IPCS

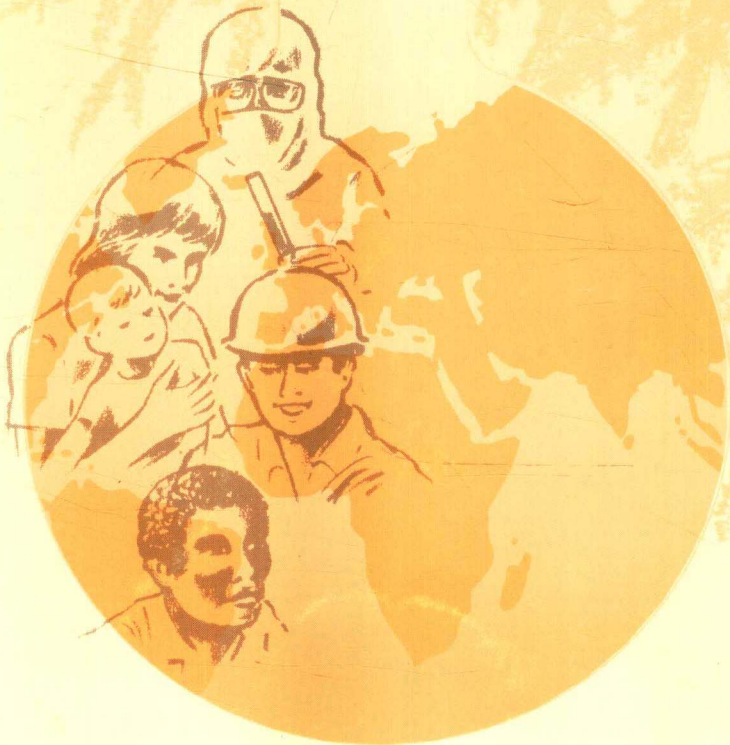
INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

UNEP

CONCISE INTERNATIONAL CHEMICAL ASSESSMENT DOCUMENT

N° 31

N,N-Dimethylformamide



IOMC

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS

A cooperative agreement among UNEP, ILO, FAO, WHO, UNIDO, UNITAR and OECD

WORLD HEALTH ORGANIZATION

Concise International Chemical Assessment Document 31

N,N-DIMETHYLFORMAMIDE

First draft prepared by
G. Long and M.E. Meek, Environmental Health Directorate, Health Canada, Ottawa, Canada, and
M. Lewis, Commercial Chemicals Evaluation Branch, Environment Canada, Ottawa, Canada

Published under the joint sponsorship of the United Nations Environment Programme, the International Labour Organization, and the World Health Organization, and produced within the framework of the Inter-Organization Programme for the Sound Management of Chemicals.

World Health Organization
Geneva, 2001

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.

WHO Library Cataloguing-in-Publication Data

N,N-Dimethylformamide.

(Concise international chemical assessment document ; 31)

1.Dimethylformamide - toxicity 2.Risk assessment 3.Environmental exposure
I.International Programme on Chemical Safety II.Series

ISBN 92 4 153031 6 (NLM Classification: QV 633)
ISSN 1020-6167

The Federal Ministry for the Environment, Nature Conservation and Nuclear Safety, Germany, provided financial support for the printing of this publication.

Printed by Wissenschaftliche Verlagsgesellschaft mbH, D-70009 Stuttgart 10

TABLE OF CONTENTS

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

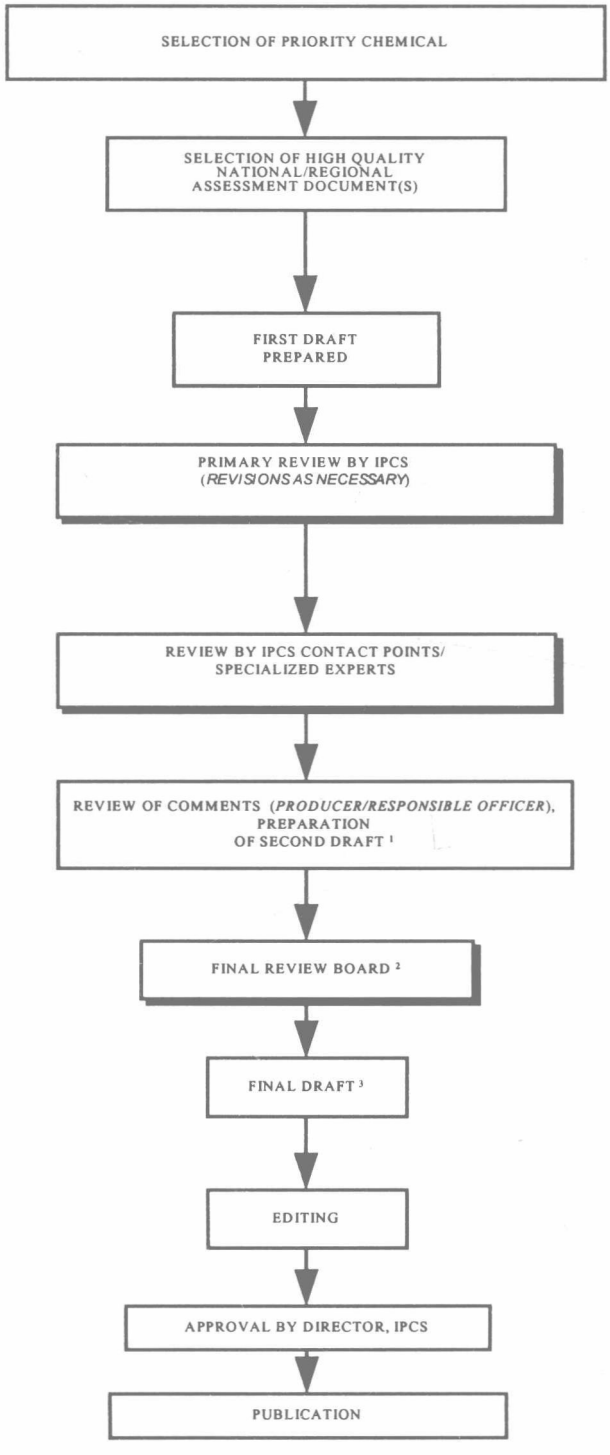
The flow chart shows the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world — expertise that is required to produce the high-quality evaluations of toxicological, exposure, and other data that are necessary for assessing 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, γ-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).

[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.

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) 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]

---

[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.

This is 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/m³. 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/m³).

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/m³ (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/m³) 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/m³). At six facilities where plastic was manufactured, concentrations ranged from 0.1 to 0.7 ppm (0.3 to 2.1 mg/m³). At 11 facilities for plastics processing, the range of concentrations was from 4 to 44 ppm (12 to 132 mg/m³); the range of 8-h threshold limit values (TLVs) at six of the facilities was 5–38 ppm (15–114 mg/m³).

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/cm² 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.