3.1 Inhalation exposure

3.1.1 *Mouse*

Groups of 78 male and 78 female Crl: CD-1 (ICR) BR mice, 55 days old, were administered dimethylformamide (purity, 99.9%) at 0, 25, 100 or 400 ppm [0, 75, 300 or 1200 mg/m^3] in air by whole-body vapour exposure for 6 h per day on five days a week for 18 months. Five males and five females per group were killed at 2 weeks, 3 months and 12 months. No compound-related effect on survival was evident. At termination, the 100- and 400-ppm males and 400-ppm females had higher liver weights. In both sexes, at the two highest exposures, centrilobular hepatocellular hypertrophy and hepatic single-cell necrosis were increased. No increased tumour incidence was observed (Malley *et al*., 1994).

3.1.2 *Rat*

Groups of 87 male and 87 female Crl:CD BR rats, 47 days old were administered dimethylformamide (purity, 99.9%) at 0, 25, 100 or 400 ppm [0, 75, 300 or 1200 mg/m^3] in air by whole-body vapour exposure for 6 h per day on five days a week for two years. Exposure to the highest concentration reduced body weight gain in both sexes but did not affect survival. The highest concentration also increased liver weights in both sexes. Ten males and ten females per group were killed at 12 months. In both sexes of the two highest concentration groups, incidences of minimal to mild centrilobular hepatocellular hypertrophy and centrilobular accumulation of lipofuscin/haemosiderin were increased. No increase in tumours occurred, but a 14.8% incidence of uterine endometrial stromal polyps in high-dose females was observed compared to 1.7% in controls [numerical data not given]. However, the range of historical control incidence for the laboratory was 2.0–15.0% (Malley *et al*., 1994).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

The penetration of dimethylformamide through excised human skin *in vitro* was evaluated by Bortsevich (1984), who showed that dimethylformamide was much better absorbed (51% in 4 h) than its aqueous solutions (15–60% v/v, < 1% in 4 h).

Percutaneous absorption *in vivo* was examined by Mráz and Nohová (1992a) in two ways, from liquid dimethylformamide and from dimethylformamide vapour. The first was evaluated by dipping one hand into undiluted dimethylformamide for up to 20 min and by

the application of 2 mmol dimethylformamide over an area of 100 cm^2 on the forearm (approximately 1.5 mg/cm^2). In both studies, the absorption rate was 9 $mg/cm^2/h$.

Percutaneous uptake of dimethylformamide vapour was evaluated in volunteers exposed to an atmosphere of 50 mg/m^3 dimethylformamide for 4 h, while wearing light clothing and breathing fresh air through masks. The percutaneous uptake of dimethylformamide increased with increasing ambient temperature and humidity and contributed some 13–36% of the urinary *N*-hydroxymethyl-*N*-methylformamide excreted during combined inhalation and percutaneous exposure to the same concentration of dimethylformamide vapour (Mráz & Nohová, 1992a).

Mráz and Nohová (1992b) placed 10 volunteers (5 men, 5 women) in atmospheres of 10, 30 and 60 mg/m^3 dimethylformamide for 8 h and measured the metabolites in urine collected for up to five days. In addition, two men and two women were exposed to 30 mg/m^3, for 8 h per day on five consecutive days. The uptake from the respiratory tract was 90% and the various urinary metabolites examined accounted for 49% of the retained dose. The half-lives of excretion and the urinary recoveries of the metabolites were: dimethylformamide, 2 h (0.3% of dose); *N*-hydroxymethyl-*N*-methylformamide, 4 h (22%); *N*-hydroxymethylformamide, 7 h (13%); and the mercapturic acid conjugate, *N*-acetyl-*S*-(*N*-methylcarbamoyl)cysteine, 23 h (13%).

A number of studies of workplace exposure to dimethylformamide have been performed to search for the most appropriate biomarkers of dimethylformamide exposure. These all showed a good and linear correlation between the amounts of dimethylformamide and *N*-hydroxymethyl-*N*-methylformamide in the urine at the end of an 8-h shift and the atmospheric concentration of dimethylformamide. Kawai *et al*. (1992) studied over 200 workers exposed to up to 9 ppm [27 mg/m^3] dimethylformamide alone or with toluene; Sakai *et al*. (1995) examined 10 workers exposed in different ways to up to 8 ppm [24 mg/m^3] dimethylformamide; while Casal Lareo and Perbellini (1995) evaluated 22 workers exposed to individual mean dimethylformamide concentrations of 10–20 mg/m^3 over three working days. The latter two studies also found that excretion of the mercapturic acid conjugate provides a good indication of the total exposure to dimethylformamide over a prolonged period, as a result of its slower excretion relative to other major metabolites.

4.1.2 *Experimental systems*

Hundley *et al*. (1993a) exposed rats and mice to atmospheres of 10, 250 and 500 ppm [30, 750 and 1500 mg/m^3] dimethylformamide for single 1-, 3- and 6-h periods or for 6 h per day on 10 days over two weeks. Dimethylformamide was not detected in the plasma after the 10 ppm dose, while at the 250 ppm dose, steady-state plasma levels were approached after 6 h of exposure; this was not the case at 500 ppm, where plasma levels increased two-fold in rats and three-fold in mice between 3 and 6 h of exposure. The area under the plasma concentration curve (AUC) values for dimethylformamide after a single 6-h exposure increased disproportionately (8-fold and 29-fold increases in rats and mice, respectively) compared with the increase in dimethylformamide exposure concentration (from 250 ppm to 500 ppm). Multiple 500 ppm dimethylformamide exposures resulted in

lower dimethylformamide AUC values for both rats (to 34%) and mice (to 23%) compared with the AUC values following a single 500 ppm exposure. These authors also presented data on plasma levels of '*N*-methylformamide', representing the total of *N*-hydroxymethyl-*N*-methylformamide and *N*-methylformamide, determined by gas chromatography. '*N*-Methylformamide' levels increased with time of exposure to single 250 ppm doses but did not increase further at 500 ppm.

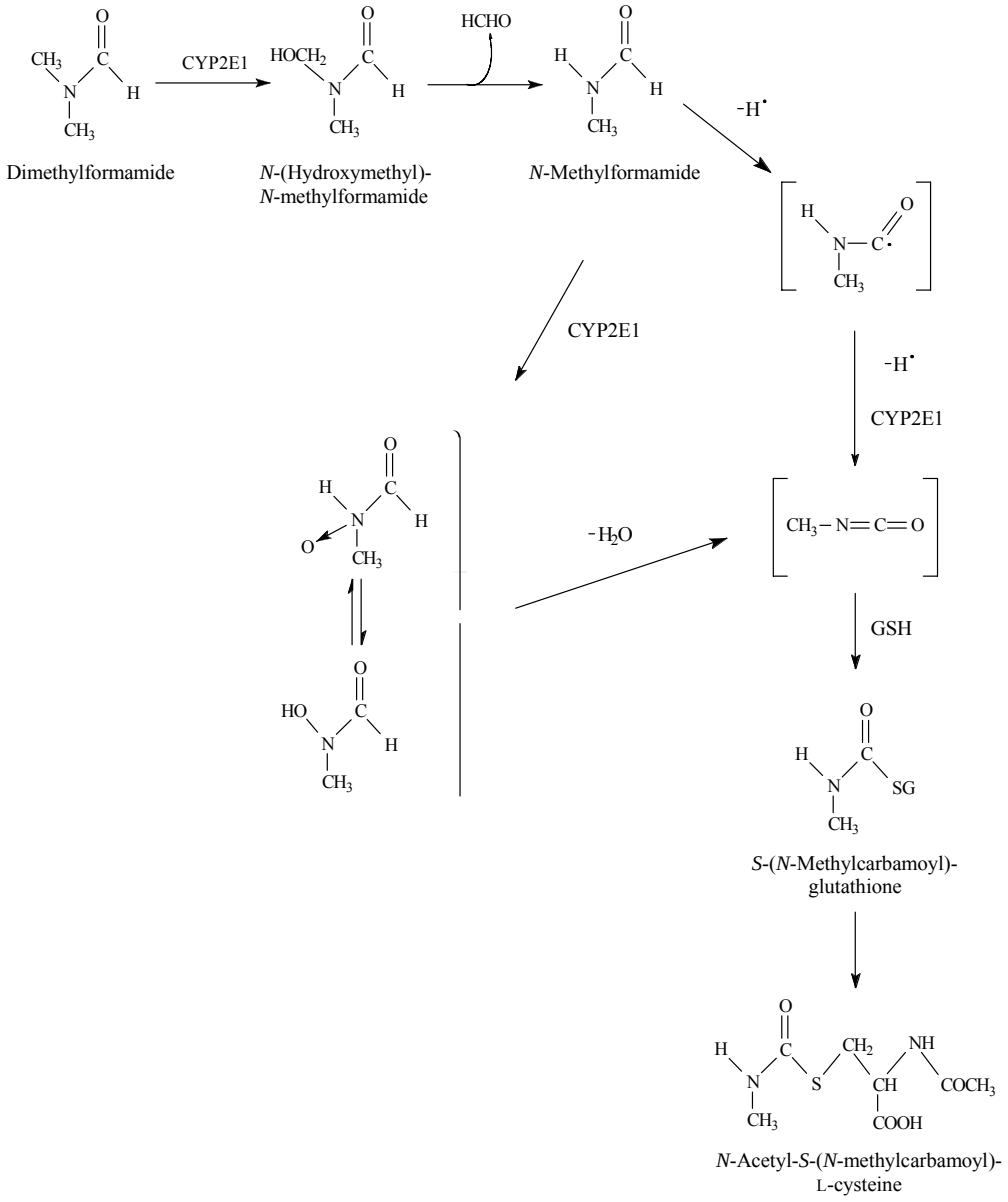
Serial blood and urine samples were collected from two cynomolgus monkeys of each sex in groups subjected to whole-body exposure to atmospheres of 30, 100 or 500 ppm [90, 300 or 1500 mg/m^3] dimethylformamide for 6 h per day on five days per week for 13 weeks (Hundley *et al.*, 1993b). As was found in rats and mice, there were disproportionate increases in plasma AUC values of 19- to 37-fold in male monkeys and 35- to 54-fold in females as the atmospheric concentrations increased five-fold from 100 to 500 ppm. Plasma half-lives ranged from 1–2 h for dimethylformamide and 4–15 h for '*N*-methylformamide'. There was rapid metabolism, the plasma '*N*-methylformamide' concentration being higher than that of dimethylformamide at 0.5 h. *N*-(Hydroxymethyl)-*N*-methylformamide formed 56–95% of the urinary metabolites, depending upon the exposure level and duration of the study.

There have been numerous studies of the metabolism of dimethylformamide in the past 25 years and these have been summarized by Gescher (1993). The major pathway of dimethylformamide metabolism is hydroxylation of one of the methyl groups, giving *N*-hydroxymethyl-*N*-methylformamide, which is unstable in many analytical manipulations and readily decomposes to *N*-methylformamide. *N*-Hydroxymethyl-*N*-methylformamide was underestimated, or not detected at all, in a number of early studies for this reason (see, for example, Kawai *et al*., 1992; Rosseel *et al*., 1993). The formation of *N*-hydroxymethyl-*N*-methylformamide is a cytochrome P450-dependent reaction mediated by CYP2E1 in rat liver microsomes. The reaction mediated by human liver microsomes was inhibited by a monospecific antibody against rat liver CYP2E1 (Mráz *et al.*, 1993).

Both *N*-hydroxymethyl-*N*-methylformamide and *N*-methylformamide formed from dimethylformamide undergo further oxidative metabolism, *N*-demethylation giving formamide and oxidation of the formyl group giving a reactive intermediate (Cross *et al*., 1990) probably methyl isocyanate, which acylates glutathione. The resulting *S*-(*N*-methylcarbamoyl)glutathione undergoes the usual further transformations to give the mercapturic acid *N*-acetyl-*S*-(*N*-methylcarbamoyl)-L-cysteine (AMCC), which is a major metabolite of dimethylformamide in animals and humans. The formyl group oxidation which is the key step in the formation of AMCC is mediated by CYP2E1 (Mráz *et al*., 1993) (Figure 1).

There occur marked differences between rodent species and humans in the proportions of a dose excreted as these various major metabolites, and the dose size introduces further variables. Mráz *et al*. (1989) gave male Sprague-Dawley rats, BALB/c mice and Syrian hamsters 0.1, 0.7 and 7 mmol/kg bw dimethylformamide (approximately 7, 50 and 500 mg/kg bw) by intraperitoneal injection and collected urine for 60 h (rat), 24 h (mice) and 36 h (hamster). In all cases, dimethylformamide and AMCC were very minor urinary metabolites, while the amounts of substances analysed as '*N*-methylformamide'

Figure 1. Metabolism of dimethylformamide



From Cross *et al.* (1990) and Gescher (1993)

and a formamide precursor varied with dose, with 8–47% of dose as the former and 8–37% as the latter. In comparison, human subjects exposed to dimethylformamide by inhalation excreted 16–49% of the dose as '*N*-methylformamide', 8–24% as 'formamide' and 10–23% as AMCC.

These data suggest a quantitative difference in the formation of AMCC between species, most likely in the formation of the reactive carbamoylating intermediate which acylates glutathione.

Purified CYP2E1 from mouse and rat liver microsomes in a reconstituted system is a very active catalyst of dimethylformamide oxidation, the turnover being about 10 nmol/min per nmol P450 for both species; however, the affinities are very different. The K_m values for mouse and rat CYP2E1, respectively, were about 0.08 mM and 1.1 mM (Chieli *et al.*, 1995).

4.2 Toxic effects

4.2.1 *Humans*

An outbreak of liver disease in a fabric-coating factory was investigated by Redlich *et al*. (1988). Dimethylformamide was used as a solvent for fabric coating in poorly ventilated areas without appropriate skin protection. Overall, 36 of 58 workers had elevations of either aspartate aminotransferase or alanine aminotransferase serum activity. Among 46 workers, the following symptoms were reported: anorexia, abdominal pain or nausea by 31 workers; headaches and dizziness by 18 workers; alcohol intolerance (facial flushing and palpitations) by 11 workers. Liver biopsies of workers exposed to several organic solvents, predominantly to dimethylformamide, showed focal hepatocellular necrosis and microvesicular steatosis with prominence of smooth endoplasmic reticulum, complex lysosomes and pleomorphic mitochondria with crystalline inclusions (Redlich *et al*., 1990). Among workers with longer exposure, no signs of liver fibrosis were found.

In 183 out of 204 employees in a synthetic leather factory, Wang *et al*. (1991) found a significant corrrelation between high exposure concentrations of dimethylformamide (25–60 ppm) and elevated serum alanine aminotransferase and creatine phosphokinase levels. Furthermore, high dimethylformamide exposure concentrations were correlated with symptoms such as dizziness, anorexia, nausea and epigastric pain.

In a group of 318 workers exposed to dimethylformamide levels of up to 7 ppm (geometric mean [21 mg/m^3]), no significant alterations in haematological and biochemical blood parameters were found compared with a non-exposed group (143 controls) (Cai *et al*., 1992). However, a dose-dependent increase in complaints of subjective symptoms was found, including nausea and abdominal pain in particular during work. Furthermore, the prevalence of alcohol intolerance was also elevated depending on the calculated dose. A prolonged susceptibility to alcohol-induced flushing after dimethylformamide exposure was reported in a case report by Cox and Mustchin (1991). A cluster of toxic liver disease among workers exposed to dimethylformamide was reported by Fleming *et al*. (1990). Thirty-five out of 45 exposed production workers had abnormalities of their liver transaminases, compared with one of 12 unexposed, nonproduction workers.

4.2.2 *Experimental systems*

In acetone-pretreated male CD-1 mice, dimethylformamide, given as a single intraperitoneal dose of 1000 mg/kg bw, resulted in liver necrosis and a strong increase in serum alanine aminotransferase activity (Chieli, 1995). In contrast, no signs of hepatotoxicity were found in non-pretreated mice given the same dose or in pretreated or non-pretreated male Sprague-Dawley rats given up to 2000 mg/kg bw as a single intraperitoneal dose. These differences are probably related to the highly different substrate affinities of CYP2E1 in rats and mice (see Section 4.1.2). The hepatotoxicity of dimethylformamide was also investigated by Imazu *et al*. (1992) who treated male Wistar rats by daily subcutaneous injections of 0.5 mL/kg bw dimethylformamide for one week. Treated rats showed a significant increase in serum glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, cholinesterase and total cholesterol. Hepatic microsomal cytochrome P450 and hepatic glutathione reductase activity were decreased, while glutathione *S*-transferase activity using 1-chloro-2,4-dinitrobenzene as a substrate was induced by about 66%. In male Wistar rats, Van der Bulcke *et al*. (1994) found increased serum sorbitol dehydrogenase activity after intraperitoneal administration of 4.1 but not of 1.4 mmol/kg bw dimethylformamide. They also found that dimethylformamide is more hepatotoxic than either of two of its metabolites, *N*-hydroxymethyl-*N*-methylformamide and *N*-methylformamide, which are similar and express their hepatotoxicity earlier.

Cynomolgus monkeys showed no measurable adverse effect following inhalation of 500 ppm [1500 mg/m^3] dimethylformamide for 6 h per day on five days per week for two weeks (Hurtt *et al*., 1991). In a 13-week inhalation study, cynomolgus monkeys received whole-body exposures of 0, 30, 100 or 500 ppm [0, 90, 300 or 1500 mg/m^3] dimethylformamide for 6 h per day on five days per week (Hurtt *et al*., 1992). No exposure-related effect on body weight or a number of haematological parameters and serum chemistry including transaminases occurred.

In a number of human and rodent cell lines (Hoosein *et al*., 1988a,b; Levine *et al.*, 1989; Guilbaud *et al*., 1990; Grunt *et al*., 1992; Levine & Chakrabarty, 1992), relatively high concentrations of dimethylformamide (in the range of 0.5–1% in the medium), initiated differentiation and led to simultaneous growth inhibition. These effects upon the differentiation state were shown to be associated in certain confluent, transformed cell cultures with a reduction of c-*myc* levels (Mulder *et al*., 1989).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

SPF (Mol:Wist) rats were administered up to 2 mL/kg bw dimethylformamide per day applied in a porous dressing placed on shaved skin either on gestation days 6–15 or on gestation days 1–20 (Hansen & Meyer, 1990). Body weight, weight gain and preg-

nancy rate were reduced in those rats receiving 2 mL/kg bw per day on days 6–15. A reduction in the number of live fetuses and in fetal weight, as well as an increase in post-implantation loss, were also observed at this dose level. Similar but more pronounced effects were observed in rats treated on days 1–20 with the same daily dose. The lowest effect level in this study was 1 mL/kg bw per day.

In a 13-week inhalation study, male cynomolgus monkeys received whole-body exposures of 0, 30, 100 or 500 ppm [0, 90, 300 or 1500 mg/m^3] dimethylformamide for 6 h per day on five days per week (Hurtt *et al*., 1992). No significant effect on semen volume, percentage of motile sperm, sperm count or abnormal sperm morphology was found.

4.4 Genetic and related effects

4.4.1 *Humans*

In a study of chromosomal aberrations in peripheral blood lymphocytes, 20 workers exposed to mono-, di- and trimethylamines as well as dimethylformamide in the then 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. The frequency of chromosomal gaps and breaks was 1.4% in the exposed group compared with 0.4% in the controls (Berger *et al.*, 1985). The authors commented that the value in the control group was low, in comparison with other studies. [The Working Group noted that the possible effect of smoking was not taken into account.]

Chromosomal aberrations in peripheral lymphocytes were also reported in a study of about 40 workers who had been occupationally exposed to trace quantities of 2-butanone (methyl ethyl ketone), butyl acetate, toluene, cyclohexanone and xylene in addition to dimethylformamide. Blood samples were taken at two four-month intervals, when exposure was to an average of 180 and 150 mg/m^3 dimethylformamide, respectively. The frequencies of chromosomal aberrations were 3.82% and 2.74% at these two sampling times. Subsequent sampling at three six-month intervals, when average dimethylformamide exposures were to 50, 40 and 35 mg/m^3, gave lower aberration frequencies of 1.59%, 1.58% and 1.49%. Aberration frequencies in two control groups were 1.61% and 1.10% (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).

Seiji *et al.* (1992) studied the effects of occupational exposure to dimethylformamide on sister chromatid exchange rates in peripheral lymphocytes from 22 dimethylformamide-exposed women (aged 22–52 years) in comparison with 22 sex-, age- and residence-matched controls. All subjects were non-smokers and non-drinkers of alcohol as confirmed by medical interview. The 22 pairs were divided into three subgroups according to the intensity of their exposure to dimethylformamide: high exposure (8 pairs with mean exposure of

5.8 ppm [17.4 mg/m^3]), medium exposure (5 pairs at 0.7 ppm [2.1 mg/m^3] in combination with toluene at 0.9 ppm) and low exposure (9 pairs at 0.3 ppm [0.9 mg/m^3]). Sister chromatid exchange frequencies per cell were significantly higher in the high- and medium-exposure groups than in their matched pairs (8.26 ± 1.76 *vs* 5.63 ± 1.56 and 7.24 ± 1.53 *vs* 4.66, respectively), but not in the low-exposure group (5.67 ± 1.35 *vs* 6.57 ± 1.12) (Seiji *et al.*, 1992). [The Working Group noted the incomplete reporting of the data.]

4.4.2 *Experimental systems* (see Table 1 for references)

Dimethylformamide was one of 42 chemicals selected for study in the International Collaborative Program for the Evaluation of Short-term Tests for Carcinogens, in which 30 assay systems were included and more than 50 laboratories contributed data (de Serres & Ashby, 1981). Since then, the database has been expanded. In most of the in-vitro studies, dimethylformamide was tested in both the presence and absence of an exogenous metabolic system. It was reported to induce mutation in *Salmonella typhimurium* TA1538 and TA98 in one test with metabolic activation, but the response occurred at a single, intermediate dose and, in many other studies, dimethylformamide did not induce gene mutation in any strain of *S. typhimurium* or in *Escherichia coli* WP2*uvrA* and did not induce differential toxicity indicative of DNA damage in bacteria. In one study, dimethylformamide enhanced the mutagenicity of tryptophan-pyrolysate in *S. typhimurium* TA98 in the presence of an exogenous metabolic system (Arimoto *et al.*, 1982). It induced aneuploidy in *Saccharomyces cerevisiae* D6 in both the presence and absence of an exogenous metabolic system in a single study and gave positive results in another study for mitotic recombination in yeast, but most results for gene mutation or mitotic recombination were negative.

Dimethylformamide induced a slight increase in unscheduled DNA synthesis in primary rat hepatocyte cultures in one study but not in two others or in studies with mouse and Syrian hamster hepatocytes.

Dimethylformamide did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster* in experiments where it was used as a solvent for other substances to be tested and the responses were, therefore, compared with those of untreated controls.

Dimethylformamide was not mutagenic in L5178Y *tk*$^{+/-}$ mouse lymphoma cells in three studies, while an increased mutation frequency of about two-fold was observed at the highest dose level in one experiment.

Gene mutations were not induced in a single study with human fibroblasts. In no study were sister chromatid exchanges induced in either Chinese hamster or human cells and no chromosomal aberrations were induced in rodent cells. Chromosomal aberrations were reported to be induced in one study with cultured human lymphocytes, at a dose level of 0.007 μg/mL, but not in another study at a dose level of 80 000 μg/mL.

In mouse experiments *in vivo*, dimethylformamide did not induce sister chromatid exchanges in mouse bone-marrow cells in a single study or micronuclei in mouse bone-marrow cells in four studies, in which intraperitoneal doses up to 2000 mg/kg bw were used; in one study, micronuclei were reported to be induced at a dose of 1 mg/kg bw.

Table 1. Genetic and related effects of *N,N*-dimethylformamide

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
PRB, SOS repair test, *Salmonella typhimurium* TA1535/pSK1002	–	–	32	Nakamura *et al.* (1987)
ECL, *Escherichia coli pol* A/W3110-P3478, differential toxicity (liquid suspension test)	–	–	2300	Rosenkranz *et al.* (1981)
ERD, *Escherichia coli* DNA-repair deficient strains, differential toxicity	–	–	NG	Tweats (1981)
ERD, *Escherichia coli* DNA-repair deficient strains, differential toxicity	–	NT	NG	Ichinotsubo *et al.* (1981b)
ERD, *Escherichia coli* DNA-repair deficient strains, differential toxicity	–	–	NG	Green (1981)
BSD, *Bacillus subtilis rec* strains, differential toxicity	–	–	19000	Kada (1981)
SAF, *Salmonella typhimurium*, forward mutation	NT	–	1000	Skopek *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	NT	–	1250	Purchase *et al.* (1978)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500	Baker & Bonin (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	1000	Brooks & Dean (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	?	500	Hubbard *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	NT	NG	Ichinotsubo *et al.* (1981a)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	2500	MacDonald (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	NG	Nagao & Takahashi (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	5000	Richold & Jones (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	1000	Rowland & Severn (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	NG	Simmon & Shepherd (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	1250	Trueman (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	250	Venitt & Crofton-Sleigh (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	94	Antoine *et al.* (1983)

Table 1 (cond)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	NT	–	1000	Falck *et al.* (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	5000	Mortelmans *et al.* (1986)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	NT	–	1250	Purchase *et al.* (1978)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	500	Baker & Bonin (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	1000	Brooks & Dean (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	1000	Gatehouse (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	5000	Richold & Jones (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	1000	Rowland & Severn (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	NG	Simmon & Shepherd (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	1250	Trueman (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	94	Antoine *et al.* (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	NT	–	1000	Falck *et al.* (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	5000	Mortelmans *et al.* (1986)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	500	Baker & Bonin (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1000	Brooks & Dean (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1000	Gatehouse (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	5000	MacDonald (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	NG	Nagao & Takahashi (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	5000	Richold & Jones (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1000	Rowland & Severn (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	NG	Simmon & Shepherd (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1250	Trueman (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	94	Antoine *et al.* (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	NT	–	500	Falck *et al.* (1985)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	5000	Mortelmans *et al.* (1986)

Table 1 (cond)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA8, *Salmonella typhimurium* TA1538, reverse mutation	NT	–	1250	Purchase *et al.* (1978)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	500	Baker & Bonin (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	1000	Brooks & Dean (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	5000	Richold & Jones (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	1000	Rowland & Severn (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	NG	Simmon & Shepherd (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	+	NG	Trueman (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	94	Antoine *et al.* (1983)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	NT	–	1000	Falck *et al.* (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	NT	-	1250	Purchase *et al.* (1978)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500	Baker & Bonin (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1000	Brooks & Dean (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1000	Gatehouse (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	?	500	Hubbard *et al.* (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	NT	NG	Ichinotsubo *et al.* (1981a)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	5000	MacDonald (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	NG	Nagao & Takahashi (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	5000	Richold & Jones (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1000	Rowland & Severn (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	NG	Simmon & Shepherd (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	+	250	Trueman (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	250	Venitt & Crofton-Sleigh (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	94	Antoine *et al.* (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	NT	–	1000	Falck *et al.* (1985)

Table 1 (cond)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	5000	Mortelmans *et al.* (1986)
SAS, *Salmonella typhimurium* (other miscellaneous strains), reverse mutation	NT	–	73000	Green & Savage (1978)
SAS, *Salmonella typhimurium*, TA92, reverse mutation	–	–	1000	Brooks & Dean (1981)
ECF, *Escherichia coli* K-122/343/113 forward or reverse mutation	NT	–	4000	Mohn *et al.* (1981)
ECW, *Escherichia coli* WP2 *uvr*A, reverse mutation	–	–	500	Gatehouse (1981)
ECW, *Escherichia coli* WP2 *uvr*A, reverse mutation	–	–	NG	Matsushima *et al.* (1981)
ECW, *Escherichia coli* WP2 *uvr*ApKM101, reverse mutation	–	–	NG	Matsushima *et al.* (1981)
ECW, *Escherichia coli* WP2 *uvr*A, reverse mutation	–	–	250	Venitt & Crofton-Sleigh (1981)
ECW, *Escherichia coli* WP2 *uvr*ApKM101, reverse mutation	–	–	250	Venitt & Crofton-Sleigh (1981)
ECW, *Escherichia coli* WP2 *uvr*A, reverse mutation	NT	–	1000	Falck *et al.* (1985)
SSB, *Saccharomyces cerevisiae* 'race XII', DNA damage in DNA-repair strains	–	–	1000	Kassinova *et al.* (1981)
SSD, *Saccharomyces cerevisiae* rad strains, differential toxicity in DNA repair-deficient strains	+	+	500	Sharp & Parry (1981a)
SCH, *Saccharomyces cerevisiae*, 'race XII', homozygosis by mitotic recombination or gene conversion	–	–	1000	Kassinova *et al.* (1981)
SCH, *Saccharomyces cerevisiae* D4, homozygosis by mitotic recombination or gene conversion	–	–	167	Jagannath *et al.* (1981)
SCH, *Saccharomyces cerevisiae* D7, homozygosis by mitotic recombination or gene conversion	+	+	4700	Zimmermann & Scheel (1981)
SCH, *Saccharomyces cerevisiae* JD1, homozygosis by mitotic recombination or gene conversion	–	–	500	Sharp & Parry (1981b)

Table 1 (cond)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SCF, *Saccharomyces cerevisiae* XV185-14C, forward mutation	–	–	800	Mehta & von Borstel (1981)
SZF, *Schizosaccharomyces pombe*, forward mutation	–	–	20	Loprieno (1981)
SCN, *Saccharomyces cerevisiae* D6, aneuploidy	+	+	100	Parry & Sharp (1981)
ASM, *Arabidopsis* species, mutation	–	NT	300000	Gichner & Veleminsky (1987)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	–		900	Wurgler & Graf (1981)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	–		40 000 ppm feed	Foureman *et al.* (1994)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	–		40 000 ppm inj	Foureman *et al.* (1994)
URP, Unscheduled DNA synthesis, Fischer 344 rat primary hepatocytes *in vitro*	(+)	NT	700	Williams (1977)
URP, Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	–	NT	7300	Williams & Laspia (1979)
URP, Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	–	NT	70	Ito (1982)
UIA, Unscheduled DNA synthesis, mouse and hamster hepatocytes *in vitro*	–	NT	700	McQueen *et al.* (1983)
UIA, Unscheduled DNA synthesis, mouse hepatocytes *in vitro*	–	NT	70	Klaunig *et al.* (1984)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	–	–	3000	Jotz & Mitchell (1981)
G5T Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	(+)	–	5000	McGregor *et al.* (1988)

Table 1 (cond)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
G5T Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	–	–	4700	Mitchell *et al.* (1988)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	–	–	4700	Myhr & Caspary (1988)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–	–	900	Evans & Mitchell (1981)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–	–	6300	Natarajan & van Kesteren-van Leeuwen (1981)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–	–	100	Perry & Thomson (1981)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	–	–	6300	Natarajan & van Kesteren-van Leeuwen (1981)
CIR, Chromosomal aberrations, rat liver RL_1 cells *in vitro*	–	NT	300	Dean (1981)
TCS, Cell transformation, Syrian hamster embryo cells, clonal assay	–	NT	10 000	Pienta *et al.* (1977)
GIH, Gene mutation, diphtheria toxin HF Dip^r, human fibroblasts *in vitro*	–	–	500	Gupta & Goldstein (1981)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	–	NT	80000	Antoine *et al.* (1983)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	+	NT	0.007	Koudela & Spazier (1979)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	–	NT	80000	Antoine *et al.* (1983)
SVA, Sister chromatid exchange, CBA/J mouse bone-marrow cells *in vivo*	–		2500 ip × 1	Paika *et al.* (1981)
MVM, Micronucleus test, ICR mice *in vivo*	–		1600 ip × 1	Kirkhart (1981)
MVM, Micronucleus test, $B6C3F_1$ mice *in vivo*	–		2.5 ip × 1	Salamone *et al.* (1981)
MVM, Micronucleus test, CD mice *in vivo*	–		1500 ip × 2	Tsuchimoto & Matter (1981)

Table 1 (cond)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
MVM, Micronucleus test, BALB/c mice *in vivo*	–		2000 ip × 1	Antoine *et al.* (1983)
MVM, Micronucleus test, mice *in vivo*	+		1 ip × 1	Ye (1987)
TVI, Cell transformation, Syrian hamster embryo cells treated *in vivo*	–		3 ip × 1	Quarles *et al.* (1979)
ICR, Inhibition of intercellular communication, Chinese hamster lung V79 fibroblasts *in vitro*	+	NT	3800	Chen *et al.* (1984)
SPM, Sperm morphology, (CBA × BALB/c) F_1 mice *in vivo*	–		900 ip × 5	Topham (1981)
SPM, Sperm morphology, BALB/c mice *in vivo*	–		667 ip × 1	Antoine *et al.* (1983)

[a] +, positive; (+), weak positive; –, negative; NT, not tested; ?, inconclusive

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw/day; NG, not given; inj, injection; ip, intraperitoneal

As reported in an abstract, no dominant-lethal effect was observed in groups of ten Sprague-Dawley rats exposed by inhalation to 300 ppm [900 mg/m^3] dimethylformamide for 6 h per day for five consecutive days (Lewis, 1979).

No morphologically transformed colonies were observed in Syrian hamster embryo cell cultures, either after treatment *in vitro* or after exposure of the dams to dimethylformamide (3 mL/kg bw) by intraperitoneal injection.

Dimethylformamide inhibited intercellular communication (as measured by metabolic co-operation) between Chinese hamster V79 *hprt* $^{+/-}$ cells.

The Working Group was also aware of inhalation studies with dimethylformamide conducted for the United States National Institute of Occupational Health. These involved exposure to 400 ppm [1200 mg/m^3] for 7 h in a rat bone-marrow cell cytogenetic study, for 7 h per day for five days in a rat bone-marrow cell cytogenetic study, a male rat dominant lethal assay and a mouse sperm morphology assay and for 2.25 h in a *Drosophila melanogaster* sex-linked recessive lethal assay. All results were negative.

4.4.3 *Mechanistic considerations*

Dimethylformamide does not appear to be genotoxic as judged from results of a variety of in-vitro and in-vivo assays. The positive data for cytogenetic damage in humans occupationally exposed to it are not very convincing. If dimethylformamide is carcinogenic, it is extremely unlikely that it owes its carcinogenicity to a genotoxic mechanism.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposures to dimethylformamide occur during its production and during the production of inks, adhesives, resins, fibres, pharmaceuticals, synthetic leather, and its use as a purification or separation solvent in organic synthesis. It has been detected in ambient air and water.

5.2 Human carcinogenicity data

Case reports of testicular cancer in aircraft repair and leather tannery facilities suggested possible association with dimethylformamide. Further research has failed to confirm this relationship. A screening effort at a leather tannery, where a cancer cluster had been noted, identified no additional cases. Mortality and cancer incidence studies and nested case–control investigations of testicular cancer and several other anatomical sites at several facilities with exposure to dimethylformamide noted no convincing associations.

5.3 Animal carcinogenicity data

Dimethylformamide was adequately tested for carcinogenicity by inhalation in one study in mice and one study in rats. No increase in tumours was found.

5.4 Other relevant data

Acute exposure of humans or experimental animals to relatively high concentrations of dimethylformamide causes hepatotoxicity as a major toxic effect.

Reports on chromosomal damage in workers exposed to dimethylformamide either failed to take into account smoking as a bias factor or were documented incompletely.

Dimethylformamide has been extensively tested in a broad range of in-vitro and in-vivo genotoxicity assays. Results have been consistently negative in well controlled studies.

5.5 Evaluation

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

There is *evidence suggesting lack of carcinogenicity* of dimethylformamide in experimental animals.

Overall evaluation

Dimethylformamide is *not classifiable as to its carcinogenicity to humans (Group 3)*.

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