CHRONIC TOXICITY SUMMARY

N,N-DIMETHYLFORMAMIDE

(N-formyldimethylamine)

CAS Registry Number: 68-12-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**80 µg/m^3** (30 ppb)
Critical effect(s)	Liver dysfunction and respiratory irritation in humans
Hazard index target(s)	Alimentary system, respiratory system

II. Chemical Property Summary (HSDB, 1994)

Description	Colorless to very slightly yellow liquid
Molecular formula	C_3H_7NO
Molecular weight	73.09 g/mol
Boiling point	153°C
Melting point	–61°C
Vapor pressure	3.7 torr @ 25°C
Solubility	Soluble in alcohol, ether, acetone, benzene, and chloroform; miscible with water
Conversion factor	2.99 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

Dimethylformamide (DMF) is primarily used as a solvent in the production of polyurethane products and acrylic fibers. It is also used in the pharmaceutical industry, in the formulation of pesticides, and in the manufacture of synthetic leathers, fibers, films, and surface coatings (Howard, 1993; Gescher, 1993; Redlich *et al.*, 1988). DMF may be emitted to the environment as a result of its use in a variety of petrochemical industries (Howard, 1993). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 18,249 pounds of DMF (CARB, 2000).

IV. Effects of Human Exposure

Among 100 workers occupationally exposed to DMF for at least one year (mean exposure of 5 years; range = 1-15 years), a statistically significant incidence of hepatic impairment, as indicated by elevated gamma-glutamyl transpeptidase levels and digestive disturbances, was noted (Cirla *et al.*, 1984). Other changes, that were not statistically significant, included

increased SGOT and SGPT and enlarged livers. The mean time-weighted average concentration of DMF was 22 mg/m^3 (range = 8-58 mg/m^3). Symptoms of irritation occurring only during work at statistically significantly higher incidences included watery eyes, dry throat, and coughing. Also, the exposed workers reported a reduced sense of smell and dry coughs at home with a statistically significant difference as compared to controls. Several of the DMF exposed workers also reported alcohol intolerance characterized by a disulfiram-type reaction (facial flushing and palpitations following alcohol ingestion). Alcohol consumption, a potential confounder, was controlled for in the study design.

A similar study was conducted on workers who had been employed in an acrylic acid fiber plant for more than 5 years (Cantenacci *et al.*, 1984). Concentrations to which the workers were exposed were characterized as either an 8-hour TWA of 18 mg/m^3 or an 8-hour TWA of 3 mg/m^3. Measures of liver function including SGOT, SGPT, gamma-glutamyl transferase, and alkaline phosphatase levels were not significantly different between exposed and unexposed workers. However, the U.S. EPA cautions that because only 54 matched pairs of workers were examined, the power of this study was not high enough to reliably detect a difference in enzyme levels.

Redlich *et al*. (1988) characterized a plant-wide outbreak of liver disease among workers in a factory coating fabric with polyurethane. Fifty-eight of 66 (88%) workers participated and each had standard liver screening function tests done at least once. At the work site DMF was being used in poorly ventilated areas without appropriate skin protection. No other major known hepatotoxic exposure was identified. Overall, 36 of 58 (62%) workers tested had elevations of either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels. Enzyme abnormalities occurred almost exclusively in production workers (35 out of 46 abnormal). Only 1 of 12 non-production workers showed elevations in enzyme levels ($p < 0.0001$). Serologic tests excluded known infectious causes of hepatitis in all but 2 workers. Changes, characteristic of liver injury, were confirmed by histologic examination of biopsy specimens from 4 workers. Improvement in liver enzyme abnormalities and symptoms in most patients were seen, after modification of work practices and removal of workers most severely affected from exposure. However, some patients showed persistent elevations of enzyme levels. No measurements or estimates of DMF exposure levels were reported.

Wang *et al*. (1991) investigated the prevalence of liver injury associated with DMF exposure in 183 of 204 (76%) employees of a synthetic leather factory by performing medical examinations, liver function tests, and creatine phosphokinase (CPK) determinations. Air concentrations were measured with personal samplers and gas chromatography. The concentration of DMF in air to which each worker was exposed was categorized as high (DMF exposure index 2: 25-60 ppm; 75-180 mg/m^3), medium (index 1: 10-40 ppm), and low (index 0: <10 ppm). High exposure concentrations were significantly associated with elevated alanine aminotransferase (ALT) levels (i.e., greater than or equal to 35 International Units/liter), a result that did not change after stratification by hepatitis B carrier status. Logistic regression analysis indicated that exposure to high DMF levels was associated with elevated ALT ($p = 0.01$), whereas hepatitis B surface antigen (HBsAg) was slightly but independently associated with elevated ALT ($p = .07$). Workers with normal ALT values had significantly higher mean ALT and aspartate aminotransferase (AST) activities, especially

among those who were not HBsAg carriers. A significant association existed between elevated CPK levels and exposure to DMF. However, an analysis of the CPK isoenzyme among 143 workers did not reveal any specific damage to muscles. Thus the authors ascribed the liver injury to DMF.

U.S. EPA (1994) states that subjective evidence of liver toxicity, such as digestive impairment and alcohol intolerance, is often observed at exposures below those that cause clinical changes in liver enzymes. Thus, the symptoms may be more sensitive indicators of hepatic impairment.

Three unexplained cases of small-for-date third trimester intrauterine deaths were observed in a group of women working as quality control analysts in the pharmaceutical industry (Farquhason *et al.*, 1983). This represented a 30% stillbirth rate as compared with the average for the general population of about 0.26%. While the authors concluded that the occurrence of stillbirth in these women was not likely due to chance, the effects cannot be solely attributed to DMF because the women were exposed to other agents in addition to DMF.

V. Effects of Animal Exposure

Malley *et al*. (1994) exposed male and female Crl:CD rats and mice to 0, 25, 100, or 400 ppm DMF for 6 hr/day, 5 days/week for 18 months (mice) or 2 years (rats). No compound-related effects on clinical observations or survival were observed. Body weights of rats exposed to 100 (males only) and 400 ppm were reduced, while body weights were increased in 400 ppm mice. No hematologic changes were observed in either species. Serum sorbitol dehydrogenase activity was increased in rats exposed to 100 or 400 ppm. DMF-related morphological changes were observed only in liver. Exposure of rats to 100 and 400 ppm produced increased relative liver weights, centrilobular hepatocellular hypertrophy, lipofuscin/hemosiderin accumulation in Kupffer cells, and centrilobular single cell necrosis (400 ppm only). In mice, increased liver weights (100 ppm males, 400 ppm both sexes), centrilobular hepatocellular hypertrophy, accumulation of lipofuscin/hemosiderin in Kupffer cells, and centrilobular single cell necrosis were observed in all exposure groups. These observations occurred in a dose-response fashion and were minimal at 25 ppm. No increase in hepatic cell proliferation was seen in mice or female rats. Slightly higher proliferation was seen in male rats exposed to 400 ppm at 2 weeks and 3 months but not at 12 months. Thus 25 ppm was a chronic NOAEL for both rats and mice.

A developmental toxicity study using three species (mice, rabbits, and rats) and four routes of administration (oral, inhalation, dermal, and intraperitoneal) identified the rabbit as the most sensitive of the three species. Groups of 15 pregnant rabbits were exposed for 6 hours per day on days 8-20 of gestation to 50, 150, or 450 ppm (150, 449, or 1350 mg/m^3) DMF (Hellwig *et al.*, 1991). Slight maternal toxicity, as indicated by non-statistically significant decreases in maternal body weight gain, was observed in the 450 ppm exposure group. An increased number of total malformations per litter was observed in the 450 ppm exposure group. Malformations observed at statistically higher incidences compared to controls included hernia umbilicalis, external variations, pseudoankylosis of the forelimbs, and skeletal

variation and retardation. The authors conclude that there was a clear teratogenic effect in rabbits following maternal exposure to 450 ppm DMF and a marginal effect following exposure to 150 ppm DMF. A NOAEL of 50 ppm for fetal and maternal effects was reported. Inhalation exposure to 150 ppm was calculated by the authors to approximate a daily dose of 45 mg/kg/day, which coincides with previous work on this compound in this species.

VI. Derivation of Chronic Reference Exposure Level

Study	Cirla *et al.*, 1984; Catenacci *et al.*, 1984
Study population	Occupationally exposed workers
Exposure method	Discontinuous inhalation exposures
Critical effects	Digestive disturbances and slight hepatic changes
LOAEL	22 mg/m^3
NOAEL	Not observed
Exposure continuity	8 hr/day (10 m^3/day), 5 days/week (assumed)
Average occupational exposure	7.9 mg/m^3 for LOAEL group (22 x 10/20 x 5/7)
Human equivalent concentration	7.9 mg/m^3
Exposure duration	5 years (mean exposure duration)
LOAEL uncertainty factor	3
Subchronic uncertainty factor	3
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	0.08 mg/m^3 (80 $\mu g/m^3$, 0.03 ppm, 30 ppb)

The U.S. EPA (1994) based its RfC of 30 $\mu g/m^3$ on the same study but included a Modifying Factor (MF) of 3 due to lack of reproductive toxicity data in the DMF database. The criteria for use of modifying factors are not well specified by U.S. EPA. Such modifying factors were not used by OEHHA. Intermediate uncertainty factors were used for LOAEL to NOAEL and subchronic to chronic extrapolation because of the mild nature of the effects observed and the less than chronic exposure duration.

For comparison Hellwig *et al*. (1991) found a developmental NOAEL of 50 ppm in rabbits exposed 6 hours per day on gestation days 8-20, equivalent to continuous exposure of 12.5 ppm. Multiplication by an RGDR of 1 and division by a UF of 30 (3 for interspecies and 10 for intraspecies) results in a REL estimate of 400 ppb. The NOAEL of 25 ppm for rats and mice in the chronic study of Malley *et al*. (1994) leads to a REL estimate of 150 ppb.

VII. Data Strengths and Limitations for Development of the REL

The major strength of the REL for N,N-dimethylformamide is the availability of human health effects data over several years of exposure. The major uncertainties are the difficulty

in estimating exposure patterns and magnitude, the lack of a NOAEL observation, and the lack of complete reproductive and developmental toxicity data.

VIII. References

CARB. 2000. California Air Resources Board. California Emissions Inventory Development and Reporting System (CEIDARS). Data from Data Base Year 1998. February 12, 2000.

Catenacci G, Grampella D, Terzi R, Sala A, and Pollini G. 1984. Hepatic function in subjects exposed to environmental concentrations of DMF lower than the actually proposed TLV. G. Ital. Med. Lav. 6(3-4):157-158.

Cirla AM, Pisati G, Invernizzi E, and Torricelli P. 1984. Epidemiological study on workers exposed to low dimethylformamide concentrations. G. Ital. Med. Lav. 6(3-4):149-156.

Farquharson RG, Hall MH, and Fullerton WT. 1983. Poor obstetric outcome in three quality control laboratory workers. Lancet 1(8331):983-984. [cited in U.S. EPA, 1994].

Gescher A. 1993. Metabolism of N,N-dimethylformamide: key to the understanding of its toxicity. Chem. Res. Toxicol. 6(3):245-251.

HSDB. 1994. Hazardous Substances Data Bank. National Library of Medicine, Bethesda, MD (TOMES® CD-ROM Version). Denver, CO: Micromedex, Inc. (Edition expires 11/31/94).

Hellwig J, Merkle J, Klimisch HJ, and Jackh R. 1991. Studies on the prenatal toxicity of N,N-dimethylformamide in mice, rats and rabbits. Food Chem. Toxicol. 29(3):192-201.

Howard PH. (ed) 1993. Handbook of Environmental Fate and Exposure Data for Organic Chemicals. Vol. IV: Solvents 2. Chelsea, MI: Lewis Publishers Inc.

Malley LA, Slone TW Jr, Van Pelt C, Elliott GS, Ross PE, Stadler JC, and Kennedy GL Jr. 1994. Chronic toxicity/oncogenicity of dimethylformamide in rats and mice following inhalation exposure. Fundam. Appl. Toxicol. 23(2):268-279.

Redlich C, Beckett WS, Sparer J, Barwick KW, Riely CA, Miller H, Sigal SL, Shalat SL, and Cullen MR. 1988. Liver disease associated with occupational exposure to the solvent dimethylformamide. Ann. Intern. Med. 108:680-686.

U.S. EPA. 1994. U.S. Environmental Protection Agency. IRIS. 1994. Integrated Risk Information System (IRIS). Reference concentration for chronic inhalation exposure (RfC) for N,N,-Dimethylformamide. Available online at http://www.epa.gov/ngispgm3/iris

Wang JD, Lai MY, Chen JS, Lin JM, Chiang JR, Shiau SJ, and Chang WS. 1991. Dimethylformamide-induced liver damage among synthetic leather workers. Arch. Environ. Health 46(3):161-166.