Concise International Chemical Assessment Document 31

N,*N*-DIMETHYLFORMAMIDE

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The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organization (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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FOREWORD

Concise International Chemical Assessment Documents (CICADs) are the latest in a family of publications from the International Programme on Chemical Safety (IPCS) — a cooperative programme of the World Health Organization (WHO), the International Labour Organization (ILO), and the United Nations Environment Programme (UNEP). CICADs join the Environmental Health Criteria documents (EHCs) as authoritative documents on the risk assessment of chemicals.

International Chemical Safety Cards on the relevant chemical(s) are attached at the end of the CICAD, to provide the reader with concise information on the protection of human health and on emergency action. They are produced in a separate peer-reviewed procedure at IPCS. They may be complemented by information from IPCS Poison Information Monographs (PIM), similarly produced separately from the CICAD process.

CICADs are concise documents that provide summaries of the relevant scientific information concerning the potential effects of chemicals upon human health and/or the environment. They are based on selected national or regional evaluation documents or on existing EHCs. Before acceptance for publication as CICADs by IPCS, these documents undergo extensive peer review by internationally selected experts to ensure their completeness, accuracy in the way in which the original data are represented, and the validity of the conclusions drawn.

The primary objective of CICADs is characterization of hazard and dose–response from exposure to a chemical. CICADs are not a summary of all available data on a particular chemical; rather, they include only that information considered critical for characterization of the risk posed by the chemical. The critical studies are, however, presented in sufficient detail to support the conclusions drawn. For additional information, the reader should consult the identified source documents upon which the CICAD has been based.

Risks to human health and the environment will vary considerably depending upon the type and extent of exposure. Responsible authorities are strongly encouraged to characterize risk on the basis of locally measured or predicted exposure scenarios. To assist the reader, examples of exposure estimation and risk characterization are provided in CICADs, whenever possible. These examples cannot be considered as representing all possible exposure situations, but are provided as guidance only. The reader is referred to EHC 170[1] for advice on the derivation of health-based tolerable intakes and guidance values.

While every effort is made to ensure that CICADs represent the current status of knowledge, new information is being developed constantly. Unless otherwise stated, CICADs are based on a search of the scientific literature to the date shown in the executive summary. In the event that a reader becomes aware of new information that would change the conclusions drawn in a CICAD, the reader is requested to contact IPCS to inform it of the new information.

Procedures

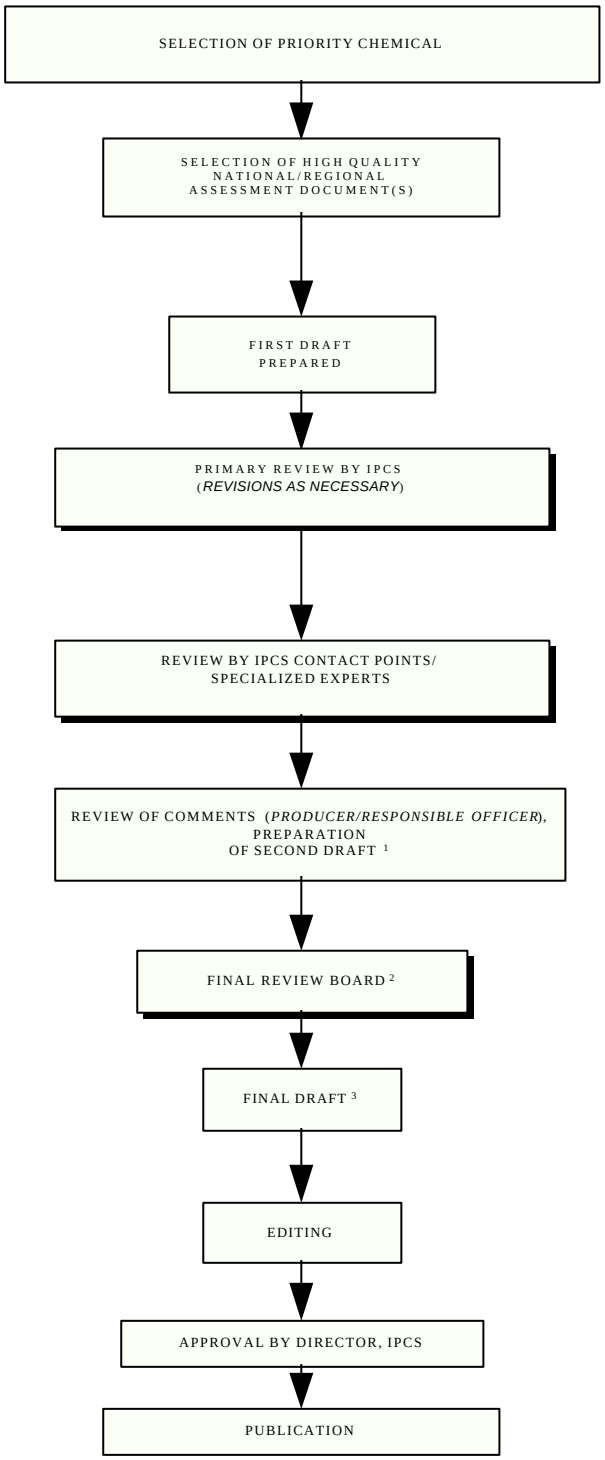
The flow chart shows the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world — expertise that is required to produce the high-quality evaluations of toxicological, exposure, and other data that are necessary for assessing risks to human health and/or the environment. The IPCS Risk Assessment Steering Group advises the Co-ordinator, IPCS, on the selection of chemicals for an IPCS risk assessment, whether a CICAD or an EHC is produced, and which institution bears the responsibility of the document production, as well as on the type and extent of the international peer review.

The first draft is based on an existing national, regional, or international review. Authors of the first draft are usually, but not necessarily, from the institution that developed the original review. A standard outline has been developed to encourage consistency in form. The first draft undergoes primary review by IPCS and one or more experienced authors of criteria documents in order to ensure that it meets the specified criteria for CICADs.

The draft is then sent to an international peer review by scientists known for their particular expertise and by scientists selected from an international roster compiled by IPCS through recommendations from IPCS national Contact Points and from IPCS Participating Institutions. Adequate time is allowed for the selected experts to undertake a thorough review. Authors are required to take reviewers' comments into account and revise their draft, if necessary. The resulting second draft

[1] International Programme on Chemical Safety (1994) *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits.* Geneva, World Health Organization (Environmental Health Criteria 170).

CICAD PREPARATION FLOW CHART



1 Taking into account the comments from reviewers.
2 The second draft of documents is submitted to the Final Review Board together with the reviewers' comments.
3 Includes any revisions requested by the Final Review Board.

is submitted to a Final Review Board together with the reviewers' comments.

A consultative group may be necessary to advise on specific issues in the risk assessment document.

The CICAD Final Review Board has several important functions:

- to ensure that each CICAD has been subjected to an appropriate and thorough peer review;
- to verify that the peer reviewers' comments have been addressed appropriately;
- to provide guidance to those responsible for the preparation of CICADs on how to resolve any remaining issues if, in the opinion of the Board, the author has not adequately addressed all comments of the reviewers; and
- to approve CICADs as international assessments.

Board members serve in their personal capacity, not as representatives of any organization, government, or industry. They are selected because of their expertise in human and environmental toxicology or because of their experience in the regulation of chemicals. Boards are chosen according to the range of expertise required for a meeting and the need for balanced geographic representation.

Board members, authors, reviewers, consultants, and advisers who participate in the preparation of a CICAD are required to declare any real or potential conflict of interest in relation to the subjects under discussion at any stage of the process. Representatives of nongovernmental organizations may be invited to observe the proceedings of the Final Review Board. Observers may participate in Board discussions only at the invitation of the Chairperson, and they may not participate in the final decision-making process.

1. EXECUTIVE SUMMARY

This CICAD on *N*,*N*-dimethylformamide (DMF) was prepared jointly by the Environmental Health Directorate of Health Canada and the Commercial Chemicals Evaluation Branch of Environment Canada based on documentation prepared concurrently as part of the Priority Substances Program under the *Canadian Environmental Protection Act* (CEPA). The objective of assessments on Priority Substances under CEPA is to assess potential effects of indirect exposure in the general environment on human health as well as environmental effects. Occupational exposure was not addressed in this source document. Data identified as of the end of September 1999 (environmental effects) and February 2000 (human health effects) were considered in this review. Information on the nature of the peer review and availability of the source document is presented in Appendix 1. Other reviews that were also consulted include IARC (1999) and BUA (1994). Information on the peer review of this CICAD is presented in Appendix 2. This CICAD was approved as an international assessment at a meeting of the Final Review Board, held in Helsinki, Finland, on 26–29 June 2000. Participants at the Final Review Board meeting are presented in Appendix 3. The International Chemical Safety Card (ICSC 0457) for *N*,*N*-dimethylformamide, produced by the International Programme on Chemical Safety (IPCS, 1999), has also been reproduced in this document.

N,*N*-Dimethylformamide (CAS No. 68-12-2) is an organic solvent produced in large quantities throughout the world. It is used in the chemical industry as a solvent, an intermediate, and an additive. It is a colourless liquid with a faint amine odour. It is completely miscible with water and most organic solvents and has a relatively low vapour pressure.

When emitted into air, most of the DMF released remains in that compartment, where it is degraded by chemical reactions with hydroxyl radicals. Indirect releases of DMF to air, such as transfers from other environmental media, play only a small role in maintaining levels of DMF in the atmosphere. DMF in air is estimated to be photooxidized over a period of days. However, some atmospheric DMF can reach the aquatic and terrestrial environment, presumably during rain events. When DMF is released into water, it degrades there and does not move into other media. When releases are into soil, most of the DMF remains in the soil — presumably in soil pore water — until it is degraded by biological and chemical reaction. Releases to water or soil are expected to be followed by relatively rapid biodegradation (half-life 18–36 h). If DMF reaches groundwater, its anerobic degradation will be slow. The use pattern of DMF is such that exposure of the general population is probably very low.

Since most DMF appears to be released to air in the sample country, and based on the fate of DMF in the ambient environment, biota are expected to be exposed to DMF primarily in air; little exposure to DMF from surface water, soil, or benthic organisms is expected. Based on this, and because of the low toxicity of DMF to a wide range of aquatic and soil organisms, the focus of the environmental risk characterization is terrestrial organisms exposed directly to DMF in ambient air.

DMF is readily absorbed following oral, dermal, or inhalation exposure. Following absorption, DMF is uniformly distributed, metabolized primarily in the liver, and relatively rapidly excreted as metabolites in urine. The major pathway involves the hydroxylation of methyl moieties, resulting in *N*-(hydroxymethyl)-*N*-methylformamide (HMMF), which is the major urinary metabolite in humans and animals. HMMF in turn can decompose to *N*-methylformamide (NMF). In turn, enzymatic *N*-methyl oxidation of NMF can produce *N*-(hydroxymethyl)formamide (HMF), which further degenerates to formamide. An alternative pathway for the metabolism of NMF is oxidation of the formyl group, resulting in *N*-acetyl-*S*-(*N*-methylcarbamoyl)cysteine (AMCC), which has been identified as a urinary metabolite in rodents and humans. A reactive intermediate, the structure of which has not yet been determined (possibly methyl isocyanate), is formed in this pathway; while direct supporting experimental evidence was not identified, this intermediate is suggested to be the putatively toxic metabolite. Available data indicate that a greater proportion of DMF may be metabolized by the putatively toxic pathway in humans than in experimental animals. There is metabolic interaction between DMF and alcohol, which, though not well understood, may be due, at least in part, to its inhibitory effect on alcohol dehydrogenase.

Consistent with the results of studies in experimental animals, available data from case reports and cross-sectional studies in occupationally exposed populations indicate that the liver is the target organ for the toxicity of DMF in humans. The profile of effects is consistent with that observed in experimental animals, with gastrointestinal disturbance, alcohol intolerance, increases in serum hepatic enzymes (aspartate aminotransferase, alanine aminotransferase, (-glutamyl transpeptidase, and alkaline phosphatase), and histopathological effects and ultrastructural changes (hepatocellular necrosis, enlarged Kupffer cells, microvesicular steatosis, complex

lysosomes, pleomorphic mitochondria, and fatty changes with occasional lipogranuloma) being observed.

Based on the limited data available, there is no convincing, consistent evidence of increases in tumours at any site associated with exposure to DMF in the occupational environment. Case reports of testicular cancers have not been confirmed in a cohort and case–control study. There have been no consistent increases in tumours at other sites associated with exposure to DMF.

There is also little consistent, convincing evidence of genotoxicity in populations occupationally exposed to DMF, with results of available studies of exposed workers (to DMF and other compounds) being mixed. The pattern of observations is not consistent with variations in exposure across studies. However, in view of the positive dose–response relationship observed in the one study in which it was investigated, this area may be worthy of additional work, although available data on genotoxicity in experimental systems are overwhelmingly negative.

DMF has low acute toxicity and is slightly to moderately irritating to the eyes and skin. No data were identified regarding the sensitization potential of DMF. In acute and repeated-dose toxicity studies, DMF has been consistently hepatotoxic, inducing effects on the liver at lowest concentrations or doses. The profile of effects includes alterations in hepatic enzymes characteristic of toxicity, increases in liver weight, progressive degenerative histopathological changes and eventually cell death, and increases in serum hepatic enzymes. A dose–response has been observed for these effects in rats and mice following inhalation and oral exposure. Species variation in sensitivity to these effects has been observed, with the order of sensitivity being mice > rats > monkeys.

Although the database for carcinogenicity is limited to two adequately conducted bioassays in rats and mice, there have been no increases in the incidence of tumours following chronic inhalation exposure to DMF. The weight of evidence for genotoxicity is overwhelmingly negative, based on extensive investigation in *in vitro* assays, particularly for gene mutation, and a more limited database *in vivo.*

In studies with laboratory animals, DMF has induced adverse reproductive effects only at concentrations greater than those associated with adverse effects on the liver, following both inhalation and oral exposure. Similarly, in well conducted and reported primarily recent developmental studies, fetotoxic and teratogenic effects have been consistently observed only at maternally toxic concentrations or doses.

Available data are inadequate as a basis for assessment of the neurological or immunological effects of DMF.

The focus of this CICAD and the sample risk characterization is primarily effects of indirect exposure in the general environment.

Air in the vicinity of point sources appears to be the greatest potential source of exposure of the general population to DMF. Based on the results of epidemiological studies of exposed workers and supporting data from a relatively extensive database of investigations in experimental animals, the liver is the critical target organ for the toxicity of DMF. A tolerable concentration of 0.03 ppm (0.1 mg/m^3) has been derived on the basis of increases in serum hepatic enzymes.

Data on the toxicity of DMF to terrestrial vascular plants have not been identified. Effect concentrations for indicators of the potential sensitivities of trees, shrubs, and other plants are high; hence, it is unlikely that terrestrial plants are particularly sensitive to DMF. For other terrestrial organisms, an estimated no-effects value of 15 mg/m^3 has been derived based on a critical toxicity value for hepatic toxicity in mice divided by an application factor. Comparison of this value with a conservative estimated exposure value indicates that it is unlikely that DMF causes adverse effects on terrestrial organisms in the sample country.

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

N,*N*-Dimethylformamide (CAS No. 68-12-2) is a colourless liquid at room temperature with a faint amine odour (BUA, 1994). There are many synonyms for this compound, the most common being the acronym DMF. The molecular mass of DMF is 73.09, as calculated from its empirical formula (C_3H_7NO). DMF sold commercially contains trace amounts of methanol, water, formic acid, and dimethylamine (BUA, 1994).

DMF is miscible in all proportions with water and most organic solvents (Syracuse Research Corporation, 1988; Gescher, 1990; BUA, 1994; SRI International, 1994). DMF is also a powerful solvent for a variety of organic, inorganic, and resin products (SRI International, 1994). At temperatures below 100 °C, DMF

Table 1: Physical and chemical properties of DMF.

Property	Value	Reference	Values used in fugacity calculations[a]
Molecular mass	73.09		73.09
Vapour pressure (Pa at 25 °C)	490	Riddick et al. (1986)	490
Solubility (g/m^3)	miscible	BUA (1994)	1.04×10^6
Log K_{ow}	!1.01	Hansch et al. (1995)	!1.01
Henry's law constant (Pa•m^3/mol at 25 °C)	0.0345 0.0075	Bobra[b] BUA (1994)	0.034 53[c]
Density/specific gravity (g/ml at 25 °C)	0.9445	WHO (1991)	
Melting point (°C)	!60.5	WHO (1991)	!60.5 °C
Boiling point (°C)	153.5	WHO (1991)	
Half-life in air (h)	approx. 192	estimated from propane	170
Half-life in water (h)	18 36	Dojlido (1979) Ursin (1985)	55
Half-life in soil (h)	assumed to be equivalent to that in water		55
Half-life in sediment (h)	–		170
Half-life in suspended sediment (h)	–		55
Half-life in fish (h)	–		55
Half-life in aerosol (h)	–		5
Odour threshold	0.12–60 mg/m^3	WHO (1991)	

[a] Discussed in section 11.1.3, Sample risk characterization.

[b] Collection of notes and modelling results submitted by A. Bobra, AMBEC Environmental Consultant, to Chemicals Evaluation Division, Commercial Chemicals Evaluation Branch, Environment Canada, 1999.

[c] Based upon vapour liquid equilibrium data (Hala et al., 1968), as calculated in DMER & AEL (1996).

remains stable in relation to light and oxygen (BUA, 1994). Temperatures in excess of 350 °C are required for DMF to decompose into carbon monoxide and dimethylamine (Farhi et al., 1968).[1]

Some important physical and chemical properties of DMF are summarized in Table 1. A vapour pressure of 490 Pa was recommended by Riddick et al. (1986). Because DMF is a miscible compound, it is preferable to determine the Henry's law constant experimentally. However, no experimental data were identified in the literature, and the calculated Henry's law constant of DMF remains uncertain (DMER & AEL, 1996).[2] The octanol/water partition coefficient (K_{ow}) was determined by a shake flask experiment (Hansch et al., 1995).

The conversion factor for DMF in air is as follows (WHO, 1991): 1 ppm = 3 mg/m^3.

3. ANALYTICAL METHODS

The following information on analytical methods for the determination of DMF in workplace air and biological media has been derived from WHO (1991) and Environment Canada (1999a).

3.1 DMF in workplace air

Colorimetric methods (based on the development of a red colour after the addition of hydroxylamine chloride as alkaline solution) that have often been utilized in the past are not specific (Farhi et al., 1968). Methods of choice more recently are high-performance liquid chromatography (HPLC) or gas chromatography – mass spectrometry (GCMS). Lauwerys et al. (1980)

[1] Also notes from N.J. Bunce, University of Guelph, Guelph, Ontario, to A. Chevrier, Environment Canada, 1 June 1998.

[2] Also collection of notes and modelling results submitted by A. Bobra, AMBEC Environmental Consultant, to Chemicals Evaluation Division, Commercial Chemicals Evaluation Branch, Environment Canada, 1999.

described a simple spectrophotometric method for measuring DMF vapour concentrations. Gas–liquid chromatography (GLC) is now the method of choice (Kimmerle & Eben, 1975a; NIOSH, 1977; Muravieva & Anvaer, 1979; Brugnone et al., 1980; Muravieva, 1983; Stransky, 1986). Detector tubes, certified by the US National Institute for Occupational Safety and Health, or other direct-reading devices calibrated to measure DMF (Krivanek et al., 1978; NIOSH, 1978) can be used. HPLC analysis (Lipski, 1982) can also be used. Mass spectrometric analysis for DMF in expired air has been described by Wilson & Ottley (1981), with a lower limit of detection of 0.5 mg/m^3. Figge et al. (1987) reported determination in air involving the enrichment of an organic polymer, thermal desorption of the adsorbed species, and qualitative determination by GCMS. The lower limit of detection was 5 ng/m^3. A NIOSH (1994) gas chromatographic (GC) method has an estimated detection limit of 0.05 mg per sample.

3.2 DMF and metabolites in biological media

DMF is extensively absorbed through the skin, its metabolism and kinetics are well known, and urinary metabolites exist that can be accurately measured. As a result, biological monitoring has been extensively used in the assessment of the absorbed amounts in occupationally exposed populations. The metabolite most often analysed is *N*-methylformamide (NMF), and several GC methods exist (Ikeda, 1996). Using nitrogen-sensitive detection, the limit of detection is 0.1 mg/litre.

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

4.1 Natural sources

BUA (1994) identified no known natural sources of DMF. However, DMF is a possible product of the photochemical degradation of dimethylamine and trimethylamine (Pellizzari, 1977; Pitts et al., 1978; US EPA, 1986). Both are commonly occurring natural substances and are also used in industrial applications (European Chemicals Bureau, 1996a, 1996b).

4.2 Anthropogenic sources

Identified data on releases are restricted to the country of origin of the source document (Canada). They are presented here in the context of an example of an emissions profile.

In 1996, just over 16 tonnes of DMF were released from various industrial locations in Canada, of which 93% (15 079 kg) were emitted to the atmosphere and the remainder to water (245 kg), wastewater (204 kg), landfill sites (26 kg), or deep-well injection (669 kg) (Environment Canada, 1998). The Canadian market for DMF is quite small, with an estimated domestic consumption in the range of less than 1000 tonnes/year (SRI International, 1994; Environment Canada, 1998). The petrochemical sector was responsible for 84% (12.7 tonnes) of the reported atmospheric releases. Releases from the pharmaceutical industry accounted for 87% (0.212 tonnes) of total releases to water. Total release volumes from Canadian industrial sectors include 13.3 tonnes from the petrochemical sector, 1.2 tonnes from manufacture of pharmaceuticals, 0.7 tonnes from dye and pigment manufacture, 0.6 tonnes from polyvinyl chloride coating operations, 0.1 tonnes from its use as a solvent in pesticide manufacture, 0.07 tonnes from paint/finisher and paint remover manufacture, and 0.09 tonnes from other miscellaneous industrial sectors. For 1996, a reported total quantity of 0.056 tonnes was released (0.023 tonnes to air, 0.033 tonnes to water) by the producer during chemical synthesis of DMF (Environment Canada, 1998). Less than 1 tonne of DMF was released from wastewater treatment facilities and in landfills (Environment Canada, 1998). With a few exceptions, most industries reported little to no seasonal variation in releases (Environment Canada, 1998).

In the USA, between 23 and 47 million kilograms of DMF were produced in 1990 (US EPA, 1997).

World production of DMF is estimated to be 125 000 tonnes (Marsella, 1994).

The total consumption of DMF in Western Europe in 1989 was reported to be 55 000 tonnes (BUA, 1994). The production capacity was estimated to be 60 000 and 19 000 tonnes in the former Federal Republic of Germany and German Democratic Republic, respectively, 16 000 tonnes in Belgium, 15 000 tonnes in England, and 5000 tonnes in Spain (BUA, 1994).

Although small accidental releases (e.g., leakage of a storage tank or spill from a barrel) may remain unreported, available information suggests that spills of DMF during use, storage, or transport are not a significant route of entry to the environment (Environment Canada, 1999a).

The quantity of DMF in landfill sites should be small. The total quantity of DMF used in formulation of products (other than pesticides) appears to be small in comparison to its use as a manufacturing aid, cleaner, or degreaser (Environment Canada, 1998). As such,

consumer products deposited in landfill sites should contain little or no DMF. The industrial DMF deposited directly in landfill sites consists only of residues remaining after incineration (Environment Canada, 1998).

4.3 Uses

DMF is used commercially as a solvent in vinyl resins, adhesives, pesticide formulations, and epoxy formulations; for purification and/or separation of acetylene, 1,3-butadiene, acid gases, and aliphatic hydrocarbons; and in the production of polyacrylic or cellulose triacetate fibres and pharmaceuticals (WHO, 1991; IARC, 1999). DMF is also used in the production of polyurethane resin for synthetic leather (Fiorito et al., 1997).

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

5.1 Air

The atmospheric pathway is particularly important in determining exposure to DMF. This is due to the fact that industrial releases of DMF into air appear to be considerably larger than releases to other environmental media (BUA, 1994; Environment Canada, 1998).

Because of the complete miscibility of DMF in water, atmospheric DMF may be transported from air into surface water or soil pore water during rain events (DMER & AEL, 1996).[1] Atmospheric DMF should be present in the vapour phase and therefore should be readily available for leaching out by rainfall (US EPA, 1986).[2] Although the efficiency and rate of washout are unknown, precipitation events (i.e., rain, snow, fog) likely shorten the residence time of DMF in the atmosphere. As water has an atmospheric half-life of approximately 4 days at Canadian latitudes, this can be considered the minimum atmospheric half-life of DMF in relation to precipitation.[1]

Chemical degradation of DMF in air is likely due to reaction with hydroxyl radicals (Hayon et al., 1970). The possibility of photochemical decomposition (i.e., direct photolysis) of DMF is extremely small (Grasselli, 1973; Scott, 1998). Other chemical degradation processes — for example, reaction with nitrate radicals — are not known to significantly affect the fate of DMF in air.

The reaction rate constant (k_{OH}) for the formamide functional group is unknown. However, the degradation half-life of DMF can be roughly estimated by comparing DMF with other compounds in terms of their relative atmospheric reactivity.

Based on experiments in chambers, reactivity for DMF relative to propane is low (Sickles et al., 1980). The k_{OH} of propane is 1.2×10^{-12} cm^3/molecule per second (Finlayson-Pitts & Pitts, 1986). Using the global average hydroxyl radical concentration of 7.7×10^5 molecules/cm^3 (Prinn et al., 1987) and the calculation method proposed by Atkinson (1988), the half-life of propane is estimated at approximately 8 days.

Although the degradation half-life of DMF in air cannot be estimated with certainty, the available evidence therefore suggests that the half-life is at least 8 days (192 h). The mean half-life used for fugacity-based fate modelling was 170 h, as it is frequently used to represent a half-life range of 100–300 h (DMER & AEL, 1996). This half-life may be underestimated; however, sensitivity analysis on the fugacity-based results indicates that percent partitioning estimates are not sensitive to this parameter, but estimated concentrations are affected.[3]

5.2 Surface water and sediment

Once released into surface water, DMF is unlikely to transfer to sediments, biota, or the atmosphere. With a K_{ow} of !1.01 (Hansch et al., 1995), DMF remains in the dissolved form and is not expected to adsorb to the organic fraction of sediments or suspended organic matter. This K_{ow} also suggests that DMF does not concentrate in aquatic organisms (BUA, 1994); indeed, no bioaccumulation was observed in carp during an 8-week bioaccumulation test (Sasaki, 1978). With a Henry's law constant of 0.0345 Pa@m^3/mol, volatilization from water is expected to be slight (BUA, 1994).[3]

The overall rate of chemical degradation is expected to be very slow in surface water.

[1] Also letter from D.R. Hastie, York University, Toronto, Ontario, to P. Doyle, Environment Canada, 1998.

[2] Also technical note from N.J. Bunce, University of Guelph, Guelph, Ontario, to B. Scott, Environment Canada, dated 10 February 1998.

[3] Collection of notes and modelling results submitted by A. Bobra, AMBEC Environmental Consultant, to Chemicals Evaluation Division, Commercial Chemicals Evaluation Branch, Environment Canada, 1999.

Photochemical decomposition is unlikely in water (Grasselli, 1973; US EPA, 1986). The photooxidation half-life of DMF in water was estimated experimentally at 50 days and would be even longer in the natural environment where other compounds compete for reaction with hydroxyl radicals (Hayon et al., 1970). The rate of hydrolysis of amides like DMF at normal temperatures in laboratory studies is extremely slow, even under strong acid or base conditions (Fersht & Requena, 1971; Eberling, 1980). The low temperature (generally less than 20 °C) and near-neutral pH of natural surface water therefore limit and almost preclude the hydrolysis of DMF under normal environmental conditions (Frost & Pearson, 1962; Langlois & Broche, 1964; Scott, 1998).

Biodegradation appears to be the primary degradation process in surface water. Under experimental conditions, DMF was degraded, either aerobically or anaerobically, by various microorganisms and algae in activated sludges, over a wide range of concentrations (Hamm, 1972; Begert, 1974; Dojlido, 1979). Intermediate biodegradation products include formic acid and dimethylamine, which further degrade to ammonia, carbon dioxide, and water (Dojlido, 1979; Scott, 1998). In some studies, acclimation periods of up to 16 days preceded quantitative degradation (Chudoba et al., 1969; Gubser, 1969). Extended adaptation under specific experimental conditions may also account for negative degradation results observed in a few studies with incubation times #14 days (Kawasaki, 1980; CITI, 1992). Limited degradation was reported in seawater (range 1–42%) (Ursin, 1985), and no degradation was found after 8 weeks' incubation under anaerobic conditions (Shelton & Tiedje, 1981).

Biodegradation of DMF in receiving surface waters is unlikely to be affected by the inherent toxicity of DMF and its biodegradation products. Concentrations above 500 mg/litre in effluent reduced the efficiency of treatment systems using activated sludge (Thonke & Dittmann, 1966; Nakajima, 1970; Hamm, 1972; Begert, 1974; Carter & Young, 1983). However, even with continuous releases, such high concentrations of DMF are not anticipated in natural waters.

In a river die-away test, an initial concentration of 30 mg DMF/litre completely disappeared within 3 and 6 days from unacclimated and acclimated water, respectively (Dojlido, 1979). The mineralization rate of DMF in seawater was less than 3% in 24 h for initial concentrations of 10 µg/litre and 100 µg/litre. However, 20% was mineralized in 24 h at a concentration of 0.1 µg/litre (Ursin, 1985). A half-life of 55 h was used for water in the fugacity-based fate modelling described in section 5.4 (DMER & AEL, 1996).[1,2] No information is available on the half-life of DMF in sediments. DMER & AEL (1996) recommend a half-life in sediment of 170 h based on the assumption that reactivity in sediment is slower than in soil.

5.3 Soil and groundwater

Fugacity-based fate modelling and the miscibility of DMF indicate that some of the DMF released into the atmosphere can reach the ground, in part, at least, through rainfall (DMER & AEL, 1996).[1,2] Once in soils, DMF will be degraded by chemical and biological processes or leached into groundwater.

As rain fills the available pore space in soils, DMF is incorporated into the pore water. With an octanol/water partition coefficient of !1.01 (Hansch et al., 1995), DMF will not tend to adsorb to humic material. Weak bonds with the mineral phase are possible but likely insignificant because of the high solubility of DMF.[3]

Biological degradation and, to a lesser extent, chemical processes operating in surface water would also likely affect DMF contained in soil pore water (Scott, 1998). As for surface water, biodegradation should therefore be the primary breakdown mechanism in soils. A soil bacterial culture acclimated to small amounts of petroleum and petroleum products degraded DMF under aerobic conditions within 18 h (Romadina, 1975), indicating a soil biodegradation half-life similar to the one observed in water. A somewhat longer conservative half-life of 55 h was used in fugacity-based fate modelling (DMER & AEL, 1996).[1,2]

The miscibility of DMF and its low Henry's law constant indicate limited volatilization from moist soils (BUA, 1994). However, DMF will be efficiently removed from soils by leaching into groundwater, likely at the same speed as water percolates through the soil.[4] This is

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[1] Also technical note sent from R. Beauchamp, Health Canada, to A. Chevrier, Environment Canada, 1998.

[2] Also collection of notes and modelling results submitted by A. Bobra, AMBEC Environmental Consultant, to Chemicals Evaluation Division, Commercial Chemicals Evaluation Branch, Environment Canada, 1999.

[3] Letter from K. Bolton, University of Toronto, Toronto, Ontario, to A. Chevrier, Environment Canada, dated 8 June 1998.

[4] Technical note from S. Lesage to B. Elliott, Environment Canada, dated 26 November 1997.

supported by a calculated organic carbon/water partition coefficient (K_{oc}) of 7 (Howard, 1993) and a soil sorption coefficient (K_{om}) of about 50, estimated from quantitative structure–activity relationships (Sabljic, 1984; US EPA, 1986), which both indicate that DMF is mobile in soils. If it reaches groundwater, DMF will be slowly degraded anaerobically (Scott, 1998).[1]

5.4 Environmental distribution

Fugacity modelling was conducted to provide an overview of key reaction, intercompartment, and advection (movement out of a system) pathways for DMF and its overall distribution in the environment. A steady-state, non-equilibrium model (Level III fugacity modelling) was run using the methods developed by Mackay (1991) and Mackay & Paterson (1991). Assumptions, input parameters, and results are summarized in Environment Canada (1999a) and presented in detail in DMER & AEL (1996) and by Beauchamp[2] and Bobra.[3] Modelling predictions do not reflect actual expected concentrations in the environment but rather indicate the broad characteristics of the fate of the substance in the environment and its general distribution among the media.

Modelling results identify air as an important exposure medium. If DMF is emitted into air, fugacity modelling predicts that 61% of the chemical will be present in air, 32% in soil, and only 7% in water. These results suggest that most of the DMF released into air will remain in that compartment, where it will be degraded by chemical reactions. They also indicate that some atmospheric DMF can reach the aquatic and terrestrial environment — presumably in rain and runoff (Scott, 1998).[4] However, the quantity of DMF available for entrainment in rain and runoff is limited by degradation in the atmosphere.

Fugacity modelling also indicates that when DMF is continuously discharged into either water or soil, most of it can be expected to be present in the receiving medium. For example, if it is released into water, 99% of the DMF is likely to be present in the water, and subsequent transport into sediment or bioconcentration in biota is not likely to be significant. When releases are into soil, 94% of the material remains in the soil — presumably in soil pore water (Scott, 1998). Therefore, indirect releases of DMF to air, such as transfers from other environmental media, play only a small role in maintaining levels of DMF in the atmosphere.

It is important to note that fugacity-based partitioning estimates are significantly influenced by input parameters such as the Henry's law constant, which, in this case, is highly uncertain. Therefore, the above partitioning estimates are also uncertain.

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

6.1 Environmental levels

6.1.1 Ambient air

Concentrations of DMF in stack emissions of two Canadian industries were less than 7.5 mg/m^3 (Environment Canada, 1998, 1999b). Data on concentrations in ambient air around these sources are not available.

In Lowell, Massachusetts, USA (Amster et al., 1983), DMF was detected in the air over an abandoned chemical waste reclamation plant (0.007 mg/m^3), a neighbouring industry (>0.15 mg/m^3), and a residential area (0.024 mg/m^3). Ambient air samples collected in the northeastern USA in 1983 ranged from less than 0.000 02 to 0.0138 mg DMF/m^3 (Kelly et al., 1993, 1994). In samples taken in 1983, levels of DMF were generally less than 0.02 mg/m^3 at a hazardous waste site in unsettled wind conditions, possibly as high as 9 mg/m^3 at nearby industrial sites, and less than 0.02 mg/m^3 in adjoining residential areas (Clay & Spittler, 1983).

A range of 0.000 11 – 0.0011 mg/m^3 was reported in Japan in 1991, but specific locations and proximity to sources were not provided (Environment Agency Japan, 1996). In Germany, a concentration of $0.005 µg DMF/m^3 was detected in air (Figge et al., 1987).

[1] Technical note from S. Lesage to B. Elliott, Environment Canada, dated 26 November 1997.

[2] Technical note sent from R. Beauchamp, Health Canada, to A. Chevrier, Environment Canada, 1998.

[3] Collection of notes and modelling results submitted by A. Bobra, AMBEC Environmental Consultant, to Chemicals Evaluation Division, Commercial Chemicals Evaluation Branch, Environment Canada, 1999.

[4] Also letter from S. Lei, Atomic Energy Control Board of Canada, to A. Chevrier, Environment Canada, dated 11 June 1998.

6.1.2 Surface water and sediment

DMF was detected (detection limit 0.002 mg/litre) in only 1 of 204 surface water samples collected between August 1975 and September 1976 from 14 heavily industrialized river basins in the USA (Ewing et al., 1977). The Environment Agency Japan (1996) reported concentrations between 0.0001 and 0.0066 mg/litre in 18 out of 48 water samples taken in 1991. In addition, in 24 water samples collected in 1978, levels were below the detection limits of 0.01–0.05 mg/litre (Environment Agency Japan, 1985). The proximity of these measurements to industrial sources is not known.

In Canada, monitoring data are available for effluents at one southern Ontario location, which released less than ~0.03 tonnes into surface water in 1996 (Environment Canada, 1998). The facility reported a range of <1–10 mg DMF/litre in effluents, but has since established a wastewater treatment plant, which reduced its effluent concentrations to non-detectable levels (detection limit 0.5 mg/litre). DMF was detected in 1 of 63 industrial effluents in the USA at a detection limit of approximately 0.01 mg/litre (Perry et al., 1979). The US Environmental Protection Agency (EPA)[1] also cited an effluent concentration of 0.005 mg/litre at a sewage treatment plant in 1975.

The properties of DMF and fugacity modelling indicate negligible accumulation of DMF in sediments (BUA, 1994; Hansch et al., 1995; DMER & AEL, 1996).[2,3] However, concentrations of 0.03–0.11 mg/kg were reported in sediments (9 out of 48 samples) in Japan (Environment Agency Japan, 1996). No information was provided on proximity to sources of DMF, sediment characteristics, or hydrological regimes. In addition, because information on sampling and analytical methods was not provided, the quality of these data cannot be assessed. In 24 sediment samples collected in 1978 at unspecified locations in Japan, levels were below the detection limits of 0.1–0.3 mg/kg (Environment Agency Japan, 1985).

6.1.3 Soil and groundwater

In 3 of 23 groundwater samples collected in the USA, concentrations ranged from 0.05 to 0.2 mg/litre, with an average value of 0.117 mg/litre (Syracuse Research Corporation, 1988).[1]

6.2 Human exposure

6.2.1 Drinking-water

Although DMF was listed as a contaminant in a survey of drinking-water in the USA, quantitative data were not reported (Howard, 1993).

6.2.2 Food

Data on concentrations of DMF in foods were not identified.

6.2.3 Multimedia study

A Health Canada-sponsored multimedia exposure study for DMF and other volatile organic compounds was conducted in 50 homes in the Greater Toronto Area in Ontario, Nova Scotia, and Alberta (Conor Pacific Environmental, 1998). DMF was not detected in indoor air samples from the 50 residences (detection limit 3.4 µg/m^3). It was also not detected in tap water samples, although the limit of detection was high (0.34 µg/ml). DMF was not recovered reproducibly in composite food or beverage samples in this study.

6.2.4 Exposure of the general population

Identified data on concentrations of DMF in environmental media in Canada were insufficient to allow estimates of population exposure to be developed; for water, either quantitative data on concentrations are unreliable[4] or DMF has not been detected, using analytical methodology with poor sensitivity (Conor Pacific Environmental, 1998).

Non-pesticidal use of DMF in Canada is small and restricted primarily to industrial applications. Most DMF released into the environment in Canada during such use is emitted to air. Most DMF remains in the medium of release prior to degradation. Therefore, the greatest potential for exposure of the general population to DMF

[1] Group STORET search on DMF, obtained from J. Boyd, US EPA (storet@epamail.eap.gov), on 30 July 1999.

[2] Also technical note sent from R. Beauchamp, Health Canada, to A. Chevrier, Environment Canada, 1998.

[3] Also collection of notes and modelling results submitted by A. Bobra, AMBEC Environmental Consultant, to Chemicals Evaluation Division, Commercial Chemicals Evaluation Branch, Environment Canada, 1999.

[4] Technical notes regarding data from Environmental Monitoring and Reporting Branch, Ontario Ministry of Environment and Energy, sent to J. Sealy, Health Canada, 1996.

from non-pesticidal sources is in air in the vicinity of industrial point sources.

Based upon dispersion modelling of releases in Canada from the highest emitter over a 1-km radius, 100 m in height, the estimated ambient concentration is 110 µg/m^3. Although this value is comparable to levels measured under similar conditions in other countries, it is based on very conservative assumptions; taking into account more likely conditions, including some loss due to advection, estimated concentrations would be 10- to 100-fold less (i.e., 11 or 1.1 µg/m^3).

Based on lack of detection in a multimedia study, levels of DMF in indoor air of 50 homes in Canada were less than 3.4 µg/m^3 (Conor Pacific Environmental, 1998).

6.2.5 Occupational exposure

Occupational exposure to DMF may occur in the production of the chemical itself, other organic chemicals, resins, fibres, coatings, inks, and adhesives (IARC, 1999). Exposure may also occur during use of these coatings, inks, and adhesives in the synthetic leather industry, in the tanning industry, and as a solvent in the repair of aircraft (Ducatman et al., 1986; IARC, 1989).

Based on data from the National Exposure Data Base, maintained by the United Kingdom Health and Safety Executive, concentrations of DMF in workplace air in the manufacture of textiles ranged from 0.1 to 10.5 ppm (0.3 to 7.5 mg/m^3) in 16 facilities.[1] For the six facilities where data were reported, the 8-h time-weighted average (TWA) concentration ranged from 4 to 12.4 ppm (12 to 37.2 mg/m^3). At six facilities where plastic was manufactured, concentrations ranged from 0.1 to 0.7 ppm (0.3 to 2.1 mg/m^3). At 11 facilities for plastics processing, the range of concentrations was from 4 to 44 ppm (12 to 132 mg/m^3); the range of 8-h threshold limit values (TLVs) at six of the facilities was 5–38 ppm (15–114 mg/m^3).

In the USA between 1981 and 1983, approximately 125 000 workers were potentially exposed to DMF, with 13 000 workers potentially exposed for more than 20 h/week (NIOSH, 1983).

[1] Data retrieval by J. Tickner from National Exposure Data Base, Health and Safety Executive (hse.gsi.gov.uk), 2000.

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Available data indicate that DMF is readily absorbed following oral, dermal, and inhalation exposure in both humans and animals. The rate of dermal absorption was estimated to be 57 mg/cm^2 per 8 h in a rat tail model. DMF is metabolized primarily in the liver and is relatively rapidly excreted as metabolites in urine, primarily as *N*-(hydroxymethyl)-*N*-methylformamide (HMMF).

7.1 Experimental animals

The major metabolic pathway for DMF in mammalian species is oxidation by the cytochrome P-450-dependent mixed-function oxidase system to HMMF (Figure 1). This can generate NMF and formaldehyde (see review by Gescher, 1993). Further cytochrome P-450-mediated oxidation of NMF and/or HMMF results in the formation of *S*-(*N*-methylcarbamoyl)glutathione (SMG), the conjugate of the presumed reactive (toxic) intermediate, methyl isocyanate, excreted *in vivo* as *N*-acetyl-*S*-(*N*-methylcarbamoyl)cysteine (AMCC). Results of studies with liver microsomes from acetone-treated rats (Mráz et al., 1993; Chieli et al., 1995) and mice (Chieli et al., 1995) and with reconstituted enzyme systems indicate that cytochrome P-450 2E1 mediates the metabolism of DMF to HMMF and, subsequently, to the proposed reactive intermediate, methyl isocyanate.

The most informative of the toxicokinetic and metabolic studies relevant to consideration of interspecies and dose-related variations in toxicokinetics and metabolism include investigations following oral administration to rats and inhalation exposure of rats, mice, and monkeys.[2]

In female Sprague-Dawley rats administered a single oral dose of 100 mg ^{14}C-labelled DMF/kg body weight on day 12 or 18 of pregnancy, 60–70% of the radioactivity was excreted in urine and 3–4% in faeces at 48 h (Saillenfait et al., 1997). Approximately 4% of the dose was present in the liver at 0.5 h after dosing at both gestation times, with 8 and 13% in the gastrointestinal tract (stomach and intestine) and 0.7 and 0.8% in

[2] In early studies, HMMF was not reported, since it degraded to NMF thermolytically in GLC conditions; hence, in early investigations, NMF = HMMF + NMF. HMMF is stable in aqueous solutions of neutral or mildly acidic pH but undergoes thermal decomposition to NMF during routine GC analysis. Therefore, it was first identified as NMF.

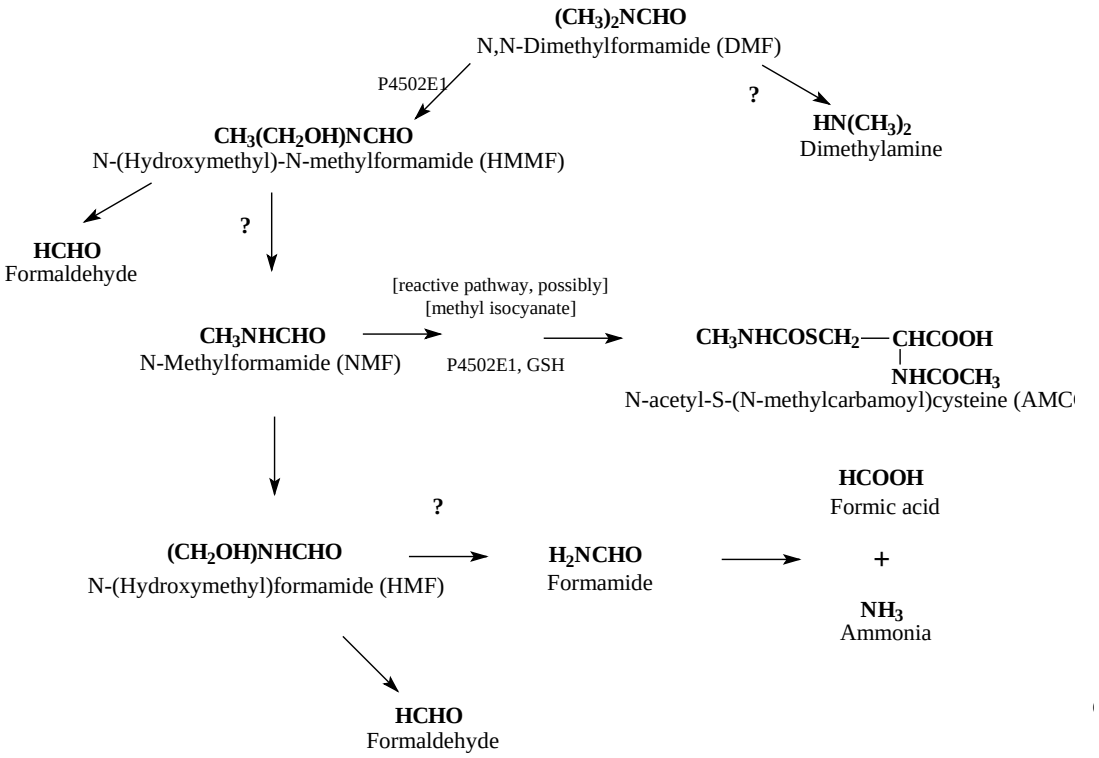

Fig. 1. Biotransformation of DMF (adapted from WHO, 1991; Gescher, 1993).

the kidneys, respectively. Plasma radioactivity was relatively constant from 0.5 to 4 h after dosing (approximately 0.4–0.5% of the dose) but declined rapidly thereafter. By 48 h, only the liver (0.5 and 0.6%) and intestine (0.2 and 0.3%) retained any significant activity. In animals exposed on day 12 of gestation, approximately 1.5% of the dose was present in the uterus, placenta, embryo, and amniotic fluid at between 0.5 and 4 h, which rapidly declined to less than 0.1% at 24 h. In rats exposed on day 18 of gestation, fetal tissues accounted for 6% of the administered dose. HPLC analysis performed at intervals from 1 to 24 h indicated that unchanged DMF and metabolites were readily transferred to the embryonic and fetal tissues, where levels were generally equal to those in maternal plasma. The parent compound accounted for most of the radioactivity until 4–8 h and then decreased.

Levels of parent compound and metabolites were determined in the plasma, amniotic fluid, placenta, and embryo in this investigation. Unchanged DMF initially accounted for the major proportion of radiolabelled carbon in the plasma or tissues, 61–77% for the first 4 h and 73–93% for the first 8 h after treatment on days 12 and 18, respectively. The decline in DMF levels corresponded with an increase in the levels of HMMF and NMF. HMMF accounted for 40–47% of ^{14}C at 8 h (day 12) and for 41–55% at 16 h (day 18). The equivalent figures for NMF were 9–13% and 16–18%, respectively. The amounts of AMCC and formamide in plasma or tissues were <4% of total radioactivity at all time points (Saillenfait et al., 1997). Other investigators have reported that DMF also crosses the placenta of pregnant rats after inhalation exposure (Sheveleva et al., 1977; Shumilina, 1991).

In another of the few recent investigations, levels of DMF, NMF, and HMMF were determined in the blood and urine of B6C3F1 mice and Crl:CD BR rats exposed to 10, 250, or 500 ppm (30, 750, or 1500 mg/m^3) for either single exposures of 1, 3, or 6 h or for 6 h/day, 5 days/week, for 2 weeks (Hundley et al., 1993a). The values for area under the plasma concentration curve (AUC) for DMF increased disproportionately in comparison with exposure, following single 6-h exposures to 250 and 500 ppm (750 and 1500 mg/m^3) (8- and 28-fold for rats and mice, respectively), while levels of NMF in the blood did not increase, which the authors considered to be indicative of saturation of metabolism of DMF. In contrast, multiple exposures increased the capacity of both rats and mice to metabolize DMF; repeated exposures to 500 ppm (1500 mg/m^3) resulted in a 3- and 18-fold reduction in AUC values for rats and mice, respectively. Peak plasma levels for NMF were elevated. HMMF represented over 90% of the total of DMF and determined metabolites.

In a similar investigation, DMF, NMF, and HMMF in blood and urine were determined in male and female cynomolgus monkeys exposed to 30, 100, or 500 ppm (90, 300, or 1500 mg/m^3) for 6 h/day, 5 days/week, for 13 weeks (Hundley et al., 1993b). The values for the AUC increased disproportionally between 100 and 500 ppm (300 and 1500 mg/m^3) (19- to 37-fold in males and 35- to 54-fold in females), data consistent with saturation of metabolism. However, there was no corresponding decrease in NMF levels; rather, they increased proportionally with increases in exposure concentrations. For each concentration, AUC values, peak plasma concentration, and plasma half-lives were consistent throughout the duration of exposure. HMMF was the main urinary metabolite (56–95%), regardless of exposure level or duration of exposure. DMF was not readily excreted in the urine, and NMF was more prevalent in plasma than in urine, suggesting that it was metabolized to compounds not determined in the study.

In comparative analyses of the two studies, the authors indicated that toxicokinetic differences may, in part, contribute to the observed species differences in toxicity. The AUC values and peak plasma levels for DMF for rats and mice following a single 500 ppm (1500 mg/m^3) exposure are substantially greater than the respective values in monkeys following a similar exposure. Whereas repeated exposures to 500 ppm (1500 mg/m^3) in rats and mice enhanced metabolism, as indicated by diminished AUC values for DMF and increased plasma concentrations of NMF, this effect was not clearly demonstrated in monkeys.

Results of the more recent study in rats were qualitatively similar to earlier investigations in which plasma DMF and "NMF" levels were determined in the plasma of rats exposed to DMF by inhalation for single 3- or 6-h exposures (Kimmerle & Eben, 1975a; Lundberg et al., 1983). Results of several of these earlier studies were also suggestive that at very high concentrations, DMF inhibits its own biotransformation. For example, 3 h following a single 4-h inhalation exposure of rats to 1690 or 6700 mg/m^3, levels of NMF in blood were lower in the higher exposure group (Lundberg et al., 1983). Similarly, Kimmerle & Eben (1975a) reported lower concentrations of NMF in the blood of rats exposed to 6015 mg/m^3 for 3 h than in rats exposed to 513 mg/m^3 for 6 h.

In a number of early studies, the effects of co-administration of ethanol on blood concentrations of DMF, NMF, ethanol, and acetaldehyde were investigated. Although there were variations in results depending on dose, time interval between administration of DMF and ethanol, and routes of exposure, there were increases in concentrations of DMF, NMF, ethanol, or acetaldehyde in blood upon co-exposure. These results may be attributable to inhibition by DMF of the activity of alcohol dehydrogenase observed both *in vitro* and *in vivo* (Eben & Kimmerle, 1976; Hanasono et al., 1977; Sharkawi, 1979) and of aldehyde dehydrogenase observed *in vivo* (Elovaara et al., 1983).

7.2 Humans

7.2.1 Studies in human volunteers

There were a number of early investigations in which the parent compound and some metabolites (not including that of the putatively toxic pathway) in blood and urine were determined in volunteers following short-term exposure to DMF (26 or 87 ppm [78 or 261 mg/m^3] for 4 h or 4 h/day for 5 days) (Kimmerle & Eben, 1975b). Results of these investigations indicated that DMF was rapidly excreted (the majority in 24 h), primarily as HMMF. Results of an additional early study in volunteers indicated that co-exposure to ethanol had a "slight influence" on the metabolism of DMF in volunteers receiving 19 g of ethanol 10 min prior to exposure to 82 ppm (246 mg/m^3) DMF for 2 h, based on lower concentrations of NMF in blood upon co-exposure. Contrary to the results in animals, there were no significant differences in the blood levels of ethanol and acetaldehyde upon co-exposure, which the authors attributed to the relatively low concentrations of DMF (Eben & Kimmerle, 1976).

In a recent study in which the product of the putatively toxic pathway of metabolism (AMCC) was determined, 10 volunteers were exposed to 10, 30, or 60 mg DMF/m^3, for either single 8-h exposures or five daily exposures of 30 mg/m^3 (Mráz & Nohová, 1992a, 1992b). Urine was collected for 5 days and analysed for DMF, HMMF, HMF, and AMCC. In a separate protocol, three volunteers ingested 20 mg AMCC dissolved in water, and metabolites were determined for a period of 8 h after exposure. After single exposure to 30 mg/m^3, the proportions of metabolites eliminated in the urine were 0.3% parent compound, 22.3% HMMF, 13.2% HMF, and 13.4% AMCC. The half-times of excretion for these various metabolites were approximately 2, 4, 7, and 23 h, respectively. In contrast to this slow elimination after exposure to DMF, AMCC was rapidly eliminated after ingestion of AMCC, with a half-time of 1 h. These results were considered to be consistent with rate-limiting reversible protein binding of a reactive metabolic intermediate of DMF, possibly methyl isocyanate. Following repeated exposures, AMCC accumulated in urine. Although quantitative data were not presented, urinary elimination 16 h following the fifth exposure was approximately 14% HMMF, 32% HMF, and 54% AMCC.

7.2.2 Occupational environment

Exposure in the occupational environment may occur through both the dermal and inhalation routes. Lauwerys et al. (1980) reported that dermal absorption was more important than inhalation in the overall exposure, in the absence of personal protective devices.

There have been a number of reports of levels of DMF and metabolites in the blood and/or urine of workers. With the exception of more recent studies involving personal air sampling (Wrbitzky & Angerer, 1998),[1] few provide reliable quantitative data on relationship with exposure, though still not accounting for additional dermal exposure. Results of such studies have confirmed, however, the presence of AMCC (the product of the putatively toxic metabolic pathway) in the urine of workers.

Wrbitzky & Angerer (1998) noted a weak association between the concentration of DMF in workplace air and urinary concentration of NMF. Kawai et al. (1992) considered the relationship to be linear. In 116 workers exposed to TWA concentrations of 0.2, 0.4, 0.6, 3.9, or 9.1 ppm (0.6, 1.2, 1.8, 11.7, or 27.3 mg/m^3), the corresponding concentrations of NMF in urine were 0.7, 0.9, 2.6, 7.8, and 19.7 mg/litre.

Mráz et al. (1989) reported the detection of HMMF in urine samples from 12 DMF-exposed workers (extent of exposure not specified). Casal Lareo & Perbellini (1995) reported that AMCC accumulated throughout the work week in the urine of workers exposed to approximately 3–8 ppm (9–24 mg/m^3). Sakai et al. (1995) reported that levels of urinary AMCC remained constant over consecutive work days and increased after the end of exposure, with the peak concentration observed at 16–40 h after the end of exposure. Kafferlein[1] reported that urinary NMF concentrations were highest in post-shift samples, with a median half-time of 5.1 h. Concentrations of urinary AMCC reached a steady state 2 days after the beginning of exposure, with a half-time greater than 16 h.

7.2.3 Other relevant data

Angerer et al. (1998) reported that haemoglobin from individuals occupationally exposed to DMF contained *N*-carbamoylated valine residues derived from methyl isocyanate, the likely precursor of AMCC. The metabolism of DMF to HMMF by human liver microsomes *in vitro* has also been demonstrated. The addition of an antibody against rat liver cytochrome P-450 2E1 to the incubation mixture strongly inhibited DMF metabolism (Mráz et al., 1993).

7.3 Interspecies comparisons

In one of the few identified studies in which the product of the putatively toxic metabolic pathway (i.e., AMCC) was determined in animal species, Mráz et al. (1989) reported data on metabolites of DMF (DMF, HMMF, "HMF," AMCC) in 72-h urine samples following intraperitoneal administration of 0.1, 0.7, or 7 mmol/kg body weight to mice, rats, and hamsters. In addition, 10 healthy volunteers (5 males, 5 females) were exposed for 8 h to 20 ppm (60 mg/m^3). (The mean of the amount of DMF absorbed via the lung was reported to be half of the lowest dose administered in rodents.) Urine was collected and analysed for the same metabolites at 2- to 8-h intervals for 8 h for 4–5 days. The proportion of the total metabolites eliminated as AMCC was greatest in the rat (1.7–5.2%) and less in the hamster (1.5–1.9%) and mouse (1.1–1.6%). In rats exposed to the highest dose, excretion of DMF metabolites (including AMCC) was delayed. There was no clear dose-related variation in proportion of the metabolites determined excreted as AMCC in the animal species. In humans, a greater proportion of the absorbed dose (14.5%) following

[1] Also written comments provided by H. Kafferlein, Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine, Friedrich-Alexander University Erlangen-Nuremberg, Germany, 2000.

inhalation was present as AMCC in the urine. Absorption through the skin was not taken into account.

8. EFFECTS ON LABORATORY MAMMALS AND *IN VITRO* TEST SYSTEMS

8.1 Single exposure

Following oral, dermal, inhalation, or parenteral administration, the acute toxicity of DMF in a number of species is low. Lethal doses are generally in the g/kg body weight range for oral, dermal, and parenteral routes and in the g/m^3 range for inhalation exposure. Clinical signs following acute exposure include general depression, anaesthesia, loss of appetite, loss of body weight, tremors, laboured breathing, convulsions, haemorrhage at nose and mouth, liver injury, and coma preceding death. Where protocols included histopathological examination, damage was observed primarily in the liver (WHO, 1991). In the rat, oral LD_{50}s range from 3000 to 7170 mg/kg body weight, dermal LD_{50}s range from 5000 to >11 520 mg/kg body weight, and inhalation LC_{50}s range from 9432 to 15 000 mg/m^3 (WHO, 1991).

8.2 Irritation and sensitization

Standard tests for dermal irritation by DMF have not been identified, and data on its sensitization potential are conflicting. Hence, only limited conclusions can be drawn concerning the potential of DMF to induce these effects.

IARC (1999), WHO (1991), and Kennedy (1986) reviewed the effects of DMF on the skin and eyes and reported only mild to moderate effects. A single application of neat DMF to the shaved skin of mice at 1–5 g/kg body weight (precise exposure conditions not specified) produced slight transient skin irritation at 2.5–5 g/kg body weight, while similar treatment of rabbits at up to 0.5 g/kg body weight was without effect (Kennedy, 1986; WHO, 1991). Repeated (15- or 28-day) applications of 1–2 g/kg body weight did not induce marked local effects on the skin of rats or rabbits. The instillation of neat or 50% aqueous DMF into the rabbit eye produced moderate corneal injury and moderate to severe conjunctivitis, with some damage still evident 14 days later (Kennedy, 1986; WHO, 1991; IARC, 1999).

In a murine local lymph node assay predictive for identification of contact allergens, cell proliferation (based on [^{3}H]thymidine incorporation in lymph nodes) was significantly increased (324 vs. 193 decompositions per minute per lymph node in exposed and control groups, respectively) in mice (strain not specified) receiving a daily topical application of 25 µl on the dorsum of both ears for 3 consecutive days (Montelius et al., 1996). In subsequent assays, thymidine incorporation in DMF-exposed mice was up to 3-fold higher than in naive mice. However, statistical analyses were not presented, and the increase was not considered to be significant (Montelius et al., 1998). The naive (non-treated) mice were included in the protocol to measure the magnitude of vehicle (DMF)-induced proliferation. In contrast, Kimber & Weisenberger (1989) detected no difference in proliferation in a lymph node assay in which lymph node cells from DMF (the solvent)-exposed mice were compared with those from naive mice.

8.3 Short-term exposure

While there have been a number of primarily early short-term studies, these have generally been restricted to examination of specific effects following exposure to single dose levels. They are not additionally informative concerning the toxicity of DMF but confirm a range of effects in the liver, which, when considered collectively across studies, are consistent with a profile in rats of alterations in hepatic enzymes and increases in liver weight at lowest concentrations and degenerative histopathological changes, cell death, and increases in serum hepatic enzymes at higher concentrations. Although results of a short-term study in monkeys also indicate that this species is less sensitive to the effects of DMF than rats, the protocol had only one exposure concentration, and there were only two monkeys in the experiment (Hurtt et al., 1991).

In the only short-term investigation in which a dose–response relationship for hepatic effects was characterized, there was a dose-related increase in liver to body weight ratio, significant at all levels of exposure, and in activity of uridine disphosphate glucuronosyltransferase in male Wistar rats exposed for 2 weeks via drinking-water to approximately 0, 14, 70, or 140 mg/kg body weight per day (Elovaara et al., 1983). Such changes have not been observed at such low doses in more recent, longer-term studies.

Available data from acute and short-term studies also indicate that there are effects on metabolizing enzymes at very high doses (i.e., 475 mg/kg body weight per day and above administered subcutaneously to rats). These include glutathione metabolism (although reported changes at two different doses were not

consistent) and decreases in hepatic microsomal P-450 content (Imazu et al., 1992, 1994; Fujishiro et al., 1996).

8.4 Medium-term exposure

Information on the incidences of lesions in the critical medium-term exposure studies is presented in Tables 2 and 3.

8.4.1 Inhalation

The NTP (1992a) carried out a subchronic bioassay in F344 rats, exposing males and females to 0, 50, 100, 200, 400, or 800 ppm (0, 150, 300, 600, 1200, or 2400 mg/m^3) for 6 h/day, 5 days/week, for 13 weeks. The authors designated 200 ppm (600 mg/m^3) as a no-observed-adverse-effect level (NOAEL) for both sexes, based upon the absence of histopathological lesions in liver. Minimal to moderate hepatocellular necrosis in both sexes was observed at 400 and 800 ppm (1200 and 2400 mg/m^3), with the lesion more severe in females. However, in males, both the absolute and relative weights of liver were significantly increased at 100 ppm (300 mg/m^3) and greater, although there was no clear dose–response, as weights declined at the highest dose. Serum cholesterol was increased at all levels of exposure; again, there was no clear dose–response. In males at day 24, there was a dose-related increase in serum alanine aminotransferase (ALT) (significant at all levels of exposure); however, at day 91, the increase was significant only at 400 ppm (1200 mg/m^3). At day 91, there was also a dose-related increase in serum sorbitol dehydrogenase in males (significant at 200 ppm [600 mg/m^3]). In females, relative liver weight was significantly increased at all levels of exposure, with the weight declining at the highest dose. Serum cholesterol was significantly increased at all levels of exposure in females, with no clear dose–response. At day 91 in females, serum sorbitol dehydrogenase and isocitrate dehydrogenase were significantly increased at 200 ppm (600 mg/m^3) and greater.

Craig et al. (1984) exposed male and female F344 rats to 0, 150, 300, 600, or 1200 ppm (0, 450, 900, 1800, or 3600 mg/m^3) for 6 h/day, 5 days/week, for 12 weeks. There were few overt signs of toxicity. Body weight was significantly decreased in both sexes at the highest dose. There were some changes in clinical chemistry and haematological parameters at the highest doses. In males, serum cholesterol was significantly increased at the highest concentration only. Serum alkaline phosphatase (AP) was reduced in a dose-related manner, beginning at 300 ppm (900 mg/m^3). In females, cholesterol was significantly increased at 600 and 1200 ppm (1800 and 3600 mg/m^3). In contrast to males, serum AP was increased in a dose-related manner (significant at the two highest concentrations). Data on organ weights were not presented. Histopathological changes were observed in the liver at the highest doses, were "barely discernible" at 300 ppm (900 mg/m^3), and were not observed at 150 ppm (450 mg/m^3). The lowest-observed-adverse-effect concentration (LOAEC) for both sexes is 300 ppm (900 mg/m^3), based upon slight histopathological changes in the liver (no-observed-effect concentration [NOEC] = 150 ppm [450 mg/m^3]).

B6C3F1 mice were exposed to 0, 50, 100, 200, 400, or 800 ppm (0, 150, 300, 600, 1200, or 2400 mg/m^3) for 6 h/day, 5 days/week, for 13 weeks (NTP, 1992a). Relative liver weight was significantly increased in both sexes at all levels of exposure, although the dose–response was not clear. Absolute liver weight was significantly increased in females at all dose levels, although the dose–response was not clear. Centrilobular hepatocellular hypertrophy (minimal to mild) was observed in all exposed males and in females at 100 ppm (300 mg/m^3) and higher (lowest-observed-effect concentration [LOEC] = 50 ppm [150 mg/m^3]).

Craig et al. (1984) exposed B6C3F1 mice to 0, 150, 300, 600, or 1200 ppm (0, 450, 900, 1800, or 300 mg/m^3) for 6 h/day, 5 days/week, for 12 weeks. Mortality was 10% at 600 ppm (1800 mg/m^3) and 40% at 1200 ppm (3600 mg/m^3). No adverse effects on haematology or clinical chemistry were observed. Hepatic cytomegaly was observed in all exposed mice; the incidence and severity were related to dose (LOEC = 150 ppm [450 mg/m^3]).

Hurtt et al. (1992) exposed three male and three female cynomolgus monkeys to 0, 30, 100, or 500 ppm (0, 90, 300, or 1500 mg/m^3) for 6 h/day, 5 days/week, for 13 weeks. Two males were maintained for a further 13-week observation period after exposure had ceased. The protocol included microscopic examination of a comprehensive range of organ tissues in all animals. Sperm morphology and vaginal cytology were also evaluated in all animals. There were no overt signs of toxicity and no effects on body weight gain, haematology, clinical chemistry, urinalysis, organ weights, or histopathological effects attributable to DMF in cynomolgus monkeys exposed to up to 500 ppm (1500 mg/m^3), leading the authors to conclude that the monkey is much less sensitive than the rat or mouse (Hurtt et al., 1992).

The other inhalation studies are either poorly reported or limited in their scope (Massmann, 1956; Clayton et al., 1963; Cai & Huang, 1979; Arena et al., 1982). One group of investigators reported effects on the

Table 2: Effect levels and benchmark concentrations for DMF, inhalation exposure.

Study (reference)	Effect level	Data for calculating benchmark concentration		Benchmark concentration		
		Concentration	Response	Parameter estimates[a,b]		Goodness of fit
Medium-term exposure						
B6C3F1 mice 10 males and 10 females per group 0, 50, 100, 200, 400, 800 ppm, 6 h/day, 5 days/week, for 13 weeks (NTP, 1992a)	LOEC = 50 ppm, based upon increased relative liver weight in both sexes and hepatocellular hypertrophy in males	Male, incidence (severity) of centrilobular hepatocellular hypertrophy: control 50 ppm 100 ppm 200 ppm 400 ppm 800 ppm	 0/10 4/10 (1.8) 9/10 (1.3) 10/10 (2.0) 10/10 (2.0) 10/10 (2.0)	BMC_{05} = 8.5 ppm excluding 400 and 800 ppm groups Adjusted BMC_{05} = 1.51 ppm	95% LCL_{05} = 2.5 ppm excluding 400 and 800 ppm groups Adjusted 95% LCL_{05} = 0.44 ppm	Chi-square (1) = 0.004 *P*-value = 0.99
		Female, incidence (severity) of centrilobular hepatocellular hypertrophy: control 50 ppm 100 ppm 200 ppm 400 ppm 800 ppm	 0/10 0/10 10/10 (1.3) 10/10 (1.9) 10/10 (2.0) 10/10 (2.0)	BMC_{05} = 17.9 ppm excluding 200, 400, and 800 ppm groups Adjusted BMC_{05} = 3.19 ppm excluding 200, 400, and 800 ppm groups	95% LCL_{05} = 8.1 ppm excluding 200, 400, and 800 ppm groups Adjusted 95% LCL_{05} = 1.45 ppm excluding 200, 400, and 800 ppm groups	Chi-square (1) = 7.5 *P*-value = 0.01
Long-term exposure/carcinogenicity assays						
Rat, Crl:CD BR 87 males and 87 females per group 0, 25, 100, 400 ppm, 6 h/day, 5 days/week, for 2 years (Malley et al., 1994)	LOEC = 100 ppm, based upon a significant increase in centrilobular hepatocellular hypertrophy (both sexes), hepatic accumulation of lipofuscin/haemosiderin (both sexes), and hepatic single-cell necrosis (females only) NOEC = 25 ppm	females, hepatic accumulation of lipofuscin/haemosiderin: control (*n* = 60) 25 ppm (*n* = 59) 100 ppm (*n* = 59) 400 ppm (*n* = 62)	 8% 7% 22% (*P* < 0.05) 61% (*P* < 0.05)	BMC_{05} = 37.0 ppm Adjusted BMC_{05} = 6.61 ppm	95% LCL_{05} = 19.8 ppm Adjusted 95% LCL_{05} = 3.54 ppm	Chi-square (1) = 1.01 *P*-value = 0.31
		males, hepatic accumulation of lipofuscin/haemosiderin: control (*n* = 57) 25 ppm (*n* = 59) 100 ppm (*n* = 58) 400 ppm (*n* = 60)	 4% 4% 17% (*P* < 0.05) 58% (*P* < 0.05)	BMC_{05} = 41.4 ppm Adjusted BMC_{05} = 7.39 ppm	95% LCL_{05} = 21.9 ppm Adjusted 95% LCL_{05} = 3.91 ppm	Chi-square (1) = 0.84 *P*-value = 0.36
		males, relative liver weight: control (*n* = 17) 25 ppm (*n* = 19) 100 ppm (*n* = 21) 400 ppm (*n* = 26)	 2.87 2.81 3.28 3.58 (*P* < 0.05)	BMC_{05} = 44.5 ppm Adjusted BMC_{05} = 7.95 ppm	95% LCL_{05} = 23.7 ppm Adjusted 95% LCL_{05} = 4.23 ppm	F(1,79) = 2.09 *P*-value = 0.15
		males, hepatic foci of alterations (clear cell): control (*n* = 57) 25 ppm (*n* = 59) 100 ppm (*n* = 58) 400 ppm (*n* = 60)	 11% 8% 22% (*P* < 0.05) 35% (*P* < 0.05)	BMC_{05} = 57.7 ppm Adjusted BMC_{05} = 10.3 ppm	95% LCL_{05} = 37.8 ppm Adjusted 95% LCL_{05} = 6.75 ppm	Chi-square (2) = 1.71 *P*-value = 0.42

Table 2 (contd).

Study (reference)	Effect level	Data for calculating benchmark concentration: Concentration	Response	Benchmark concentration: Parameter estimates[a,b]		Goodness of fit
		females, hepatic foci of alterations (clear cell):		BMC_{05} = 84.3 ppm Adjusted BMC_{05} = 15.1 ppm	95% LCL_{05} = 53.4 ppm Adjusted 95% LCL_{05} = 9.54 ppm	Chi-square (2) = 0.77 *P*-value = 0.68
		control (*n* = 60)	5%			
		25 ppm (*n* = 59)	5%			
		100 ppm (*n* = 59)	14%			
		400 ppm (*n* = 62)	24% (*P* < 0.05)			
Rat, Crl:CD BR 87 males and 87 females per group 0, 25, 100, 400 ppm, 6 h/day, 5 days/week, for 2 years (Malley et al., 1994)	LOEC = 100 ppm, based upon a significant increase in centrilobular hepatocellular hypertrophy (both sexes), hepatic accumulation of lipofuscin/haemosiderin (both sexes), and hepatic single-cell necrosis (females only) NOEC = 25 ppm	females, relative liver weight:		BMC_{05} = 101.6 ppm Adjusted BMC_{05} = 18.1 ppm	95% LCL_{05} = 46.2 ppm Adjusted 95% LCL_{05} = 8.25 ppm	F(1,67) = 1.12 *P*-value = 0.29
		control (*n* = 22)	3.12			
		25 ppm (*n* = 14)	3.43			
		100 ppm (*n* = 12)	3.33			
		400 ppm (*n* = 23)	3.86 (*P* < 0.05)			
		males, centrilobular hepatocellular hypertrophy:		BMC_{05} = 118.7 ppm Adjusted BMC_{05} = 21.2 ppm	95% LCL_{05} = 56.4 ppm Adjusted 95% LCL_{05} = 10.1 ppm	Chi-square (1) = 0.65 *P*-value = 0.42
		control (*n* = 57)	0			
		25 ppm (*n* = 59)	0			
		100 ppm (*n* = 58)	5% (*P* < 0.05)			
		400 ppm (*n* = 60)	30% (*P* < 0.05)			
		females, centrilobular hepatocellular hypertrophy:		BMC_{05} = 126.7 ppm Adjusted BMC_{05} = 22.6 ppm	95% LCL_{05} = 77.7 ppm Adjusted 95% LCL_{05} = 13.9 ppm	Chi-square (1) = 0.13 *P*-value = 0.72
		control (*n* = 60)	0			
		25 ppm (*n* = 59)	0			
		100 ppm (*n* = 59)	3% (*P* < 0.05)			
		400 ppm (*n* = 62)	40% (*P* < 0.05)			
		females, hepatic single-cell necrosis:		BMC_{05} = 126.9 ppm Adjusted BMC_{05} = 22.7 ppm	95% LCL_{05} = 72.9 ppm Adjusted 95% LCL_{05} = 13.0 ppm	Chi-square (1) = 0.78 *P*-value = 0.38
		control (*n* = 60)	0			
		25 ppm (*n* = 59)	0			
		100 ppm (*n* = 59)	5% (*P* < 0.05)			
		400 ppm (*n* = 62)	18% (*P* < 0.05)			
Mice, Crl:CD 1 (ICR)BR 78 males and 78 females per group 0, 25, 100, 400 ppm, 6 h/day, 5 days/week, for 18 months (Malley et al., 1994)	LOEC = 25 ppm, based upon centrilobular hepatocellular hypertrophy (males), hepatic single-cell necrosis (males and females), and hepatic Kupffer cell hyperplasia/pigment accumulation (males)	females, hepatic single-cell necrosis:		BMC_{05} = 16.8 ppm BMC_{05} = 5.9 ppm excluding 400 ppm group Adjusted BMC_{05} = 3.00 ppm BMC_{05} = 1.05 ppm excluding 400 ppm group	95% LCL_{05} = 11.9 ppm 95% LCL_{05} = 4.1 ppm excluding 400 ppm group Adjusted 95% LCL_{05} = 2.13 ppm 95% LCL_{05} = 0.73 ppm excluding 400 ppm group	Chi-square (2) = 9.7 *P*-value = 0.00 (Chi-square (1) = 0.02 *P*-value = 0.88)
		control (*n* = 61)	29%			
		25 ppm (*n* = 63)	44% (*P* < 0.05)			
		100 ppm (*n* = 61)	70% (*P* < 0.05)			
		400 ppm (*n* = 63)	76% (*P* < 0.05)			
		males, hepatic single-cell necrosis:		BMC_{05} = 10.8 ppm Adjusted BMC_{05} = 1.93 ppm	95% LCL_{05} = 7.8 ppm Adjusted 95% LCL_{05} = 1.39 ppm	Chi-square (2) = 13.4 *P*-value = 0.00
		control (*n* = 60)	24%			
		25 ppm (*n* = 62)	59% (*P* < 0.05)			
		100 ppm (*n* = 60)	68% (*P* < 0.05)			
		400 ppm (*n* = 59)	87% (*P* < 0.05)			
		males, hepatic Kupffer cell hyperplasia/pigment accumulation:		BMC_{05} = 11.1 ppm Adjusted BMC_{05} = 1.98 ppm	95% LCL_{05} = 8.2 ppm Adjusted 95% LCL_{05} = 1.46 ppm	Chi-square (2) = 7.5 *P*-value = 0.02
		control (*n* = 60)	22%			
		25 ppm (*n* = 62)	52% (*P* < 0.05)			
		100 ppm (*n* = 60)	60% (*P* < 0.05)			
		400 ppm (*n* = 59)	86% (*P* < 0.05)			

Table 2 (contd).

Study (reference)	Effect level	Data for calculating benchmark concentration		Benchmark concentration		
		Concentration	Response	Parameter estimates[a,b]		Goodness of fit
		females, hepatic Kupffer cell hyperplasia/pigment accumulation:		BMC_{05} = 13.4 ppm Adjusted BMC_{05} = 2.39 ppm	95% LCL_{05} = 9.3 ppm Adjusted 95% LCL_{05} = 1.66 ppm	Chi-square (2) = 0.35 *P*-value = 0.84
		control (*n* = 61)	51%			
		25 ppm (*n* = 63)	57%			
		100 ppm (*n* = 61)	71% (*P* < 0.05)			
		400 ppm (*n* = 63)	89% (*P* < 0.05)			
Mice, Crl:CD 1 (ICR)BR 78 males and 78 females per group 0, 25, 100, 400 ppm, 6 h/day, 5 days/week, for 18 months (Malley et al., 1994)	LOEC = 25 ppm, based upon centrilobular hepatocellular hypertrophy (males), hepatic single-cell necrosis (males and females), and hepatic Kupffer cell hyperplasia/pigment accumulation (males)	males, centrilobular hepatocellular hypertrophy:		BMC_{05} = 18.9 ppm Adjusted BMC_{05} = 3.38 ppm BMC_{05} = 2.93 ppm excluding 400 ppm group	95% LCL_{05} = 15.3 ppm Adjusted 95% LCL_{05} = 0.95 ppm 95% LCL_{05} = 1.48 ppm excluding 400 ppm group	Chi-square (2) = 0.77 *P*-value = 0.00 (Chi-square (0) = 0.00 *P*-value = 1.00)
		control (*n* = 60)	0			
		25 ppm (*n* = 62)	8% (*P* < 0.05)			
		100 ppm (*n* = 60)	41% (*P* < 0.05)			
		400 ppm (*n* = 59)	52% (*P* < 0.05)			
		females, centrilobular hepatocellular hypertrophy:		BMC_{05} = 25.1 ppm Adjusted BMC_{05} = 4.48 ppm	95% LCL_{05} = 19.9 ppm Adjusted 95% LCL_{05} = 3.55 ppm	Chi-square (2) = 0.39 *P*-value = 0.82
		control (*n* = 61)	0			
		25 ppm (*n* = 63)	6%			
		100 ppm (*n* = 61)	19% (*P* < 0.05)			
		400 ppm (*n* = 63)	54% (*P* < 0.05)			
		males, relative liver weight:		BMC_{05} = 65.6 ppm Adjusted BMC_{05} = 11.7 ppm	95% LCL_{05} = 37.5 ppm Adjusted 95% LCL_{05} = 6.69 ppm	F(1,143) = 1.94 *P*-value = 0.17
		control (*n* = 31)	5.85			
		25 ppm (*n* = 42)	5.94			
		100 ppm (*n* = 38)	7.06 (*P* < 0.05)			
		400 ppm (*n* = 36)	7.80 (*P* < 0.05)			
		females, relative liver weight:		BMC_{05} = 144.7 ppm Adjusted BMC_{05} = 25.8 ppm	95% LCL_{05} = 76.3 ppm Adjusted 95% LCL_{05} = 13.6 ppm	F(1,156) = 0.34 *P*-value = 0.56
		control (*n* = 42)	5.59			
		25 ppm (*n* = 35)	5.71			
		100 ppm (*n* = 36)	5.99			
		400 ppm (*n* = 47)	6.35 (*P* < 0.05)			

[a] Adjusted from intermittent exposure (h/day, days/week) to continuous exposure.
[b] LCL = Lower confidence limit.

Table 3: Effect levels and benchmark doses for DMF, oral exposure.

		Data for calculating benchmark dose		Benchmark dose		
Study (reference)	**Effect level**	**Dose (mg/kg body weight per day)**	**Response**	**Parameter estimates**		**Goodness of fit**
Medium-term exposure						
Rat, Wistar 25 males and 25 females per group Dietary administration for 15 weeks (Becci et al., 1983)	LOEL = 69 mg/kg body weight per day, based upon a significant increase in relative liver weight in females at the two highest doses (NOEL = 20 mg/kg body weight per day)	males, relative liver weight: control (*n* = 25) 18 (*n* = 23) 61 (*n* = 25) 210 (*n* = 23)	 4.30 ± 0.09 4.51 ± 0.11 4.59 ± 0.08 4.99 ± 0.10 (*P* < 0.05)	BMD_{05} = 23.1 mg/kg body weight per day	95% LCL_{05} = 12.7 mg/kg body weight per day	F(1,92) = 0.73 *P*-value = 0.39
		females, relative liver weight: control (*n* = 25) 20 (*n* = 25) 69 (*n* = 24) 235 (*n* = 24)	 86 ± 0.06 89 ± 0.08 24 ± 0.12 (*P* < 0.05) 00 ± 0.12 (*P* < 0.05)	BMD_{05} = 35.9 mg/kg body weight per day	95% LCL_{05} = 15.7 mg/kg body weight per day	F(1,94) = 0.13 *P*-value = 0.72
Mouse, CD-1 30 males and 30 females per group dietary administration for 17 weeks (Becci et al., 1983)	LOEL = 96 mg/kg body weight per day, based upon statistically significant increase in relative liver weight in females (NOEL = 28 mg/kg body weight per day)	males, relative liver weight: control (*n* = 30) 22 (*n* = 28) 70 (*n* = 29) 246 (*n* = 29)	 5.3 ± 0.1 5.6 ± 0.1 5.8 ± 0.1 6.6 ± 0.1 (*P* < 0.01)	BMD_{05} = 21.3 mg/kg body weight per day	95% LCL_{05} = 7.6 mg/kg body weight per day	F(1,112) = 1.17 *P*-value = 0.28
		females, relative liver weight: control (*n* = 30) 28 (*n* = 29) 96 (*n* = 29) 326 (*n* = 30)	 5.1 ± 0.2 5.5 ± 0.1 5.9 ± 0.1 (*P* < 0.01) 6.6 ± 0.3 (*P* < 0.01)	BMD_{05} = 36.8 mg/kg body weight per day	95% LCL_{05} = 21.3 mg/kg body weight per day	F(1,114) = 0.14 *P*-value = 0.71

liver of rats exposed to DMF vapour for 18 weeks at a concentration of just 7.3 ppm (21.9 mg/m^3) (no further details provided in the citation) (Cai & Huang, 1979). Myocardial changes occurred in rabbits exposed to 40 ppm (120 mg/m^3) for 50 days (Arena et al., 1982).

8.4.2 Oral

In a 90-day dietary study, Crl:CD rats were exposed to 0, 10, 50, or 250 mg/kg body weight per day (Haskell Laboratory, 1960; Kennedy & Sherman, 1986). Mild effects on the liver (enlargement of hepatic cells) and haematological effects (anaemia, leukocytosis) were observed at 50 mg/kg body weight per day; at the top dose of 250 mg/kg body weight per day, weight gain was reduced, and the animals had slight anaemia, leukocytosis, and liver cell enlargement. Although there was an apparent increase in serum cholesterol in both sexes at the highest dose, statistical analyses were not presented. The no-observed-effect level (NOEL) was 10 mg/kg body weight per day. The lowest-observed-effect level (LOEL) is 50 mg/kg body weight per day, based upon a significant increase in relative liver weight in males.

In a second study involving larger group sizes, a different strain (Wistar), and more comprehensive tissue examination, growth was inhibited but no tissue lesions were observed in rats administered DMF in the diet for 15 weeks (Becci et al., 1983). Males received 0, 18, 61, or 210 mg/kg body weight per day, and females received 0, 20, 69, or 235 mg/kg body weight per day. The LOEL is 69 mg/kg body weight per day, based upon a significant increase in relative liver weight in females at the two highest doses (NOEL = 20 mg/kg body weight per day).

In the corresponding study in CD-1 mice involving dietary administration (males: 0, 22, 70, or 246 mg/kg body weight per day; females: 0, 28, 96, or 326 mg/kg body weight per day) for 17 weeks, there were no overt signs of toxicity and no notable effects on blood morphology, blood biochemistry, or urinary parameters (Becci et al., 1983). Microscopic examination of an extensive range of organ tissues revealed only mild effects on the liver in the majority of high-dose males and females. There was a dose-related increase in relative liver weight at all dose levels, although this was statistically significant only in the mid- and high-dose females and in the high-dose males. On this basis, the LOEL is 96 mg/kg body weight per day, based upon a significant increase in relative liver weight in females (NOEL = 28 mg/kg body weight per day).

In a submission to the US EPA Office of Toxic Substances, BASF (1984) reported that there were no adverse effects observed in beagle dogs (four males and four females per group) administered 0, 1.4, 7.0, or 34.8 mg/kg body weight per day (NOEL) in the diet for 13 weeks. The protocol included measurement of food consumption, measurement of body weight gain, hearing tests, ophthalmoscopic examination, clinical laboratory investigations, measurement of organ weights, and histopathological observations.

8.5 Long-term exposure and carcinogenicity

Information on the incidences of lesions in critical long-term studies is presented in Tables 2 and 3.

8.5.1 Inhalation

Malley et al. (1994) exposed Crl:CD BR rats for 6 h/day, 5 days/week, to 0, 25, 100, or 400 ppm (0, 75, 300, or 1200 mg/m^3) DMF vapour for 24 months. There were no overt signs of toxicity other than a reduction in weight gain in the rats exposed at 400 ppm (1200 mg/m^3) and, to a lesser extent and towards the end of the study, in males exposed at 100 ppm (300 mg/m^3). Haematological findings were normal, as were urinary analyses. There was a concentration-related increase in serum sorbitol dehydrogenase activity (indicative of hepatic effects) in the male and female rats at 100 and 400 ppm (300 and 1200 mg/m^3). Relative liver weights were increased in both sexes at 400 ppm (1200 mg/m^3), and microscopic examination revealed hepatic lesions (centrilobular hepatocellular hypertrophy, lipofuscin/haemosiderin accumulation, clear cell foci, and single-cell necrosis in males and high-dose females and focal cystic degeneration in males) at 100 and 400 ppm (300 and 1200 mg/m^3). Microscopic examination of an extensive range of tissues from the high-dose animals (and of selected tissues from the lower dose groups) revealed no other treatment-related lesions except in females, in which there was an increased incidence of uterine endometrial stromal polyps (1.7%, 5.1%, 3.4%, and 14.8% for control, low-, mid-, and high-dose females, respectively). Historical control data from the same laboratory indicated a highly variable incidence of endometrial stromal polyps (2–15% for 14 control groups, average 6.6%). The investigators concluded that DMF was not carcinogenic to rats under the conditions of exposure. The LOEC was 100 ppm (300 mg/m^3) (NOEC = 25 ppm [75 mg/m^3]), based upon a significant increase in centrilobular hepatocellular hypertrophy (both sexes), significant increase in hepatic accumulation of lipofuscin/haemosiderin (both sexes), and hepatic single-cell necrosis (females only).

Mice [Crl:CD 1 (ICR)BR] were exposed to 0, 25, 100, or 400 ppm (0, 75, 300, or 1200 mg/m^3) DMF for 6 h/day, 5 days/week, for 18 months (Malley et al., 1994). Haematological observations were normal. Relative liver weight was significantly increased at the two highest concentrations in males. Microscopic alterations in liver were observed at all levels of exposure. The authors concluded that DMF was not carcinogenic to mice under the conditions of the bioassay. The LOEC is 25 ppm (75 mg/m^3), based upon centrilobular hepatocellular hypertrophy (males), hepatic single-cell necrosis (males and females), and hepatic Kupffer cell hyperplasia/pigment accumulation (males).

8.5.2 Oral

An inadequate carcinogenicity study involving the administration of DMF in the drinking-water of BD rats at approximately 10 or 20 mg/kg body weight per day for 500 or 250 days, respectively, provided no evidence of tumour formation, although the extent of tissue examination was not specified (Druckrey et al., 1967). In female Mongolian gerbils administered DMF in the drinking-water at concentrations of 1.0–6.6% (around 5–40 mg/kg body weight per day) for up to 200 days, there were many early deaths at concentrations of 1.7% (around 7–11 mg/kg body weight per day) and above, and all DMF-exposed groups had liver degeneration and kidney congestion (Llewellyn et al., 1974).

8.5.3 Injection

In a study in hamsters investigating the carcinogenic activity of aflatoxins, there was no mention of any tumours in the DMF-treated controls. These animals (five males and five females) received weekly intraperitoneal injections of 0.1 ml of a 50% DMF solution (equivalent to approximately 47 mg DMF/kg body weight per injection) for 6–8.5 months and were then maintained untreated until they died (average life span 19 months) (Herrold, 1969). Although there were no increases in tumours following repeated intraperitoneal injections of DMF to rats for 10 weeks in a study reported in a secondary source, available information was inadequate to permit critical review (Kommineni, 1973).

8.6 Genotoxicity and related end-points

The following discussion is limited to results of assays for gene mutation and cytogenesis, i.e., those assays in which the end-points are most relevant to the assessment of DMF with respect to human health.

The results of assays for gene mutation *in vitro* were almost entirely negative. Of 20 identified assays in *Salmonella*, results were negative in 18 (Green & Savage, 1978; Purchase et al., 1978; Baker & Bonin, 1981; Brooks & Dean, 1981; Garner et al., 1981; Gatehouse, 1981; Ichinotsubo et al., 1981; MacDonald, 1981; Martire et al., 1981; Nagao & Takahashi, 1981; Richold & Jones, 1981; Rowland & Severn, 1981; Simmon & Shepherd, 1981; Skopek et al., 1981; Venitt & Crofton-Sleigh, 1981; Antoine et al., 1983; Falck et al., 1985; Mortelmans et al., 1986), and two had equivocal results (Hubbard et al., 1981; Trueman, 1981). Results in six assays in *Escherichia coli* were all negative (Gatehouse, 1981; Matsushima et al., 1981; Mohn et al., 1981; Thomson, 1981; Venitt & Crofton-Sleigh, 1981; Falck et al., 1985).

Although fewer assays for cytogenetic effects and genotoxicity *in vitro* were identified than for gene mutation, results were also predominantly negative. In assays for chromosomal aberrations (CAs), results were negative for human lymphocytes (Antoine et al., 1983) and Chinese hamster ovary (CHO) (Natarajan & van Kesteren-van Leeuwen, 1981) and weakly positive in human peripheral lymphocytes (Koudela & Spazier, 1979). In three mouse lymphoma assays, results were negative (Jotz & Mitchell, 1981; Mitchell et al., 1988; Myhr & Caspary, 1988) and one was weakly positive (McGregor et al., 1988). Results of *in vitro* tests for sister chromatid exchange (SCE) were negative in three assays in CHO (Evans & Mitchell, 1981; Natarajan & van Kesteren-van Leeuwen, 1981; Perry & Thomson, 1981) and one in human lymphocytes (Antoine et al., 1983). Assays for unscheduled DNA synthesis (UDS) were negative in human fibroblasts (Agrelo & Amos, 1981; Robinson & Mitchell, 1981), mouse hepatocytes (Klaunig et al., 1984), and HeLa cells (Martin & McDermid, 1981), while in assays in rat hepatocytes, results were both negative (Ito, 1982) and positive (Williams, 1977). Results of assays for DNA repair in mouse (McQueen et al., 1983) and hamster (McQueen et al., 1983) hepatocytes were also negative. An assay for DNA repair in human hepatocytes had negative results (McQueen et al., 1988).

The database for genotoxicity studies *in vivo* is more limited than that for *in vitro* studies.

In two adequate assays for micronucleus induction, results were negative (Kirkhart, 1981; Antoine et al., 1983). In the latter study, dose levels were too widely spaced, and the top dose was 2000 mg/kg body weight. Results were also negative in two assays in which there were no positive controls (Salamone et al., 1981; Tsuchimoto & Matter, 1981). It should be noted that Salamone et al. (1981) observed no effect at doses up to 80% of the LD_{50}. An assay in which an increase in

micronuclei was observed in bone marrow of mice was reported only as an abstract (Ye, 1987), although a dose–response was not clear. Although six dose levels were included in the protocol, the highest dose was only 20 mg/kg body weight (oral LD_{50} values in laboratory animals range from 2000 to 7000 mg/kg body weight).

Negative results were reported in assays for chromosomal damage in bone marrow of rats (Sheveleva et al., 1979; McGregor, 1981) and dominant lethal assays in rats (Lewis et al., 1979; McGregor, 1981; Cragin et al., 1990). Limited reporting (abstracts, secondary sources) precluded critical review of these studies.

Quantitative data were not presented in a report of an assay in which SCEs were not observed in bone marrow of mice (Paika et al., 1981).

8.7 Reproductive toxicity

8.7.1 Effects on fertility

Effects on organ weights or histopathological effects in the reproductive organs have not been observed in medium-term or long-term studies in rats or mice following inhalation or oral exposure (Becci et al., 1983; Craig et al., 1984; Kennedy & Sherman, 1986; NTP, 1992a; Malley et al., 1994). In several of these bioassays, additional reproductive end-points were examined. These included sperm density, motility, or count and length of diestrus in rats and mice exposed for 13 weeks to concentrations up to 800 ppm (2400 mg/m^3) (NTP, 1992a) and semen volume and sperm motility, morphology, or count in a limited number of monkeys exposed to 500 ppm (1500 mg/m^3) (Hurtt et al., 1992). In none of these investigations, however, were there adverse effects on reproductive parameters at concentrations or doses less than those at which hepatic effects were observed; indeed, the only effect reported was prolonged diestrus in female rats exposed to 800 ppm (2400 mg/m^3) for 13 weeks (NTP, 1992a).

Few studies were identified in which the protocols were designed specifically to address reproductive toxicity. In a study reported as abstracts (Lewis et al., 1979; Cragin et al., 1990), exposure of male Sprague-Dawley rats to 30 or 300 ppm (90 or 900 mg/m^3) for 6 h/day for 5 days did not result in histopathological changes in reproductive organs after 6 weeks. Pairing of the exposed males with unexposed females for 6 weeks after exposure resulted in a reduced number of viable fetuses per dam in the low-dose group only.

In a multi-generation study in Swiss mice, DMF was administered in the drinking-water at concentrations of 0, 1000, 4000, or 7000 mg/litre (NTP, 1992b; Fail et al., 1998). Litters from F0 animals were sacrificed immediately. At week 16, pairs were separated and the final litters reared to postnatal day 21, then entered into an F1 fertility assessment. A crossover mating trial was also carried out with the F0 mice. The lowest level of exposure (1000 mg/litre; average 219 mg/kg body weight per day) was designated by the authors as the maximum tolerated dose (LOEL) for the F0 mice, based upon increased relative liver weight in males and females and increased relative kidney and adrenal weight in females. Reproductive effects in F0 mice included reduced fertility and fecundity at 4000 and 7000 mg/litre. The crossover trial identified females as the affected sex. Following F1 mating, both F2 litter size and live pup weight were reduced at all doses. At necropsy, the body weight of F1 males and females was reduced at the two highest doses, and both absolute and relative liver weights were increased at all doses. The authors concluded that both reproductive and developmental toxicity occurred at the two highest doses (4000 and 7000 mg/litre) in the F0 mice and at all dose levels ($\$$1000 mg/litre) in the F1 mice.

No abnormalities were observed in sperm in an adequate single-injection study in mice, for which few details were presented (Antoine et al., 1983). Although negative results were reported in other assays in mice, quantitative data were not presented (Topham, 1980, 1981) or only a secondary source was available (McGregor, 1981).

8.7.2 Developmental toxicity

The database on developmental toxicity is more extensive, with numerous studies having been conducted in various species by the inhalation, oral, and dermal routes. Emphasis here is on the most recent studies for which protocols and reporting are most extensive.

In studies in which DMF has been administered by inhalation or ingestion, it has been, at most, weakly teratogenic, with malformations being observed only at high doses that were maternally toxic (450 ppm [1350 mg/m^3] by inhalation in rabbits; 503 mg/kg body weight per day following ingestion in rats), based on consideration of maternal body weight and signs of overt toxicity (Hellwig et al., 1991). In general, DMF has induced primarily fetotoxic effects most often at maternally toxic concentrations or doses (100 mg/kg body weight per day by stomach tube in rats) (Saillenfait et al., 1997) but occasionally in the absence of maternal toxicity, based on determination of body weight gain and overt signs. For example, Lewis et al. (1992) reported maternal weight gain in Crl:CD rats at 300 ppm (900

mg/m^3) (maternal LOEC), but not at 30 ppm (90 mg/m^3), at which concentration there was a slight but significant reduction in fetal weight. The mean fetal weights of control, low-dose, and high-dose groups were 5.5 ± 0.2, 5.5 ± 0.4, and 5.3 ± 0.2 g, respectively ($P < 0.05$ for both low- and high-dose groups).

The pattern of results of studies by the dermal route was similar, with malformations being observed in rats only at doses that were maternally toxic based on examination of weight gain and overt signs of toxicity only (944 mg/kg body weight per day in rats; 400 mg/kg body weight per day in rabbits; 944 mg/kg body weight per day in mice) (Hellwig et al., 1991). In one of the relatively recent investigations by other authors (Hansen & Meyer, 1990), fetotoxic effects (delayed ossification) only were observed at doses (945 mg/kg body weight per day) at which there were no effects on maternal weight gain and no overt signs of maternal toxicity.

Klug et al. (1998) carried out a mouse limb bud assay with DMF, HMMF, NMF, SMG (a synthesis product of glutathione and methyl isocyanate), *S*-(*N*-methyl-carbamoyl)cysteine (SMC), *N*-acetoximethyl-*N*-methylformamide (AMMF), AMCC, L-cysteine, and glutathione. There were no signs of adverse developmental effects caused by DMF, NMF, HMMF, AMMF, L-cysteine, or glutathione. However, a pronounced impact upon growth and development was observed for AMCC, SMC, and SMG (metabolites resulting from the glutathione binding pathway). The authors concluded that the developmental toxicity of DMF in different species is related to the magnitude of glutathione binding.

8.8 Neurological effects

In male Wistar rats exposed to 0, 7, 35, or 65 mg DMF/kg body weight per day in drinking-water for either 2 or 7 weeks, glial cell fractions were isolated from the left cerebral hemisphere and assayed for activity of acid proteinase and 2',3'-cyclic nucleotide 3'-phosphohydrolase (Savolainen, 1981). The right cerebral hemisphere was assayed for RNA, glutathione, and activities of succinate dehydrogenase and azoreductase. After 2 weeks, there was a dose-related increase in activity of 2',3'-cyclic nucleotide 3'-phosphohydrolase, which was significant ($P < 0.001$) at all levels of exposure. After 7 weeks of exposure to 0, 8, 39, or 75 mg/kg body weight per day, the intake of drinking-water was significantly reduced at all levels of exposure. There was also a significant reduction in activity of azoreductase and succinate dehydrogenase (uneven dose–response).

9. EFFECTS ON HUMANS

Consistent with the results of studies in experimental animals, available data from case reports and cross-sectional studies in occupationally exposed populations consistently indicate that the liver is the target organ for the toxicity of DMF in humans. The profile of effects is consistent with that observed in experimental animals, with related symptoms, increases in serum hepatic enzymes, and histopathological effects being reported.

9.1 Effects on the liver

Case reports in workers acutely exposed to DMF confirm that the liver is the target organ, with hepatic effects and associated disorders of the digestive system being reported. Symptoms include abdominal pain, anorexia, incoordination, and jaundice, as well as nausea, vomiting, and diarrhoea; nasal and skin irritation have also been reported (Tolot et al., 1968; Potter, 1973; Chary, 1974; Chivers, 1978; Guirguis, 1981; Paoletti et al., 1982a, 1982b; Riachi et al., 1993; Drouet D'Aubigny et al., 1998; Huang et al., 1998). Changes in both liver function (Weiss, 1971; Potter, 1973; Guirguis, 1981; Paoletti et al., 1982b; Riachi et al., 1993; Drouet D'Aubigny et al., 1998) and morphology (Tolot et al., 1968; Riachi et al., 1993) have also been observed. In one of the few reports where there was some indication of magnitude of exposure, hepatic impairment (marked increases in serum levels of ALT, aspartate aminotransferase [AST], AP, and bilirubin, together with fulminant hepatitis and jaundice) was reported in a woman who ingested about 0.6 g DMF/kg body weight (in a formulation containing other ingredients) in a suicide attempt (Nicolas et al., 1990). Similarly, clinical measurements were carried out in a patient who intravenously injected (presumably) 50 ml of a veterinary euthanasia drug containing DMF as a solvent (Buylaert et al., 1996). Serum AST and ALT increased, there was a transient rise in total serum bilirubin, and prothrombin time decreased. AP levels remained within the normal range.

Alcohol intolerance, characterized by flushing of the face, dizziness, nausea, and tightness of the chest, has been widely reported among DMF-exposed workers (Lyle, 1979; Lyle et al., 1979; Lauwerys et al., 1980; Yonemoto & Suzuki, 1980; Paoletti & Iannaccone, 1982; Paoletti et al., 1982a; Tomasini et al., 1983; Cirla et al., 1984; Redlich et al., 1988, 1990; Wang et al., 1989, 1991; Cai et al., 1992; Fiorita et al., 1997; Wrbitzky, 1999). While it is difficult to establish with

Table 4: Effects of DMF exposure on hepatic function in humans.[a]

Concentration[b]	Effect on liver enzymes	Exposed population	Confounders	Reference
<10–60 ppm; random area sampling	increase	183 workers	some workers were also exposed to solvents	Wang et al. (1989, 1991)
10–42 ppm; area monitoring	increase	13 workers	few details reported	Yang et al. (1994)
1–27 ppm	no effect	27 workers		Paoletti & Iannaconne (1982)
5–20 ppm	increase (significance not reported)	13 workers	exposure to solvents	Tomasini et al. (1983)
3–20 ppm (TWA, 7 ppm); personal sampling	significant increase	100 workers		Cirla et al. (1984)
0.3–15.5 ppm (usually <10 ppm); static area sampling	no effect	22 workers		Lauwerys et al. (1980)
1–5 ppm; personal and area sampling	no effect	6 workers		Yonemoto & Suzuki (1980)
4–8 ppm (mean 6 ppm); sampling not specified	no effect	28 workers		Catenacci et al. (1984)
0.2–8 ppm; area sampling	increase (significance not reported)	26 workers	concomitant exposure to acrylonitrile	Major et al. (1998)
7 ppm; area sampling at different workplaces	significant increase	75 workers		Fiorito et al. (1997)
0.1–7 ppm; personal sampling	no effect	207 workers	some workers were also exposed to toluene	Cai et al. (1992)
up to 2.3 ppm; personal sampling	no effect	126 workers		Wrbitzky & Angerer (1998); Wrbitzky (1999)

[a] See text for more detailed descriptions of highlighted studies.
[b] 1 ppm = 3 mg/m^3.

any certainty a lowest concentration at which increases in these subjective symptoms first appear, they have been associated with mean or median levels of 10 ppm (30 mg/m^3) (Lauwerys et al., 1980; Yonemoto & Suzuki, 1980; Cai et al., 1992; Fiorito et al., 1997); in a recent study, some workers reported symptoms upon exposure to concentrations for which the median value was as low as 1.2 ppm (3.6 mg/m^3) (Wrbitzky, 1999).

Levels of serum hepatic enzymes in populations occupationally exposed to DMF have been determined in several cross-sectional studies. A brief overview of the information on exposure–response derived from these studies is summarized in Table 4.

While there have been considerable variations in the size of study populations, magnitude and duration of exposure, extent of exposure to other substances, and adequacy of reporting in these investigations, there is a consistent pattern of increase in serum enzymes in workers with relatively higher exposures in these investigations, some of which included individual monitoring. In summary, the results concerning exposure–response are consistent across studies, with increases in serum hepatic enzymes not being observed at concentrations in the range of 1–6 ppm (3–18 mg/m^3). At higher levels of exposure (>7 ppm [>21 mg/m^3]), increased serum levels of hepatic enzymes have been observed consistently.

There were three studies identified (highlighted in Table 4) for which TWA exposures were presented and which can serve, therefore, as the basis for at least crude estimates of exposure–response. These are described in more detail here. It should be noted, though, that the monitored levels in these studies do not take into account potential additional dermal exposure.

In a carefully conducted investigation of liver function in 75 workers in a synthetic leather factory, geometric mean levels of DMF in the air based on 8-h area sampling in various working locations were approximately 20 mg/m^3 (~7 ppm) (range 2–40 mg/m^3) (Fiorito et al., 1997). It was reported that the study subjects worked in a factory that produces synthetic leather using polyurethane resin, pigments, and large amounts of DMF (about 14 tonnes/day), where skin contact with liquid DMF was also possible. The mean duration of employment was 3.8 years. The control group consisted of 75 unexposed workers similar in age, sex, social status, and residence. Confounding by

alcohol consumption and pre-existing liver disease was minimized through selection criteria for study subjects. Analysis of paired enzymes was also conducted. All workers underwent a complete physical examination, with liver function tests for serum AST, ALT, (-glutamyl transpeptidase ((-GT), AP, bile acids (BA), bilirubin, serum cholesterol and triglycerides, and markers for hepatitis A, B, and C. Gastrointestinal symptoms (stomach pain, nausea, appetite loss) were reported by 50% of the DMF-exposed workers, and 40% had symptoms such as face flushing, palpitation, headache, dizziness, or tremors following alcohol consumption. (Many avoided alcohol as a result.) Mean serum ALT (28.8 vs. 21.9 IU/litre), AST (26.5 vs. 21.1 IU/litre), (-GT (29.5 vs. 14.2 IU/litre), and AP (75.7 vs. 60.8 IU/litre) were significantly higher in 12 of 75 workers in the exposed group ($P < 0.001$); 17/75 (23%) had abnormal liver function, compared with only 4% of controls. Multivariate analyses confirmed that ALT, AST, and (-GT were significantly correlated with cumulative DMF exposure. The analyses controlled for factors such as body mass index, alcohol intake, serum cholesterol, and hepatitis markers, which did not explain the observed effects.

Catenacci et al. (1984) investigated liver function (serum glutamate–oxalate transaminase [SGOT], serum glutamate–pyruvate transaminase [SGPT], (-GT, and AP) in workers employed for at least 5 years in an acrylic fibre plant; no mention was made of exposure to other solvents. The first group of 28 subjects worked in the spinning department, where DMF exposure (8-h TWA) ranged from 12 to 25 mg/m^3, with a mean of 18 mg/m^3 (4–8 ppm, mean 6 ppm). The second group consisted of 26 subjects exposed, in the polymer department, to DMF at (8-h TWA) 1.8–5 mg/m^3, with a mean of 3 mg/m^3 (0.6–1.8 ppm, mean 1 ppm). A control group consisted of 54 subjects matched for age, smoking/alcohol consumption, and history of liver disease, who had never been occupationally exposed to solvents. The data on which the estimated TWA exposures were based were not reported. Mean serum values for SGOT (20.74, 21.06, and 20.17 mU/ml for 6 ppm, 1 ppm, and control groups, respectively), SGPT (19.76, 21.26, and 26.09 mU/ml for 6 ppm, 1 ppm, and control groups, respectively), (-GT (36.37, 28.34, and 40.76 mU/ml for 6 ppm, 1 ppm, and control groups, respectively), and AP (154.42, 150.35, and 153.07 mU/ml for 6 ppm, 1 ppm, and control groups, respectively) did not differ among the three groups and were within the normal ranges. Few additional details were presented in the published account of this study.

Cirla et al. (1984) carried out a clinical evaluation of 100 workers in synthetic polyurethane leather production exposed to a mean TWA concentration (determined by personal sampling) of 22 mg/m^3 (range 8–58 mg/m^3) (mean TWA 7 ppm; range 3–19 ppm). The mean exposure period was 5 years (range 1–15 years). The workers were also exposed to small (but unspecified) quantities of toluene, methyl ethyl ketone (MEK), ethyl acetate, and isopropyl and isobutyl alcohol. Study subjects were selected to minimize large variations in exposure; those with histories of possible accidental exposures were also excluded. The referent group was 100 workers at the same or similar factories, without exposure to any solvents or toxic metals, matched by sex, age group, alcohol history, smoking habits, coffee intake, socioeconomic status, residence, and dietary customs. Clinical evaluation was carried out and a laboratory assessment was performed for blood cell counts and serum AP, AST, ALT, and (-GT. Serum (-GT was abnormally high in 25/100 exposed and only 10/100 referents ($P < 0.01$). Higher prevalences in the exposed group for abnormally high serum levels of AST (9 vs. 3) and ALT (12 vs. 8) were not statistically significant. AP values were normal in all subjects. When subjects who had not modified their alcohol consumption upon working with DMF were considered, the effect was still evident. Several symptoms, including headache, dyspepsia, and digestive impairment, characteristic of effects on the liver were also associated with exposure to DMF.

Histopathological changes in liver have also been reported in occupationally exposed workers, although quantitative data on levels of exposure are not well documented. Tomasini et al. (1983) reported hepatic pain and palpable liver in 4 of 13 workers exposed to 5–20 ppm (15–60 mg/m^3) DMF (and other solvents), ranging from a few weeks to 4 years. Redlich et al. (1990) carried out biopsies of liver from workers heavily exposed to DMF (and other solvents; quantitative data not reported). Workers exposed for less than 3 months had hepatocellular necrosis, enlarged Kupffer cells, microvesicular steatosis, complex lysosomes, and pleomorphic mitochondria. The livers of workers exposed for longer terms (14–120 months) had fatty changes with occasional lipogranuloma.

9.2 Cardiac effects

Excess mortality from ischaemic heart disease in DMF-exposed workers in a US acrylonitrile fibre plant was observed in a historical cohort study (Chen et al., 1988b). Between 1950 and 1982, there were 62 deaths due to ischaemic heart disease (40.3 expected from company rates; $P < 0.01$). The increase was not significant in comparison with the state (South Carolina) rates. A similar observation was made for a second group of 1329 employees at the plant who were potentially exposed to

both DMF and acrylonitrile (65 deaths observed, 48.3 expected from company rates; $P < 0.05$). However, the observed number of deaths was not significantly higher than that which would be expected from either state or national rates, possibly due to a "healthy worker effect." Lifestyle factors such as alcohol and tobacco consumption were suggested to be more likely causes than exposure to DMF, although the specific basis for this contention was not specified (Chen et al., 1988b). The authors noted that South Carolina has a higher ischaemic heart disease mortality rate than the USA.

No convincing evidence of adverse effects on cardiac function was seen in a limited study in which electrocardiographic (ECG) monitoring was carried out on workers at a small synthetic leather plant where DMF was used. Monitoring of eight workers over a workshift revealed possible mild effects (isolated ventricular premature beats after 2 h of work, without "pathological alteration" of the ECG) in one worker (Taccola et al., 1981). In a brief report, ECG changes in workers exposed to DMF were reported (<3 ppm [<9 mg/m^3], with peaks up to 1500 ppm [4500 mg/m^3], plus skin exposure), but little detail was provided (Kang-De & Hui-Lan, 1981).

Cardiac disturbances, including tachycardia and palpitations, have occasionally been observed in cross-sectional studies of DMF-exposed workers (Lyle, 1979; Lyle et al., 1979; Kang-De & Hui-Lan, 1981; Cirla et al., 1984; Fiorito et al., 1997). Sometimes, the palpitations followed alcohol ingestion (Lyle, 1979; Lyle et al., 1979; Fiorito et al., 1997).

9.3 Cancer

Data on the incidence or mortality of cancer associated with exposure to DMF are limited to case reports of testicular tumours and single well conducted and reported cohort and case–control studies of occupationally exposed populations (Chen et al., 1988a; Walrath et al., 1989). In the cohort study of 3859 actively employed workers with potential exposure to DMF and to DMF and acrylonitrile in an acrylonitrile fibre production facility, the incidences of cancer of the buccal cavity/pharynx, lung, prostate, stomach, nervous system, and bladder were considered in relation to level of and, for some tumours, duration of exposure and were compared with company and national rates. Level of exposure was classified as low (approximately <10 ppm (<30 mg/m^3)), moderate (sometimes above 10 ppm [30 mg/m^3]), or high, although quantitative data were not reported (Chen et al., 1988a). In an additional case–control study, cancers of the buccal cavity/pharynx (n = 39), liver (n = 6), prostate (n = 43), and testis (n = 11) and malignant melanoma of the skin (n = 39) were examined in approximately 8700 workers from four plants, which included a DMF production plant, two acrylic fibre plants that used DMF as a spinning solvent, and a plant using the chemical as a solvent for inks (Walrath et al., 1989).

Three cases of testicular germ cell tumours that occurred during 1981–1983 among 153 white men who repaired the exterior surfaces and electrical components of F4 Phantom jets in the USA were reported by Ducatman et al. (1986), which led to surveys of two other repair shops at different locations, one in which F4 Phantom jets were repaired and one where other types of aircraft were repaired. Four of 680 workers in the F4 Phantom shop had testicular germ cell cancers (approximately one expected) diagnosed during 1970–1983. No cases were reported in the other facility. All seven men had long histories in aircraft repair; although there were many common exposures to solvents in the three facilities, the only one identified as unique to the F4 Phantom jet aircraft repair facilities was to a solvent mixture containing 80% DMF (20% unspecified). Three of the cases had been exposed to this mixture with certainty, and three had probably been exposed. Of the seven cases, five were seminomas and two were embryonal cell carcinomas.

Levin et al. (1987) and Frumin et al. (1989) reported three cases of embryonal cell carcinoma of the testis in workers at one leather tannery in the USA, where it was reported that DMF as well as a wide range of dyes and solvents were used, including such testicular toxins as 2-ethoxyethanol and 2-ethoxyethanol acetate. The latency period ranged from 8 to 14 years. No additional cancers were reported in a screening effort undertaken to identify additional testicular cancers in 51 of the 83 workers at the leather tannery where the three cases were reported (Calvert et al., 1990).

In an investigation of cancer incidence at a plant producing acrylonitrile fibres, compared with company and national rates, there was no increase in the incidence of testicular cancer in 2530 actively employed workers exposed to DMF only. When the data from this cohort were grouped with data from 1329 workers exposed to both DMF and acrylonitrile, there was only one case of testicular cancer, versus 1.7 expected (confidence interval [CI] not reported) (Chen et al., 1988a).

There was no increase in cancer of testis (odds ratio = 0.91; 95% CI = 0.1–8.6; observed number of cases = 11) in the case–control study described above in which the cases were drawn from a population of

approximately 8700 workers involved in production or use of DMF at four plants (Walrath et al., 1989, 1990). For each case, two controls were selected, matched for age, sex, payroll class, and plant. Potential exposure to DMF was classified as low or moderate based on job title/work area combinations and monitoring data.

Chen et al. (1988a) observed a significant increase in prostate cancer (10 observed vs. 5.1 expected from company rates and 5.2 expected from national rates; $P < 0.10$ for both comparisons) in the 3859 workers exposed either to DMF or to both DMF and acrylonitrile. However, when only DMF-exposed workers (2530) were considered, the standardized incidence rate (SIR) (4 observed vs. 2.4 expected from company rates) was not significant. The odds ratio for prostate cancer in the case–control study of the 8700 DMF-exposed workers from four plants was not significantly elevated (1.48; 95% CI = 0.59–3.74; 43 cases) (Walrath et al., 1989, 1990). When analyses were carried out separately for each of the four plants, an increased incidence was observed only at one plant, where the exposure to DMF was lower and the number of cases was fewer than at the other plants. Adjustment for assumed latency period did not alter the odds ratio. There was no relationship with duration of exposure.

Chen et al. (1988a) also reported a significant increase of cancer of the buccal cavity/pharynx (9 observed vs. 1.6 expected from company rates; $P < 0.10$) in the 2530 DMF-exposed workers (confidence intervals not reported). When combined with data from 1329 workers exposed to both DMF and acrylonitrile, the increase (11 observed) was significant when compared with the company rate (3.2 expected; $P < 0.01$), but not compared with the national rate (6.6 expected). There was no relation to either level or duration of exposure. All cases were heavy, long-term smokers. There was no increase in risk of cancer of the buccal cavity/pharynx in the case–control study of workers at the four plants mentioned above (odds ratio = 0.89; 90% CI = 0.35–2.29; 39 cases) (Walrath et al., 1989, 1990).

9.4 Genotoxicity

Seven studies were identified in which the genotoxicity of DMF in humans has been examined. Four of these studies were critically reviewed by IARC (1999) and were described therein as follows.

Berger et al. (1985) reported that the prevalence of CAs was higher in the blood lymphocytes of 20 workers exposed to DMF, NMF, and dimethylamine than in 18 unexposed workers at the same factory (1.4% vs. 0.4%; statistical significance not provided). The mean concentrations 1 year prior to blood sampling were 12.3 mg/m^3 for DMF, 5.3 mg/m^3 for NMF, and 0.63 mg/m^3 for dimethylamine. However, the control group had an unusually low level of chromosome breaks. The IARC Working Group noted that the possible effect of smoking was not addressed.

A higher incidence of CAs was observed in the lymphocytes of about 40 workers exposed to DMF than in an unspecified control group (2.74–3.82% vs. 1.10–1.61%; $P < 0.05$). The range of exposure to DMF was 150–180 mg/m^3. Workers were also exposed to trace amounts of MEK, butyl acetate, toluene, cyclohexanone, and xylene. After technological improvements designed to reduce DMF exposure levels (range 35–50 mg/m^3), the frequency of aberrant cells decreased to 1.49–1.59% (Koudela & Spazier, 1981).

Although Sram et al. (1985) reported in an abstract that there was no evidence of increased frequency of CA in peripheral lymphocytes in workers exposed to DMF, no details were provided.

Seiji et al. (1992) reported that the mean SCE rate was higher in the blood cells of 22 women exposed to three concentrations of DMF (0.3–5.8 ppm [0.9–17.4 mg/m^3]) in a leather production factory than in 22 unexposed controls from the same factory, matched by sex, age, and residence. None of the women smoked tobacco or drank alcohol. The incidence of SCEs was significantly increased in a dose-related manner in the mid- and high-exposure groups.

Based on review of these studies, IARC (1999) concluded that "The positive data for cytogenetic damage in humans occupationally exposed to it are not very convincing."

Three relevant reports, including one for which only an abstract was identified in which few details were provided (Haber et al., 1990), were identified in addition to those reviewed by IARC (1999). The two investigations for which reporting was adequate are described here.

Major et al. (1998) reported that for workers with 3–10 years of occupational exposure to undefined levels of DMF and/or acrylonitrile, the prevalence of peripheral lymphocytes with CAs was increased compared with unexposed controls (see below). After a further 7 months of exposure (to DMF at 0.2–8 ppm [0.6–24 mg/m^3] and to acrylonitrile at 0–17.6 mg/m^3), the incidence in the exposed group increased to 5.1% but did not increase further up to 20 months. The incidence of SCEs was also

higher than control values at the start of the 20-month study and remained higher at 7 and 20 months. The UDS level was similar to that in controls when the study started, but had increased in the exposed group by month 7. In addition to concomitant exposure to acrylonitrile, current smoking was also a confounding factor, with CA and SCE yields being significantly higher in exposed smokers than in exposed non-smokers. Nevertheless, CA yields at 7 months were significantly higher in exposed non-smokers than in control non-smokers and in exposed smokers than in control smokers.

Cheng et al. (1999) measured SCE frequency in peripheral lymphocytes of workers at a resin synthesis plant. Nine workers had low exposure (median 5.2 ppm [15.6 mg/m^3]; range 0.9–5.3 ppm [2.7–15.9 mg/m^3]), and 20 workers had high exposure (median 24.8 ppm (74.4 mg/m^3); range 11.4–83.3 ppm [34.2–249.9 mg/m^3]). There were no differences between the two groups; there was no additional control population.

Results of studies on genotoxicity conducted since the IARC evaluation have not contributed materially to the database, which was considered by IARC (1999) not to provide convincing evidence. Certainly, the results, when taken as a whole, are inconsistent and not readily explained by variations in exposure.

10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

DMF has been the focus of several toxicity studies conducted on a range of species. The most sensitive end-points for terrestrial and aquatic organisms are presented below and are summarized in Table 5.

10.1 Aquatic environment

A number of studies are available for a range of taxa, including protozoa, blue-green algae, diatoms, green algae, macrophytes, molluscs, oligochaetes, crustaceans, insect larvae, and fish.

For four species of fish, EC_{50} and LC_{50} values ranged from approximately 7100 to 12 000 mg/litre (Batchelder, 1976; Johnson & Finley, 1980; Call et al., 1983; Poirier et al., 1986; Groth et al., 1994). The most sensitive fish species appears to be the bluegill (*Lepomis macrochirus*), with an LC_{50} of 7100–7500 mg/litre.

Aquatic invertebrates tested include the water flea (*Daphnia magna*) and various species of insect larvae. The water flea appears to be the most sensitive invertebrate, with a NOEL of 1140 mg/litre. Acute end-points (EC_{50} and LC_{50}) for *Daphnia magna* range from 12 400 to 15 700 mg/litre, whereas chronic studies provide end-points for mortality between 1140 and 3721 mg/litre (Call et al., 1983; Leblanc & Surprenant, 1983; Adams & Heidolph, 1985; Poirier et al., 1986; Ziegenfuss et al., 1986; Sebaugh et al., 1991). The 48-h LC_{50}s obtained for various species of insect larvae were much higher and ranged from 33 500 to 36 200 mg/litre (Call et al., 1983; Poirier et al., 1986; Ziegenfuss et al., 1986).

The most sensitive alga appears to be *Selenastrum capricornutum*, with a 14-day NOEC value for growth inhibition of 480 mg/litre (Hughes & Vilkas, 1983). Results for two other green algae range from 8900 to 10 000 mg/litre (Stratton & Smith, 1988; El Jay, 1996). Peterson et al. (1997) obtained an IC_{25} for growth inhibition of 6200 mg/litre for the diatom *Nitzschia* sp. In the same study, blue-green algae appeared to be the least sensitive, with IC_{25}s for growth inhibition ranging from 7000 to 15 100 mg/litre for three tested species (Peterson et al., 1997), a finding that differs from earlier data (Stratton, 1987). Because of the high degree of quality assurance/quality control associated with the Peterson et al. (1997) study, these data are considered as definitive levels of toxicity to blue-green algae.

Rajini et al. (1989) measured the lethal response of the ciliated protozoan *Paramecium caudatum* to acute (10-min and 4-h) exposures to DMF. The 4-h LC_{50} was found to be 20 465 mg/litre. A recent paper reports EC_{50}s of 8190–9870 mg/litre for deformations and LC_{50}s of 19 700–31 700 mg/litre for the protozoan *Spirostomum ambiguum* (Nalecz-Jawecki & Sawicki, 1999).

Marine organisms tested include the bacteria *Vibrio fischeri*, the common shrimp (*Crangon crangon*), and a fish, the winter flounder (*Pleuronectes americanus*). For the decrease in luminescence in *Vibrio fischeri*, the 5-min EC_{50} value of 20 000 mg/litre (Curtis et al., 1982) is in the same order of magnitude as the values (13 260–14 830 mg/litre) obtained by Harwood[1] with a 15-min exposure. IC_{25} values calculated by Harwood[1] with the same data set range from 5830 to 6730 mg/litre.

[1] Personal communications from M. Harwood, Environment Canada, to A. Chevrier, Environment Canada, dated 2 and 5 December 1997.

Table 5: Toxicity of DMF to various organisms.

Test species	Latin name	End-point	Range	References
Bacteria	*Vibrio fischeri*	5-min EC_{50} light production	20 000 mg/litre	Curtis et al. (1982)
Bacteria	*Vibrio fischeri*	15-min IC_{50} light inhibition 15-min IC_{25} light inhibition	13 260–14 830 mg/litre 5830–6730 mg/litre	Harwood[a]
Protozoan	*Paramecium caudatum*	4-h LC_{50} mortality	20 465 mg/litre	Rajini et al. (1989)
Protozoan	*Spirostomum ambiguum*	24-h EC_{50} deformations 24-h LC_{50} mortality 48-h EC_{50} deformations 48-h LC_{50} mortality	9870 mg/litre 31 700 mg/litre 8190 mg/litre 19 700 mg/litre	Nalecz-Jawecki & Sawicki (1999)
Blue-green algae	*Nostoc* sp.	10- to 14-day EC_{50} growth inhibition test	<480 mg/litre	Stratton (1987)
Blue-green algae	*Anabaena* sp.	10- to 14-day EC_{50} growth inhibition test	<480 mg/litre	Stratton (1987)
Blue-green algae	*Anabaena cylindrica*	10- to 14-day EC_{50} growth inhibition test	<480 mg/litre	Stratton (1987)
Blue-green algae	*Anabaena variabilis*	10- to 14-day EC_{50} growth inhibition test	<480 mg/litre	Stratton (1987)
Blue-green algae	*Anabaena inaequalis*	10- to 14-day EC_{50} growth inhibition test	5700 mg/litre	Stratton (1987)
Blue-green algae	*Anabaena flos-aquae*	48-h IC_{25} growth inhibition	15 100 mg/litre	Peterson et al. (1997)
Blue-green algae	*Microcystis aeruginosa*	48-h IC_{25} growth inhibition	7000 mg/litre	Peterson et al. (1997)
Blue-green algae	*Oscillatoria* sp.	48-h IC_{25} growth inhibition	10 400 mg/litre	Peterson et al. (1997)
Diatom	*Nitzschia* sp.	48-h IC_{25} growth inhibition	6200 mg/litre	Peterson et al (1997)
Green algae	*Selenastrum capricornutum*	48-h IC_{25} growth inhibition	7700 mg/litre	Peterson et al. (1997)
Green algae	*Selenastrum capricornutum*	72-h IC_{25} growth as cell numbers	3420–6280 mg/litre	Harwood[a]
Green algae	*Selenastrum capricornutum*	growth at day 4	inhibition at 5000 mg/litre	El Jay (1996)
Green algae	*Selenastrum capricornutum*	growth inhibition NOEC	480 mg/litre	Hughes & Vilkas (1983)
Green algae	*Selenastrum capricornutum*	growth at day 4	stimulation at 1000 mg/litre	El Jay (1996)
Green algae	*Chlorella vulgaris*	growth at day 4	inhibition at 10 000 mg/litre	El Jay (1996)
Green algae	*Chlorella vulgaris*	growth at day 4	stimulation at 1000 mg/litre	El Jay (1996)
Green algae	*Chlorella pyrenoidosa*	10- to 14-day EC_{50} reduction in growth	8900 mg/litre	Stratton & Smith (1988)
Duckweed	*Lemna minor*	7-day IC_{25} growth inhibition	4900 mg/litre	Peterson et al. (1997)
Water flea	*Daphnia magna*	acute 48-h EC_{50} immobilization	14 500 mg/litre	Poirier et al. (1986)
Water flea	*Daphnia magna*	acute 48-h EC_{50} survival and mortality	15 700 mg/litre	Adams & Heidolph (1985)
Water flea	*Daphnia magna*	acute 48-h LC_{50} mortality	14 400 mg/litre	Ziegenfuss et al. (1986)
Water flea	*Daphnia magna*	acute 48-h LC_{50} mortality	14 530 mg/litre	Call et al. (1983)
Water flea	*Daphnia magna*	acute 48-h EC_{50} immobilization	13 100 mg/litre	Sebaugh et al. (1991)

Table 5 (contd).

Test species	Latin name	End-point	Range	References
Water flea	*Daphnia magna*	chronic 21-day EC_{50} survival and mortality	3721 mg/litre	Adams & Heidolph (1985)
Water flea	*Daphnia magna*	chronic 21-day NOEL/LOEC survival and mortality	1500–3000 mg/litre	Adams & Heidolph (1985)
Water flea	*Daphnia magna*	chronic 28-day NOEL survival and mortality	1140 mg/litre	Leblanc & Surprenant (1983)
Water flea	*Daphnia magna*	acute 48-h EC_{50} survival and mortality	12 400 mg/litre	Leblanc & Surprenant (1983)
Insect larvae	*Paratanytarsus parthenogeneticus*	48-h EC_{50}	36 200 mg/litre	Poirier et al. (1986)
Insect larvae	*Tanytarsus dissimilis*	48-h LC_{50}	36 000 mg/litre	Call et al. (1983)
Insect larvae	*Chironomus tentans*	acute 48-h LC_{50} mortality	33 500 mg/litre	Ziegenfuss et al. (1986)
Shrimp	*Crangon crangon*	LC_{50}	>100 mg/litre	Portmann & Wilson (1971)
Rainbow trout	*Oncorhynchus mykiss*	acute 96-h LC_{50} mortality	9800–12 000 mg/litre	Johnson & Finley (1980); Call et al. (1983); Poirier et al. (1986)
Winter flounder	*Pleuronectes americanus*	inhibition of the enzyme activity in intestinal mucosae	50 000 mg/litre	Janicki & Kinter (1971)
Zebrafish	*Brachydanio rerio*	acute 96-h LC_{50} mortality	8840 mg/litre	Groth et al. (1994)
Fathead minnow	*Pimephales promelas*	acute 96-h LC_{50} mortality	9080–11 400 mg/litre	Batchelder (1976); Call et al. (1983); Poirier et al. (1986)
Bluegill	*Lepomis macrochirus*	acute 96-h LC_{50} mortality	7100–7500 mg/litre	Call et al. (1983); Poirier et al. (1986)
Soil fungi	*Sclerotinia homeocarpa*	EC_{50} inhibition of fungal growth, compared with a control growth of 50–70 mm	4840 mg/litre	Stratton (1985)
Soil fungi	*Pythium ultimum*	EC_{50} inhibition of fungal growth, compared with a control growth of 50–70 mm	10 250 mg/litre	Stratton (1985)
Soil fungi	*Pestalotia* sp.	EC_{50} inhibition of fungal growth, compared with a control growth of 50–70 mm	5970 mg/litre	Stratton (1985)
Wheat and bean seeds		inhibition of germination	50 000 mg/litre	Szabo (1972)
Rat		2-year inhalational NOEL, 6 h/day, 5 days/week exposure changes in body weight and clinical chemistry parameters	75 mg/m^3	Malley et al. (1994)

[a] Personal communications from M. Harwood, Environment Canada, to A. Chevrier, Environment Canada, dated 2 and 5 December 1997.

Portmann & Wilson (1971) reported an LC_{50} of >100 mg/litre for *Crangon crangon*.

10.2 Terrestrial environment

There is little information available on the toxicity of DMF to terrestrial vascular plants. Szabo (1972) reported that DMF did not inhibit germination of wheat and bean seeds at 1% (approximately 10 000 mg/litre), but did at 5% (approximately 50 000 mg/litre); however, little methodological information is provided with which to assess the quality of the data. The IC_{25} of 4900 mg/litre for the duckweed (*Lemna minor*), an aquatic angiosperm, indicates that terrestrial angiosperms may not be sensitive to DMF (Peterson et al., 1997). The most sensitive organism in the terrestrial

compartment appears to be the soil fungus *Sclerotinia homeocarpa*, with an EC_{50} of 4840 mg/litre for growth inhibition (Stratton, 1985).

Although information on effects of DMF on wild-life has not been identified, a review of laboratory studies on experimental animals (WHO, 1991) concludes that acute toxicity of DMF in a variety of species is low. Only one chronic (2-year) inhalation assay was identified in recent literature (Malley et al., 1994). In that study, a LOEC of 25 ppm (75 mg/m^3) following inhalation of DMF was reported, based on changes in body weight and clinical chemistry.

11. EFFECTS EVALUATION

11.1 Evaluation of health effects

11.1.1 Hazard identification and dose–response assessment

11.1.1.1 Effects in humans

Consistent with the results of studies in experimental animals, available data from case reports and cross-sectional studies in occupationally exposed populations indicate that the liver is the target organ for the toxicity of DMF in humans. The profile of effects is consistent with that observed in experimental animals, with gastrointestinal disturbance, alcohol intolerance, increases in serum hepatic enzymes (AST, ALT, (-GT, and AP), and histopathological effects (hepatocellular necrosis, enlarged Kupffer cells, microvesicular steatosis, complex lysosomes, pleomorphic mitochondria, and fatty changes with occasional lipogranuloma) being observed. Effects observed at lowest concentrations in cross-sectional studies in occupationally exposed populations for which there is some information on dose–response are increases in serum hepatic enzymes.

Based on the limited data available, there is no convincing, consistent evidence of increased risk of cancer at any site associated with exposure to DMF in the occupational environment. Case reports of testicular cancers have not been confirmed in a cohort and case–control study. There have been no consistent increases in tumours at other sites associated with exposure to DMF.

There is also little consistent, convincing evidence of genotoxicity in populations occupationally exposed to DMF, with results of available studies of exposed workers (to DMF and other compounds) being mixed. The pattern of observations is not consistent with variations in exposure across studies. However, in view of the positive dose–response relationship observed in the one study in which it was investigated, this area may be worthy of additional work, although available data on genotoxicity in experimental systems are overwhelmingly negative.

11.1.1.2 Effects in experimental animals

DMF has low acute toxicity and is slightly to moderately irritating to the eyes and skin, based on limited data acquired in non-standard assays. Available data are inadequate as a basis for characterization of the potential of DMF to induce sensitization. In acute and repeated-dose toxicity studies, DMF has been consistently hepatotoxic, inducing effects on the liver at lowest concentrations or doses. The profile of effects includes alterations in hepatic enzymes, increases in liver weight, progressive degenerative histopathological changes and eventually cell death, and increases in serum hepatic enzymes. Species variation in sensitivity to these effects has been observed, with the order of sensitivity being mice > rats > monkeys.

Although the database for carcinogenicity is limited to two adequately conducted bioassays in rats and mice, there have been no increases in the incidence of tumours following chronic inhalation exposure to DMF. The weight of evidence for genotoxicity is overwhelmingly negative, based on extensive investigation in *in vitro* assays, particularly for gene mutation, and a more limited database *in vivo.*

DMF has induced adverse reproductive effects only at concentrations considerably greater than those associated with adverse effects on the liver. In adequately conducted and reported primarily recent developmental studies, fetotoxic and teratogenic effects have been consistently observed only at maternally toxic concentrations or doses.

Available data are inadequate as a basis for assessment of the neurological, immunological, or skin sensitizing effects of DMF.

The following guidance is provided as a possible basis for derivation of limits of exposure and judgement of the quality of environmental media by relevant authorities.

11.1.2 Criteria for setting tolerable concentrations or guidance values

In both humans and experimental animals exposed to DMF, the target organ has been the liver, consistent with local action of a reactive intermediate in the tissue where it is primarily metabolized. Available data indicate that there are considerable variations between experimental animals and humans in the proportion of

DMF metabolized by the putatively toxic pathway, with the resulting implication that humans may be more sensitive to the effects of DMF. Also, since there are data available to serve as the basis for at least crude characterization of exposure–response for parameters associated with hepatic toxicity in workers, the tolerable concentration (TC) is based on data on inhalation in humans, although it should be noted that these values do not account for likely additional exposure by dermal absorption. Analyses of dose–response for hepatic effects in the studies in experimental animals are presented for comparison. Since exposure in the general environment is likely to be primarily through air, emphasis in this section is on the generally more extensive database on toxicity by the inhalation route.

Effects on the liver observed at lowest concentration in cross-sectional studies in occupationally exposed populations for which there is some information on exposure–response are increases in serum hepatic enzymes. The results concerning exposure–response are consistent across studies, with increases in serum hepatic enzymes not being observed at concentrations in the range of 1–6 ppm (3–18 mg/m^3). At higher levels of exposure (>7 ppm [>21 mg/m^3]), increased serum levels of hepatic enzymes have been observed consistently. Cirla et al. (1984) reported significant increases in serum (-GT in 100 workers exposed to 7 ppm (21 mg/m^3). Similarly, Fiorito et al. (1997) reported significant increases in serum ALT, AST, (-GT, and AP in workers exposed to 7 ppm (21 mg/m^3).

Catenacci et al. (1984) did not observe differences between serum levels of SGOT, SGPT, and (-GT in workers employed for more than 5 years. In view of the small number of subjects exposed to the mean TWA of 6 ppm (18 mg/m^3) DMF (n = 28), negative results reported therein may be a function of lack of power of the study to detect a meaningful effect and are not, therefore, necessarily inconsistent with the results of Cirla et al. (1984) and Fiorito et al. (1997).

Based on the lowest-observed-adverse-effect level (LOAEL) of 7 ppm (21 mg/m^3), a TC[1] has been derived as follows:

$$TC = \frac{7\text{ppm}}{50} \times 8/24 \times 5/7$$

= 0.03 ppm (0.1 mg/m^3)

where:

- 7 ppm (21 mg/m^3) is the LOAEL for increases in serum hepatic enzymes in workers exposed primarily to DMF, reported by Cirla et al. (1984) and Fiorito et al. (1997); it should be noted that the observed small increases in a few serum hepatic enzymes are considered to be only minimally adverse, with associated hepatic damage likely being reversible upon cessation of exposure;
- 8/24 and 5/7 are the factors to convert exposure during 8 h/day and 5 days/week, respectively, to continuous exposure;
- 50 is the uncertainty factor (×10 for intraspecies [interindividual][2] variation, including sensitive subgroups; ×5 to account primarily for less than lifetime exposure; although the TC is based on a LOAEL, observed effects are considered to be only minimally adverse).

Although not the basis of the TC developed here, there are several important observations from dose–response analyses of the results of the studies in animals (see Appendix 4). The lowest reported benchmarks for a range of hepatic effects in rats and mice following inhalation are those for histopathological lesions in the liver of both rats and mice, which are higher but in the same range as those reported to induce effects on hepatic function in the studies in workers. It should be noted, though, that, due to the nature of the effects on which they were based (increases in serum hepatic enzymes versus histological effects), the benchmarks in humans are not strictly comparable.

It is also evident that there is progression of effects from the medium-term to long-term studies, with effects being more severe following long-term exposure (although quantitative values for the lowest benchmarks for different types of lesions in the medium-term and long-term studies are similar).

11.1.3 Sample risk characterization

Due to the nature of use, patterns of release, and environmental fate of DMF, the focus of the human health risk characterization for indirect exposure is populations exposed through air in the vicinity of industrial point sources.

With a reported annual loading of less than 20 tonnes and generally less than 1 tonne at any location in the sample country (i.e., Canada), continuous releases of consistent magnitude likely result in long-term expo-

[1] The term “tolerable concentration” is used here in the same sense as the term “tolerable intake” as defined by IPCS (1994), i.e., “an estimate of the intake of a substance over a lifetime that is considered to be without appreciable health risk.”

[2] Available quantitative data are insufficient to replace default values for the component of this uncertainty factor with data-derived values (IPCS, 1994).

sure to small concentrations (worst-case estimate in Canada, 0.11 mg/m^3) of DMF near point sources. Because of the absence of empirical data on concentrations of DMF in air in Canada, an estimated exposure value (EEV) was calculated based on release data for the largest Canadian emitter, making several conservative assumptions.

The largest annual release reported at one location can be expressed on a daily basis (12.7 tonnes/year = 0.0348 tonnes/day or 3.48×10^7 mg/day). As a conservative estimate, it will be assumed that daily releases of DMF are contained within a cylinder having a radius of 1 km centred on the point source. Dispersion within 1 km is likely a conservative assumption for a number of reasons. First, the greatest reported emissions are occurring in a mixed industrial and agricultural area (Environment Canada, 1999b). The site is paved with asphalt; as such, wild plants and mammals will not likely be found in the immediate vicinity of the source. Finally, although the specific dispersal behaviour of DMF has not been documented near the source, results of dispersion modelling indicate that concentrations of other contaminants released to air elsewhere tend to decrease rapidly within a few kilometres of industrial point sources (e.g., Davis, 1997; Thé, 1998).

Upward movement of organic compounds generally does not exceed 100 m at night and may exceed 1000 m during the day.[1] The more conservative value of 100 m will be used as a ceiling for estimating the exposure concentrations throughout the day.

This provides a dispersal volume of 3.14×10^8 m^3 in the form of a cylinder 100 m in height and 1 km in radius. With a daily release of 3.48×10^7 mg/day, the daily increase in the concentration of DMF in air is estimated at 0.11 mg/m^3. Since ambient levels in the cylinder are likely to be lower than this daily increase of 0.11 mg/m^3, it will be used as a conservative EEV. Reaction with hydroxyl radicals will tend to reduce the concentrations of DMF in the daytime. Since the degradation half-life of DMF could be a week or more, continuous daily inputs would lead to buildup of DMF within the cylinder in the absence of any other loss process. However, fugacity-based modelling suggests that advection processes, i.e., rain and wind, are the major factors in determining concentrations in the atmosphere. Even under essentially stagnant conditions, with a wind speed of 1 km/h, the rate of advection of DMF out of the cylinder is so fast that the steady-state concentration would be 0.01 mg/m^3 or less. At a typical average wind speed of 10 km/h, the concentration of DMF in the cylinder would be reduced by a factor of approximately 100. The EEV of 0.11 mg/m^3 is generally higher than or comparable to measurements made in other countries.

Worst-case estimates of airborne levels in the immediate vicinity of the largest emitter in the sample country (0.11 mg/m^3), which are likely 10- to 100-fold greater than those anticipated under most conditions, do not appreciably exceed the TC (0.1 mg/m^3) derived on the basis of increases in serum hepatic enzymes in exposed workers.

11.1.4 Uncertainties and degree of confidence in human health risk characterization

Quantitative estimates of ambient levels of DMF in the vicinity of point sources in the sample country on which the human health risk characterization is based are highly uncertain (see discussion of uncertainty in section 11.2.3) and likely conservative, although consistent with highest consentrations measured in other countries. The proximity of these predicted concentrations in the vicinity of point sources to residential areas is also unknown. Available monitoring data are inadequate as a basis for characterization of the exposure of the general population to DMF.

There is a high degree of confidence based on studies in both humans and experimental animals that the liver is the target organ for the toxicity of DMF. Cross-sectional studies on hepatic effects in workers, limited principally to males, were complicated by co-exposures to other substances and limitations of available data on exposure, including, in some cases, lack of monitoring data for individuals. However, the levels that induced minimally adverse effects were remarkably consistent across a large number of studies. The TC developed on the basis of increases in serum hepatic enzymes in occupationally exposed populations is likely conservative, since it does not take into account additional exposure by the dermal route.

Although cases of testicular cancer among people exposed to DMF have been reported, these findings have not been corroborated in (limited) epidemiological studies, and it is thus unlikely that DMF is carcinogenic to humans.

11.2 Evaluation of environmental effects

11.2.1 Terrestrial assessment end-points

Since most DMF appears to be released to air in the sample country, and based on the fate of DMF in the ambient environment, biota are expected to be exposed to DMF primarily in air; little exposure to DMF from surface water, soil, or benthic organisms is expected. Based on this, and because of the low toxicity of DMF to

[1] Notes from N.J. Bunce, University of Guelph, Guelph, Ontario, to A. Chevrier, Environment Canada, dated 1 June 1998.

a wide range of aquatic and soil organisms, it is unlikely that organisms will be exposed to harmful levels of DMF in Canadian surface waters, soils, or groundwater. Therefore, the focus of the environmental risk characterization will be on terrestrial organisms exposed directly to DMF in ambient air.

Terrestrial plants can be exposed to DMF by direct contact with the atmosphere, but also conceivably by diffusion from raindrops deposited on leaves. No data are available on the toxicity of DMF to terrestrial vascular plants. Seeds, soil fungi, and aquatic angiosperm macrophytes can be used as indicators of the potential sensitivities of trees, shrubs, and other plants. The most sensitive of these organisms appears to be the soil fungus *Sclerotinia homeocarpa*, with an EC_{50} of 4840 mg/litre for growth inhibition (Stratton, 1985). In view of the generally high effect concentrations, it is unlikely that terrestrial plants are particularly sensitive to DMF.

As most DMF is released to air and bioaccumulation is not expected, effects on wildlife will occur mainly through direct exposure by inhalation in the vicinity of the point source. Based on the available information, the home range of common small to medium-sized eastern Canadian mammals is generally much less than 1 km^2 (Banfield, 1974; Burt & Grossenheider, 1976; Forsyth, 1985; US EPA, 1999). By contrast, the home range of the raccoon, a common suburban visitor, is quite variable in size, reportedly ranging from a few square kilometres to thousands of square kilometres (Burt & Grossenheider, 1976; US EPA, 1999). Therefore, small mammals are likely exposed over long periods to highest concentrations of DMF within a few kilometres of the site, while the more mobile medium-sized mammals are probably exposed over time to lower average levels of DMF.

No information has been found on effects of DMF on wildlife. Experimental animals used in laboratory studies will be used as surrogates for small and medium-sized mammals exposed to DMF through inhalation.

11.2.2 Sample environmental risk characterization

The calculation of the EEV is presented in section 11.1.3.

Analysis of exposure pathways and subsequent identification of sensitive receptors are the basis for selection of environmental assessment end-points (e.g., adverse reproductive effects on sensitive fish species in a community). For each end-point, a conservative EEV is selected and an estimated no-effects value (ENEV) is determined by dividing a critical toxicity value (CTV) by an application factor. A hyperconservative or conservative quotient (EEV/ENEV) is calculated for each of the assessment end-points in order to determine whether there is potential ecological risk.

The long-term (18-month) inhalation LOAEC of 75 mg/m^3 measured for mice is used as a CTV for exposure of small mammals. This value was selected from a large data set composed of acute and long-term studies conducted on a number of laboratory species. Although no direct effects related to survival were observed at the exposure concentrations (up to 1200 mg/m^3), nor were any haematological changes or effects on the estrous cycle observed, the incidence of hepatocellular hypertrophy, hepatic single-cell necrosis, and hepatic Kupffer cell hyperplasia/pigment accumulation was increased at 75 mg/m^3 (Malley et al., 1994). Such effects may not directly manifest themselves as population-level effects in wildlife species; therefore, the ENEV is derived by dividing the CTV by a reduced application factor of 5. This factor also accounts for the extrapolation from a low-effect level to a no-effect level, as well as the uncertainty surrounding the extrapolation from laboratory to field conditions and interspecies and intraspecies variations in sensitivity. As a result, the ENEV is 15 mg/m^3. Therefore, using the EEV of 0.11 mg/m^3, the quotient EEV/ENEV= 0.007. Since this conservative quotient is less than 1, it is unlikely that DMF causes adverse effects on terrestrial organisms in the sample country.

11.2.3 Discussion of uncertainty

There are a number of potential sources of uncertainty in this environmental risk assessment.

The calculated Henry's law constant is uncertain, as solubility cannot be measured. Based on sensitivity analysis, the fugacity-based partitioning estimates can be sensitive to the value used as the Henry's law constant.[1]

Ambient levels near Canadian sources are not available. The EEV was therefore estimated based on available information on releases. This calculated EEV is, however, generally consistent with the highest concentrations measured in other countries. It is unlikely that there are concentrations of DMF in the sample country that are higher than those calculated and used in this assessment. For air, reported releases at the selected location by far exceed reported releases to air at any other location and as such likely constitute a worst-case scenario. For water, concentrations are expected to

[1] Collection of notes and modelling results submitted by A. Bobra, AMBEC Environmental Consultant, to Chemicals Evaluation Division, Commercial Chemicals Evaluation Branch, Environment Canada, 1999.

be low because of the limited releases identified to this medium and the limited partitioning of DMF from air into water. Small spills and leakage could increase levels of DMF in soil and groundwater; however, the available information suggests that such releases would be small and infrequent.

Regarding effects of DMF on terrestrial organisms, although no toxicity data were identified for vascular plants, data for effects on seeds and aquatic macrophytes suggest that terrestrial vegetation is not particularly sensitive to DMF. Additional evidence of effects on terrestrial plants would strengthen the conclusion that DMF is not expected to damage gymnosperms, angiosperms, and other vascular plants.

There is uncertainty concerning the extrapolation from available toxicity data for laboratory mammals to potential effects on wildlife populations. To account for these uncertainties, an application factor was used in the environmental risk analysis to derive ENEVs.

12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

IARC (1999) has classified DMF in Group 3 (not classifiable as to its carcinogenicity to humans). There was inadequate evidence for carcinogenicity of DMF in humans. There was evidence suggesting lack of carcinogenicity of DMF in experimental animals.

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APPENDIX 1 — SOURCE DOCUMENT

Government of Canada (in press)

Copies of the *Canadian Environmental Protection Act Priority Substances List Assessment Report* (Government of Canada, in press) and unpublished supporting documentation for *N,N*-dimethylformamide may be obtained from:

Commercial Chemicals Evaluation Branch
Environment Canada
14th floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
Canada K1A 0H3

or

Environmental Health Centre
Health Canada
Address Locator: 0801A
Tunney's Pasture
Ottawa, Ontario
Canada K1A 0L2

Initial drafts of the supporting documentation and Assessment Report for DMF were prepared by staff of Health Canada and Environment Canada.

The environmental sections were reviewed externally by:

D. Andrews, Golder Associates Ltd.
K. Bolton, University of Toronto
N. Bunce, University of Guelph
R. Gensemer, Boston University
D. Hastie, York University
S. Mabury, University of Toronto
M. Mumtaz, Chinook Group Ltd.
C. Nalewajko, University of Toronto
M. Sheppard, EcoMatters Inc.

Sections of the supporting documentation pertaining to human health were reviewed externally by G. Kennedy, DuPont Haskell Laboratory for Toxicology and Industrial Medicine, to address adequacy of coverage.

Accuracy of reporting, adequacy of coverage, and defensibility of conclusions with respect to hazard identification and dose–response analyses were considered at a panel of the following members, convened by Toxicology Excellence in Risk Assessment on 14 February 2000 in Ottawa, Canada:

M.S. Abdel-Rahman, University of Medicine & Dentistry of New Jersey
C. Abernathy, US Environmental Protection Agency
J.P. Christopher, California Environmental Protection Agency
J.C. Collins, Solutia, Inc.
J.T. Colman, Syracuse Research Corporation
M. Mumtaz, Agency for Toxic Substances and Disease Registry
K.A. Poirier, Toxicology Excellence in Risk Assessment
J.E. Whalen, US Environmental Protection Agency

APPENDIX 2 — CICAD PEER REVIEW

The draft CICAD on *N,N*-dimethylformamide was sent for review to institutions and organizations identified by IPCS after contact with IPCS National Contact Points and Participating Institutions, as well as to identified experts. Comments were received from:

A. Aitio, International Programme on Chemical Safety, World Health Organization, Switzerland

M. Baril, Institut de Recherche en Santé et en Sécurité du Travail du Québec (IRSST), Canada

R. Benson, Drinking Water Program, US Environmental Protection Agency, USA

R.S. Chhabra, National Institute for Environmental and Health Sciences/National Institutes of Health (NIEHS/NIH), USA

R. Hertel, Federal Institute for Health Protection of Consumers and Veterinary Medicine (BgVV), Germany

C. Hiremath, US Environmental Protection Agency, USA

H. Kafferlein, Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine, Friedrich-Alexander University Erlangen-Nuremberg, Germany

F. Larese, Institute of Occupational Medicine, University of Trieste, Italy

H. Lendle, Product Safety, BASF AG, Germany

I. Mangelsdorf, Fraunhofer Institute for Toxicolgy and Aerosol Research, Germany

J. Mraz, Centre of Industrial Hygiene and Occupational Diseases, National Institute of Public Health, Czech Republic

P. Ridgeway, Health and Safety Executive, United Kingdom

P. Schulte, National Institute for Occupational Safety and Health, USA

E. Soderlund, Department of Environmental Medicine, National Institute of Public Health, Norway

D. Willcocks, National Industrial Chemicals Notification and Assessment Scheme (NICNAS), Australia

P. Yao, Chinese Academy of Preventive Medicine, People's Republic of China

K. Ziegler-Skylakakis, Beratergremium für Umweltrelevante Altstoffe (BUA), Germany

APPENDIX 3 — CICAD FINAL REVIEW BOARD

Helsinki, Finland, 26–29 June 2000

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APPENDIX 4 — BENCHMARK DOSE CALCULATIONS

In subchronic inhalation assays in F344 rats, there was an increase in relative liver weight in females and increased cholesterol in both sexes at 50 ppm (150 mg/m³), with no clear dose–response (LOEC) (NTP, 1992a), progressive histopathological hepatic changes in both sexes at 400 and 800 ppm (1200 and 2400 mg/m³) (Craig et al., 1984), and hepatocellular necrosis in both sexes at 400 ppm (1200 mg/m³) (NTP, 1992a). B6C3F1 mice had hepatocellular hypertrophy at 50 ppm (150 mg/m³) (LOEC), in addition to significantly increased relative liver weight in both sexes without clear dose–response (NTP, 1992a) and hepatic cytomegaly at 150 ppm (450 mg/m³) and higher (Craig et al., 1984). No signs of toxicity were observed in monkeys exposed to up to 500 ppm (1500 mg/m³) (Hurtt et al., 1992).

In a chronic inhalation bioassay in Crl:CD BR rats, at 100 ppm (300 mg/m³), there were significant increases in centrilobular hepatocellular hypertrophy (both sexes), hepatic accumulation of lipofuscin/haemosiderin (both sexes), and hepatic single-cell necrosis (females only). In mice [Crl:CD 1 (ICR)BR], at 25 ppm (75 mg/m³), there was centrilobular hepatocellular hypertrophy (males), hepatic single-cell necrosis (males and females), and hepatic Kupffer cell hyperplasia/pigment accumulation (males) (Malley et al., 1994).

Data on dose–response following ingestion are limited to medium-term exposure studies. At 250 mg/kg body weight per day, liver cell enlargement was reported in Crl:CD rats; at 50 mg/kg body weight per day, relative liver weight was significantly increased in males (Kennedy & Sherman, 1986). In Wistar rats, relative liver weight was significantly increased at 69 mg/kg body weight per day, but no histopathological lesions were observed at doses up to 235 mg/kg body weight per day (Becci et al., 1983). In CD-1 mice, only mild histopathological changes were observed in the liver at 246 mg/kg body weight per day; at 96 mg/kg body weight per day, relative liver weight was significantly increased in females. No adverse effects were observed in beagle dogs administered up to 34.8 mg/kg body weight day in the diet for 13 weeks.

It should be noted that the lowest concentration (50 ppm [150 mg/m³]) at which effects were observed in the liver of rats (NTP, 1992a) in an inhalation assay is equivalent to an intake of 46.5 mg/kg body weight per day in rats,[1] which is consistent with the effects levels in Crl:CD rats (Kennedy & Sherman, 1986) and Wistar rats (Becci et al., 1983) following dietary exposure. The lowest concentration (50 ppm [150 mg/m³]) to which mice were exposed in the NTP (1992a) is equivalent to an intake of 200 mg/kg body weight per day,[2] which is consistent with the effect levels in the dietary assay in mice reported by Becci et al. (1983).

Reported incidence, benchmark concentrations (BMCs) at the 5% level, and associated *P*-values and goodness of fit statistics for effects on the liver for relevant end-points in the most robust medium- and long-term exposure studies for ingestion and inhalation, respectively, are presented in Tables 2 and 3.

For the discrete end-points, the BMC_{05} is defined as the concentration of chemical that causes a 5% increase in incidence over the background response rate. It is calculated by first fitting the following model to the dose–response data (Howe, 1995):

$$P(d) = q_0 + (1 - q_0) \cdot [1 - e^{-q_1 d - \ldots - q_k d^k}]$$

where d is dose, k is the number of dose groups in the study, $P(d)$ is the probability of the animal developing the effect at dose d, and $q_i > 0$, $i = 1,\ldots, k$ is a parameter to be estimated.

The models were fit to the incidence data using THRESH (Howe, 1995), and the BMC_{05}s were calculated as the concentration C that satisfies

$$\frac{P(C) - P(0)}{1 - P(0)} = 0.05$$

A chi-square lack of fit test was performed for each of the model fits. The degrees of freedom for this test are equal to k minus the number of q_i's whose estimates are non-zero. A *P*-value less than 0.05 indicates a significant lack of fit.

For the continuous end-points, the BMC_{05} is defined as the dose that causes a 5% increase in the absolute risk of seeing an "adverse" response. This method utilizes the "hybrid" method of Crump (1995), in which the adverse response level in the control group is specified as 5%. That is, 5% of the animals in the control group would, by natural variation, have a response that would be considered adverse. Then, the probability of being adverse, as opposed to the response itself, is modelled.

The Weibull model was fit to each of the end-points using BENCH_C (Crump & Van Landingham, 1996):

$$P(d) = p_0 + (1 - p_0) [1 - e^{(-\beta d)^k}]$$

where d is dose, $P(d)$ is the probability of an adverse response at dose d, and k, β, and p_0 are parameters to be estimated. The BMC_{05} was then calculated as the concentration C such that

$$P(C) - P(0) = 0.05$$

An F-test was used to assess lack of fit of the model. A *P*-value less than 0.05 indicates lack of fit.

[1] 1 mg/m³ = 0.31 mg/kg body weight per day in rats (Health Canada, 1994).

[2] 1 mg/m³ = 1.33 mg/kg body weight per day in mice (Health Canada, 1994).

N,N-DIMETHYLFORMAMIDE

0457
October 2000

CAS No: 68-12-2
RTECS No: LQ2100000
UN No: 2265
EC No: 616-001-00-X

Dimethylformamide
DMF
DMFA
N-formyldimethylamine
C_3H_7NO / $HCON(CH_3)_2$
Molecular mass: 73.09

TYPES OF HAZARD/ EXPOSURE	ACUTE HAZARDS/SYMPTOMS	PREVENTION	FIRST AID/FIRE FIGHTING
FIRE	Flammable. Gives off irritating or toxic fumes (or gases) in a fire.	NO open flames, NO sparks, and NO smoking. NO contact with oxidizing agents.	Powder, alcohol-resistant foam, water spray, carbon dioxide.
EXPLOSION	Above 58°C explosive vapour/air mixtures may be formed.	Above 58°C use a closed system, ventilation.	In case of fire: keep drums, etc., cool by spraying with water.
EXPOSURE		**PREVENT GENERATION OF MISTS! AVOID EXPOSURE OF (PREGNANT) WOMEN!**	
Inhalation	Abdominal pain. Diarrhoea. Nausea. Vomiting. Facial flushing.	Ventilation, local exhaust, or breathing protection.	Fresh air, rest. Refer for medical attention.
Skin	MAY BE ABSORBED!	Protective gloves. Protective clothing.	Remove contaminated clothes. Rinse and then wash skin with water and soap. Refer for medical attention.
Eyes	Redness. Pain.	Safety goggles, or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion		Do not eat, drink, or smoke during work.	Rinse mouth.

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Ventilation. Remove all ignition sources. Collect leaking and spilled liquid in sealable containers as far as possible. Absorb remaining liquid in sand or inert absorbent and remove to safe place. (Extra personal protection: complete protective clothing including self-contained breathing apparatus).	T Symbol R: 61-20/21-36 S: 53-45 Note: E UN Hazard Class: 3 UN Pack Group: III

EMERGENCY RESPONSE	STORAGE
Transport Emergency Card: TEC (R)-30G35 NFPA Code: H1; F2; R0	Separated from strong oxidants, halogens.

IPCS
International Programme on Chemical Safety

Prepared in the context of cooperation between the International Programme on Chemical Safety and the European Commission

SEE IMPORTANT INFORMATION ON THE BACK.

IMPORTANT DATA

Physical State; Appearance
COLOURLESS TO YELLOW LIQUID, WITH CHARACTERISTIC ODOUR.

Chemical dangers
The substance decomposes on heating or on burning producing toxic fumes including nitrogen oxides.
Reacts violently with oxidants, nitrates and halogenated hydrocarbons. Attacks some plastic and rubber.

Occupational exposure limits
TLV: 10 ppm; (skin) (ACGIH 2000).
MAK: 10 ppm; 30 mg/m^3; skin, Re2 (1999)

Routes of exposure
The substance can be absorbed into the body by inhalation and through the skin.

Inhalation risk
A harmful contamination of the air will be reached rather slowly on evaporation of this substance at 20°C.

Effects of short-term exposure
The substance is irritating to the eyes.
The substance may cause effects on the liver, resulting in jaundice. See Notes.

Effects of long-term or repeated exposure
The substance may have effects on the liver, resulting in impaired functions.
Animal tests show that this substance possibly causes toxic effects upon human reproduction.

PHYSICAL PROPERTIES

Boiling point: 153°C
Melting point: -61°C
Relative density (water = 1): 0.95
Solubility in water: miscible
Vapour pressure, Pa at 25°C: about 492
Relative vapour density (air = 1): 2.5
Relative density of the vapour/air-mixture at 20°C (air = 1): 1.00
Flash point: 58°C c.c.
Auto-ignition temperature: 445°C
Explosive limits, vol% in air: 2.2-15.2 at 100°C
Octanol/water partition coefficient as log Pow: -0.87

ENVIRONMENTAL DATA

NOTES

Use of alcoholic beverages enhances the harmful effect.
Resulting symptoms could be delayed from several hours up to several days.
Environmental effects from the substance have been investigated, but none has been found.

ADDITIONAL INFORMATION

RÉSUMÉ D'ORIENTATION

Ce CICAD sur le *N*,*N*-diméthylformamide (DMF) a été préparé conjointement par la Direction de l'hygiène du milieu de Santé Canada et la Direction de l'évaluation des produits chimiques commerciaux d'Environnement Canada, sur la base d'une documentation préparée simultanément dans le cadre du Programme d'évaluation des substances prioritaires, en application de la Loi canadienne sur la protection de l'environnement (LCPE). Les évaluations sanitaires des substances prioritaires effectuées en application de cette loi portent sur les effets que pourraient avoir ces produits sur la santé humaine en cas d'exposition indirecte dans l'environnement. L'exposition professionnelle n'est pas abordée dans le document de base. La présente mise au point prend en compte les données sur les effets environnementaux jusqu'à septembre 1999 et les données sur les effets sanitaires jusqu'à février 2000. L'appendice 1 donne des informations sur la nature de l'examen par des pairs et sur les sources documentaires. D'autres études ont également été utilisées, à savoir celle l'IARC/CIRC (1999) et celle du BUA (1994). Des renseignements sur l'examen par des pairs du présent CICAD sont donnés à l'appendice 2. Ce CICAD a été adopté en tant qu'évaluation internationale lors de la réunion du Comité d'évaluation finale qui s'est tenue à Helsinki du 26 au 29 juin 2000. La liste des participants à cette réunion figure à l'appendice 3. La fiche internationale sur la sécurité chimique (ICSC 0457) du *N*,*N*-diméthylformamide, établie par le Programme international sur la sécurité chimique (IPCS, 1999), est également reproduite dans le présent document.

Le *N*,*N*-diméthylformamide (No CAS 68-12-2) est un solvant organique produit en grande quantité dans l'ensemble du monde. On utilise dans l'industrie chimique comme solvant, comme intermédiaire ou comme additif. Il se présente sous la forme d'un liquide incolore dégageant une faible odeur qui rappelle celle des amines. Il est miscible en toutes proportions à l'eau et à la plupart des solvants organiques. Sa tension de vapeur est relativement faible.

Une fois libéré dans l'air, le DMF y demeure en majeure partie jusqu'à décomposition par réaction avec des radicaux hydroxyles. La libération indirecte de DMF dans l'air, notamment à partir d'autres milieux, ne contribue guère au maintien de la concentration de ce composé dans le compartiment atmosphérique. On estime que le DMF présent dans l'air est photo-oxydé en l'espace de quelques jours. Une partie du DMF atmosphérique peut cependant atteindre le milieu aquatique ou terrestre, vraisemblablement à la faveur des précipitations. Le DMF qui passe dans l'eau subit une décomposition *in situ* sans transfert vers d'autres compartiments. Libéré dans le sol, il y demeure en majeure partie - probablement dans l'eau des pores - jusqu'à dégradation par voie chimique ou biologique. En cas de décharge dans les eaux ou au sol, on peut s'attendre à une biodégradation relativement rapide (demi-vie de 18 à 36 h). Si le composé parvient jusqu'aux nappes souterraines, sa décomposition anaérobie sera lente. Compte tenu du mode d'utilisation du DMF, l'exposition de la population générale à ce composé est vraisemblablement très faible.

Etant donné que dans le pays témoin, la majeure partie du DMF est effectivement libérée dans l'air et compte tenu du devenir de ce composé dans l'environnement, l'exposition des organismes vivants est essentiellement atmophérique et les organismes benthiques, comme ceux qui peuplent les eaux de surface ou le sol, sont sans doute peu exposés. Compte tenu de cela et étant donné la faible toxicité du DMF pour nombre d'organismes aquatiques ou terricoles, la caractérisation du risque vise essentiellement les organismes terrestres directement exposés au DMF présent dans l'air ambiant.

Le DMF est rapidement absorbé en cas d'exposition par voie orale, percutanée ou respiratoire. Une fois absorbé, le composé se répartit de façon uniforme dans l'organisme et après avoir été métabolisé principalement au niveau du foie, il est assez rapidement excrété par la voie urinaire sous la forme de métabolites. La principale voie métabolique consiste en une hydroxylation du groupement méthyle conduisant au *N*-(hydroxyméthyl)-*N*-méthylformamide (HMMF), qui est le principal métabolite urinaire chez l'Homme et l'animal. Le HMMF peut à son tour subir une décomposition en *N*-méthylformamide (NMF), dont l'hydroxylation enzymatique au niveau du groupement *N*-méthyle va entraîner la formation de *N*-(hydroxyméthyl)formamide (HMF), qui se décompose ensuite en formamide. Il existe également une possibilité de bifurcation métabolique à partir du NMF qui consiste en une oxydation du groupement formyle conduisant à la *N*-acétyl-*S*-(*N*-méthylcarbamoyl)cystéine (AMCC), métabolique dont on a décelé la présence dans l'urine humaine et l'urine de rongeurs. Au cours de ce processus, il se forme également un intermédiaire réactif dont la structure n'est pas encore élucidée (peut-être de l'isocyanate de méthyle). Bien qu'on ne dispose pas de preuve expérimentale directe, il se pourrait que ce composé soit le métabolite présumé toxique. A la lumière des données existantes, il semblerait que chez l'Homme, la proportion de DMF métabolisée par la voie présumée toxique soit plus importante que chez l'animal de laboratoire. Il existe une interaction métabolique entre le DMF et l'alcool, qui, bien qu'encore mal élucidée, pourrait être due à l'action inhibitrice de ce composé sur l'alcool-déshydrogénase.

Les données tirées d'analyses de cas individuels ou d'études transversales sur des populations professionnellement exposées, montrent, en accord avec

les résultats de l'expérimentation animale, que chez l'Homme, c'est le foie qui est l'organe-cible du DMF. L'ensemble des effets correspond à ce qui s'observe chez l'animal de laboratoire, c'est-à-dire des troubles digestifs, une intolérance à l'alcool, l'augmentation du taux sérique des enzymes hépatiques (aspartate-aminotransférase, alanine-aminotransférase, γ-glutamyltranspeptidase et phosphatase alcaline) accompagnés d'anomalies histopathologiques et de modifications ultrastructurales (nécrose hépatocellulaire, hypertrophie des cellules de Kupffer, stéatose microvésiculaire, lysosomes complexes, mitochondries pléomorphes et dégénérescence graisseuse avec présence occasionnelle de lipogranulomes).

A la lumière des données disponibles, il n'existe pas de faits probants ni cohérents qui témoignent d'une augmentation des tumeurs de toutes localisations imputable à l'exposition au DMF sur le lieu de travail. Les cas de cancer du testicule qui avaient été rapportés n'ont pas été confirmés par une étude de cohorte cas-témoins. Pour ce qui est d'autres localisations, aucune augmentation systématique de la fréquence tumorale n'a pu être associée à une exposition au DMF.

En ce qui concerne la génotoxicité du composé pour des populations professionnellement exposées, les données ne sont pas non plus très probantes ni cohérentes, les résultats des études effectuées sur des travailleurs exposés (au DMF et à d'autres composés) étant mitigés. L'ensemble des observations ne cadre pas avec les variations de l'exposition d'une étude à l'autre. Cependant, en raison de la relation dose-réponse positive observée lors de l'étude où cette possibilité avait été explorée, il s'agit là d'un domaine qui mériterait des études supplémentaires, même si les résultats obtenus dans des systèmes d'épreuve expérimentaux sont très largement négatifs en ce qui concerne la génotoxicité du DMF.

La toxicité aiguë du DMF est faible et il n'est que légèrement à modérément irritant pour les yeux et la peau. On n'a pas trouvé de données sur son pouvoir sensibilisateur. Les études de toxicité aiguë ou chronique par administration de doses répétées mettent invariablement en évidence l'hépatotoxicité du DMF, même aux concentrations ou aux doses les plus faibles. Au nombre des effets constatés figurent des modifications touchant les enzymes hépatiques qui sont caractéristiques d'une action toxique, l'augmentation du poids du foie, une dégénérescence histopathologique progressive pouvant conduire à la mort cellulaire et l'accroissement du taux sérique des enzymes hépatiques. Après avoir exposé des rats et des souris par la voie respiratoire et la voie orale, on a constaté l'existence d'une relation dose-réponse pour l'ensemble de ces effets. Par ailleurs, l'ordre de sensibilité des diverses espèces relativement à ces effets est le suivant : souris > rat > singe.

La base de données relative à la cancérogénicité du DMF ne comporte en tout et pour tout que deux épreuves biologiques sur le rat et la souris, mais il en ressort néanmoins que l'inhalation prolongée de ce composé n'entraîne pas d'augmentation de l'incidence tumorale. Comme on l'a vu, les résultats des tests de génotoxicité sont très largement négatifs; ils proviennent d'études approfondies *in vitro*, consistant notamment à rechercher la présence de gènes mutés, ainsi que d'une base de données plus limitée constituée à partir d'épreuves *in vivo.*

L'expérimentation animale montre que le DMF n'a d'effets nocifs sur la reproduction qu'à des concentrations plus fortes que celles qui sont hépatotoxiques, après exposition tant par la voie respiratoire que par la voie orale. De même, lors d'études sur le développement bien conduites et publiées tout récemment, on n'a observé d'effets foetotoxiques et tératogènes systématiques qu'aux doses ou aux concentrations toxiques pour la mère.

Les données existantes sont insuffisantes pour permettre une évaluation des effets neurologiques et immunologiques du DMF.

Le présent CICAD et la caractérisation du risque que constitue le DMF ont essentiellement pour objet les effets de ce composé lors d'une exposition indirecte dans l'environnement.

C'est l'air au voisinage de sources ponctuelles de DMF qui fait courir à la population générale le risque d'exposition le plus important. D'après les études épidémiologiques effectuées sur des travailleurs exposés et les informations tirées de la base de données relativement fournie qui a été constituée à partir des résultats de l'expérimentation animale, c'est le foie qui constitue l'organe cible de l'action toxique du DMF. En se basant sur l'augmentation du taux sérique des enzymes hépatiques, on a fixé à 0,03 ppm (0,1 mg/m^3) la concentration tolérable.

On n'a pas trouvé de données sur la toxicité du DMF pour les plantes vasculaires terrestres. Pour les indicateurs de sensibilité potentielle des arbres et des arbustes, les concentrations agissantes sont élevées, aussi est-il peu probable que les végétaux terrestres soient particulièrement sensibles à ce composé. En ce qui concerne les autres organismes terrestres, on est parvenu à une valeur de 15 mg/m^3 pour la concentration sans effet en prenant la valeur limite pour l'hépatotoxicité chez la souris divisée par un coefficient d'application. En comparant cette valeur avec une estimation prudente de l'exposition on peut conclure que

dans le pays témoin, le DMF n'a vraisemblablement aucun effet nocif sur les organismes terrestres.

RESUMEN DE ORIENTACIÓN

Este CICAD sobre la *N*,*N*-dimetilformamida (DMF), preparado conjuntamente por la Dirección de Higiene del Medio del Ministerio de Salud del Canadá y la División de Evaluación de Productos Químicos Comerciales del Ministerio de Medio Ambiente del Canadá, se basó en la documentación preparada al mismo tiempo como parte del Programa de Sustancias Prioritarias en el marco de la *Ley Canadiense de Protección del Medio Ambiente* (CEPA). Las evaluaciones de sustancias prioritarias previstas en la CEPA tienen por objeto valorar los efectos potenciales para la salud humana de la exposición indirecta en el medio ambiente general, así como los efectos ecológicos. En este documento original no se abordó la exposición ocupacional. En este examen se analizaron los datos identificados hasta el final de septiembre de 1999 (efectos ecológicos) y febrero de 2000 (efectos en la salud humana). La información relativa al carácter del examen colegiado y la disponibilidad del documento original figura en el apéndice 1. También se consultaron otros exámenes, entre ellos el del IARC (1999) y el del BUA (1994). La información sobre el examen colegiado de este CICAD aparece en el apéndice 2. Este CICAD se aprobó como evaluación internacional en una reunión de la Junta de Evaluación Final celebrada en Helsinki (Finlandia) del 26 al 29 de junio de 2000. La lista de participantes en esta reunión figura en el apéndice 3. La Ficha internacional de seguridad química (ICSC 0457) para la *N*,*N*-dimetilformamida, preparada por el Programa Internacional de Seguridad de las Sustancias Químicas (IPCS, 1999), también se reproduce en este documento.

La *N*,*N*-dimetilformamida (CAS Nº 68-12-2) es un disolvente orgánico que se produce en grandes cantidades en todo el mundo. Se utiliza en la industria química como disolvente, intermediario y aditivo. Es un líquido incoloro con un ligero olor a amina. Es completamente miscible con el agua y la mayoría de los disolventes orgánicos y su presión de vapor es relativamente baja.

Cuando se libera en el aire, la mayor parte de las emisiones de *N*,*N*-dimetilformamida se mantienen en este compartimento, donde se degrada por reacción química con radicales hidroxilo. Las emisiones indirectas de *N*,*N*-dimetilformamida al aire, por ejemplo por desplazamiento desde otros compartimentos del medio ambiente, desempeñan sólo una pequeña función en el mantenimiento de los niveles de *N*,*N*-dimetilformamida en la atmósfera. Se estima que la fotooxidación de la *N*,*N*-dimetilformamida en el aire dura unos días. Sin embargo, parte de la *N*,*N*-dimetilformamida atmosférica puede alcanzar los medios acuático y terrestre, posiblemente con la lluvia. Cuando se libera *N*,*N*-dimetilformamida en el agua, se degrada allí y no pasa a otros compartimentos. Cuando se libera al suelo, la mayor parte de

la *N,N*-dimetilformamida se mantiene allí - posiblemente en el agua intersticial del suelo - hasta que se degrada por reacción biológica y química. Se supone que las emisiones al agua o al suelo van seguidas de una biodegradación relativamente rápida (semivida de 18-36 h). Si la *N,N*-dimetilformamida alcanza el agua freática, su degradación anaerobia será lenta. Las pautas de uso de la *N,N*-dimetilformamida hacen suponer que la exposición de la población general es probablemente muy baja.

Habida cuenta de que en el país de muestra la mayor parte de la *N,N*-dimetilformamida parece que se libera al aire y teniendo cuenta su destino en el medio ambiente, se supone que la biota está expuesta fundamentalmente a la *N,N*-dimetilformamida del aire; la exposición a la presente en las aguas superficiales, el suelo o los organismos bentónicos se supone que es escasa. Sobre esta base y debido a su baja toxicidad para una gran variedad de organismos acuáticos y del suelo, la caracterización del riesgo ambiental se concentra en los organismos terrestres expuestos directamente a la *N,N*-dimetilformamida del aire ambiente.

La *N,N*-dimetilformamida se absorbe fácilmente tras la exposición oral, cutánea o por inhalación. Después de la absorción, la *N,N*-dimetilformamida se distribuye de manera uniforme, se metaboliza sobre todo en el hígado y se excreta con relativa rapidez como metabolitos en la orina. En la vía principal interviene la hidroxilación de los grupos metilo, produciendo *N*-(hidroximetil)-*N*-metilformamida, que es el principal intermediario urinario en las personas y en los animales. La *N*-(hidroximetil)-*N*-metilformamida se puede descomponer a su vez para formar *N*-metilformamida. Luego, la oxidación enzimática del *N*-metilo de la *N*-metilformamida puede dar lugar a *N*-(hidroximetil)formamida, que a continuación se degrada a formamida. Una vía alternativa para el metabolismo de la *N*-metilformamida es la oxidación del grupo formilo, produciendo *N*-acetil-*S*-(*N*-metilcarbamoil)-cisteína, que ha sido identificado como un metabolito urinario en los roedores y en las personas. En esta vía se forma un intermediario reactivo, cuya estructura aún no se ha determinado (posiblemente metilisocianato); aunque no se han encontrado pruebas experimentales directas que lo respalden, parece que este intermediario es el metabolito supuestamente tóxico. Los datos disponibles indican que la proporción de *N,N*-dimetilformamida que se puede metabolizar por la vía supuestamente tóxica es mayor en las personas que en los animales de experimentación. Se ha detectado una interacción metabólica entre la *N,N*-dimetilformamida y el alcohol, lo cual, aunque no se conoce del todo, se puede deber, al menos en parte, a que inhibe la alcohol deshidrogenasa.

Coincidiendo con los resultados de los estudios en animales de experimentación, los datos disponibles de informes de casos y de estudios de muestras representativas de poblaciones expuestas ocupacionalmente indican que en las personas es el hígado el órgano destinatario de la toxicidad de la *N,N*-dimetilformamida. El perfil de los efectos está en consonancia con el observado en los animales de experimentación, habiéndose detectado trastornos gastrointestinales, intolerancia al alcohol, aumento de las enzimas hepáticas en el suero (aspartato aminotransferasa, alanina aminotransferasa, (-glutamil transpeptidasa y fosfatasa alcalina) y efectos histopatológicos y cambios ultraestructurales (necrosis hepatocelular, agrandamiento de las células de Kupffer, esteatosis microvesicular, lisosomas complejos, mitocondrías pleomórficas y cambios en la grasa con lipogranulomas ocasionales).

Teniendo en cuenta los limitados datos disponibles, no hay pruebas sistemáticas convincentes de un aumento del número de tumores en los lugares asociados con la exposición a la *N,N*-dimetilformamida en el entorno ocupacional. Las notificaciones de casos de cáncer testicular no se han confirmado en un estudio de cohortes y de casos y testigos. No se ha observado un aumento constante de tumores en otros lugares asociados con la exposición a la *N,N*-dimetilformamida.

Hay también pocas pruebas sistemáticas convincentes de genotoxicidad en las poblaciones expuestas ocupacionalmente a la *N,N*-dimetilformamida, con resultados desiguales en los estudios disponibles sobre trabajadores expuestos (a la *N,N*-dimetilformamida y a otros compuestos). La pauta de las observaciones no es coherente con las variaciones de la exposición en los diversos estudios. Sin embargo, a la vista de la relación dosis-respuesta positiva observada en el único estudio en el cual se investigó, convendría estudiar más este aspecto, aunque los datos disponibles sobre genotoxicidad en sistemas experimentales son abrumadoramente negativos.

La *N,N*-dimetilformamida tiene una toxicidad aguda baja y una actividad irritante ocular y cutánea entre ligera y moderada. No se identificaron datos relativos a su potencial de sensibilización. En estudios de toxicidad aguda y de dosis repetidas, la *N,N*-dimetilformamida ha sido siempre hepatotóxica, induciendo efectos en el hígado a las concentraciones o dosis más bajas. El perfil de los efectos incluye alteraciones en las enzimas hepáticas características de la toxicidad, aumento de peso del hígado, cambios histopatológicos de degeneración progresiva y a la larga muerte celular, así como aumento de las enzimas hepáticas en el suero. Tras la exposición por inhalación y por vía oral se ha observado una relación dosis-respuesta para estos efectos en ratas y ratones. Se ha detectado una variación de la sensibilidad entre especies para estos efectos, siendo el orden de sensibilidad ratones > ratas > monos.

Aunque la base datos para la carcinogenicidad se limita a dos biovaloraciones debidamente realizadas en ratas y ratones, no se ha registrado un aumento de la incidencia de tumores tras la exposición por inhalación crónica a la *N,N*-dimetilformamida. El valor probatorio para la genotoxicidad es totalmente negativo, basándose en una investigación amplia mediante valoraciones *in vitro,* en particular para la mutación genética, y en una base de datos más limitada *in vivo*.

En estudios con animales de laboratorio, tras la exposición tanto por inhalación como por vía oral la *N,N*-dimetilformamida indujo efectos reproductivos adversos sólo a concentraciones superiores a las asociadas con los efectos adversos en el hígado. Del mismo modo, en estudios fundamentalmente recientes sobre el desarrollo realizados y notificados de manera adecuada, se han observado sistemáticamente efectos citotóxicos y teratogénicos sólo a concentraciones o dosis con toxicidad materna.

Los estudios disponibles no son suficientes como base para la evaluación de los efectos neurológicos e inmunológicos de la *N,N*-dimetilformamida.

Este CICAD y la caracterización del riesgo en la muestra se concentran fundamentalmente en los efectos de la exposición indirecta en el medio ambiente general.

El aire en la proximidad de fuentes puntuales parece ser el principal origen potencial de exposición de la población general a la *N,N*-dimetilformamida. Sobre la base de los resultados de los estudios epidemiológicos de trabajadores expuestos y de los datos justificativos de una base de datos relativamente amplia de investigaciones en animales de experimentación, el hígado es el principal órgano destinatario de la toxicidad de la *N,N*-dimetilformamida. Se ha obtenido una concentración tolerable de 0,03 ppm (0,1 mg/m^3), teniendo en cuenta el aumento de las enzimas hepáticas en el suero.

No se han identificado datos sobre la toxicidad de la *N,N*-dimetilformamida para las plantas vasculares terrestres. Las concentraciones con efecto para los indicadores de una posible sensibilidad de los árboles, los arbustos y otras plantas son altas; por consiguiente, es poco probable que las plantas terrestres sean particularmente sensibles a la *N,N*-dimetilformamida. Para otros organismos terrestres, se ha estimado un valor sin efectos de 15 mg/m^3, basado en un valor critico de la toxicidad para la toxicidad hepática en ratones dividido por un factor de aplicación. La comparación de este resultado con un valor de exposición estimada prudente indica que es poco probable que la *N,N*-dimetilformamida provoque efectos adversos en los organismos terrestres del país de muestra.

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