

[FOREWORD](#)

[INTRODUCTION](#)

DIMETHYLFORMAMIDE
CAS N°: 68-12-2

SIDS Initial Assessment Report

For

SIAM 13

Bern, Switzerland, 6-9 November 2001

- 1. Chemical Name:** Dimethylformamide
- 2. CAS Number:** 68-12-2
- 3. Sponsor Country:** Germany
BMU (Bundesministerium für Umwelt,
Naturschutz und Reaktorsicherheit)
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- 4. Shared Partnership with:** ICCA
- 5. Roles/Responsibilities of the Partners:**
 - Name of industry sponsor /consortium
 - Process used
- 6. Sponsorship History**
 - How was the chemical or category brought into the OECD HPV Chemicals Programme? See next page
- 7. Review Process Prior to the SIAM:**
- 8. Quality check process:**
- 9. Date of Submission:** 14. September 2001
- 10. Date of last Update:** July 2003
- 11. Comments:** Last literature search (up date): 21 Feb 2001 (Human Health): databases medline, toxline; search profile CAS-No. and special search terms.

04 May 2001 (Ecotoxicology): databases CA, biosis; searchprofile CAS-No. and special search terms.

OECD/ICCA - The BUA¹ Peer Review Process

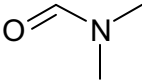
Qualified BUA personnel (toxicologists, ecotoxicologists) perform a quality control on the full SIDS dossier submitted by industry. This quality control process follows internal BUA guidelines/instructions for the OECD/ICCA peer review process and includes:

- a full (or update) literature search to verify completeness of data provided by industry in the IUCLID/HEDSET
- Review of data and assessment of the quality of data
- Review of data evaluation
- Check of adequacy of selection process for key studies for OECD endpoints, and, where relevant, for non-OECD endpoints by checking original reports/publications
- Review of key study description according robust summaries requirements; completeness and correctness is checked against original reports/publications
(if original reports are missing: reliability (4) = not assignable)
- Review of validity of structure-activity relationships
- Review of full SIDS dossier (including SIAR, SIAP and proposal for conclusion and recommendation for further work)

In case of data gaps, review of testing plan or rationale for not testing.

¹ BUA (GDCh-Beratergremium für Altstoffe): Advisory Committee on Existing Chemicals of the Association of German Chemists (GDCh).

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	68-12-2
Chemical Name	N,N-dimethylformamide
Structural Formula	
RECOMMENDATIONS	
The chemical is a candidate for further work	
SUMMARY CONCLUSIONS OF THE SIAR	
Human Health	
<p>N,N-dimethylformamide (DMF) is of low acute toxicity in mammals: LD₅₀ rat (oral) 3040 mg/kg bw, LC₅₀ rat (inhalative, 4 h) > 5900 mg/m³, LD₅₀ rat (dermal) > 3160 mg/kg bw. Main symptoms following exposure were apathy and staggering (oral) and irregular or intermittent respiration (inhalation). It was irritating to the eyes of rabbits but not irritating to the skin of rabbits and rats.</p> <p>DMF did not show a sensitizing potential when used as a vehicle in a local lymph node assay. In repeated-dose toxicity studies in rats and mice with chronic exposure over 2 years (rats) or 18 months (mice) and subchronic exposure over 13 weeks by inhalation, or in rats treated by oral administration of DMF (90 day feeding study or administration by gavage for 28 days), the predominant target organ was the liver (NOAEC: chronic inhalation rat: 25 ppm (about 80 mg/m³), LOAEC: chronic inhalation mouse: 25 ppm (about 80 mg/m³); NOAEC: subchronic inhalation rat: 100 ppm, mouse: 400 ppm (about 300 mg/m³ and 1210 mg/m³, respectively); NOAEL: rat, 90 days 200 ppm (about 12 mg/kg bw/day), 28 days about 238 mg/kg bw/day). In a 13-week inhalation study with a limited number of Cynomolgus monkeys no treatment-related effects occurred (NOAEC: 500 ppm (about 1500 mg/m³)).</p> <p>DMF does not induce chromosome aberrations or gene mutations in various test systems <i>in vivo</i> and <i>in vitro</i>. In addition, no increased tumor incidence was found in carcinogenicity studies in rats and mice that were exposed to 25, 100 and 400 ppm DMF (about 80, 300, and 1210 mg/m³) by inhalation for 2 years or 18 months, respectively.</p> <p>Reproductive toxicity was observed at the presence of some general toxicity in a continuous breeding study in mice, when DMF was administered orally in the drinking water at doses of 1000, 4000 and 7000 ppm (about 219, 820 and 1455 mg/kg bw/day). The maximal tolerated dose for generalized toxicity was 1000 ppm (about 219 mg/kg bw/day) for the F0 and the F1 generation, thus a systemic NOAEL could not be determined. Significant reproductive toxicity (e.g. reduced fertility and fecundity characterized by reduced pregnancy and mating index (the latter one only in the high dose group), reduced number of litters, reduced average litter size and</p>	

for the F1 parental males by effects on prostate weight and epididymal spermatozoa concentration, the latter finding only in the high dose group) and developmental toxicity (e.g. reduced survival and growth of pups, increase in craniofacial and sternebral malformations) occurred at 4000 ppm and above. At 1000 ppm, reduced pup weights were found in F2 pups. Thus 1000 ppm (about 219 mg/kg bw/day) was the NOAEL for reproductive and developmental toxicity in F0 and F1, and the LOAEL for developmental toxicity in F2.

Developmental toxicity and teratogenicity occurred in rats and rabbits in various studies (inhalation, oral- or dermal administration) and in mice (oral administration). In rats embryo-/fetotoxicity and teratogenicity were mostly seen at maternally toxic doses, whereas in mice and in rabbits embryo-/fetotoxicity and teratogenicity occurred also at dose levels without maternal toxicity. However, the rabbit appeared to be the most sensitive species to the developmental toxic effects of DMF.

Rabbit: NOAEC (inhalative) maternal toxicity and teratogenicity as well as embryo-/fetotoxicity 50 ppm (about 150 mg/m³); NOAEL (oral, gavage) maternal toxicity and embryo-/fetotoxicity 65 mg/kg bw/day, teratogenicity 44.1 mg/kg bw/day; NOAEL (dermal) maternal toxicity and teratogenicity as well as embryo-/fetotoxicity 200 mg/kg bw/day).

In humans, DMF is absorbed by inhalation and through the skin. After high exposures (up to 60 ppm) headaches, abdominal pain, nausea, vomiting, dizziness, elevated liver enzymes, and alcohol intolerance (facial flushing and palpitations) were seen. Case reports of testicular cancer in aircraft repair and leather tannery facilities failed to be confirmed in further studies. Reports of DNA and chromosomal damage in peripheral lymphocytes of subjects exposed to DMF either failed to take into account smoking as a confounder or coexposure to other chemicals.

With respect to the metabolism of DMF the following conclusion can be drawn: DMF is readily absorbed via all exposure routes. N-hydroxymethyl-N-methylformamide is the main urinary metabolite and to a minor extent, but with greater toxicological relevance the metabolite mono-N-methylformamide (MMF) occurs which may partially be conjugated to glutathione forming S-methylcarbamoylglutathione. The GSH and its sequel adducts (S-methylcarbamoylcystein and the corresponding mercapturic acid S-methylcarbamoyl-N-acetyl-cysteine) seem to be responsible for developmental toxic effects.

At higher doses, DMF inhibits its own metabolism, i.e. the formyloxidation to MMF which precedes the GSH binding.

Persons who repeatedly inhaled DMF excreted the mercapturic acid at levels of ~ 13% of the dose with a total half-life (i.e. DMF biotransformation and excretion) of 23 hours.

Ethanol and probably the metabolite acetaldehyde inhibit the breakdown of DMF and conversely, DMF inhibits the metabolism of ethanol and acetaldehyde. Furthermore, ethanol induces cytochrome P450 2E1 which facilitates the initial hydroxylation of DMF. Thus, exposure to DMF can cause a severe alcohol intolerance.

Environment

N,N-dimethylformamide (DMF) is a colorless liquid, which is miscible with water in all proportions and has a vapour pressure of 3.5 hPa (at 20°C). The log Kow was measured to - 0.85 (at 25°C).

Distribution modelling using Mackay Level I indicates water to be the main target compartment

for DMF (98.7%). In the atmosphere DMF is indirectly photodegraded by reacting with hydroxyl radicals with $t_{1/2} = 2$ hours. According to OECD criteria the substance is readily biodegradable. Hydrolysis is not expected under environmental conditions. Bioconcentration factor in fish was measured to 0.3 – 1.2.

In short term tests with fish, daphnids and algae DMF showed an acute toxicity EC/LC50 >100 mg/l. Hence DMF is not regarded as harmful to aquatic organisms. In the following the lowest valid EC/LC50 data of different aquatic species are summarized:

Lepomis macrochirus: LC50(96h) = 7100 mg/l

Daphnia magna: EC50(48h) > 100 mg/l; EC50(48h) = 15700 mg/l

Scenedesmus subspicatus: EC10 and EC50(96h) > 1000 mg/l (biomass and growth rate).

Long term reproduction studies with *Daphnia magna* resulted in NOECs of 1140 mg/l (28 days) and 1500 mg/l (21 d).

Applying an assessment factor of 50 on the lowest available NOEC of 1140 mg/l a $PNEC_{\text{aqua}} = 22.8$ mg/l can be derived according to the EU risk assessment procedure.

Exposure

In Germany 50,000 to 100,000 t DMF were produced in 2000 at BASF AG, Ludwigshafen. Further producers are located in Belgium, Korea, Japan, Spain and USA. The total production volume in the EU (including Germany) is in the range of 50,000 to 100,000 t/a. In Asia, the production volume is 100,000 to 500,000 tonnes per year and in North America it is 50,000 to 100,000 tonnes per year. DMF is predominately used as a solvent in synthesis of fine chemicals, in polyacrylonitrile fibre production, polyurethane coating and in the electronics industry. The remaining is split into various applications like varnishing, surface coating, polyamide coating, absorbents, cleaners and extractants. In addition, DMF is also used as a solvent in crop protection agents.

Releases into the environment may occur during production of DMF and during its use as solvent or cleaning agent. In 1991 the maximum annual release of DMF into the hydrosphere from production and processing in pre-unification Germany was estimated to 352 t. Approximately 9000 t/a were emitted into the atmosphere. More recent data about environmental releases are not available. Releases into the terrestrial compartment may occur from use of DMF as solvent in plant protection products. However, this release is not quantifiable.

Product register information indicates that there are several products that contain the substance in significant amounts (up to 100 %). The product types are solvents, intermediates, paints, lacquers and varnishes. Among the products there are some products for private use. Therefore consumer and occupational exposure can not be excluded. Exposure to workers during production is well controlled in the industry of the sponsor country (Germany).

NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is a candidate for further work. In occupational settings where exposure is not controlled and, due to information of European product registers, exposure to consumers and workers cannot be excluded. As the extent of exposure cannot be estimated and the substance is a developmental toxicant, a human exposure and if then indicated a risk assessment should be performed.

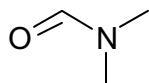
Environment: Concerning the aquatic compartment, DMF is of low concern due to the low toxicity to aquatic organisms, the low bioaccumulation potential and the classification as readily biodegradable. However, high releases of DMF into the atmosphere are described in the BUA report from 1991. Although the substance has a half-life in the atmosphere of 2 hours, these very high emissions may pose a local problem in the vicinity of point sources. In addition releases into the soil result from the use of the substance in plant protection products. Therefore, exposure data gathering should be performed. Depending on the exposure information further information on toxicity to terrestrial organisms may be required, for example a plant fumigation test.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 68-12-2
IUPAC Name: Dimethylformamide
Molecular Formula: C₃ H₇ NO
Structural Formula:



Synonyms: dimethylformamide
DMF
DMFA
formdimethylamide
N-Formyldimethylamine

Substance type: organic

Physical status: liquid

1.2 Purity/Impurities/Additives

Purity: ≥ 99.9 % w/w

1.3 Physico-Chemical properties

N,N-Dimethylformamide (DMF) is miscible with water in all proportions (Bipp and Kieczka, 1989). The vapour pressure at 20°C is 3.5 hPa (IPCS, 1991). A Henry's law constant of $7.47 \cdot 10^{-5}$ hPa·m³/mol can be deduced from an experimentally determined equilibrium constant at 25°C (Taft et al., 1985). The partition coefficient $\log P_{OW}$ is measured to -0.85 (BASF, 1987). Since the density of DMF (0.95 g/cm³ at 20°C; Bipp and Kieczka, 1989) is very similar to that of water, significant flotation or stratification in surface waters in case of accidental losses is not expected.

2 GENERAL INFORMATION ON EXPOSURE

In Germany 50,000 to 100,000 t DMF were produced in 2000 at BASF AG, Ludwigshafen. Further producers are located in Belgium, Korea, Japan, Spain and USA. The production volume in the EU (including Germany) is in the range of 50,000 to 100,000 t/a. In Asia the production volume is 100,000 to 500,000 t/a and in North America it is 50,000 to 100,000 t/a. DMF is predominately used as a solvent in synthesis of fine chemicals, in polyacrylonitrile fibre production, in polyurethane coating and in electronics industry. The remaining is split into various applications like varnishing, surface coating, polyamide coating, absorbents, cleaners and extractants (BUA, 1991). The former use of DMF as a solvent in crop protection agent formulations of BASF has been abandoned. However, there is recent information from the Finnish product register on the use of DMF as solvent in pesticides used for fungi in tomatoes, cucumbers and decorative plants.

The Danish product register (August 2001) gives the information that there is a total number of 42 products that contain the substance in amounts up to 100 %. Product types are solvents, intermediates and paint, lacquers and varnishes. Among the products there are 5 products for private use.

In the Swedish product register (September 2001) there are 37 products that contain the substance, among them 3 consumer products. Main uses of these products are solvents and intermediates.

The Swiss product register (July 2001) gives the information that there are 145 products that contain the substance in concentrations up to 100 %. Among them there are 33 products for public use. Product types are e.g. paint, lacquers and varnishes, solvents, cleaning agents, herbicides.

Releases into the environment may occur during production of DMF and during its use e.g. as solvent, cleaning agent. In 1991 the maximum annual release of DMF into the hydrosphere from production and processing in pre-unification Germany was estimated to 352 t. Approximately 9000 t/a were emitted into the atmosphere (BUA, 1991). More recent data about environmental releases are not available.

Releases into the terrestrial compartment may occur from use of DMF as solvent in plant protection products. However, this release is not quantifiable.

2.1 Environmental Exposure and Fate

Distribution modelling using Mackay Level I (BASF, 2001) indicates water to be the main target compartment for DMF (98.7%). In the atmosphere DMF is expected to be indirectly photodegraded with a half life of 2 hours (BUA, 1991). Under OECD 301E test conditions DMF turned out to be readily biodegradable (100% after 21 days; BASF, 1989). A lag-phase of 14 days was observed in this study. In a MITI I test a degradation of 4.4 % after 14 days was found (CITI, 1992). However, considering the long lag-phase found in the OECD 301E study there is no discrepancy between these two studies and DMF can be classified as readily biodegradable. In a sewage treatment plant simulation test using activated sludge from a municipal sewage treatment plant as inoculum an acclimation phase of 35 days was necessary before an elimination of DMF took place. After this period DMF was almost completely removed (analysis of substance concentration) from the synthetic waste water used in the study (Dojlido, 1979). Photodegradation in water occurs with a half life of 50 days (BUA, 1991). However, as DMF is classified as readily biodegradable this elimination pathway is not predominant for the substance. Hydrolysis is not expected under environmental conditions.

Bioaccumulation studies on fish (*Cyprinus carpio*) showed no significant accumulation potential (BCF = 0.3 – 1.2 after 56 days; CITI, 1992), which corresponds to the experimentally determined $\log K_{ow} = -0.85$ (BASF, 1987).

Geoaccumulation is also not expected from the log Kow of -0.85 .

2.2 Human Exposure

Exposure measurements (personal sampling) have been performed at different sites within the facilities of the producer in the Sponsor Country during 1996 – 2001:

- production: 4 measurements; result: all values below detection limit (0.02 ppm)
- use: 219 measurements; result: 1.05 ppm (90% percentile)

Higher workplace exposures have been reported in the literature (cf section 3.1)

In the European Union, DMF may not be used in substances or preparations placed on the market for sale to the general public in concentrations equal or greater than 0.5% (EU directive 76/769/EEC on restrictions of marketing and use of dangerous substances and preparations), since the substance may cause harm to the unborn child. Due to information from European product registers, consumer exposure cannot be excluded.

3 HUMAN HEALTH HAZARDS

3.1 Hazard Assessment Experience with Human Exposure

Percutaneous absorption of liquid and N,N-dimethylformamide (DMF) vapor was shown in human volunteers (Mraz et al., 1992a, b). A good and linear correlation of DMF concentrations in the air of the workplace and N-hydroxymethyl-N-methylformamide in the urine at the end of an 8-h shift was found (Kawai et al.; 1992; Sakai et al., 1995; Lareo and Perbellini, 1995). Workers with high DMF workplace exposure concentrations up to 60 ppm reported headaches, dizziness, anorexia, nausea, abdominal pain, and alcohol intolerance (facial flushing and palpitations). Clinical investigations showed elevated liver enzyme values for serum aspartate aminotransferase (ASAT) and serum alanine aminotransferase (ALAT) (Redlich et al., 1988, 1990; Wang et al., 1991; Cai et al., 1992; Cox and Mustchin, 1991; Fleming et al., 1990). One case of positive patch test reaction (0.1-1.0 % in pet.) was reported in a woman using DMF in her laboratory work. However DMF (0.1% in pet.) was negative in 20 controls (Camarasa, 1987).

Case reports of testicular cancer in aircraft repair and leather tannery facilities suggested possible association with DMF. Further research has failed to confirm this relationship. A screening effort at a leather tannery, where a cancer cluster had been noted, identified no additional cases. Mortality and cancer incidence studies and nested case-control investigations of testicular cancer and several other anatomical sites at several facilities with exposure to DMF noted no convincing associations (IARC, 1999, Ducatman et al.; 1986; Levin et al., 1987; Calvert et al., 1990; Chen et al., 1988 a,b; Walrath et al., 1989).

Increases in chromosome aberration (CA), sister chromatid exchange (SCE) and UV-induced unscheduled DNA synthesis (UDS) in peripheral lymphocytes was observed in 26 viscose rayon plant workers exposed to acrylonitrile (ACN) and DMF during a 20-month period compared to controls. The range of peak ACN and DMF concentrations in ambient air were 0-5.9 and 0.2-7.7 ppm at the start of the study and 0.1-1.7 and 1.2-7.6 ppm seven months later, respectively. No data were available for twenty months (Major et al, 1998). Since workers were exposed to ACN and DMF at the same time no assignment of the effects to a single compound is possible. Investigation of frequency of premature centromere division (PCD) in peripheral lymphocytes in 18 of the 26 workers did not show a significant increase compared to controls. However, analysis of correlation indicated that PCD is probably independent from CA (Major, 1999).

No association of exposure to DMF and SCE frequency in peripheral lymphocytes was found in an investigation in 85 workers from a resin synthesis plant (Cheng et al, 1999).

Frequency of chromosomal gaps and breaks in peripheral lymphocytes was 1.4 % in 20 workers exposed to mono-, di-, and trimethylamine as well as DMF compared to 0.4 % in controls. Workplace concentrations were 1.9-8.8 ppm for DMF and 0.005-1.7 ppm for dimethylamine. The authors commented the frequency of chromosomal gaps and breaks was low compared to other studies. Possible effect of smoking was not taken into account (Berger et al, 1985).

Chromosomal aberrations in peripheral lymphocytes were investigated in about 40 workers occupationally exposed to DMF and several other chemicals were found to be increased when compared to controls. At DMF concentrations in ambient air of 60 and 50 ppm frequencies of chromosomal aberrations was 3.82 and 2.74 %. At DMF concentrations of 16.7, 13.3, and 11.7 ppm frequencies were 1.59, 1.58, and 1.49 %. Aberration frequencies in the controls were 1.61 and 1.10 %. Ambient air concentrations of the coexposures were not given (Koudela and Spazier, 1981).

Sister chromatid exchange rates in peripheral lymphocytes in 22 female workers in a leather production factory were investigated in comparison to a control group of 22 females from the clerical or business department. Workers were divided into three subgroups according to DMF concentration in ambient air. SCE frequencies was significantly higher in the high (5.8 ppm) and the medium (0.7 ppm) exposure group than the in matched controls, but not in the low exposure group (0.3 ppm). Workers were also exposed to toluene (concentration in ambient air up to 0.9 ppm) (Seiji et al, 1992).

Reports of chromosomal and DNA damage in peripheral lymphocytes of subjects occupationally exposed to DMF either failed to take into account smoking as a confounder (Berger et al, 1985) or coexposure to other chemicals (Major et al, 1998, 1999, Seiji et al, 1992, Koudela and Spazier, 1981). No association of exposure to DMF and SCE frequency in peripheral lymphocytes of workers was found by Cheng et al, 1999.

Summary

DMF is absorbed by inhalation and through the skin. After high exposures (up to 60 ppm) headaches, abdominal pain, nausea, vomiting, dizziness, elevated liver enzymes, and alcohol intolerance (facial flushing and palpitations) were seen. Case reports of testicular cancer in aircraft repair and leather tannery facilities failed to be confirmed in further studies. Reports of DNA and chromosomal damage in peripheral lymphocytes of subjects exposed to DMF either failed to take into account smoking as a confounder or co-exposure to other chemicals.

3.2 Effects on Human Health

3.2.1 Toxicokinetics, Metabolism and Distribution

DMF (DMF) is readily absorbed via all exposure routes in human beings and animals. Dermal absorption from the vapour phase may even exceed pulmonary absorption.

The first metabolic step in humans and animals is hydroxylation of one of the methylgroups, mediated by Cytochrom P450 2E1. The resulting N-hydroxymethyl-N-methylformamide is also the main urinary metabolite. (MMF was once considered to be the predominant urinary metabolite of DMF; later it was revealed that N-hydroxymethyl-N-methylformamide forms MMF on the gas chromatographic column and GC analysis does not reflect the true pattern of metabolites in the urine (Scailteur et al., 1984 cited in Klug et al., 1998).)

To a minor extent, yet with greater toxicological relevance, a second pathway (of lower capacity) exists, namely P450 2E1 dependent hydroxylation and subsequent formylation to mono-N-methylformamide (MMF). MMF is then partially conjugated to glutathione forming S-methylcarbamoylglutathione. As glutathione carbamoylating species, an intermediary formation of methyl isocyanate was postulated but not proven. The GSH- and its sequel adducts (S-methylcarbamoyl-cystein and the corresponding mercapturic acid S-methylcarbamoyl-N-acetyl-cysteine) appeared to be responsible for developmental toxic effects in an in vitro assay (Klug et al., 1998). In this in vitro assay with limb bud organ cultures DMF and its major metabolites were investigated for their developmental toxicity in the mouse. Neither DMF nor the predominant urinary metabolite N-hydroxymethyl-N-methylformamide exhibited developmental activity, whereas the metabolites mentioned before and resulting from the glutathione binding pathway showed potent developmental activity on growth and development of day 12 old mouse limb buds after 24 hours as well as 6 days in culture.

S-methylcarbamoyl-N-acetyl-cysteine was found at levels of 1% to 5% of the dose in the urine of mice, hamsters and rats after parenteral administration. Interestingly, higher doses of DMF were converted to a lesser extent to S-methylcarbamoyl-N-acetyl-cysteine, than lower doses. At higher

doses, DMF inhibits its own metabolism, i.e. the formyloxidation to MMF which precurses the GSH binding (Mráz et al., 1993).

Persons who had inhaled DMF (8 hours daily for 5 days at concentrations of 10, 30 or 60 mg/m³) excreted the mercapturic acid at levels of ~13% of the dose with a total half-life (i.e. DMF biotransformation and excretion) of 23 hours (Mráz and Nohová, 1992).

When comparing these data from different species including man, the different doses, administration routes and rates (inhalation in man versus i.v. treatment of animals) as well as the peak levels of the parent substance DMF have to be taken into account.

When the sum of all three N-methylcarbamoylthioesters in plasma ('SMGs') were assessed as a function of exposure concentration in rats (after inhalation) the following pattern was obtained:

At 25 and 84 ppm DMF there was a linear relation between DMF exposure and 'SMGs'. At both levels, the 'SMG'-levels obtained were in a range that was shown to produce embryotoxic effects in vitro. At 25 ppm the steady state levels for 'SMGs' (~50 µmol/l) was obtained after 12 hours of exposure and stayed in that range during a continuing exposure up to 48 hours. After exposure termination the 'SMGs' were excreted with a half-life of approximately 2.8 hours. At 84 ppm the steady state 'SMG' level was ~200 µmol/l; excretion half-life was ~2.2 hours. At 213 ppm, however, no 'SMGs' were found until 6 hours following a 72 hours exposure time, presumably because of the inhibition of biotransformation (Filser et al., 1994).

A delayed biotransformation of DMF at high dose levels was also observed by other authors (Hundley et al., 1993a, b; Lundberg et al., 1983).

These data may explain why in prenatal toxicity studies in rats the slope of the dose response relation was so low (Hellwig et al., 1991). The data underline the correlation of the internal 'SMG' doses with the risk of prenatal toxicity.

Mutual interaction occurs between the degradation steps of DMF and alcohol. Ethanol and probably the metabolite acetaldehyde inhibit the breakdown of DMF and conversely, DMF inhibits the metabolism of ethanol and acetaldehyde. Furthermore, ethanol induces cytochrome P450 2E1 which facilitates the initial hydroxylation of DMF. Exposure to DMF, therefore, causes a severe alcohol intolerance which may show up even after termination of working shift (Greim, 1992).

Conclusion

DMF is readily absorbed via all exposure routes in human beings and animals.

N-hydroxymethyl-N-methylformamide is the main urinary metabolite.

To a minor extent, yet with greater toxicological relevance the metabolite mono-N-methylformamide (MMF) occurs which may partially be conjugated to glutathione forming S-methylcarbamoylglutathione. In an in vitro assay indications were found that the GSH- and its sequel adducts (S-methylcarbamoylcystein and the corresponding mercapturic acid S-methylcarbamoyl-N-acetyl-cysteine) seem to be responsible for developmental toxic effects.

At higher doses, DMF inhibits its own metabolism, i.e. the formyloxidation to MMF which precurses the GSH binding.

After repeated inhalation of DMF, persons excreted the mercapturic acid at levels of ~13% of the dose with a total half-life (i.e. DMF biotransformation and excretion) of 23 hours.

Ethanol and probably the metabolite acetaldehyde inhibit the breakdown of DMF and conversely, DMF inhibits the metabolism of ethanol and acetaldehyde. Furthermore, ethanol induces

cytochrome P450 2E1 which facilitates the initial hydroxylation of DMF. Thus, exposure to DMF can cause a severe alcohol intolerance.

3.2.2 Acute Toxicity

After single oral administration by gavage the LD₅₀ for rats was determined to be 3040 mg/kg bw (BASF, 1972). Main symptoms observed were apathy and staggering after oral intake. Further studies in rats revealed LD₅₀ values in the range between 2200 and 7550 mg/kg bw (BUA, 1991).

Acute inhalation of the maximum technically attainable concentration of 5900 mg N,N-dimethylformamide/m³ by rats resulted in a LC₅₀-value of > 5900 mg/m³/ 4 h; (BASF, 1979). Irregular or intermittent respiration were observed in the treated animals.

The LD₅₀ for dermal application was determined in the rat and resulted in a value of > 3160 mg/kg bw (Toxic Substances Control Act Test Submission (TSCATS): OTS 0516779, 1978); no substance-related clinical findings were reported in the study.

Conclusion

DMF is of low acute toxicity in mammals.

3.2.3 Irritation

The undiluted substance (about 0.5 ml) led to faint redness in one of four rabbits on the first day after removal of the bandage (after a 20 hour semi-occlusive exposure). On the second day there were no more findings, thus DMF was not regarded to be irritating to the skin of rabbits (BASF, 1952). The undiluted substance was even not irritating to the skin of rats (mean primary irritation score: 0) under occlusive conditions on abraded skin after a 24 hour exposure (TSCATS: OTS 0516779, 1978); but it was irritating to the eyes of rabbits administered at a dose of 0.1 ml or following administration of one drop of the test substance twice at an interval of 5 minutes, respectively (TSCATS: OTS 0516779, 1978; BASF, 1952).

With respect to irritation of the eyes, in one study severe signs of inflammation (redness, chemosis and purulent secretion) as well as transient opacity of the cornea in one of two animals were observed (BASF, 1952); in the other study (TSCATS: OTS 0516779, 1978) the primary irritation index (scoring was done according to the method of Draize et al. 1944) was 50.8 after 1h, decreasing to 35.8 after 72 h and 35.0 on day 4, decreasing to 3.3 on day 13. All animals in the latter study showed large blisters on the inside of upper and lower lids at the 1 and 4 hour readings. Blisters decreased in size at the 24 hour reading and they were gone at 48 hours.

Conclusion

DMF causes no skin irritation but it is irritating to the eyes.

3.2.4 Sensitisation

In a murine local lymph node assay DMF was used as a vehicle. 25 µl were applied on the dorsum of both ears of mice for three consecutive days. The treatment led to slight ear-draining lymph node activation as expressed by increased weight and cell count. However, there was no clear indication of a sensitizing potential of DMF (Ulrich et al., 2001).

3.2.5 Repeated Dose Toxicity

In **chronic inhalation** studies Crl:CD BR **rats** were exposed over a period of 2 years and Crl:CD-1 (ICR)BR **mice** were exposed for 18 months at concentrations of 25, 100 and 400 ppm (about 80, 300 and 1210 mg/m³) 5 d/w and 6 h/d (Malley et al., 1994). In the **rats** body weight and body weight gain were reduced in both sexes at 400 ppm and in the male animals at 100 ppm. Moreover, the animals in these groups showed increased enzyme activity (serum sorbitol dehydrogenase), increased liver weights and some histopathological findings in the liver. There was no compound-related increase of tumors. Estrous cycles were not altered in the females. Similar findings were observed in **mice**. At 400 ppm liver weights were increased in both sexes and at 100 ppm in the males. At all concentrations tested minimal to mild hepatocellular hypertrophy was observed (incidence being dose-related). Individual hepatocellular necrosis together with some other histopathological findings (minimal to moderate kupffer cell hyperplasia with pigment accumulation of lipofuscin and hemosiderin) were seen in all groups (also control, incidence being greater in N,N-dimethylformamide-treated animals). A compound-related increase in tumors was not observed and there was no effect on estrous cycles in female mice. According to the authors, a NOEC (no-observable-effect level) was not achieved in mice due to morphological changes seen in the liver at all three test concentrations, nevertheless they expected the NOEC to be close to 25 ppm due to the minimal changes observed at this concentration.

These minimal changes included a slightly (for the males significantly) increased incidence of hepatocellular hypertrophy, dose-related and statistically significantly increased incidence of hepatic single cell necrosis in both sexes, and dose-related (for the males significantly) increased incidences of hepatic kupffer cell hyperplasia and pigment accumulation.

Rat	NOAEC:	25 ppm	Mouse LOAEC:	25 ppm
Rat	LOAEC:	100 ppm		

In **13 week-inhalation** studies (NTP, 1992) Fischer 344 **rats** and B6C3F1 **mice** were exposed to concentrations of 50, 100, 200, 400 and 800 ppm (about 150, 300, 610, 1210 and 2430 mg/m³) for 6 hours/days, 5 days per week.

In the **rats** body weight gain was reduced at the two highest concentrations tested. Hepatocellular injury was biochemically characterized by increased activities of liver-specific enzymes in serum in both sexes at 200-800 ppm. Relative liver weights were increased in the females at all concentrations and in the males at 100 ppm and above. Hepatocellular necrosis occurred in both sexes at 400 and 800 ppm and pigment accumulation was found in both sexes at the highest concentration. Although liver histopathology findings were absent, the NOAEC was 100 ppm based on the findings observed in the liver function assays (i.e. increased serum cholesterol).

In the **mice** body weights were slightly reduced in the females at 800 ppm. Relative liver weights were increased in both sexes at all exposure concentrations, however this finding did not show a clear dose-response relationship. Hepatocellular hypertrophy was found in all treated groups of male mice and at 100 ppm and above in the females. Since in chronic inhalation studies in rats and mice (see above (Malley et al., 1994)) no increased incidence of hepatic tumors occurred, the hepatocellular hypertrophy can be regarded as the result of an adaptive process, thus the NOAEC for mice is expected to be at about 400 ppm.

Rat	NOAEC:	100 ppm	Mouse NOAEC:	400 ppm
Rat	LOAEC:	200 ppm	Mouse LOAEC:	800 ppm

A limited number of **Cynomolgus monkeys** (i.e. 3 female and 5 male monkeys/group) were used; for the males 2 animals/group were designated as the post exposure groups, that

were held for additional 13 weeks with no exposure and were then necropsied) was treated with DMF by **inhalation for 13 weeks** at concentrations of 30, 100 and 500 ppm (about 90, 300, 1500 mg/m³) (TSCATS: OTS 0000750-1, 1990; TSCATS: OTS 0528444, 1990).

No treatment-related findings were observed. Increased length of the estrous cycle was observed in one female in the low, two females in the mid and all females in the high concentration group, but not assessed as treatment-related given the importation history and lack of pre-exposure data.

Monkey NOAEC: 500 ppm

In a **90-day feeding study** Charles River CD strain **rats** received 200, 1000 and 5000 ppm DMF (about 12, 60 and 300 mg/kg bw/day) (TSCATS: OTS 0520880, 1960; TSCATS: OTS 0571664, 1960; TSCATS: OTS 0572893, 1960). Relative liver weights were slightly increased at 1000 ppm, a histopathological correlate was not found but hypercholesterolemia and elevated phospholipid values were observed in females. Leucocytosis and a decrease in the red blood cell count were observed. At 5000 ppm both sexes showed depressed body weight gain and reduced food consumption. Slight anemia, leukocytosis, hypercholesterolemia and elevated phospholipid concentrations were seen. Increased relative liver weights together with mild liver injury in the histological examination were found in both sexes.

Increased relative liver weights at 1000 and 5000 ppm were dose-related.

Rat NOAEL: 200 ppm

Rat LOAEL: 1000 ppm

In a **28-day study**, Sprague–Dawley **rats** received 250, 500, 1000 and 2000 µl N,N-dimethylformamide/kg bw (about 238, 475, 950 and 1900 mg/kg bw/day) **by gavage** on 5 days/week (BASF, 1977). In the highest dose group all animals died, mostly at the beginning of the study. At 1000 µl/kg bw/day all animals were affected by reduced food consumption and reduced body weight, males already at the beginning, females at the end of the study. Hepatic injury was characterized by changes in clinical chemistry values, e.g. increased enzyme activities. Relative liver weights were increased in both sexes. Histological examination revealed an acute to subacute hemorrhagic liver dystrophy with necrosis in both sexes in the two high dose groups. Disturbances in kidney function were characterized by elevated urea (females) and creatinine values, the latter one in both sexes. Relative kidney weights were increased in the males.

At 250 and 500 µl/kg bw/day reduced food consumption in the males and at 500 µl/kg bw/day reduced body weight was observed in the males. For the observation of increased relative liver weights in both sexes and of increased relative kidney weights in the males no histopathological correlate was found.

Rat NOAEL: 238 mg/kg bw/day

Rat LOAEL: 475 mg/kg bw/day

Conclusion

The liver is the predominant target organ of DMF toxicity.

The substance may also cause damage to the hematological system and the kidneys after repeated uptake as shown in animal studies.

3.2.6 Mutagenicity

DMF is often used as negative control substance (solvent) in mutagenicity and genetic toxicity studies without showing any conspicuous effects.

In vitro Studies

DMF was negative in the standard plate-incorporation Ames-Test with *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and TA1538, both with and without metabolic activation (rat liver S-9 mix) and even when tested at cytotoxic concentrations (concentrations tested: 9400 – 470 000 µg/plate (TSCATS: OTS 0520905, 1977).

Negative results were also obtained with and without metabolic activation in the SCE assay with CHO-cells (conc. tested 0.0625 -1mg/ml), the UDS Test in human diploid fibroblasts (conc. tested: up to 9220 mg/l) and a chromosome aberration/SCE assay (conc. tested 1.6, 3.2, 6.3 mg/ml) again with CHO-cells (Evans and Mitchell, 1981; TSCATS: OTS 0516796, 1981; Natarajan and Kesteren-van Leeuwen, 1981).

Although the vast majority of mutagenicity and genetic toxicity studies led to negative results, single *in vitro* investigations with a positive result were reported in the literature. The positive results observed in tests with *S. cerevisiae* (i.e. induction of mitotic aneuploidy and increased inhibition of cell growth in a repair-defective strain of yeast) were regarded as false positive by the authors due to specific effects related to the use of fungal cells and/or the absence of the appropriate detoxification mechanisms or the need of further development of the assay. With respect to a marginal mutagenic response in a mouse lymphoma cell forward mutation assay without S9 mix at concentrations of 5000 µg N,N-dimethylformamide/ml that was abolished by the use of S9 mix, there are reproducible negative results at the same concentration in some other publications. The same is true for cytogenetic tests with human peripheral lymphocytes. Taking into account the aforementioned aspects, the single studies with positive results are not regarded to be plausible or consistent.

In vivo Studies

In two dominant lethal assays (one in NMRI mice by single *i.p.* administration of the substance at a dose of about 380 mg/kg bw, and another one in Sprague-Dawley rats by inhalation exposure over a period of 5 days, 6 h/d at concentrations of 30 and 300 ppm (about 90 and 910 mg/m³)) DMF exposure did not result in mutagenic effects (BASF, 1976 a/b; TSCATS: OTS 0516779, 1978).

In two Micronucleus assays in which Balb/c or ICR mice were treated by a single *i.p.* administration of DMF (Balb/c mice were treated with doses of 0.2, 20 and 2000 mg/kg bw and the ICR mice were treated with 12.5, 25 or 50% of the LD₅₀, i.e. doses of about 404, 808 and 1615 mg/kg bw) no increases in micronuclei in bone marrow were seen (Antoine et al., 1983; Kirkhart, 1981).

Conclusion

DMF does not induce chromosome aberrations or gene mutations in various test systems *in vivo* and *in vitro*.

3.2.7 Carcinogenicity

In the chronic inhalation studies in rats (2 years) and mice (18 months) already described under 3.2.4 (Malley et al., 1994), in which the animals were exposed to 25, 100 and 400 ppm (5 d/w, 6 h/d) no compound-related lesions were noted in the nose or respiratory tract and the incidences of hepatic tumors and testicular tumors in both species were similar to control values.

Cell-labelling indices in the liver (measured in 5 randomly selected animals per sex and group after 2 weeks, 3 months and 12 months of testing) showed no substance-related effect at any exposure level in the mice; in the rat cell-labelling indices for hepatocytes were not statistically different

between control and 400 ppm animals, but rates were slightly higher for 400 ppm males at 2 weeks and 3 months but not at 12 months.

Conclusion

Chronic exposure to DMF did not cause a compound-related increase of tumors in rats or mice, thus DMF was not oncogenic at concentrations up to 400 ppm.

3.2.8 Toxicity for Reproduction

In a continuous breeding study CD-1 mice were treated orally with DMF in the drinking water at doses of 1000, 4000 and 7000 ppm (about 219, 820 and 1455 mg/kg bw/day) (Fail et al., 1998). The maximal tolerated dose (MTD) for generalized toxicity was 1000 ppm for the F0 and the F1 generation, thus a systemic NOAEL could not be determined.

At all dose levels in the F0 generation liver weights were increased. At necropsy body weight was significantly depressed in the females at 7000 ppm. Reproductive toxicity was observed in the mid and high dose groups represented by reduced fertility. Monitoring of the estrous cycle in control and high dose females revealed a decreased number of females in the high dose group having normal cycles. F1 pup postnatal survival was reduced during pre- and postweaning and body weights of F1 pups in the mid and high dose were also reduced, moreover the surviving pups of these dose groups exhibited craniofacial and sternebral malformations.

Data generated by a crossover mating trial in the course of the continuous breeding study suggested that the female was the sex affected by DMF treatment because females treated with 7000 ppm DMF produced smaller litters compared to control pairs or the group of control females mated to treated males. In addition, pups born by treated females mated to controls exhibited malformations similar to those observed in the F1 pups of the F0 parental generation.

The selected animals for the F1 parental generation showed reduced body weights in the mid and high dose groups. The F1 animals of all DMF treated groups had increased liver weights associated with hepatocellular hypertrophy. F1 estrous cycle length was significantly longer in the high dose females compared to the control animals. Histopathology did not reveal any findings in the reproductive tissues of the females. Male animals showed decreased relative prostate weight at all doses and epididymal spermatozoa concentration was reduced at the high dose. Affected reproductive performance was seen at the high dose by reduced mating index and at the high and mid dose by reduced pregnancy index and reduced litter size. Live F2 pup body weights were reduced at all doses and malformations observed in F2 pups of all DMF treated groups were similar to those observed for F1 litters. Craniofacial and sternebral malformations at the mid and high doses were characteristic and occurred in offspring of both generations.

Mouse:

F0, F1 parental generation, systemic toxicity	LOAEL: 1000 ppm (appr. 219 mg/kg bw/day)
F0, F1 fertility	NOAEL: 1000 ppm (appr. 219 mg/kg bw/day)
F1 developmental toxicity	NOAEL: 1000 ppm (appr. 219 mg/kg bw/day)
F2 developmental toxicity	LOAEL: 1000 ppm (appr. 219 mg/kg bw/day)

Conclusion

Significant reproductive toxicity (e.g. reduced fertility and fecundity characterized by reduced pregnancy and mating index (the latter one only in the high dose group), reduced no. of litters,

reduced average litter size and for the F1 parental males by effects on prostate weight and epididymal spermatozoa concentration, the latter finding only in the high dose group) occurred at ≥ 4000 ppm (mean exposure of 820 mg/kg bw/day) in the presence of some general toxicity (i.e. increased liver weights, hepatocellular hypertrophy and decreased body weights in the females at 7000 ppm). Developmental toxicity (e.g. reduced survival and growth of pups, increase in craniofacial and sternebral malformations) was observed in both generations. Reduced F2 pup weight was observed at ≥ 1000 ppm (appr. 219 mg/kg bw/day) and reduced F1 pup weight at 4000 ppm. At ≥ 4000 ppm an increase in cranio-facial and sternebral malformations was observed in offspring of both generations.

3.2.9 Developmental Toxicity / Teratogenicity

In two inhalation studies Long-Evans rats (Kimmerle and Machemer, 1975) and Sprague-Dawley rats (TSCATS: OTS 0516779, 1978) were exposed from day 6 to day 15 of gestation, 6 hours/day to exposure levels of 18 and 172 ppm (about 55 and 520 mg/m³) and to 30 and 300 ppm (about 90 and 910 mg/m³), respectively. In both studies teratogenicity was not observed, however fetotoxicity occurred at 172 ppm in the Long-Evans fetuses without signs of maternal toxicity whereas maternal toxicity and fetotoxicity were observed in the Sprague-Dawley rats at the exposure level of 300 ppm. In the Long-Evans fetuses fetotoxicity was represented by significantly reduced body weights in comparison to the control fetuses and in the Sprague-Dawley fetuses by significantly reduced fetal weights and a significant higher incidence of fetuses with ossification variations in comparison to the control fetuses.

Rat	NOAEC maternal Toxicity:	172 ppm (Kimmerle and Machemer, 1975)
Rat	NOAEC Teratogenicity:	172 ppm (Kimmerle and Machemer, 1975)
Rat	NOAEC Fetotoxicity:	18 ppm (Kimmerle and Machemer, 1975)
Rat	NOAEC maternal Toxicity:	30 ppm (TSCATS: OTS 0516779, 1978)
Rat	NOAEC Teratogenicity:	300 ppm (TSCATS: OTS 0516779, 1978)
Rat	NOAEC Fetotoxicity:	30 ppm (TSCATS: OTS 0516779, 1978)

In an inhalation developmental toxicity study with rabbits performed according to OECD Guideline 414 (1981) Himalayan rabbits were exposed to 50, 150 and 450 ppm (about 150, 450 and 1360 mg/m³) DMF from day 7 – 19 post insemination for 6 hours/day (BASF, 1989; Hellwig et al., 1991).

Maternal toxicity was observed at 150 and 450 ppm represented by impairment of body weight gain during the exposure period. At the highest concentration tested, clear signs of embryo-/fetotoxicity (e.g. reduced fetal body weights, increased incidence of variations) including teratogenicity (increased number of malformations, especially hernia umbilicalis) were observed.

At 150 ppm a toxic/teratogenic effect on the fetuses cannot be excluded due to an increased number of skeletal variations and one hernia umbilicalis, a malformation that was typically increased at 450 ppm.

Rabbit	NOAEC maternal Toxicity:	50 ppm
Rabbit	NOAEC Teratogenicity:	50 ppm
Rabbit	NOAEC Embryo-/Fetotoxicity:	50 ppm

In a developmental toxicity study Sprague-Dawley rats received doses of 176, 533 and 1600 μ l/kg bw/day (about 167, 506 and 1520 mg DMF/kg bw/day) by gavage from gestation day 6 – 15

(Hellwig et al., 1991; BASF, 1976 c). The study was performed in accordance with the FDA Guidelines (1966).

Maternal toxicity occurred at the mid and the high dose in the form of a dose-dependent decrease in body weight gain during the time of substance application. At both maternal toxic doses embryo-/fetotoxicity and teratogenicity were observed.

At the low dose neither maternal toxicity nor teratogenicity occurred. The only finding was a slight but significant and dose-related reduction of mean placental weight, however the number of live fetuses and fetal weights at the low dose were comparable to the control or even higher.

Rat	NOAEL maternal Toxicity (gavage):	167 mg/kg bw/day
Rat	NOAEL Teratogenicity (gavage):	167 mg/kg bw/day
Rat	NOAEL Embryo-/Fetotoxicity (gavage):	167 mg/kg bw/day

In another developmental toxicity study with Sprague-Dawley rats, the animals received 50, 100, 200 and 300 mg DMF/kg bw/day by gavage from gestation day 6 – 20 (Saillenfait et al., 1997). Maternal toxicity was observed at doses from 100 up to 300 mg/kg bw/day characterized by dose-dependent impairment of body weight gain and food consumption. Fetotoxicity occurred also at these dose levels (e.g. dose-related decrease in fetal body weight/litter, dose-dependent increase in the total number with skeletal variations, statistically significant at 200 and 300 mg/kg bw/day). The total number of skeletal variations was also slightly (but not statistically significant) increased at 50 mg/kg bw/day, thus suggesting slight indications for fetotoxicity at this dose level.

Teratogenicity was not observed.

Rat	NOAEL maternal Toxicity (gavage) :	50 mg/kg bw/day
Rat	NOAEL Teratogenicity (gavage):	300 mg/kg bw/day
Rat	LOAEL Embryo-/Fetotoxicity (gavage):	50 mg/kg bw/day

A developmental toxicity study with NMRI mice, receiving 193 and 580 µl of 20-30% aqueous solutions of DMF/kg bw/day (about 183 and 551 mg/kg bw/day) by gavage was carried out according to FDA Guidelines (1966). 24 pregnant females were treated from day 6 to 15 of gestation. Caesarian section took place on day 18 of gestation (Hellwig et al., 1991; BASF, 1976 d). Two concurrent control groups of 23 pregnant females/group run in parallel. Maternal toxicity did not occur at both dose levels investigated, whereas embryo-/fetotoxicity was seen in the form of reduced fetal body weights and reduced fetal growth in both dose groups. A dose-response relationship was not seen for these findings. However, the number of retardations and variations was increased in both substance-treated groups and clear signs of teratogenicity (statistically significant increase in malformations, mostly related to the head) were seen at the high dose. At the low dose a slight but not statistically significant increase in malformations (mostly cleft palate, a very common malformation in mice) was observed in comparison to the control group (1.63% of the live fetuses versus 0.48% of the live control fetuses).

Mouse	NOAEL maternal Toxicity (gavage):	551 mg/kg bw/day
Mouse	NOAEL Teratogenicity (gavage):	183 mg/kg bw/day
Mouse	LOAEL Embryo-/Fetotoxicity (gavage):	183 mg/kg bw/day

In a developmental toxicity study with rabbits performed according to FDA Guidelines (1966), animals were treated by gavage at dose levels of 46.4, 68.1 and 200 µl/kg bw/day (about 44.1, 65 and 190 mg/kg bw/day) from day 6 – 18 post insemination (BASF, 1976 e).

Maternal toxicity was observed at the high dose where food consumption, body weight and body weight gain were impaired and 3 dams had abortions. At this dose level clear signs of embryo-/fetotoxicity and teratogenicity were observed (e.g. decreased placental and fetal weights, increased incidence of malformed fetuses showing mainly hydrocephalus internus, hernia umbilicalis and/or ectopia visceralis).

In the mid dose group no maternal toxicity was observed but three malformed fetuses in two litters with hydrocephalus internus indicated a substance-related teratogenic effect.

At the low dose one fetus showed hydrocephalus internus, however, this incidence was in the range of control data.

Rabbit	NOAEL maternal Toxicity (gavage):	65 mg/kg bw/day
Rabbit	NOAEL Teratogenicity (gavage):	44.1 mg/kg bw/day
Rabbit	NOAEL Embryo-/Fetotoxicity (gavage):	65 mg/kg bw/day

In a dermal developmental toxicity study (OECD Guideline 414, (1981)) with rabbits, doses of 100, 200 and 400 mg/kg bw/day were administered on the shaved dorsal skin for 6 hours/day from day 6 to 18 post insemination (Hellwig et al., 1991; BASF, 1984).

A dose-dependent skin irritation occurred in all DMF treated animals. At the dose of 400 mg bw/day there were if at all, only very mild signs of maternal toxicity, i.e. a slight but statistical significant decrease in body weight at the end of the treatment period and one dam that showed abortion on day 21 post insemination. One dead fetus and several malformations (e.g. hernia umbilicalis, skeletal malformations) were found at this dose level. No embryo-/fetotoxic effects were found at the low and mid dose. The 3 fetuses with malformations seen in the low dose were regarded to be incidental, since no malformations occurred in the fetuses at the mid-dose. Thus, according to the authors, disregarding the skin reactions, the NOAEL for maternal toxicity was 200 mg/kg bw/day.

Rabbit	NOAEL maternal Toxicity (dermal):	200 mg/kg bw/day
Rabbit	NOAEL Teratogenicity (dermal):	200 mg/kg bw/day
Rabbit	NOAEL Embryo-/Fetotoxicity (dermal):	200 mg/kg bw/day

Conclusion:

In various developmental toxicity studies in rats embryo-/fetotoxicity was mostly seen at maternal toxic doses/concentrations and teratogenicity was observed at maternal toxic doses/concentrations only, whereas in mice and in rabbits embryo-/fetotoxicity and/or indications for teratogenicity were found at dose levels without maternal toxicity.

However, the rabbit appeared to be the most sensitive species to the developmental toxic effects of DMF.

3.3 Initial Assessment for Human Health

In Germany 50,000 to 100,000 t DMF were produced in 2000 at BASF AG, Ludwigshafen. Further producers are located in Belgium, Korea, Japan, Spain and USA. The production volume in the EU (including Germany) is in the range of 50,000 to 100,000 t/a. In Asia, the production volume is 100,000 to 500,000 t/a and in North America it is 50,000 to 100,000 t/a. DMF is predominately used as a solvent in synthesis of fine chemicals, in polyacrylonitrile fibre production, polyurethane coating and in the electronics industry. The remaining is split into various applications like

varnishing, surface coating, polyamide coating, absorbents, cleaners and extractants. The former use of DMF as a solvent in crop protection agent formulations of BASF has been abandoned. However, there is recent information from the Finnish product register on the use of DMF as solvent in pesticides.

Product register information indicates that there are several products that contain the substance in significant amounts (up to 100 %). The product types are solvents, intermediates, paints, lacquers and varnishes. Among the products there are some products for private use. Therefore consumer and occupational exposure can not be excluded. Exposure to workers during production is well controlled in the industry of the sponsor country (Germany).

DMF is of low acute toxicity in mammals: LD₅₀ rat (oral) 3040 mg/kg bw, LC₅₀ rat (inhalative, 4 h) > 5900 mg/m³, LD₅₀ rat (dermal) > 3160 mg/kg bw.

It was irritating to the eyes of rabbits but not irritating to the skin of rabbits and rats.

DMF did not show a sensitizing potential when used as a vehicle in a local lymph node assay.

In various repeated dose toxicity studies in rats and mice with chronic and subchronic exposure by inhalation, or in rats treated subchronically by oral administration, the predominant target organ was the liver (NOAEC: chronic inhalation rat: 25 ppm, LOAEC: chronic inhalation mouse: 25 ppm (a NOAEC was not achieved); NOAEC: subchronic inhalation rat 100 ppm, mouse 400 ppm; NOAEL: rat, 90 days 200 ppm, 28 days about 238 mg/kg bw/day). In a 13-week inhalation study with Cynomolgus monkeys no treatment-related effects occurred (NOAEC: 500 ppm).

DMF did not induce chromosome aberrations or gene mutations in various test systems in vivo and in vitro. In addition, no increased tumor incidence was found in carcinogenicity studies in rats and mice that were exposed from 25 up to 400 ppm DMF by inhalation for 2 years or 18 months, respectively.

Reproductive toxicity, i.e. reduced fertility and fecundity, was observed in the presence of some general toxicity in a continuous breeding study in mice, when DMF was administered orally in the drinking water at doses \geq 4000 ppm (appr. 820 mg/kg bw/day). The maximal tolerated dose (MTD) for generalized toxicity was 1000 ppm (appr. 219 mg/kg bw/day) for the F0 and the F1 generation, thus a systemic NOAEL could not be determined. Developmental toxicity (e.g. reduced survival and growth of pups, increase in craniofacial and sternebral malformations) was observed in both off-spring generations at \geq 4000 ppm. Reduced F2 pup weight was observed at \geq 1000 ppm.

(NOAEL F0, F1 fertility: 1000 ppm; NOAEL, F1 developmental toxicity 1000 ppm; LOAEL, F2 developmental toxicity: 1000 ppm).

Developmental toxicity and teratogenicity occurred in rats and rabbits in various studies (inhalation, oral or dermal administration) and in mice (oral administration). In rats embryo-/fetotoxicity and teratogenicity were mostly seen at maternal toxic doses, whereas in mice and in rabbits embryo-/fetotoxicity and teratogenicity occurred also at dose levels without maternal toxicity. However, the rabbit appeared to be the most sensitive species to the developmental toxic effects of DMF.

(Rabbit: NOAEC (inhalative) maternal toxicity and teratogenicity as well as embryo-/fetotoxicity 50 ppm; NOAEL (oral, gavage) maternal toxicity and embryo-/fetotoxicity 65 mg/kg bw/day, teratogenicity 44.1 mg/kg bw/day; NOAEL (dermal) maternal toxicity and teratogenicity as well as embryo-/fetotoxicity 200 mg/kg bw/day).

With respect to the metabolism of DMF the following conclusion can be drawn: DMF is readily absorbed via all exposure routes. N-hydroxymethyl-N-methylformamide is the main urinary metabolite and to a minor extent, but with greater toxicological relevance the metabolite mono-N-methylformamide (MMF) occurs which may partially be conjugated to glutathione forming

S-methylcarbamoylglutathione. The GSH- and its sequel adducts (S-methylcarbamoylcystein and the corresponding mercapturic acid S-methylcarbamoyl-N-acetyl-cysteine) seem to be responsible for developmental toxic effects.

At higher doses, DMF inhibits its own metabolism, i.e. the formyloxidation to MMF which precurses the GSH binding.

Persons who repeatedly inhaled DMF excreted the mercapturic acid at levels of ~13% of the dose with a total half-life (i.e. DMF biotransformation and excretion) of 23 hours.

Ethanol and probably the metabolite acetaldehyde inhibit the breakdown of DMF and conversely, DMF inhibits the metabolism of ethanol and acetaldehyde. Furthermore, ethanol induces cytochrome P450 2E1 which facilitates the initial hydroxylation of DMF. Thus, exposure to DMF can cause a severe alcohol intolerance.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Acute Toxicity Test Results

In the following a selection of results from acute aquatic toxicity tests relevant to risk assessment is summarized:

Fish

The acute toxicity of DMF to three fresh water fish species ranges from EC/LC50(96h) = 7100 – 10600 mg/l. The tests were performed applying the US-EPA test protocol EPA-660/3-75-009 (1975) under flow-through conditions with analytical monitoring of the DMF concentration. *Lepomis macrochirus* turned out to be the most sensitive species, showing a LC50(96h) = 7100 mg/l (Poirier et al., 1986).

Toxicity data from TSCATS (1971, 1974) were not taken into consideration, because mixtures containing DMF were tested. Specific effects solely related to DMF cannot be derived from these results. Due to insufficient documentation or secondary quotation results from TSCATS (1976) and Cardwell cited in Poirier, S.H. et al. (1986) were also not taken into account.

Invertebrates

The reported acute toxicity of DMF to *Daphnia magna* ranges from EC50(48h) >100 – 15700 mg/l. Additional investigations on the freshwater crayfish *Orconectes immunis* result in NOEC(24h) = 3680 mg/l (Phipps and Holcombe, 1985).

Summarising, with EC50(48h) > 100 mg/l the study of BASF (1992) on acute toxicity to *Daphnia magna* following the OECD 202 test protocol represents for formal reasons the lowest valid EC50 value. However, as this was only a limit test and also the long-term toxicity of DMF to daphnids is much higher than 100 mg/l, the value of 15700 mg/l is used for the hazard assessment because this value is from the most reliable test.

Algae

There is only one reliable study available on toxicity to unicellular green algae. The acute toxicity to *Scenedesmus subspicatus* was determined according to DIN 38412 (part 9) test protocol resulting in EC10 and EC50 (96h) > 1000 mg/l related to both inhibition of biomass and growth rate (BASF, 1988). In a long-term test with *Selenastrum capricornutum* a NOEC (14d) of 470 mg/l was found (Hughes and Vilkas, 1983). However, this test is not used for the hazard assessment as the algae growth was not longer in the exponential phase at test end and at the highest test concentration an increase in algal growth was found.

Chronic Toxicity Test Results

In a two-generation study with *Pimephales promelas* a MATC of 5 - 11 mg/l was found for the endpoint development of F1 generation (data presented by the Environ. Res. Laboratory-Duluth, USA). However, this value cannot be used for the hazard assessment, as the study is only available as draft with hand-written corrections. The report provided limited information which was not sufficient to evaluate the associated study. According to information from US-EPA the study was never finalized. Therefore, a validation was not possible.

Chronic toxicity of DMF to *Daphnia magna* was investigated by LeBlanc and Surprenant (1983) yielding a MATC(28d) = 1200 – 2500 µl/l (1140 – 2375 mg/l). MATC is defined in this investigation as the maximum acceptable toxic concentration, which did not adversely affect survival or reproduction during chronic exposure. Adams and Heidolph (1985) determined a GM-MATC = 2121 mg/l after 21d exposure of *Daphnia magna* to DMF (GM-MATC stands for geometric mean of the highest concentration producing no significant effects and the lowest concentration producing a statistically significant effect). According to the EU TGD a NOEC can be derived from this value by dividing it by $\sqrt{2}$. Therefore a NOEC of about 1500 mg/l is determined. This value is in the same order of magnitude with the MATC derived by LeBlanc et al.

A PNECaqua of 22.8 mg/l can be derived from the lowest NOEC (1140 mg/l) found in a reproduction test with *Daphnia magna* and using an assessment factor of 50. This factor is chosen because long-term tests with species representing two different trophic levels are available (daphnids and algae).

Toxicity to Microorganisms

Curtis et al. (1982) studied the inhibition of the bioluminescence of the marine bacterium *Photobacterium phosphoreum* in presence of DMF (EC₅₀/5min = 20000 mg/l).

4.2 Terrestrial Effects

The impact of DMF on colony growth of three different fungi (*Pythium ultimum*, *Sclerotinia homeocarpa*, *Pestalotia sp.*) were investigated by measuring the growth of colonies after control growth reached a diameter of 50 – 70 mm (Stratton, 1985).

EC₅₀ = 0.51 – 1.08 v/v (4794 – 10152 mg/l). This study is not relevant for an environmental hazard assessment. No PNECsoil can be derived from this study.

4.3 Initial Assessment for the Environment

Releases into the environment may occur during production of DMF and during its use e.g. as solvent, cleaning agent. In 1991 the maximum annual release of DMF into the hydrosphere from production and processing in pre-unification Germany was estimated to 352 t. Approximately 9000 t/a were emitted into the atmosphere. More recent data about environmental releases are not available. Releases into the terrestrial compartment may occur from use of DMF as solvent in plant protection products. However, this release is not quantifiable.

From the physico-chemical properties of DMF the hydrosphere was identified as target compartment. DMF is classified as readily biodegradable. In aqueous solution the substance photolyses with a half-life of 50 days. Hydrolysis is not expected to occur under environmental conditions. In the atmosphere DMF is expected to be indirectly photodegraded with a half life of 2 hours.

The log Kow of –0.85 does not indicate a potential for bio- or geoaccumulation. Also in studies with fish no bioaccumulation was found.

In short term tests with fish, daphnids and algae DMF showed a acute toxicity EC/LC₅₀ >100 mg/l. Hence DMF is not regarded as harmful to aquatic organisms. In the following the lowest valid EC/LC₅₀ data of different aquatic species are summarized:

Lepomis macrochirus: LC₅₀(96h) = 7100 mg/l

Daphnia magna: EC₅₀(48h) > 100 mg/l; EC₅₀ (48h) = 15700 mg/l

Scenedesmus subspicatus. EC10 and EC50(96h) > 1000 mg/l (biomass and growth rate)

Long term reproduction studies with *Daphnia magna* resulted in NOECs of 1140 mg/l (28 days) and 1500 mg/l (21 d)

A PNECaqua of 22.8 mg/l was derived from the lowest NOEC (1140 mg/l) using an assessment factor of 50. This factor was chosen because long-term tests with species representing two different trophic levels are available (daphnids and algae).

5 RECOMMENDATIONS

Human Health: The chemical is a candidate for further work. In occupational settings where exposure is not controlled, and due to information from European product registers, exposures cannot be excluded. As the extent of occupational and consumer exposure cannot be estimated and the substance is a developmental toxicant, a human exposure assessment, and, if then indicated, a risk assessment should be performed.

Environment: Concerning the aquatic compartment, DMF is of low concern due to the low toxicity to aquatic organisms, the low bioaccumulation potential and the classification as readily biodegradable. However, high releases of DMF into the atmosphere are described in the BUA report from 1991. Although the substance has a half-life in the atmosphere of 2 hours, these very high emissions may pose a local problem in the vicinity of point sources. In addition, releases into the soil result from the use of the substance in plant protection products. Therefore, exposure data gathering should be performed. Depending on the exposure information further information on toxicity to terrestrial organisms may be required, e.g. a plant fumigation test.

6 REFERENCES

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I U C L I D D a t a S e t

Existing Chemical ID: 68-12-2
CAS No. 68-12-2
EINECS Name N,N-dimethylformamide
EC No. 200-679-5
Molecular Formula C3H7NO

Producer Related Part

Company: BASF AG
Creation date: 12-NOV-1992

Substance Related Part

Company: BASF AG
Creation date: 12-NOV-1992

Memo: master

Printing date: 28-MAY-2003
Revision date:
Date of last Update: 28-MAY-2003

Number of Pages: 238

Chapter (profile): Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile): Reliability: without reliability, 1, 2, 3, 4
Flags (profile): Flags: without flag, SIDS

1.0.1 Applicant and Company Information

Type: lead organisation
Name: BASF AG
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Flag: Critical study for SIDS endpoint
22-MAY-2003

Type: cooperating company
Name: Air Products and Chemicals, Inc.
Country: United States

Flag: Critical study for SIDS endpoint
12-MAY-2003

Type: cooperating company
Name: Celanese
Country: United States

Flag: Critical study for SIDS endpoint
12-MAY-2003

Type: cooperating company
Name: DuPont
Country: United States

Flag: Critical study for SIDS endpoint
12-MAY-2003

Type: cooperating company
Name: Ertisa S.A.
Country: Spain

Flag: Critical study for SIDS endpoint
12-MAY-2003

Type: cooperating company
Name: Mitsubishi Gas Chemical Company, INC.
Country: Japan

Flag: Critical study for SIDS endpoint
12-MAY-2003

Type: cooperating company
Name: Mitsubishi Rayon Co., LTD.
Country: Japan

Flag: Critical study for SIDS endpoint
12-MAY-2003

Type: cooperating company
Name: Samsung Fine Chemicals Co. Ltd.
Country: other: Korea

Flag: Critical study for SIDS endpoint
12-MAY-2003

Type: cooperating company
Name: UCB SA/NV
Country: Belgium

Flag: Critical study for SIDS endpoint
12-MAY-2003

1.0.2 Location of Production Site, Importer or Formulator

1.0.3 Identity of Recipients

1.0.4 Details on Category/Template

1.1.0 Substance Identification

Mol. Formula: C3 H7 N O
Mol. Weight: 73.09 g/mol

Flag: non confidential, Critical study for SIDS
endpoint
27-JUN-2002

1.1.1 General Substance Information

Purity type: typical for marketed substance
Substance type: organic
Physical status: liquid
Purity: >= 99.9 - % w/w
Colour: colourless
Odour: faint specific odour amine-like

Flag: non confidential, Critical study for SIDS
endpoint

27-JUN-2002

(1)

1.1.2 Spectra

1.2 Synonyms and Tradenames

Dimethylformamid

Flag: non confidential, Critical study for SIDS
endpoint

02-DEC-1992

Dimethylformamide

Flag: non confidential, Critical study for SIDS
endpoint

02-DEC-1992

DMF

Flag: non confidential, Critical study for SIDS
endpoint

02-DEC-1992

DMF (amide)

Flag: non confidential, Critical study for SIDS
endpoint

02-DEC-1992

DMFA

Flag: non confidential, Critical study for SIDS
endpoint

02-DEC-1992

Formamide, N,N-dimethyl- (8CI, 9CI)

Flag: non confidential, Critical study for SIDS
endpoint

02-DEC-1992

N,N-Dimethylformamide

Flag: non confidential, Critical study for SIDS
endpoint

02-DEC-1992

N,N-Dimethylmethanamide

Flag: non confidential, Critical study for SIDS
endpoint

02-DEC-1992

N-Formyldimethylamine

Flag: non confidential, Critical study for SIDS
endpoint

02-DEC-1992

1.3 Impurities

Purity type: typical for marketed substance

CAS-No: 67-56-1

EC-No: 200-659-6

EINECS-Name: methanol

Mol. Formula: C H4 O

Contents: <= .005 - % w/w

Flag: non confidential, Critical study for SIDS
endpoint

12-MAY-2003

Purity type: typical for marketed substance

CAS-No: 124-40-3

EC-No: 204-697-4

EINECS-Name: dimethylamine, in aqueous solution

Mol. Formula: C2 H7 N

Contents: < .001 - % w/w

Flag: non confidential, Critical study for SIDS
endpoint

12-MAY-2003

1.4 Additives

1.5 Total Quantity

Quantity: 10000 - 50000 tonnes produced in 1999

Remark: Production volume refers to BASF production in Ludwigshafen (Germany)
Flag: non confidential, Critical study for SIDS endpoint
12-MAY-2003

1.6.1 Labelling

Labelling: as in Directive 67/548/EEC
Symbols: (T) toxic
Nota: (E) For substances ascribed Nota E the risk phrases R20, R22 to R28 and all combinations of these risk phrases shall be preceded by the word 'also'. E.g. R23 'also' toxic by inhalation
Specific limits: no
R-Phrases: (61) May cause harm to the unborn child
(20/21) Harmful by inhalation and in contact with skin
(36) Irritating to eyes
S-Phrases: (53) Avoid exposure - obtain special instructions before use
(45) In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible)
Remark: INDEX-No. 616-001-00-X
Flag: non confidential, Critical study for SIDS endpoint
01-JUL-2002 (2)

1.6.2 Classification

Classified: as in Directive 67/548/EEC
Class of danger: harmful
R-Phrases: (20/21) Harmful by inhalation and in contact with skin
Remark: INDEX-No. 616-001-00-X
Flag: non confidential, Critical study for SIDS endpoint
01-JUL-2002 (2)
Classified: as in Directive 67/548/EEC
Class of danger: irritating
R-Phrases: (36) Irritating to eyes
Remark: INDEX-No. 616-001-00-X

Flag: non confidential, Critical study for SIDS
endpoint
01-JUL-2002 (2)

Classified: as in Directive 67/548/EEC
Class of danger: toxic for reproduction, category 2
R-Phrases: (61) May cause harm to the unborn child

Remark: INDEX-No. 616-001-00-X
Flag: non confidential, Critical study for SIDS
endpoint
01-JUL-2002 (2)

1.6.3 Packaging

1.7 Use Pattern

Type: type
Category: Non dispersive use

Flag: non confidential, Critical study for SIDS
endpoint
16-FEB-1994

Type: industrial
Category: Basic industry: basic chemicals

Flag: non confidential, Critical study for SIDS
endpoint
16-FEB-1994

Type: industrial
Category: Electrical/electronic engineering industry

Flag: non confidential, Critical study for SIDS
endpoint
16-FEB-1994

Type: industrial
Category: Leather processing industry

Flag: non confidential, Critical study for SIDS
endpoint
16-FEB-1994

Type: industrial
Category: Paints, lacquers and varnishes industry

Flag: non confidential, Critical study for SIDS
endpoint

11-JUL-2002

Type: use
Category: Solvents

Flag: non confidential, Critical study for SIDS
endpoint

16-FEB-1994

1.7.1 Detailed Use Pattern

1.7.2 Methods of Manufacture

1.8 Regulatory Measures

1.8.1 Occupational Exposure Limit Values

Type of limit: BAT (DE)
Limit value: 15 other: mg/l

Country: Germany
Remark: testing material: urine
time of sampling: end of exposure
Flag: non confidential, Critical study for SIDS
endpoint

23-MAY-2003 (3)

Type of limit: MAK (DE)
Limit value: 10 ml/m³

Country: Germany
Flag: non confidential, Critical study for SIDS
endpoint

12-MAY-2003 (4)

Type of limit: MAK (DE)
Limit value: 30 mg/m³

Country: Germany
Remark: absorbable to the skin
exceeding factor: 4
Flag: non confidential, Critical study for SIDS
endpoint

12-MAY-2003 (4)

1.8.2 Acceptable Residues Levels

1.8.3 Water Pollution

Classified by: other: VwVwS (Germany) of 17.05.1999, Annex 2
Labelled by: other: VwVwS (Germany) of 17.05.1999, Annex 2
Class of danger: 1 (weakly water polluting)

Country: Germany
Remark: ID-Number: 83
Flag: non confidential, Critical study for SIDS
endpoint

12-MAY-2003 (5)

1.8.4 Major Accident Hazards

1.8.5 Air Pollution

1.8.6 Listings e.g. Chemical Inventories

Type: EINECS
Additional Info: EINECS No. 200-679-5

Flag: non confidential, Critical study for SIDS
endpoint

12-MAY-2003 (6)

Type: ENCS
Additional Info: ENCS No. 2-680

Remark: ENCS CLASSIFICATION:
Low Molecular Chain-like Organic Compounds.
Flag: non confidential, Critical study for SIDS
endpoint

12-MAY-2003 (6)

Type: ECL
Additional Info: ECL Serial No. KE-11411

Flag: non confidential, Critical study for SIDS
endpoint

12-MAY-2003 (6)

Type: other: SWISS
Additional Info: SWISS No. G-1559

Remark: SWISS CLASSIFICATION:
Giftliste 1 (List of Toxic Substances 1), 31 May
1999.
Toxic Category 3: Acute oral lethal dose of 50 -
500 mg/kg.

Flag: non confidential, Critical study for SIDS
endpoint
12-MAY-2003 (6)

Type: other: TAIWAN
Additional Info: TAIWAN No. 98-01

Remark: TAIWAN CLASSIFICATION:
This is a Class II toxic chemical. Regulated
Threshold quantity is 50 Kg. Minimum control
level is 1 w/w%.

Flag: non confidential, Critical study for SIDS
endpoint
12-MAY-2003 (6)

Type: TSCA

Flag: non confidential, Critical study for SIDS
endpoint
12-MAY-2003 (6)

Type: DSL

Flag: non confidential, Critical study for SIDS
endpoint
12-MAY-2003 (6)

Type: AICS

Flag: non confidential, Critical study for SIDS
endpoint
12-MAY-2003 (6)

Type: PICCS

Flag: non confidential, Critical study for SIDS
endpoint
12-MAY-2003 (6)

1.9.1 Degradation/Transformation Products

1.9.2 Components

1.10 Source of Exposure

1.11 Additional Remarks

1.12 Last Literature Search

Type of Search: Internal and External
Chapters covered: 5.10
Date of Search: 06-NOV-2002

06-FEB-2003

Type of Search: Internal and External
Date of Search: 18-JUL-2001

Flag: Critical study for SIDS endpoint
12-MAY-2003

1.13 Reviews

Memo: BUA report No.: 84 of 1991

Flag: Critical study for SIDS endpoint
20-JUL-2001

Memo: IPCS Environmental Health Criteria 114 of 1991
25-MAR-2003

2.1 Melting Point

Value: = -61 degree C

Remark: Key study selected for robust summary

Reliability: (4) not assignable
Secondary quotation

Flag: Critical study for SIDS endpoint

19-JUN-2001 (7)

Value: = -61 degree C

Reliability: (4) not assignable
Handbook

27-NOV-2000 (8)

Value: = -60.5 degree C

Reliability: (4) not assignable
Secondary quotation

28-NOV-2000 (9)

2.2 Boiling Point

Value: = 152 - 153 degree C

Reliability: (4) not assignable
Handbook

27-NOV-2000 (8)

Value: = 152.5 - 153.5 degree C

Remark: Key study selected for robust summary

Reliability: (4) not assignable
Secondary quotation

Flag: Critical study for SIDS endpoint

30-JUL-2001 (7)

Value: = 153 degree C

Reliability: (4) not assignable
Secondary quotation

28-NOV-2000 (9)

2.3 Density

Value: = .94 g/cm³ at 20 degree C

Reliability:	(4) not assignable Manufacturer/producer data without proof	
05-MAY-2000		(10)
Type:	density	
Value:	= .95 g/cm ³ at 20 degree C	
Remark:	Key study selected for robust summary	
Reliability:	(4) not assignable Secondary quotation	
Flag:	Critical study for SIDS endpoint	
12-MAY-2003		(7)
Value:	= .9445 g/cm ³ at 25 degree C	
Reliability:	(4) not assignable Secondary quotation	
18-JUN-2001		(11)
Value:	= .9445 g/cm ³ at 25 degree C	
Reliability:	(4) not assignable Secondary quotation	
18-JUN-2001		(9)
Value:	= .95	
Remark:	sp.gr.	
Reliability:	(4) not assignable Handbook	
18-JUN-2001		(8)

2.3.1 Granulometry

2.4 Vapour Pressure

Value:	= 3.5 hPa at 20 degree C	
Remark:	= 4.8 hPa at 25 °C = 34.6 hPa at 60 °C Key study selected for robust summary	
Reliability:	(4) not assignable Secondary quotation	
Flag:	Critical study for SIDS endpoint	
18-JUN-2001		(9)
Value:	= 3.6 hPa at 20 degree C	
Reliability:	(4) not assignable	

27-NOV-2000 Handbook (8)

Value: = 3.77 hPa at 20 degree C

Reliability: (4) not assignable
Manufacturer/producer data without proof

19-JUN-2001 (10)

2.5 Partition Coefficient

Partition Coeff.: octanol-water

log Pow: = -.85 at 25 degree C

Method: other (measured): GC

Remark: log Pow: mean value of three measurements

Key study selected for robust summary

Reliability: (2) valid with restrictions

Scientifically acceptable study

Flag: Critical study for SIDS endpoint

12-MAY-2003 (12)

log Pow: = -1.028

Method: other (calculated): Increment method by Rekker
with computer programme of firm CompuDrug Ltd.

Reliability: (2) valid with restrictions

Calculated value in accordance with generally
accepted standard methods

28-NOV-2000 (13)

log Pow: = -1.01

Method: other (measured)

Reliability: (2) valid with restrictions

Scientifically verified data

27-NOV-2000 (14) (15) (16)

log Pow: = -.89

Remark: n-Octanol/water partition coefficient = 0.13

Reliability: (4) not assignable

Secondary quotation

28-NOV-2000 (9)

log Pow: =

Result: log Pow -0.87/-0.59 (calculated)
Reliability: (4) not assignable
Handbook
19-JUL-2001 (8)

2.6.1 Solubility in different media

Solubility in: Water
Descr.: miscible
Remark: Key study selected for robust summary
Reliability: (4) not assignable
Secondary quotation
Flag: Critical study for SIDS endpoint
12-MAY-2003 (7)

Solubility in: Water
Value: at 20 degree C
pH value: 7
Conc.: 200 g/l at 20 degree C
Descr.: miscible
Reliability: (4) not assignable
Manufacturer/producer data without proof
Flag: Critical study for SIDS endpoint
12-MAY-2003 (10)

Descr.: miscible
Method: other: measured
Reliability: (4) not assignable
Abstracts
18-JUN-2001 (17)

Descr.: miscible
Reliability: (4) not assignable
Secondary quotation
28-NOV-2000 (9)

2.6.2 Surface Tension

Value: = 35.2 mN/m at 25 degree C
Remark: Key study selected for robust summary

Result: Original data: 35.2 dyn/cm at 25 °C
Reliability: (4) not assignable
Secondary quotation
Flag: Critical study for SIDS endpoint
19-JUN-2001 (18)

Value: = 35.5 mN/m at 20 degree C
Reliability: (4) not assignable
Secondary quotation
27-NOV-2000 (7)

2.7 Flash Point

Value: = 57.5 degree C
Type: closed cup
Method: other: DIN 51 755
Remark: Key study selected for robust summary
Test substance: N,N-dimethylformamide pure
Reliability: (2) valid with restrictions
National standard method without detailed
documentation
Flag: Critical study for SIDS endpoint
19-JUL-2001 (19)

Value: = 58 degree C
Type: closed cup
Method: other: DIN 51 755
Reliability: (4) not assignable
National standard method without detailed
documentation
30-JUL-2001 (10)

Value: = 58 degree C
Type: closed cup
Method: other: DIN 51 755
Reliability: (4) not assignable
Secondary quotation
27-NOV-2000 (7)

Value: = 58 degree C
Type: closed cup

Reliability: (4) not assignable
Secondary quotation
28-NOV-2000 (9)

2.8 Auto Flammability

Value: = 410 degree C
Method: other: DIN 51 794
Remark: Ignition temperature
Reliability: (4) not assignable
Secondary quotation
28-NOV-2000 (7)

Value: = 435 degree C
Method: other: DIN 51 794
Remark: Key study selected for robust summary
Test substance: N,N-dimethylformamide pure
Reliability: (1) valid without restriction
National standard specification
Flag: Critical study for SIDS endpoint
18-JUN-2001 (19)

Value: = 445 degree C
Remark: Auto-ignition temperature
Reliability: (4) not assignable
Secondary quotation
28-NOV-2000 (9)

2.9 Flammability

2.10 Explosive Properties

Result: not explosive
Remark: because of chemical structure
Key study selected for robust summary
Reliability: (2) valid with restrictions
Expert judgment
Flag: Critical study for SIDS endpoint
19-JUN-2001 (20)

2.11 Oxidizing Properties

Result: no oxidizing properties

Remark: because of chemical structure
Key study selected for robust summary

Reliability: (2) valid with restrictions
Expert judgment

Flag: Critical study for SIDS endpoint
19-JUN-2001 (20)

2.12 Dissociation Constant

2.13 Viscosity

Test type: other

Value: .87 mPa s (dynamic) at 15 degree C

Reliability: (2) valid with restrictions
Secondary quotation

Flag: Critical study for SIDS endpoint
12-MAY-2003 (7)

2.14 Additional Remarks

Remark: Dangerous reactions when mixed with nitrate and
Strong oxidizing agents. Dangerous reactions
when mixed with halogenated hydrocarbons in the
presence of certain metals, particularly at
elevated temperatures. Key study selected for
robust summary

Reliability: (4) not assignable
Manufacturer/producer data without proof

Flag: Critical study for SIDS endpoint
19-JUN-2001 (10)

Remark: explosive limits in air: 2.2 - 16 vol%

Reliability: (4) not assignable
Secondary quotation

Flag: Critical study for SIDS endpoint
27-NOV-2000 (7)

3.1.1 Photodegradation**Type:** air**INDIRECT PHOTOLYSIS****Sensitizer:** OH**Conc. of sens.:** 500000 molecule/cm³**Rate constant:** = .00000000021 cm³/(molecule * sec)**Degradation:** = 50 % after 2 hour(s)**Method:** other (calculated): according to Atkinson**Reliability:** (2) valid with restrictions

Accepted calculation method

Flag: Critical study for SIDS endpoint

22-MAY-2003

(21) (22)

Type: water**INDIRECT PHOTOLYSIS****Sensitizer:** OH**Degradation:** = 50 % after 50 day(s)**Result:** Conc. of Sensitizer: 1*10⁻¹⁶ mol/l;Rate Constant: (1.7 +/- 0.3)*10⁹ l/mol*sec**Test condition:** pH = 5.5, concentration of test substance 5 - 100 mmol/l**Reliability:** (2) valid with restrictions

Test procedure not in accordance with defined methods, but data are comprehensible and scientifically acceptable

Flag: Critical study for SIDS endpoint

22-MAY-2003

(23) (24)

3.1.2 Stability in Water**Method:** other**Result:** Hydrolysis of DMF is not expected in the environment.**Flag:** Critical study for SIDS endpoint

22-MAY-2003

(22)

3.1.3 Stability in Soil

3.2.1 Monitoring Data (Environment)

- Medium:** air
- Remark:** concentration: nd-14 ug/m3 (1 location, 4 samples)
03-FEB-1997 (25)
- Type of measurement:** other
Medium: other: industrial wastewater
- Remark:** USA, industrial wastewater: <10 ug/l detected using GC-MS analysis.
24-JUN-2002 (26)
- Type of measurement:** other
Medium: sediment
- Remark:** Japan, detection in sediment: <100 ng/kg.
24-JUN-2002 (27)
- Type of measurement:** other
Medium: surface water
- Remark:** Japan, detection in surface water: <10 ug/l.
24-JUN-2002 (27)

3.2.2 Field Studies

3.3.1 Transport between Environmental Compartments

- Type:** adsorption
Media: water - soil
Method: other
- Result:** No experiments have been carried out on the mobility of DMF in soil. From the partition coefficient for octanol/water, soil-sorption coefficient, Koc, can be calculated from various correlations for various contents of organic carbon (TDG, p. 539: Nonhydrophobics, $\log Koc = 0.52 \log Kow + 1.02$). The maximum value for the coefficients is lower than 10, a value which corresponds to very slight soil sorption.
- Reliability:** (2) valid with restrictions
Accepted calculation methods
- Flag:** Critical study for SIDS endpoint
22-MAY-2003 (22) (28) (29)

Type: volatility
Media: water - air
Method: other

Result: DMF is infinitely miscible with water and its vapour pressure is lower than that of water. It can be assumed that DMF shows very little tendency to evaporate from aqueous solution. Taft et al. determined the equilibrium constant experimentally at 25 °C to be $\log K_{eq} = -5.52$. Substitution into the equation, $H = H' * RT$ yields a Henry's constant of $H = 7.47 * 10^{-5}$ hPa*m³/mol.

Reliability: (2) valid with restrictions
 Accepted calculation method

Flag: Critical study for SIDS endpoint
 25-JUN-2002 (22) (30)

3.3.2 Distribution

Media: air - biota - sediment(s) - soil - water
Method: Calculation according Mackay, Level I

Method: Fugacity-Based Environmental Equilibrium Partitioning Model, V2.11, Environmental Modelling Centre, Trent University Ontario, Canada (1999)

Remark: Input Data
 Molecular Mass: 73g/mol
 Temperature: 25°C
 log Kow: -0.85
 Water solubility: 9.4E+05 g/m³
 Vapor pressure: 480 Pa
 Melting Point: -61°C

Result: water: 98.7 %; air: 1.3 %

Reliability: (2) valid with restrictions
 Accepted calculation method

Flag: Critical study for SIDS endpoint
 22-MAY-2003 (31)

3.4 Mode of Degradation in Actual Use

3.5 Biodegradation

Type: aerobic
Inoculum: activated sludge, domestic, non-adapted

Method: other: Respirometric test

Test substance: as prescribed by 1.1 - 1.4

Result: Various concentrations of DMF (80-440 mg/l) were Exposed under constant stirring to adapted and not adapted municipal waste water for at most 10 days at 20 °C. During exposure the bacterial oxygen consumption was measured once a day. The nutrient medium was supplemented with yeast extract or glucose. Under these conditions using not adapted waste water, DMF was biodegraded to 90 % within at most 9 days related to the theoretical oxygen uptake (BOD/ThOD).

Reliability: (2) valid with restrictions
Test procedure not in accordance with defined methods, but data are comprehensible and scientifically acceptable

Flag: Critical study for SIDS endpoint
22-MAY-2003 (32)

Type: aerobic
Inoculum: other: River water
Concentration: 30 mg/l related to Test substance

Test substance: no data

Remark: Primary degradation of DMF was analysed by GC
Result: To determine the biodegradability under environmental conditions, 30 mg/l DMF was treated with not acclimated river water. After passing through a lag phase of app. 2 days, DMF was completely biodegraded within 6 days at a rate of 0.55 mg/l*h.

Reliability: (2) valid with restrictions
Test procedure not in accordance with defined methods, but data are comprehensible and scientifically acceptable.

Flag: Critical study for SIDS endpoint
22-MAY-2003 (32)

Type: aerobic
Concentration: 70 mg/l

Method: other: Sewage Treatment Simulations Test
Test substance: no data

Result: In this continuous sewage treatment simulation test, synthetic waste water containing 0.6 g/l meat extract (BOD5 = 360 mg/l O2) was used as influent spiked with 70 mg/l DMF.

After 35 days of acclimation DMF was nearly completely removed from the waste water. The mean retention time of the water in the aeration chamber was about 4 hours.

Reliability: (2) valid with restrictions
Test procedure not in accordance with defined methods, but data are comprehensible and scientifically acceptable

Flag: Critical study for SIDS endpoint

22-MAY-2003 (32)

Type: aerobic
Inoculum: activated sludge
Concentration: 100 mg/l related to Test substance
Degradation: = 4.4 % after 14 day(s)

Test substance: no data

Method: The guideline corresponds to 301 C, Ready Biodegradability:

Modified MITI-(I)-Test
Test condition: Concentration of sludge: 30 mg/l

Reliability: (1) valid without restriction
Guideline study

Flag: Critical study for SIDS endpoint

22-MAY-2003 (33)

Type: aerobic
Inoculum: domestic sewage, non-adapted
Concentration: 20 mg/l related to DOC (Dissolved Organic Carbon)
Degradation: = 100 % after 21 day(s)
Result: readily biodegradable

Method: OECD Guide-line 301 E "Ready biodegradability: Modified OECD Screening Test"

Test substance: as prescribed by 1.1 - 1.4

Remark: DMF was biodegraded after a lag phase (acclimation phase) of 14 days. DMF is readily biodegradable according to OECD criteria.

Reliability: (1) valid without restriction
Guideline study

Flag: Critical study for SIDS endpoint

22-MAY-2003 (34) (22)

Type: aerobic
Inoculum: activated sludge
Degradation: 95 % after 3 day(s)

Method: OECD Guide-line 302 B "Inherent biodegradability: Modified Zahn-Wellens Test"

GLP: no

Reliability: (2) valid with restrictions
guideline study
27-MAY-2003 (35)

Type: aerobic
Inoculum: activated sludge
Degradation: = 81 % after 13 day(s)

Method: other: BOD-Test (BOD of THOD)

Reliability: (4) not assignable
18-JUN-2001 (36)

Type: aerobic
Inoculum: other: salt water
Degradation: = 42.5 % after 5 day(s)

Method: other: BOD-Test, resp. Sea Water Dilution Method; (BOD of THOD)

Test condition: concentration: 4 ppm of test substance
Reliability: (2) valid with restrictions
Test procedure not in accordance with defined methods, but data are comprehensible and scientifically acceptable
28-JUN-2002 (37)

Type: aerobic
Inoculum: other: fresh water
Degradation: = 4.7 % after 5 day(s)

Method: other: BOD-Test, resp. Standard Dilution Method; (BOD of THOD)

Test condition: concentration: 4 ppm of test substance
Reliability: (2) valid with restrictions
Test procedure not in accordance with defined methods, but data are comprehensible and scientifically acceptable
28-JUN-2002 (37)

Type: aerobic
Inoculum: activated sludge
Degradation: < 30 % after 14 day(s)

Method: other: MITI-Test

Remark: "Degradation resistant"

Test condition: 100 ppm test substance/ 30 ppm sludge

Reliability: (2) valid with restrictions
Test procedure not in accordance with defined methods, but data are comprehensible and scientifically acceptable

18-JUN-2001 (38)

3.6 BOD5, COD or BOD5/COD Ratio

3.7 Bioaccumulation

Species: Cyprinus carpio (Fish, fresh water)

Exposure period: 56 day(s) at 25 degree C

Concentration: 20 µg/l

BCF: .3 - .8

Method: OECD Guide-line 305 C "Bioaccumulation: Test for the Degree of Bioconcentration in Fish"

GLP: no data

Test substance: no data

Reliability: (1) valid without restriction
Guideline study

Flag: Critical study for SIDS endpoint

22-MAY-2003 (33)

Species: Cyprinus carpio (Fish, fresh water)

Exposure period: 56 day(s) at 25 degree C

Concentration: 2 µg/l

BCF: .3 - 1.2

Method: OECD Guide-line 305 C "Bioaccumulation: Test for the Degree of Bioconcentration in Fish"

GLP: no data

Test substance: no data

Remark: Key study selected for robust summary

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

22-MAY-2003 (33)

3.8 Additional Remarks

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: flow through
Species: Lepomis macrochirus (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** yes
LC50: 7100

Method: other: US EPA (1975) Committee on methods for toxicity tests with aquatic organisms.
EPA- 660/3-75-009

GLP: no data

Test substance: other TS: N,N-Dimethylformamide, no further data

Remark: Several test concentrations (up to 5, where appropriate) and a control were tested in duplicate in Lepomis macrochirus (average weight: 0.912 +/- 0.350 g) delivered from Lake Mills Fish Hatchery. Groups of 10 fishes were tested in glass exposure tanks (20x35x9 cm; containing 6.3L). Water was untreated Lake Superior water used at about 19.8°C (+/- 2.3°C). Water quality characteristics were measured using methods described by the American Public Health Association et al. (1975). Exposure samples were analyzed on a DB-UV spectrophotometer at a wavelength of 200 nm. Fish were not fed 24 h before or during a test. Dead fish were counted and removed at 1, 3, 6, 12, and 24 h after initial exposure and at a 24-h period thereafter.

Result: No controls died. DMF-exposed Lepomis macrochirus were stressed and showed mortality within 3 h after initial exposure, deaths continued throughout the test with all fish dead in the highest concentration at 96 h (no values given). The 96 h LC50 and its 95% confidence limits were 7100 (6700 - 7500) mg/l.

Test condition: pH: 7.04 - 7.97,
hardness: 40.4 - 56.3 mg/l as CaCO₃,
dissolved oxygen: 54.3 - 88.9%

Reliability: (1) valid without restriction
Guideline study

Flag: Critical study for SIDS endpoint

28-MAY-2003

(39)

Type: flow through
Species: Pimephales promelas (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** yes
LC50: 10600

Method: other: US EPA (1975) Committee on methods for toxicity tests with aquatic organisms.
EPA-660/3-75-009

GLP: no data

Test substance: other TS: N,N-Dimethylformamide, no further data

Remark: Several test concentrations (up to 5, where appropriate) and a control were tested in duplicate in Pimephales promelas (28- to 32-day old; average weight: 0.047 +/- 0.022 g) reared at the US EPA Environmental Research Laboratory-Duluth test facility. Groups of 20 fishes were tested in glass exposure tanks (20x35x9 cm; containing 6.3L). Water was untreated Lake Superior water used at About 23.3°C (+/- 1.7°C). Water quality characteristics were measured using methods described by the American Public Health Association et al. (1975). Exposure samples were analyzed on a DB-UV spectrophotometer at a wavelength of 200 nm. Fish were not fed 24 h before or during a test. Dead fish were counted and removed at 1, 3, 6, 12, and 24 h after initial exposure and at a 24-h period thereafter.

Result: No controls died. DMF-exposed Pimephales promelas showed mortalities immediately after initial exposure with 89.7% dead in the highest exposure at 96 h (no values given). The 96 h LC50 and its 95% confidence limits were 10600 (10400 - 10800) mg/l.

Test condition: pH: 7.04 - 7.97,
hardness: 40.4 - 56.3 mg/l as CaCO₃,
dissolved oxygen: 78.1 - 98.0%

Reliability: (1) valid without restriction
Guideline study

Flag: Critical study for SIDS endpoint

22-MAY-2003

(39)

Type: flow through
Species: Salmo gairdneri (Fish, estuary, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** yes

LC50: 9800

Method: other: US EPA (1975) Committee on methods for toxicity tests with aquatic organisms.
EPA-660/3-75-009

GLP: no data

Test substance: other TS: N,N-Dimethylformamide, no further data

Remark: Several test concentrations (up to 5, where appropriate) and a control were tested in duplicate in *Salmo gairdneri* (juvenile animals; average weight: 5.08 +/- 1.97 g) delivered from Fattig Hatcheries, Brady, NE. Groups of 10 fishes were tested in glass exposure tanks (20x35x9 cm; containing 6.3L). Water was untreated Lake Superior water used at about 12.7°C (+/- 1.0°C). Water quality characteristics were measured using methods described by the American Public Health Association et al. (1975). Exposure samples were analyzed by aqueous injection gas-liquid chromatography. Fish were not fed 24 h before or during a test. Dead fish were counted and removed at 1, 3, 6, 12, and 24 h after initial exposure and at a 24- h period thereafter.

Result: No controls died. DMF-exposed *Salmo gairdneri* were stressed and showed mortality within 3 h after initial exposure, deaths continued throughout the test with all fish dead in the highest concentration at 96 h (no values given). The 96 h LC50 and its 95% confidence limits were 9800 (9000 -10700) mg/l.

Test condition: pH: 7.04 - 7.97,
hardness: 40.4 - 56.3 mg/l as CaCO₃,
dissolved oxygen: 61.0 - 95.9%

Reliability: (1) valid without restriction
Guideline study

Flag: Critical study for SIDS endpoint
22-MAY-2003 (39)

Type: static

Species: *Brachydanio rerio* (Fish, fresh water)

Exposure period: 96 hour(s)

Unit: mg/l **Analytical monitoring:** no

LC50: = 8844

Result: The effects of the test substance on embryonal development were studied in zebrafish embryos.

The embryos were exposed to the test substance at concentrations ranging from 8.5 to 420 mmol/l (ca. 0.6 - 30.7 g/l) continuously during a period from the eight-cell stage until hatching.

According to the authors, exposure to the test substance resulted in malformations; skeletal abnormalities (curvature of spine and tail), atrophy of the heart, reduction of the heart beat rate and circulatory disorder were observed. According to the authors, these findings were different from the effects of the test substance observed in rats and mice. NOEC, LC50, and LC100 were determined as 15, 121, and 218 mmol/l (1 096, 8 844, and 15 934 mg/l), respectively.

Reliability:

(2) valid with restrictions

Test procedure not in accordance with defined methods, but data are comprehensible and scientifically acceptable

30-JUL-2001

(40)

Type:

static

Species:

Lepomis macrochirus (Fish, fresh water)

Exposure period:

96 hour(s)

Unit:

mg/l

Analytical monitoring: no data

Method:

other: static bioassay as described in the Fish Bioassay Procedure in 1970 ed. of Standard Methods (APHA)

GLP:

no data

Test substance:

other TS: Cytox 3522, a mixture containing N,N-Dimethylformamide, no further data

Remark:

The TL50 in mg active ingredient/liter for 96 hours is 2.09 and the No Effect Concentration is 1.60 mg/L.

Reliability:

(4) not assignable

Reported values result from testing a mixture containing the test substance. Specific effects solely related to the test substance cannot be derived due to unknown interactions with other components.

20-JUL-2001

(41)

Type:

static

Species:

Oncorhynchus mykiss (Fish, fresh water)

Exposure period:

96 hour(s)

Unit:

mg/l

Analytical monitoring: no data

Method: other: static bioassay as described in the Fish Bioassay Procedure in 1970 ed. of Standard Methods (APHA)
GLP: no data
Test substance: other TS: Cytox 3522, a mixture containing N,N-Diemthylformamide , no further data
Remark: The TL50 in mg active ingredient/liter for 96 hours is 1.04 and the No Effect Concentration is 0.42 mg/L.
Reliability: (4) not assignable
Reported values result from testing a mixture containing the test substance. Specific effects solely related to the test substance cannot be derived due to unknown interactions with other components.

20-JUL-2001 (41)

Type: static
Species: Pimephales promelas (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** no data
NOEC: = 3200
LC50: = 9080
LC90 : = 14500

Method: other: Standard static acute fish toxicity test method-Environmental Sciences Research Laboratory, The Dow Chemical Company
GLP: no data
Test substance: as prescribed by 1.1 - 1.4
Remark: The fishes were exposed at 12°C in dechlorinated Lake Huron water. Analyses were made for total oxygen demand, chemical oxygen demand and biochemical oxygen demand.
Reliability: (4) not assignable
insufficient documentation

20-JUL-2001 (42)

Species: Lepomis macrochirus (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:**
LC50: 6300
GLP: no data
Test substance: no data

Reliability: (4) not assignable
Secondary literature
19-JUL-2001 (43)

Species: Lepomis macrochirus (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:**
LC50: 7500

Reliability: (4) not assignable
second quotation
28-MAY-2003 (44)

Species: Leuciscus idus (Fish, fresh water)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** no
LC50: > 500
Limit Test: no

Method: other: screening-test
GLP: no

Remark: 3 fish were tested per concentration;
concentration ranged from 10 up to 10000 mg/L.
No mortality occurred at any observation time
(4, 24, 48 h).

Reliability: (3) invalid
screening-test not according to standard test
procedure
27-MAY-2003 (45)

Species: Oncorhynchus mykiss (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** no data
LC50: = .86

Method: other
GLP: no data
Test substance: other TS: Nopcocide 150 a mixture with a content
of 32.5% Dimethylformamide

Remark: Data were prepared from multiple tests, no
detailed information on test conditions with
respect to type of study are given.

Test substance: other TS: Nopcocide 150, active ingredients
bis-1,4-bromoacetoxy 2-butene 28 %, methylene
bis-thiocyanate 6.5%, inert ingredients 65.5%
(32.5% Dimethylformamide)

Reliability: (4) not assignable Reported values result from testing a mixture containing the test substance. Specific effects solely related to the test substance cannot be derived due to unknown interactions with other components.
20-JUL-2001 (46)

Species: Pimephales promelas (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:**
LC50: 9080 - 11400

Reliability: (4) not assignable second quotation
28-MAY-2003 (47) (48)

Species: Pimephales promelas (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:**
LC50: 10410

GLP: no data
Test substance: no data

Reliability: (4) not assignable Secondary literature
19-JUL-2001 (43)

Species: Salvelinus fontinalis (Fish, estuary, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:**
LC50: 8366

GLP: no data
Test substance: no data

Reliability: (4) not assignable Secondary literature
19-JUL-2001 (43)

Species: other: Bluegills
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** no data
LC50: = 1

Method: other
GLP: no data

Test substance: other TS: Nopcocide 150, mixture with a content of 32.5% Dimethylformamide

Remark: Data were prepared from multiple tests, no detailed informations on test conditions with respect to type of study are given.

Test substance: other TS: Nopcocide 150, active ingredients bis-1,4-bromoacetoxy 2-butene 28 %, methylene bis-thiocyanate 6.5%, inert ingredients 65.5% (32.5% Dimethylformamide)

Reliability: (4) not assignable
Reported values result from testing a mixture containing the test substance. Specific effects solely related to the test substance cannot be derived due to unknown interactions with other components.

20-JUL-2001 (46)

4.2 Acute Toxicity to Aquatic Invertebrates

Species: Daphnia magna (Crustacea)

Exposure period: 48 hour(s)

Unit: mg/l **Analytical monitoring:** yes

EC0: >= 100

EC50: > 100

EC100: > 100

Method: other: 79/831/EEC corresponds to OECD 202

Year: 1989

GLP: yes

Test substance: other TS: 99.8 % purity

Test condition: illumination: artificial light, day:night-rhythm = 16:8 hours light intensity: appr. 5-6 $\mu\text{E}/\text{m}^2\cdot\text{s}$ at 400 - 700 nm, test volume: 10 ml, number of animals/vessel: 5, total number of animals/concentration: 20, number of replicates and controls/concentration: 4, age of test animals: 2 - 24 hours, immobilisation was checked at 0, 3, 6, 24 and 48 h, concentration range: 100 - 12.5 mg/l, temperature: 19.8 - 20.5 °C, pH: 7.8 - 8.0, dissolved oxygen: 8.1 - 8.8 mg/l, dilution factor: 2

Reliability: (1) valid without restriction
Guideline study

Flag: Critical study for SIDS endpoint

22-MAY-2003 (49)

Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:**
EC50: = 19800

Method: other: static acute toxicity test according to ASTM E 729
Test substance: other TS: technical grade

Reliability: (1) valid without restriction
Guideline study
02-AUG-2001 (50)

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** no
NOEC: = 6000
EC50: = 15700

Method: other: static acute toxicity test according to ASTM E 729
GLP: no
Test substance: other TS: technical grade

Test condition: age of test animals: < 24 h,
endpoint: Mortality at 24 h and 48 h,
mean O2-content: 6.0 - 9.3 mg/l,
temperature: 20- 23 °C,
pH - value: 7.0 - 8.5,
hardness: 120 -250 mg/l,
feeding: no

Reliability: (1) valid without restriction
Guideline study
Flag: Critical study for SIDS endpoint
22-MAY-2003 (50)

Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:** no
LC50 : = 16150

Method: other
Test substance: other TS: analytical grade

Remark: endpoint: mortality
Result: LC50 = 17000 (13000 - 22000) µl/l corresponds to
LC50 = 16150 (12350 - 20900) mg/l
Test condition: age: < 24 h, pH 7.9 - 8.3, total hardness: 165 mg/l, temperature: 21 °C, 15 daphnids/conc. level, 16 h light/8 h dark

Reliability: (2) valid with restrictions
Test procedure not in accordance with defined methods, but data are comprehensible and scientifically acceptable
02-AUG-2001 (51)

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** no
LC50 : = 12350

Method: other
Test substance: other TS: analytical grade

Result: LC50 = 13000 (10000 - 16000) µl/l corresponds to
LC50 = 12350 (9500 - 15200) mg/l
Test condition: age: < 24 h, pH 7.9 - 8.3, total hardness: 165 mg/l,
temperature: 21 °C, 15 daphnids/conc. level, 16 h light/8 h dark

Reliability: (2) valid with restrictions
Test procedure not in accordance with defined methods, but data are comprehensible and scientifically acceptable
03-AUG-2001 (51)

Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC50: 900
EC100: > 1000
Limit Test: no

Method: other: according to DIN 38412 L 11
GLP: no

Reliability: (2) valid with restrictions guideline study without GLP and analytics
27-MAY-2003 (52)

Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:**
EC50: = 26300

Method: other: immobilisation
18-JUN-2001 (39)

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:**
EC50: = 14500

Method: other: immobilisation
Test substance: as prescribed by 1.1 - 1.4

18-JUN-2001 (39)

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:**
LC50 : = 14400

Method: other: mortality
Test substance: as prescribed by 1.1 - 1.4

31-OCT-2000 (53)

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:**
LC50 : 13100

Reliability: (4) not assignable
second quotation

27-MAY-2003 (54)

Species: other aquatic arthropod: Brown shrimp
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:**
LC50 : > 100

30-NOV-1992 (55)

Species: other aquatic arthropod: Orconectes immunis
(Crayfish)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:** yes
NOEC: = 3680

Method: other: mortality
GLP: no

Remark: No mortality was observed up to 3680 mg/l
(24/48/72/96 h).

Reliability: (2) valid with restrictions Test procedure not in accordance with defined methods, but data are comprehensible and scientifically acceptable
02-AUG-2001 (56)

Species: other aquatic arthropod: Water fleas
Exposure period: 3 hour(s)
Unit: mg/l **Analytical monitoring:**
LC50 : = 13000
30-NOV-1992 (57)

Species: other aquatic arthropod: Water fleas
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:**
LC50 : = 14530
30-NOV-1992 (58)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Scenedesmus subspicatus (Algae)
Endpoint: growth rate
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC10: > 1000
EC50: > 1000

Method: other: DIN 38412, part 9, Determination of inhibitory effect on the cell multiplication
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: EC values are given in nominal concentrations.
Test condition: number of replicates/concentration: 4
concentration of test substance: 100, 320 and 1000 mg/l algal growth was checked by determination of chlorophyll A fluorescence at 0, 24, 48, 72 and 96 h

Reliability: (2) valid with restrictions
Study conducted according to national standard method.

Flag: Critical study for SIDS endpoint
22-MAY-2003 (59)

Species: Scenedesmus subspicatus (Algae)
Endpoint: biomass
Exposure period: 96 hour(s)

Unit: mg/l **Analytical monitoring:** no
EC10: > 1000
EC50: > 1000

Method: other: DIN 38412, part 9, Determination of inhibitory effect on the cell multiplication
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: EC values are given in nominal concentrations.
Test condition: number of replicates/concentration: 4
concentration of test substance: 100, 320 and 1000 mg/l algal growth was checked by determination of chlorophyll A fluorescence at 0, 24, 48, 72 and 96 h

Reliability: (2) valid with restrictions
Study conducted according to national standard method.

Flag: Critical study for SIDS endpoint
22-MAY-2003 (59)

Species: Selenastrum capricornutum (Algae)
Endpoint: biomass
Exposure period: 14 day(s)
Unit: mg/l **Analytical monitoring:** no
NOEC: = 470

Method: other: static bottle test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: Static bottle test according to Miller, et al. (1978) or EPA-600/9-78-018
Result: The NOEC value is given in ml/l (nominal). 0.5 ml/l is equivalent to 470 mg/l. In the highest concentration (1 ml/l) a statistically significant increase of algal growth was observed with respect to dry weight.
Test condition: test vessel: 250 ml Erlenmeyer flask
concentration of test substance: 0, 0.1, 0.18, 0.32, 0.56 and 1 ml/l
temperature: 24 °C +/- 2 °C
continuous illumination: 4304 +/- 650 lumens/m²
continuous shaking at 100 rpm cell counts at day 0, 2, 3, 4, 7, 9, 11 and 14 using an Improved Neubauer Hemacytometer

Reliability: (3) invalid
The algae growth was not longer in the exponential phase a test end and an increase in

	algal growth was found at the highest test concentration.	
28-JUN-2002		(60)
Species:	Anabaena flos-aquae (Algae)	
Endpoint:	growth rate	
Exposure period:	48 hour(s)	
Unit:	mg/l	Analytical monitoring:
IC25 :	15100	
Reliability:	(4) not assignable second quotation	
27-MAY-2003		(61)
Species:	Chlorella pyrenoidosa (Algae)	
Unit:	mg/l	Analytical monitoring:
Remark:	10-14-day EC50 reduction in growth at 8900 mg/l	
Reliability:	(4) not assignable second quotation	
27-MAY-2003		(62)
Species:	Chlorella sp. (Algae)	
Endpoint:	other: chlorophyll content	
Exposure period:	7 day(s)	
Unit:	mg/l	Analytical monitoring:
TGK :	> 1890	
Method:	other: Study conducted acc. to EPA recommended method	
Reliability:	(2) valid with restrictions Study conducted according to national standard method without detailed documentation	
19-JUN-2001		(32)
Species:	Microcystis aeruginosa (Algae, blue, cyanobacteria)	
Endpoint:	growth rate	
Exposure period:	48 hour(s)	
Unit:	mg/l	Analytical monitoring:
IC25 :	7000	
Reliability:	(4) not assignable second quotation	
27-MAY-2003		(61)
Species:	Nitzschia sp. (Algae)	
Endpoint:	growth rate	
Exposure period:	48 hour(s)	

Unit: mg/l **Analytical monitoring:**
IC25 : 6200

Reliability: (4) not assignable
second quotation
27-MAY-2003 (61)

Species: Oscillatoria sp. (Algae)
Endpoint: growth rate
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:**
IC25 : 10400

Reliability: (4) not assignable
second quotation
27-MAY-2003 (61)

Species: Selenastrum capricornutum (Algae)
Endpoint: growth rate
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:**
IC25 : 7700

Reliability: (4) not assignable
second quotation
27-MAY-2003 (61)

Species: other algae: Nostoc. sp., Anabaena sp., A.
cylindrica, A.variabilis, A. inaequalis
Unit: mg/l **Analytical monitoring:**

Remark: 10- to 14 days EC50 growth inhibition:
A. inaequalis EC50 5700 mg/l; all other species
revealed an EC50 of < 480 mg/l

Reliability: (4) not assignable
second quotation
27-MAY-2003 (63)

Species: other aquatic plant: Lemna minor
Exposure period: 7 day(s)
IC25 growth inhibi4900 :4900

Reliability: (4) not assignable
second quotation
27-MAY-2003 (61)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: aquatic
Species: Paramecium caudatum (Protozoa)
Exposure period: 4 hour(s)
Unit: mg/l **Analytical monitoring:**
LC50 : 20465

Reliability: (4) not assignable
second quotation
27-MAY-2003 (64)

Type: aquatic
Species: Photobacterium phosphoreum (Bacteria)
Exposure period: 5 minute(s)
Unit: mg/l **Analytical monitoring:**
EC50: = 20000

Method: other: Bacterial bioluminescence bioassay
(Mikrotox-analyser, Beckmann)
Test substance: as prescribed by 1.1 - 1.4

Remark: The principle of the bacterial bioluminescence bioassay (Mikrotox-analyser) was a 50% reduction of the bioluminescence 5 min after incubation of test organisms with DMF

Reliability: (2) valid with restrictions
Test procedure not in accordance with defined methods, but data are comprehensible and scientifically acceptable
27-MAY-2003 (65)

Type: aquatic
Species: Pseudomonas putida (Bacteria)
Unit: mg/l **Analytical monitoring:**
EC10: = 2210

Test substance: as prescribed by 1.1 - 1.4

Reliability: (4 not assignable
Abstracts
19-JUN-2001 (66)

Type: soil
Species: Sclerotinia sp. (Fungi)
Unit: mg/l **Analytical monitoring:**
EC50: 4840

Remark: EC50 inhibition of fungal growth compared with a control growth of 50-70 mm
Reliability: (4) not assignable
second quotation
28-MAY-2003 (67)

Type: soil
Species: other fungi: Pestalotia sp.
Unit: mg/l **Analytical monitoring:**
EC50: 5970

Remark: EC50 inhibition of fungal growth compared with a control growth of 50-70 mm
Reliability: (4) not assignable
second quotation
28-MAY-2003 (67)

Type: soil
Species: other fungi: Phytium ultimum
Unit: mg/l **Analytical monitoring:**
EC50: 10250

Remark: EC50 inhibition of fungal growth compared with a control growth of 50-70 mm
Reliability: (4) not assignable
second quotation
28-MAY-2003 (67)

Species: Vibrio fisheri (Bacteria)
Exposure period: 15 minute(s)
Unit: mg/l **Analytical monitoring:**
IC50 light inhibit1320 13260 - 14830
IC25 light inhibit583:5830- 6730

Reliability: (4) not assignable
second quotation
27-MAY-2003 (68)

Species: other protozoa: Spirostomum ambiguum
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:**
EC50 deformation :9870
EC50 mortality : 31700

Reliability: (4) not assignable
second quotation
27-MAY-2003 (69)

Species: other protozoa: Spirostomum ambiguum
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:**
EC50 deformation : 8190
EC50 mortality : 19700

Reliability: (4) not assignable
second quotation

27-MAY-2003

(69)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

Species: Pimephales promelas (Fish, fresh water)

Method: other

Method: Chronic toxicity test
2-generation study U.S. EPA, Recommended
Bioassay Procedure for Fathed Minnow (Pimephales
promelas) chronic test, unpublished

Result: The F0 generation was exposed for 4 months and
the following F1 generation for 60 days to 5,
11, 20, 44, or 94 mg/l of DMF (nominal
concentrations). The exposure of the F0
generation to DMF was started, following
spawning after a 24 h period. The development of
the F1 generation was normal but an increase in
mortality was observed after a 2 month
exposure period. After a 1 month exposure period
with DMF, the animal sizes became reduced,
depending on the respective DMF concentrations.
The F0 generation started spawning from the
124th day on. In comparison, the group exposed
to the highest concentration started spawning
later. The development of the spawn (F1) was
reduced at 5 mg/l DMF and higher concentrations.
However, an increase of deformities was not
described. The authors stated that the maximal
acceptable toxic concentration (MATC) of DMF was
between 5 to 11 mg/l.

Reliability: (4) not assignable

Draft version; Final report not available

Flag: Critical study for SIDS endpoint

23-JAN-2002

(70)

Species: Salvelinus fontinalis (Fish, estuary, fresh
water)

Method: other
Year: 1972

Method: Chronic toxicity
2-generation study of U.S. EPA, Recommended Bioassay Procedure for Brook trout (*Salvelinus fontinalis*) chronic test, unpublished

Remark: The exposure of brook trout to DMF concentrations of 4.5, 10.6, 21.2, 42.8, or 98.2 mg/l had no effect on the F0-generation. Furthermore, no clear effects on reproductive parameters were determined. A concentration of 42.8 mg/l. and higher resulted in reduced survival of the F1-generation. The authors stated that the maximal acceptable toxic concentration was 42.8 - 98.2 mg/l.

Reliability: (4) not assignable
Draft version; Final report not available

Flag: Critical study for SIDS endpoint
08-JAN-2002 (70)

4.5.2 Chronic Toxicity to Aquatic Invertebrates

Species: Daphnia magna (Crustacea)
Endpoint: reproduction rate
Exposure period: 28 day(s)
Unit: mg/l **Analytical monitoring:** no
MATC : = 1140 - 2375

Method: other: Flow Through Open System
GLP: no
Test substance: other TS: analytical grade

Result: MATC = maximum acceptable toxic concentration, which did not adversely affect survival or reproduction during chronic exposure as checked by analysis of variance
Published value:
MATC = 1200 - 2500 µl/l is equivalent to
MATC = 1140 - 2375 mg/l.

Test condition: test system: flow through in open aquarium (1.75 l),
volume rate: 4 - 5 aquarium volumes/day
concentration of test substance: 600-10000 µl/l
(570 -9500 mg/l)
Dilution factor: 2
number of replicates: 4
number of animals/treatment: 20
counting of offspring: weekdays between 7 and 28
automatically with a particle counter

(offspring removed afterwards)
feeding: three times daily on weekdays and once daily on weekends with 2.5 ml Rangen Salmon Starter fish food suspension (5 mg/l) and 1.0 ml suspension of Selenastrum capricornutum (1-2e7 cells/ml)
temperature: 21 °C
total hardness: 170 mg/l CaCO₃
total alkalinity: 130 mg/l CaCO₃
conductivity: 5012 µmhos/cm
pH: 7.5 - 8.3
dissolved oxygen: 8.4 - 6.2 mg/l
illumination: artificial light (grow lux and soft white fluorescent bulbs at an intensity of 3 - 6 hlx at the solutions surface (light: dark = 16:8 hours)

Reliability: (2) valid with restrictions
Test procedure not in accordance with defined methods, but data are comprehensible and scientifically acceptable

Flag: Critical study for SIDS endpoint
25-JUN-2002 (51)

Species: Daphnia magna (Crustacea)
Endpoint: reproduction rate
Exposure period: 21 day(s)
Unit: mg/l **Analytical monitoring:** no
EC50: = 3721
GM-MATC : = 2121

Method: other: semistatic test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: GM-MATC in this investigation represents the geometric mean of the highest concentration producing no significant effect and the lowest concentration producing a statistically significant effect.

Reliability: (2) valid with restrictions
Test procedure not in accordance with defined methods, but data are comprehensible and scientifically acceptable

Flag: Critical study for SIDS endpoint
30-JUL-2001 (50)

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Sediment Dwelling Organisms

4.6.2 Toxicity to Terrestrial Plants

Species: other terrestrial plant: wheat and bean seed
Endpoint: other: inhibition of germination
Unit: mg/l
: 50000

Remark: Dimethylformamide did not inhibit germination of wheat and bean seeds at 1% (approx. 10000 mg/l) but did at 5% (approx. 50000 mg/l).

Reliability: (4) not assignable
second quotation

28-MAY-2003 (71)

4.6.3 Toxicity to Soil Dwelling Organisms

4.6.4 Toxicity to other Non-Mamm. Terrestrial Species

Species: other: Pythium ultimum (fungus)
Endpoint: other: colony growth in mm

Method: other: Growth Inhibition Test
GLP: no

Result: EC-values are given in nominal concentrations:
EC50 = 1.08 +/- 0.12 % (v/v) corresponds to
EC50 = 10152 +/- 1128 mg/l

Test condition: Exposure: funghi were exposed to different concentrations of DMF dissolved in potato dextrose agar.

Exposure time: variable
Temperature: 25 °C
Test vessel: petri dishes containing 10 ml spiked dextrose agar

Inoculum: mycelial discs taken from the outer margin of fresh stock culture plate (8 mm diameter)

Measures: growth of colonies after control growth reached a diameter of 50 - 70 mm

Concentration of test substance: 0.1 - 3.0 % (v/v)
Number of replicates: 5

Analytical
monitoring: no

Reliability: (2) valid with restrictions
Test procedure not in accordance with defined
methods, but data are comprehensible and
scientifically acceptable

Flag: Critical study for SIDS endpoint
22-MAY-2003 (72)

Species: other: Sclerotinia homeocarpa (fungus)
Endpoint: other: colony growth in mm

Method: other: Growth Inhibition Test
GLP: no

Result: EC-values are given in nominal concentrations:
EC50 = 0.51 +/- 0.02 % (v/v) corresponds to
EC50 = 4794 +/- 188 mg/l

Test condition: Exposure: funghi were exposed to different
concentrations of DMF dissolved
in potato dextrose agar.
Exposure time: variable
Temperature: 25 °C
Test vessel: petri dishes containing 10 ml
spiked dextrose agar
Inoculum: mycelial discs taken from the
outer margin of fresh stock
culture plate (8 mm diameter)
Measures: growth of colonies after control
growth reached a diameter of 50
- 70 mm
Concentration of
test substance: 0.1 - 3.0 % (v/v)
Number of
replicates: 5

Analytical
monitoring: no

Reliability: (2) valid with restrictions
Test procedure not in accordance with defined
methods, but data are comprehensible and
scientifically acceptable

Flag: Critical study for SIDS endpoint
22-MAY-2003 (72)

Species: other: Pestalotia sp. (fungus)
Endpoint: other: colony growth in mm

Method: other: Growth Inhibition Test
GLP: no

Result: EC-values are given in nominal concentrations:
EC50 = 0.63 +/- 0.10 % (v/v) corresponds to
EC50 = 5922 +/- 940 mg/l

Test condition: Exposure: funghi were exposed to different concentrations of DMF dissolved in potato dextrose agar.
Exposure time: variable
Temperature: 25 °C
Test vessel: petri dishes containing 10 ml spiked dextrose agar
Inoculum: mycelial discs taken from the outer margin of fresh stock culture plate (8 mm diameter)
Measures: growth of colonies after control growth reached a diameter of 50 - 70 mm
Concentration of test substance: 0.1 - 3.0 % (v/v)
Number of replicates: 5
Analytical monitoring: no

Reliability: (2) valid with restrictions
Test procedure not in accordance with defined methods, but data are comprehensible and scientifically acceptable

Flag: Critical study for SIDS endpoint

22-MAY-2003 (72)

4.7 Biological Effects Monitoring

4.8 Biotransformation and Kinetics

4.9 Additional Remarks

5.0 Toxicokinetics, Metabolism and Distribution

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Value: 2200 - 7550 mg/kg bw

Test substance: other TS: N,N-dimethylformamide, no further data
21-NOV-2001 (73)

Type: LD50
Species: rat
Value: = 7600 mg/kg bw

Method: other: BASF Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

03-MAR-2003 (74)

Type: LD50
Species: rat
Sex: male/female
No. of Animals: 10
Vehicle: water
Value: = 3040 mg/kg bw

Method: other: BASF Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: DMF was administered once by gavage as aqueous solution in concentrations of 25% (doses from 1520 mg/kg to 3800 mg/kg) and 50% (at a dose of 6080 mg/kg), respectively, to 10 Sprague-Dawley rats per group at the dose levels of 1520, 1900, 2375, 3040 and 3800 mg/kg and to 5 rats per group at 6016 mg/kg. Mortality and signs of toxicity were recorded 1, 24 and 48 hours and 7 days after the substance administration. Animals that died were necropsied and the surviving animals were sacrificed and necropsied after the 7-day post observation period.

Result: 48 h after substance application one animal each at both highest dose levels (6080 and 3800 mg/kg) died. After 7 days all animals were dead at 6080 mg/kg, 5 of 10 rats were dead at 3800 mg/kg and 6 of 10 rats at 3040 mg/kg. There were no dead animals at 2375 mg/kg and 2 of 10 and 1 of 10 rats were dead after 7 days at 1900 and at 1520 mg/kg, respectively. At necropsy of animals that died and those sacrificed at the end of the study, discolored livers were seen.

In relation to the dose administered the main symptoms observed were apathy and staggering.

Test substance: N,N-Dimethylformamide, purity: > 99.9%

Reliability: (2) valid with restrictions
reliable with restrictions

Flag: Critical study for SIDS endpoint

03-MAR-2003

(75)

Type: LD50

Species: rat

Value: = 3895 mg/kg bw

Method: other: BASF Test

GLP: no

Test substance: as prescribed by 1.1 - 1.4

03-MAR-2003

(76)

Type: LD50

Species: rat

GLP: no data

Test substance: other TS: N,N-dimethylformamide, no further data

Remark: DMF was more toxic in younger than in older rats, with oral LD50s of less than 1 g/kg body weight in newborn, 1,4 g/kg bw in 14-day-old, 4 g/kg bw in young adult and 6,8 g/kg bw in adult animals.

03-MAR-2003

(77)

Type: LD50

Species: rat

Sex: no data

Value: 2800 mg/kg bw

Method: other

GLP: no

Test substance: other TS: N,N-Dimethylformamide, no further data

Remark: no further data
31-AUG-2000 (78)

Type: other: ALD
Species: rat
Sex: no data
No. of Animals: 1
Vehicle: other: corn oil at the 30 through 300 mg/kg dose levels
Value: > 300 mg/kg bw

Method: other
GLP: no data
Test substance: other TS: see under remarks

Remark: The test substance containing 50% DMF was administered by gavage in dose levels of 30, 100, 300, 1.000, 3.000 and 10.000 mg/kg using 1 rat per level. At the 30 mg/kg through 300 mg/kg dose levels the substance was given as a 5% (w/v) corn oil solution and undiluted at the remaining dose levels. Food was withheld 16-hours prior to intubation.

After substance administration the animals were observed for 14 days.

Result: Animals at dose levels ≥ 1000 mg/kg of the test substance containing 50% DMF died within 6-22 hours (1000 and 10000 mg/kg animals) or within 2 days (3000 mg/kg animal) after intubation. Since the test substance was a mixture of different chemicals, clinical and necropsy findings observed in the 3 animals that died could not be attributed to DMF alone.

Test substance: other TS: CNF-623 urethane catalyst consisting of 50% N,N-dimethylformamide and 50% dibutyldichlorostannane complexation with triphenylphosphine oxide, no further data

03-MAR-2003 (79)

Type: other: ALD
Species: rat
Sex: male
No. of Animals: 1
Vehicle: other: corn oil

Method: other
GLP: no data
Test substance: other TS: N,N-Dimethylformamide, Solvent
Recovery Tar Still Residue, no further data

Remark: The test material was administered as a suspension in corn oil (in the three high doses as 80% solutions, in the three intermediate doses as 40% solutions and in the two low doses as 15% solutions) at dose levels from 25000 mg/kg - 670 mg/kg in a single dose, one animal per dose. Surviving animals were sacrificed 14 days after the day of substance administration.

Result: At lethal doses the animals showed stained mouth and nose, diarrhea and wet and stained perineal areas at 17000 mg/kg.

At sublethal doses, weight loss for 1-3 days after dosing occurred at 2250 mg/kg and above. The ALD is 11000 mg/kg.
(Note: TSCAT/Microfiche in most parts, mainly when numbers/values were given not clearly readable, thus quotation of dose levels used and ALD value are questionable)

28-AUG-2000 (80)

Type: LD50
Species: mouse
Value: 3700 - 6800 mg/kg bw

Test substance: other TS: N,N-dimethylformamide, no further data

03-SEP-1997 (73)

Type: LD50
Species: mouse
Value: = 4608 mg/kg bw

Method: other: BASF Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

03-MAR-2003 (75)

Type: LD50
Species: mouse
Value: = 2755 mg/kg bw

Method: other: BASF Test
GLP: no

Test substance: as prescribed by 1.1 - 1.4

03-MAR-2003 (81)

Type: LD50
Species: mouse
Value: > 5000 mg/kg bw

Method: other: no data
GLP: yes
Test substance: no data

Remark: Groups of 10 mice were administered the test substance at doses of 500, 890, 1580, 2810, and 5000 mg/kg. No mortality occurred until day 15 except 2 mice administered 2810 mg/kg (1 death on day 2, 1 death on day 3).

Test substance: N,N-dimethylformamide; no data on purity of the compound

25-AUG-1997 (82)

Type: LD50
Species: mouse
Value: 2900 mg/kg bw

Reliability: (4) not assignable
second quotation

27-MAY-2003 (83)

Type: other: ALD50
Species: mouse
Sex: male
No. of Animals: 1
Vehicle: water
Value: > 3200 mg/kg bw

Method: other
GLP: no
Test substance: other TS: N,N-Dimethylformamide, no further data

Remark: Study design and result are only given in tabulated form.
The test material DMF solution 10% in water was orally administered at dose levels of 50, 400 and 3200 mg/kg bw.
The tested animals survived treatment, only slight to moderate weakness and ataxia were observed.

03-MAR-2003 (84)

Type: LD50
Species: rabbit
Value: 940 - 2360 mg/kg bw

Test substance: other TS: N,N-dimethylformamide, no further data

03-SEP-1997 (73)

Type: LDLo
Species: rabbit

Method: other: BASF Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: 4750 mg/kg: single administration led to mortality
2375 mg/kg: two times administered led to mortality
950 mg/kg: " " " " " "
950 mg/kg: 4-5 times " " " "

03-MAR-2003 (76)

Type: LDLo
Species: cat
Value: = 950 mg/kg bw

Method: other: BASF Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Test substance application: 4 - 5 times

03-MAR-2003 (76)

Type: LD50
Species: dog
Value: = 940 mg/kg bw

Test substance: other TS: N,N-dimethylformamide, no further data

03-SEP-1997 (73)

Type: LDLo
Species: dog
Value: = 950 mg/kg bw

Method: other: BASF Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Mortality occurred in 1/2 animals.
03-MAR-2003 (85)

Type: LD50
Species: guinea pig
Value: 1700 - 3400 mg/kg bw

Test substance: other TS: N,N-dimethylformamide, no further data
03-SEP-1997 (73)

Type: LD50
Value: 5000 mg/kg bw

Reliability: (4) not assignable
second quotation
27-MAY-2003 (83)

5.1.2 Acute Inhalation Toxicity

Type: LC0
Species: rat
Exposure time: 4 hour(s)

GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Remark: The rats survived a 4 hour exposure period in
DMF saturated air.
03-MAR-2003 (86)

Type: LC50
Species: rat
Value: 9 - 15 mg/l

Test substance: other TS: N,N-dimethylformamide, no further data
03-MAR-2003 (87)

Type: LC50
Species: rat
Sex: male/female
No. of Animals: 20
Exposure time: 4 hour(s)
Value: > 5.9 mg/l

Method: other: BASF Test
Year: 1979
GLP: no

Test substance: as prescribed by 1.1 - 1.4

Remark: 10 male and 10 female Sprague-Dawley rats per dose group were exposed by whole-body exposure to DMF vapor for 4 hours at (analytical determined) concentrations of 2.23, 4.92, 5.10 and 5.85 mg/L. The concentration of 5.85 mg/L was the maximum technical attainable concentration.

A concurrent control group of ten male and female animals run in parallel. After the 4 h DMF-exposure, the animals were examined for 14 days. Body weight was determined before the beginning of the study, after 7 days during the study and at the end of the post observation period. The animals were daily observed for clinical signs and mortality. Animals that died during the study and the surviving animals sacrificed at the end of the post observation period were necropsied and macroscopically examined.

Result: At the analytical concentration of 2.23 mg/L all animals survived and did not show any clinical signs related to DMF exposure.

In the other three treatment groups dyspnoea (irregular or intermittent respiration) and rough fur were observed as well as in 3 females at 5.1 mg/L a minimal alopecia at the head. Deaths occurred 3 days after the start of the study; at 4.92 mg/l 2 of 10 males and 1 of 10 females died, at 5.1 mg/l all animals survived treatment and at 5.85 mg/l 3 of 10 males and no female animal died.

Surviving animals recovered 6-7 days after exposure. These animals did not show any gross lesions at necropsy, whereas the animals that died during the study had some organ findings, e.g. discoloration of the liver, hemorrhage in thymus and punctate hemorrhage in pancreas and in the gastric mucous membrane.

The LC50 for male and female animals was > 5.85 mg/L/4 hours.

Test substance: N,N-Dimethylformamide purity: 99.7%

Reliability: (2) valid with restrictions
reliable with restrictions

Flag: Critical study for SIDS endpoint

12-JUL-2001

(88)

Type: other

Species: rat

Exposure time: 6 hour(s)

GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Result: A single exposure of 6 hours duration to air saturated with DMF vapour (16,31 mg/l, 5000 ppm) at room temperature killed rats and produced injury to liver, lungs and kidneys.

03-MAR-2003 (89)

Type: other: IRT
Species: rat
Exposure time: 6 hour(s)

Method: other: BASF Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: There was no mortality after a 6 hours exposure in an enriched or saturated atmosphere at 20° C.

03-MAR-2003 (76)

Type: other: IRT
Species: rat
Exposure time: 7 hour(s)

Method: other: BASF Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: No mortality occurred after a 7 hours exposure in an enriched or saturated atmosphere (vapor) at 20° C.
Test substance: Dimethylformamide 25% and 50% in water.

03-MAR-2003 (90)

Type: other: IRT
Species: rat
Exposure time: 7 hour(s)

Method: other: based on the method described by Smyth et al: Am.Ind.Hyg.Ass.J.23,95-107 (1962)
Year: 1962
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: No mortality after 1 hour exposure in a at 20° C enriched or saturated atmosphere (vapor); lateron mortality was observed.
03-MAR-2003 (91)

Type: LC50
Exposure time: 2 hour(s)
Value: 9400 mg/m³

Reliability: (4) not assignable
second quotation
27-MAY-2003 (83)

5.1.3 Acute Dermal Toxicity

Type: LD50
Species: rat
Value: 5000 - 11000 mg/kg bw

Method: other
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data
04-MAR-2003 (87)

Type: other: lethal dose
Species: rat
Sex: male/female
No. of Animals: 4
Value: > 3160 mg/kg bw

Method: other: no data
GLP: yes
Test substance: other TS: N,N-dimethylformamide, no further data

Remark: In an acute dermal toxicity study, 2 male and 2 female Sprague-Dawley rats were treated with the undiluted test substance at a dose level of 3160 mg/kg under occlusive conditions on abraded skin for 24h.
On days 2, 4, 8, 11 and 15 exposure sites were examined and scored for erythema and edema on a graded scale of 0 to 4.
Each animal was observed for mortality and toxic effects 2 and 4 hours post-dosing and daily thereafter.

Result: In the 14-days post observation period, 1/4 animals died (one male animal) on day 4 of the study, however, gross necropsy revealed no substance-related effect.

Among the remaining animals, no signs of systemic toxicity or percutaneous absorption were observed.

Reliability: (2) valid with restrictions
reliable with restrictions

Flag: Critical study for SIDS endpoint
10-OCT-2000 (82)

Type: LD50
Species: mouse
Value: > 5000 mg/kg bw

Test substance: other TS: N,N-dimethylformamide, no further data
03-SEP-1997 (73)

Type: LDLo
Species: mouse

Method: other
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Remark: Slight skin irritation was observed after skin application of 2,5 g DMF/kg bw to mice.
04-MAR-2003 (92)

Type: LD50
Species: rabbit
Value: = 1500 mg/kg bw

Test substance: other TS: N,N-dimethylformamide, no further data

Remark: Pregnant animals were used in the present investigation.
04-MAR-2003 (87)

Type: LD50
Species: rabbit
Value: 3800 - 12350 mg/kg bw

Method: other: BASF Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Several experiments with different doses were carried out:
a) 4750- 9500 mg/kg (open application; no toxic effects)

- b) 6650-12350 mg/kg (2 applications resulted in lethality)
c) 3800- 7600 mg/kg (5 applications resulted in lethality)

04-MAR-2003

(76)

Type: LD50
Species: rabbit
Sex: no data
Value: 4720 mg/kg bw
Method: other
GLP: no
Test substance: other TS: N,N-Dimethylformamide, no further data

Remark: No further data, only secondary literature

31-AUG-2000

(93)

Type: LDLo
Species: rabbit
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Remark: No skin irritation was found after skin application of 0,5 g DMF/kg bw to rabbits.

04-MAR-2003

(92)

Type: other: ALD
Species: rabbit
Sex: no data
No. of Animals: 1
Value: > 2000 mg/kg bw
Method: other
GLP: no data
Test substance: other TS: see under TS

Remark: One day prior to dermal exposure, the backs of 3 New Zealand rabbits were shaved free of hair. One rabbit per dose level was used. Doses chosen were 200, 500 and 2.000 mg/kg of the undiluted test substance containing 50% DMF. Application was performed under occlusive conditions on abraded skin for 24 hours. The animals were examined for local skin reactions, mortality and behavioral abnormalities as well as for initial and 14-day body weights during a 14 day post observation period. Necropsy examination was conducted on all animals.

Result: The test material could not be completely removed from the skin and residual test material remained in contact with the skin for an unlimited period of time. The test material was severely irritating to the skin, however the three animals survived treatment.

Test substance: other TS: CNF-623 urethane catalyst consisting of 50% N,N-dimethylformamide and 50% dibutyldichlorostannane complexation with triphenylphosphine oxide, no further data

29-AUG-2000 (79)

Type: LDLo
Species: guinea pig

Method: other
GLP: no data

Test substance: other TS: N,N-dimethylformamide, no further data

Result: Application of 2 ml DMF to the skin of guinea pigs caused death of 10/20 animals within four days. When 0,5 ml was applied, no deaths were noted during an observation time of 35 days.

04-MAR-2003 (94)

5.1.4 Acute Toxicity, other Routes

Type: LD50
Species: rat
Route of admin.: i.p.
Value: = 4095 mg/kg bw

Method: other: BASF Test
GLP: no

Test substance: as prescribed by 1.1 - 1.4

04-MAR-2003 (75)

Type: LD50
Species: mouse
Route of admin.: i.p.
Value: = 5035 mg/kg bw

Method: other: BASF Test
GLP: no

Test substance: as prescribed by 1.1 - 1.4

04-MAR-2003 (75)

Type: LD50

Species: mouse
Route of admin.: i.p.

Method: other: BASF Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: values obtained: 1900 mg/kg and 2090 mg/kg
Two investigations were performed.

04-MAR-2003 (95) (96)

Type: LC50
Species: mouse
Route of admin.: i.p.

Method: other
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Remark: According to the authors, LD50 in mice was 1.54 ml/kg (ca. 1.46 mg/kg) for the neat test substance and 5.61 ml/kg (ca. 5.33 mg/kg) for an aqueous solution (no data on concentration)

04-MAR-2003 (97)

Type: other
Species: guinea pig
Route of admin.: i.p.

Method: other
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Result: When 2 ml DMF were given by i.p. injection, 9 of 10 guinea pigs died within 72 hours, whereas 0,5 ml caused death of 5/10 animals within 72 days.

04-MAR-2003 (98)

Type: LD50
Species: rat
Route of admin.: s.c.
Value: = 1425 mg/kg bw

Method: other: BASF Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

04-MAR-2003 (99)

Type: LD50
Species: rat
Route of admin.: s.c.
Value: = 2280 mg/kg bw

Method: other: BASF Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

04-MAR-2003

(76)

Type: LD50
Species: mouse
Route of admin.: s.c.
Value: = 3800 mg/kg bw

Method: other: BASF Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

04-MAR-2003

(76)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Concentration: undiluted
Exposure: Semiocclusive
Exposure Time: 20 hour(s)
No. of Animals: 4
Result: not irritating
EC classificat.: not irritating

Method: other: BASF Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: The neat test substance (about 0.5 ml) was administered for 20 hours on the shaved back of 4 albino rabbits. For this purpose a 2.5 cm x 2.5 cm big patch was soaked with the test substance and applied onto the skin and fixed with a bandage. After removal of the bandage the application site was examined and in case of findings, observation continued until the findings disappeared.

Result: Only one of the four animals showed faint redness on the first day after removal of the bandage. On the second day there were no more findings. The other three animals were without any findings.

Test substance: N,N-Dimethylformamide, purity 99%, about 1 (wght.)% Methanol, traces of Monomethylformamide and Formamide

Reliability: (2) valid with restrictions
reliable with restrictions

Flag: Critical study for SIDS endpoint
04-MAR-2003 (76)

Species: rabbit
Result: not irritating

Method: other: no data
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Remark: Method: 15 times repeated application of 2000 mg/kg over a time period of 4 weeks (exposure: 6 hours daily).
04-MAR-2003 (100)

Species: rabbit
Exposure: Occlusive
Exposure Time: 24 hour(s)
No. of Animals: 3
Result: irritating

Method: Draize Test
Year: 1944
GLP: no data
Test substance: other TS: see under TS

Remark: Test material containing 50% DMF (see under TS) was administered to shaved and abraded and to shaved intact skin sites of 3 New Zealand rabbits under occlusive conditions for 24 hours. Test procedures was modeled after that of Draize et al.. Application sites were examined after 24 and 72 hours.

Result: The test material containing 50% DMF and 50% dibutyldichlorostannane complexation with triphenylphosphine oxide led to severe irritation.

Test substance: other TS: CNF-623 urethane catalyst consisting of 50% N,N-dimethylformamide and 50% dibutyldichlorostannane complexation with

17-AUG-2000 triphenylphosphine oxide, no further data (79)

Species: rabbit
Exposure: Occlusive
Exposure Time: 24 hour(s)
No. of Animals: 6
Result: not irritating

Method: other
GLP: no

Test substance: other TS: p-Phenylendiamine, N,N,N',N-Tetrakis (p-Aminophenyl)-, Crude fraction mixture, TAPD solution; product is a dimethylformamide solution containing about 12% by weight of TAPD and minor amounts of impurities

Remark: Study design and results are only given in tabulated form. 0.5 ml of the product as received (see under TS) were administered for 24 hours under occlusive conditions on the intact and the abraded skin of 6 rabbits. After exposure (24 h) and after 72 hours the animals were examined for erythema and edema, scoring system used was that of Draize et al. (1944). Erythema response could not be evaluated in several instances since the product colored the skin purple.

Result: Primary irritation score was 0.1.

24-AUG-2000 (101)

Species: guinea pig
Exposure: Occlusive
No. of Animals: 1
EC classificat.: irritating

Method: other
GLP: no

Test substance: other TS: N,N-Dimethylformamide, no further data

Remark: Study design and result are only given in tabulated form. DMF was administered undiluted in an amount of 0.5 cc/animal (about 317 mg/kg when assumed that a guinea pig will have a weight of 1500 g). Information on exposure time is missing.

Result: The animal survived treatment but showed slight edema, the entire application site was gray and necrotic and dark red around the area.

04-MAR-2003 The authors deduced an ALD50 of > 0.5 cc DMF. (84)

Species: mammal
Result: not irritating
Method: other: no data
Test substance: other TS: N,N-dimethylformamide, no further data

04-MAR-2003 (87)

Species: rat
Concentration: undiluted
Exposure: Occlusive
Exposure Time: 24 hour(s)
No. of Animals: 4
Result: not irritating
EC classificat.: not irritating
Method: other: no data
GLP: yes
Test substance: other TS: N,N-dimethylformamide, no further data

Remark: Application of 3160 mg/kg under occlusive conditions on abraded skin for 24h to 2 male and 2 female Sprague-Dawley rats, 14-days post observation period.

On days 2, 4, 8, 11 and 15 the exposure sites were examined and scored for erythema and edema on a graded scale of 0 to 4. Each animal was observed for mortality and toxic effects at 2 and 4 hours post-dosing and daily thereafter. **Result:** Mean primary irritation score was 0 (max. = 8).

Reliability: (2) valid with restrictions
reliable with restrictions
Flag: Critical study for SIDS endpoint

04-MAR-2003 (82)

5.2.2 Eye Irritation

Species: rabbit
Concentration: undiluted
Comment: not rinsed
No. of Animals: 2
Result: irritating
EC classificat.: irritating
Method: other: BASF Test
GLP: no

Test substance: as prescribed by 1.1 - 1.4

Remark: One drop (about 50 µl) of the undiluted test substance was administered twice at an interval of 5 minutes into the eyes of two albino rabbits. After 10 minutes, 1, 3 and 24 hours the eyes were examined and in case of findings, observation was continued until the findings disappeared.

Result: Marked redness and chemosis as well as purulent secretion were observed in both animals. In one animal transient opacity of the cornea occurred two days after substance application. Both animals recovered and were without findings 6 and 7 days after treatment, respectively.

Test substance: N,N-Dimethylformamide, purity 99%, about 1 (wght.%) Methanol, traces of Monomethylformamide and Formamide

Reliability: (2) valid with restrictions
reliable with restrictions

Flag: Critical study for SIDS endpoint
04-MAR-2003 (76)

Species: rabbit
Result: irritating

Method: other: no data
GLP: no data

Test substance: other TS: N,N-dimethylformamide, no further data
04-MAR-2003 (87) (102)

Species: rabbit
Result: irritating

Method: other: no data
GLP: no data

Test substance: other TS: N,N-dimethylformamide, no further data

Remark: The result of the study was obtained by using concentrated Dimethylformamide.
04-MAR-2003 (103)

Species: rabbit
Result: irritating

Method: other
GLP: no data

Test substance: other TS: N,N-dimethylformamide, no further data

Remark: Moderate corneal injury and moderate to severe conjunctivitis were observed after application 0,01 ml concentrated DMF on the corneal surface or of a 50 % dilution in the conjunctival sac of rabbits.

04-MAR-2003 (103) (104)

Species: rabbit
No. of Animals: 3
Result: irritating

Method: other: no data
GLP: no
Test substance: other TS: Dimethylformamide technical, no further data

Result: The undiluted test substance was instilled into both eyes of 3 rabbits; the left eye was washed with water 20 seconds after instillation, the right eye remained without rinsing. Moderate inflammation of the mucous membranes of both eyes in all animals and transient corneal damage in the unwashed eyes of all animals were observed. These findings were reversible within 8 days. Necropsy on day 8 revealed no significant changes except one unwashed cornea which showed slight swelling of the substantia propria.

29-AUG-2000 (105) (106)

Species: rabbit
Concentration: undiluted
Comment: not rinsed
No. of Animals: 6
Result: irritating
EC classificat.: irritating

Method: other: no data
GLP: yes
Test substance: other TS: N,N-dimethylformamide, no further data

Remark: Instillation of 0.1 ml of the neat test substance into one eye of 6 New Zealand white rabbits without rinsing, the untreated eye served as control; readings 1 h, 4 h, 24 h, 48 h, 72 h, 4 d, 7 d, 10 d and 13 d after application. Scoring of ocular lesions was done according to the method of Draize et al. (1944).

Result: Primary irritation index was 50.8 after 1 h decreasing to 35.8 after 72 h and 35.0 on day 4 decreasing to 3.3 on day 13 (max. = 110). All animals in the present study showed large blisters on the inside of upper and lower lids at the 1 and 4 hour readings. Blisters decreased in size at the 24 hour reading and they were gone at 48 hours. According to the authors, the test substance was classified as severely irritating to the rabbit eyes when applied without rinsing.

Test substance: N,N-dimethylformamide; no data on purity of the compound

Reliability: (2) valid with restrictions
reliable with restrictions

Flag: Critical study for SIDS endpoint

04-MAR-2003

(82)

Species: rabbit

No. of Animals: 3

Result: irritating

Method: Draize Test

Year: 1944

GLP: no data

Test substance: other TS: see under TS

Remark: 3 New Zealand rabbits were used. The undiluted test material containing 50% DMF was instilled into the right eye of each rabbit, the left eye served as control. The test substance treated eye remained unwashed. Cornea, iris and conjunctiva were examined at 1, 24, 48, 72 hours and 7 days after test material application.

Result: The test material containing 50% DMF and 50% dibutyldichlorostannane complexation with triphenylphosphine oxide led to severe irritation.

Test substance: other TS: CNF-623 urethane catalyst consisting of 50% N,N-dimethylformamide and 50% dibutyldichlorostannane complexation with triphenylphosphine oxide, no further data

17-AUG-2000

(79)

Species: rabbit

No. of Animals: 4

Result: irritating

Method: other

GLP: no data

Test substance: other TS: Dimethylformamide, no further data

Remark: The present study was conducted to compare the effects of an old sample of DMF (at least two years old) and a fresh sample of DMF when administered to each two rabbits per sample. In a former eye irritation study, administration of the old sample resulted in severe ocular damage. 0.1 ml of the samples was administered in the right conjunctival sac of each rabbit. Twenty seconds after treatment one of the two eyes dosed with each DMF sample was rinsed with tap water for one minute. The other eye remained unwashed. The eyes were examined one and four hours and at one, two, three, seven and 14 days after treatment. Fluorescein was also used for examination after the treatment day.

Result: The fresh sample led to moderate corneal injury and moderate conjunctivitis in the unwashed eye, whereas the washed eye showed moderate but deep corneal injury, mild iritis and severe conjunctivitis. The so called old sample of DMF led in both eyes to deep corneal injury and to severe irreversible corneal damage with deep vascularization. The one-minute water wash increased ocular damage in both samples tested.

Test substance: other TS: Dimethylformamide, a fresh and an old (at least two years old) sample were used, no further data given with respect to purity

04-MAR-2003

(107)

Species: rabbit
No. of Animals: 6
Result: irritating

Method: other
GLP: no

Test substance: other TS: p-Phenylendiamine, N,N,N',N-Tetrakis (p-Aminophenyl)-, Crude fraction mixture, TAPD solution; product is a dimethylformamide solution containing about 12% by weight of TAPD and minor amounts of impurities

Remark: Study design and results are only given in tabulated form. 0.1 ml of the product as received (see under TS) were administered into

the conjunctival sac of 6 rabbits. Cornea, iris and conjunctivae were examined after 24, 48 and 72 hours. Scoring system used was that of Draize et al. (1944).

06-SEP-2000

(101)

5.3 Sensitization

Type: Guinea pig maximization test
Species: guinea pig
Result: not sensitizing

Method: other
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

04-MAR-2003

(108)

Type: Mouse local lymphnode assay
Species: mouse
No. of Animals: 6
Result: not sensitizing

Method: other: according to Ulrich, P. et al.:
Toxicology 125, 149-168
Year: 1998
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Remark: N,N-dimethylformamide was used as a vehicle in the present investigation. The publication describes the validation of a two-tiered murine local lymph node assay. Groups of 6 female BALB/C strain mice (6-8 weeks old) were used. During tier I a wide range of concentrations of test chemical solutions or vehicle (volume: 25 µl) were applied on three consecutive days to the dorsum of both ears. Mice were killed 24 hours after the last application to determine ear and local lymph node weights and lymph node cell counts. Ear weights were determined to correlate chemical induced skin irritation with the ear-draining lymph node activation potential. For comparison of the induction and challenge responses, mice were treated on the shaved back with 50 µl of test chemical or vehicle alone on three consecutive days (induction phase treatment).

Then mice were challenged 12 days after the final induction phase exposure with 25 µl of test chemical or vehicle on the dorsum of both ears for a further 3 days (challenge phase treatment). Lymph nodes were excised 24 hours after the final challenge phase treatment. A tier II LLNA protocol was used to finally differentiate between true irritants and contact allergens.

To investigate the impact of different vehicles on the primary response induced by two contact allergens, i.e. dinitrochlorobenzene (DNCB) at 0.5% and by eugenol at 35%, DAE433, DMSO, DMF and acetone /oil olive (AOO) were used. Both contact allergens were compared either to the untreated control (aqua bidest) or to the corresponding vehicle control.

Result: Topical treatment of mice with the vehicle N,N-dimethylformamide led to slight ear-draining lymph node activation as expressed by increased weights and cell counts in comparison to the untreated animals.

However, this observation was not reproducible in a second experiment (i.e. when DMF was tested as vehicle for eugenol and as vehicle alone in comparison to the respective untreated control group).

Reliability: (2) valid with restrictions

reliable with restrictions

Flag: Critical study for SIDS endpoint

09-APR-2001

(109)

5.4 Repeated Dose Toxicity

Species: rat **Sex:** male/female
Strain: Fischer 344
Route of administration: inhalation
Exposure period: 12 weeks
Frequency of treatment: 5 d/w; 6 h/d
Post exposure period: none
Doses: 150, 300, 600, 1200 ppm (ca. 0.45, 0.91, 1.82, 3.63 mg/l)
Control Group: other: air
NOAEL: 300 ppm
LOAEL: 600 ppm
Method: other
GLP: no data

Test substance: other TS: Dimethylformamide, no further data

Remark: Whole-body exposure to DMF vapor was tested in each 10 male and female rats/group. The animals were observed twice daily for mortality and overt signs of toxicity. Detailed clinical observations were obtained weekly and body weights biweekly.
At sacrifice all surviving rats were investigated for clinical laboratory tests and hematology. Gross necropsy examinations were made on all animals, histopathology was done on selected tissues (lungs, heart, liver, thymus, spleen, pancreas, kidneys, urinary bladder, testes and nasal passages).
Dunnett's t-test was used for body weights and clinical pathology parameters in comparison to controls.

Result: 3 rats died during the course of the study, one 300 ppm male and one rat of each sex at 1200 ppm.
The highest concentration tested (1200 ppm) led to significant reduced body weight gain from the second week of study onwards in the females and from study week 4 in the males. At 600 ppm there was also a trend of reduced body weight gain. In both sexes a dose-related increase of serum cholesterol was observed, significant at the highest concentration tested and at 600 ppm in the females. Due to a significant increase of serum alkaline phosphatase in female animals of the 600 and 1200 ppm groups and elevated enzyme values (SGPT, SGOT) in one animal at the highest concentration tested as well as to macroscopical and histopathological changes in the liver (fibrosis, dark stained cytoplasm of hepatocytes and in the two animals of the 1200 ppm group that died before scheduled sacrifice widespread collapse, necrosis and accumulation of yellow-brown pigment in Kupffer cells, macrophages and hepatocytes was seen), the liver seemed to be the target organ. Microscopic changes in the liver were predominantly found in the high dose group, and to a lesser extent at 600 ppm and in the form of variation in nuclear size and cytoplasmic characteristics at 300 ppm.

According to the authors the MTD was below 600 ppm.

25-OCT-2000

(110) (111)

Species: rat **Sex:**
Route of administration: inhalation
Exposure period: 27 days
Frequency of treatment: daily; 4 h/d
Doses: 0.13 mg/l
Method: other
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Result: In addition, over the same time period the effects of 300 mg/m³ (corresponding to 0.3 mg/l) were investigated when the animals were exposed 5 times daily for 15 minutes (in between always 40 minutes breaks). The effects on functional parameters of liver and kidneys as well as on blood pressure were described.

04-MAR-2003

(112)

Species: rat **Sex:** no data
Strain: no data
Route of administration: inhalation
Exposure period: 3 or 30 days
Frequency of treatment: daily; 0.5 h/d
Post exposure period: no data
Doses: no data
Method: other
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Result: Type of exposure: aerosol
Necroses in liver and kidneys and changes in lungs and in arterial vessel of the myocard were mentioned.

04-MAR-2003

(113) (114)

Species: rat **Sex:** no data
Strain: no data
Route of administration: inhalation
Exposure period: 4 weeks
Frequency of treatment: daily; 8 h/d
Post exposure period: no data
Doses: 200 ppm (0.61 mg/l)

Method: other
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Result: The present investigation compares the hepatotoxic effects of Dimethylformamide and carbon tetrachloride on rats of different ages (3 - 12 weeks). Changes in the liver were seen more often in young animals. Dimethylformamide led to a cloudy swelling of liver lobules and to a disseminated fatty infiltration around the central vein. These histological findings were reversible, whereas similar findings in a more severe intensity caused by carbon tetrachloride led to fibrosis of the liver lobules. In the Dimethylformamide treated animals increased serum levels of GOT and GPT were found.

04-MAR-2003

(115)

Species: rat **Sex:**
Route of administration: inhalation
Exposure period: 6 months
Frequency of treatment: daily; 4 h/d
Doses: 10-17, 100-167 ppm (ca. 0.03-0.05, 0.3-0.5 mg/l)

Result: The higher dose level should have caused reversible changes in the reflex response and the interneuron-binding. There were no signs of histological changes in liver and kidneys. The relevance of the described findings is questionable.

04-MAR-2003

(116)

Species: rat **Sex:**
Route of administration: inhalation
Exposure period: 4 months
Frequency of treatment: daily; 6 h/d
Doses: 0.005, 0.01 mg/l

Method: other: no data

Result: In addition, rats were treated dermally with a 30% and 60% solution of Dimethylformamide, respectively.

Changes in hematological parameters and changes in the reflex response were described for the inhalation of 10 mg/m³ and the dermal treatment with the 60% solution.

04-MAR-2003

(117)

Species: rat **Sex:** no data
Strain: no data
Route of administration: inhalation
Exposure period: 10 weeks
Frequency of treatment: no data
Post exposure period: no data
Doses: 3.03 mg/l (1000 ppm)
Control Group: yes

Method: other: no data
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Result: No clinical or histological evidence of liver injury.

04-MAR-2003

(118)

Species: rat **Sex:** male/female
Strain: Fischer 344
Route of administration: inhalation
Exposure period: 13 weeks
Frequency of treatment: 5 days/week, 6 hours/day
Post exposure period: none
Doses: 50, 100, 200, 400, 800 ppm (ca. 0.15, 0.30, 0.61, 1.21, 2.43 mg/l)
Control Group: yes, concurrent no treatment
NOAEL: 100 ppm
LOAEL: 200 ppm

Method: other: NTP study
Year: 1992
GLP: yes
Test substance: other TS: N,N-dimethylformamide, purity: > 99% according to Karl Fischer water analysis, nonaqueous amide functional group titration and two gas chromatographic systems

Remark: 30 rats per sex and group were exposed by whole-body exposure to DMF vapors at concentrations of 0, 50, 100, 200, 400 and 800 ppm 6 h/day, 5 days/week for 13 weeks.

Rats were 51 days of age at the first exposure, they were subdivided into 3 study groups, 10 of each sex for each exposure level: a base study group, a cardiovascular group (blood pressure and electrocardiograms were determined) and a renal function (urinalysis) group. Animals were observed twice daily for mortality and moribundity. Body weights were measured weekly and at necropsy. Moreover sperm morphology and vaginal cytology evaluations were performed on rats exposed to 0, 50, 200 and 800 ppm DMF. Epididymal sperm motility was evaluated at necropsy and vaginal cytology was done by vaginal lavage with saline during the 2 weeks just before necropsy. Clinical pathology investigations were performed on cardiovascular study rats at 4 and 23 days and on base-study rats at 13 weeks. Urinalysis were performed in 5 rats/sex in the 0, 50, 200 and 800 ppm groups. Kidney histology was performed on these animals. Blood pressure and electrocardiograms were measured within 24 hours of the last DMF exposure in the cardiovascular group rats. The animals were killed and the heart removed for microscopic examination. At study termination rats in the base study and the renal function groups were killed and complete necropsies were performed. Examination for gross lesions was done and weights of liver, thymus, both kidneys, both testicles, heart and lungs were recorded. The target organ, i.e. the liver was microscopically examined in all dose groups and the following tissues were examined microscopically from all control and high dose group-animals from the base study group: adrenals, brain, epididymis, seminal vesicles, prostate, testes, ovaries, uterus, esophagus, eyes (if grossly abnormal), femur with marrow, gross lesions and tissue masses with regional lymph nodes, heart, aorta, intestines, kidneys, larynx, liver, lungs, lymph nodes, mammary gland with adjacent skin, nasal cavity and turbinates, pancreas, parathyroid glands, pharynx (if grossly abnormal), pituitary, preputial or clitoral glands, salivary glands, spleen, skeletal muscle, stomach, thymus, thyroid, trachea, urinary bladder and vagina.

Result: The analytical concentrations in ppm, determined during the study by infrared analysis were 0, 50.2 +/- 1.69, 98.6 +/- 2.17, 198.1 +/- 5.34, 401.3 +/- 10.13, 804.6 +/- 19.89 for the target concentrations of 0, 50, 100, 200, 400 and 800 ppm, respectively. (remark: the analytical values were hardly readable, so that there might be some wrong numbers quoted).

There was no substance-related mortality. Body weight gains were reduced by approx. 47-65% in rats exposed to 800 ppm and to a lesser extent in the animals of the 400 ppm group.

Evidence for hepatocellular injury was seen as early as day 4 based on increases in activities of liver-specific enzymes (e.g. ALT, SDH and ICDH) in the serum of both sexes at 200-800 ppm DMF. Serum cholesterol levels were increased in all exposed rats at all time points (i.e. 4, 24 and 91 days). Relative liver weights were increased in the males at 100 ppm and above and at all concentrations in the females.

Minimal to moderate centrilobular hepatocellular necrosis was seen in both sexes at 400 and 800 ppm and pigment accumulation (hemosiderin and lipofuscin) in macrophages and Kupffer cells was found in both sexes at the highest concentration. Prolonged diestrus was observed in 7 of 10 females exposed at 800 ppm, i.e. at a concentration that produced hepatotoxicity and reduced body weight gain.

Relative testis weights were increased at 400 and 800 ppm DMF, however no microscopical findings or any adverse effects on sperm density or motility were observed.

For both sexes the NOAEC was 100 ppm, based on the findings in the liver function assays (increased activities of liver-specific enzymes).

Reliability: (2) valid with restrictions

reliable with restrictions

Flag: Critical study for SIDS endpoint

04-MAR-2003

(119)

Species: rat **Sex:** male
Strain: other: albino
Route of administration: inhalation
Exposure period: 5 days
Frequency of treatment: 6 h/d
Post exposure period: up to 10 days
Doses: ca. 7,67 mg/l (2523 ppm)

Control Group: yes, concurrent no treatment

Method: other: no data
GLP: no

Test substance: other TS: N,N-dimethylformamide technical, no further data

Result: Groups of 10 rats were used and were investigated for cumulative toxicity after repeated exposure to DMF vapor. Progressive weakness, discomfort, and body weight loss were observed in the treated animals. One rat died after the 2nd day; necropsy revealed acute pulmonary congestion and edema. Seven animals that died 1 - 3 days after the final exposure exhibited dehydration and acute liver necrosis. The remaining 2 animals survived the 10-day recovery period and one of these animals exhibited evidence of healing liver injury upon necropsy.

04-MAR-2003

(120) (105) (106)

Species: rat **Sex:** no data
Strain: no data
Route of administration: inhalation
Exposure period: 5 - 9 weeks see under remarks
Frequency of treatment: 6 hours daily, 5 days a week
Post exposure period: none
Doses: 56, 108 ppm (about 0.17, 0.33 mg/L)
Control Group: yes

Method: other
GLP: no
Test substance: other TS: Dimethylformamide, no further data

Remark: A group of nine rats received 26 exposures (5 weeks) to DMF vapor at a dose of 56 ppm followed by 20 exposures (4 weeks) at a dose of 108 ppm. 9 control animals exposed to air run in parallel. Body weight changes were recorded on Monday morning and late Friday afternoon. Urine and blood analyses were made during the exposure period. All animals were sacrificed at the end of the experiment and investigated for gross and microscopic changes.

Result: According to the authors, the treated animals were not significantly affected by their exposure.

22-AUG-2000

(121)

Species: rat **Sex:** male/female
Strain: other: Cr1:CD BR
Route of administration: inhalation
Exposure period: 2 years
Frequency of treatment: 5 d/w, 6 h/d
Post exposure period: none
Doses: 25, 100, 400 ppm (about 0.08, 0.3, 1.21 mg/l)
Control Group: yes
NOAEL: 25 ppm
LOAEL: 100 ppm

Method: other: no data
GLP: no data
Test substance: other TS: N,N-dimethylformamide, 99.9% pure, no further data

Remark: 87 male and female rats were used per group. The rats were approx. 47 days of age at the beginning of the study. They were exposed to DMF vapors by whole body exposure at dose levels of 0, 25, 100 and 400 ppm for two years. The concurrent control group animals (0 ppm) were exposed to dehumidified air alone. Clinical pathology was investigated at 3, 6, 12, 18 and 24 months in each 10 male and 10 female animals/group. At 12 months interim sacrifice of 10 male and 10 female animals per group took place, thus again 10 rats per sex and group had to be selected for the 18 and 24 months examinations. After 2 weeks, 3 months and 12 months of testing cell proliferation in the liver was evaluated in 5 randomly selected rats per sex and group. An immunohistochemical evaluation was done on livers from animals of the 0 ppm and 400 ppm groups. Estrous cycle evaluation was done in all female animals of the control and the high dose group from test day 107 through test day 131. Moreover, examinations on body weight, organ weights, ophthalmoscopy, urinalysis and a complete necropsy including microscopical examinations were carried out.

Result: There were no compound-related differences in the survival of the animals in the present study (for male rats survival was 27, 34, 40 and 44% for 0, 25, 100 and 400 ppm, respectively).

For female rats survival was 35, 23, 19 and 39%, respectively). Ophthalmologic examinations, hematology and urinalysis revealed no compound-related effects in the rats. Moreover, no compound-related effects were seen on the estrous cycles of rats exposed up to 400 ppm DMF.

Body weight and body weight gain were reduced in both sexes of the 400 ppm group and in the male animals of the 100 ppm group. Serum sorbitol dehydrogenase activity was increased in the animals of the 100 and 400 ppm groups. These animals also showed increased mean relative liver weights and centrilobular hepatocellular hypertrophy as well as an increased centrilobular accumulation of lipofuscin/hemosiderin. At 400 ppm there was also an increased incidence of hepatocellular single cell necrosis.

The incidence of clear cell foci was increased in 100 ppm males and in both sexes of the highest dose group. An increased incidence of eosinophilic foci was seen in the 400 ppm females. Cell-labeling indices for hepatocytes were not statistically significant different between control and 400 ppm rats, however, rates were slightly higher for 400 ppm males at 2 weeks and 3 months but not at 12 months.

An increased incidence of endometrial stromal polyp of the uterus (14.8%) occurred in the females of the 400 ppm group.

According to the authors endometrial stromal polyps are the most common uterine neoplasm in rats. Moreover, the incidence showed no clear dose-response relationship and was in the range of historical control incidences for the respective laboratory (2.0-15.0%) Thus, the authors concluded, that the increased incidence is probably a chance variation rather than a compound-related effect.

There were no compound-related lesions noted in the nose or respiratory tract for any exposure concentration.

Exposure to DMF for 2 years did not cause a compound-related increase of tumors in rats. According to the authors the NOEC in rats is 25 ppm.

Species: rat **Sex:** male/female
Strain: other: Charles River CD strain
Route of administration: oral feed
Exposure period: 90 days
Frequency of treatment: continuously
Post exposure period: none
Doses: 200, 1000, 5000 ppm in the diet
(according to the
authors, ca. 12, 60, 300 mg/kg)
Control Group: yes, concurrent no treatment
NOAEL: 200 ppm
LOAEL: 1000 ppm

Method: other
GLP: no
Test substance: other TS: N,N-Dimethylformamide technical grade,
no further data

Remark: 40 male and 40 female weanling rats were observed during a six-day pre-test period. At the end of this period 6 male and 6 female animals were assigned to 4 groups, one control group and 3 dose groups. Dose levels chosen were 200, 1000 and 5000 ppm. Body weight and food consumption were determined at least once weekly. Routine hematological examinations were performed for all animals on study days 30, 60 and 90. Alkaline phosphatase activity was also determined at these time points. At the end of the study for evaluation of liver function enzyme activities and phospholipid and cholesterol content were measured in the serum. At sacrifice the animals were submitted to gross and microscopic pathological appraisal and to organ weight determination (brain, liver, kidney, adrenal, lung, spleen and testis). For histology the following organs were preserved: organs that were weight and ovary, heart, pancreas, stomach and small intestine.

Result: All treated animals survived the feeding study. At a dose of 1000 ppm DMF relative liver weights were slightly increased without a histopathological correlate. Leucocytosis was observed after 60 days of DMF feeding. The red blood cell count was slightly lower in the 1000 ppm group in comparison to the control.

Hypercholesterolemia was observed in the females and elevated phospholipid values were seen in 2/6 females at 1000 ppm.

In both sexes at 5000 ppm body weight gain was depressed during the entire study period (statistically significant only in male animals), food consumption was lower during the first 5-6 weeks when compared to control animals and food efficiency were also lower during the first two weeks of the study.

Moreover slight anemia, leucocytosis, hypercholesterolemia and elevated phospholipid concentration together with mild liver injury (the latter finding in 3/6 males and 5/6 females) and increased relative liver weights were observed in both sexes of the 5000 ppm group.

The increase in relative liver weights in both sexes at 1000 and 5000 ppm were dose-related.

Reliability: (2) valid with restrictions
reliable with restrictions
Flag: Critical study for SIDS endpoint
23-MAY-2003 (123) (124) (125)

Species: rat **Sex:** male/female
Strain: Wistar
Route of administration: oral feed
Exposure period: 104 days
Frequency of treatment: continuously in the diet
Post exposure period: none
Doses: 215, 750, 2500 ppm in the diet (ca. 14.3; 50; 167 mg/kg)
Control Group: yes, concurrent no treatment
NOAEL: 750 ppm

Result: In the highest dose group depression of food consumption led to lower body weights. The authors assume, that the increased liver weights in the highest dose group are the result of a physiological adaptation reaction. The NOEL of 750 ppm was explained by the authors with the fact that relevant changes in organs were only observed in the highest dose group.
04-MAR-2003 (126) (127)

Species: rat **Sex:**
Route of administration: oral feed
Exposure period: 30 days
Frequency of treatment: continuously in the diet

Doses: 320, 640 mg/kg in the diet (ca. 26.7, 53.3 mg/kg)

Result: The test substance concentration in the food led to anorexia and body weight loss. In addition, the test substance was administered in the drinking water at dose levels of 50, 500 and 5000 ppm over a time period of 100 days. Changes in liver morphology and weight were described at 500 and 5000 ppm. NOEL was 50 ppm.

04-MAR-2003 (128)

Species: rat **Sex:**
Route of administration: drinking water
Exposure period: 14 or 49 days
Frequency of treatment: continuously in the drinking water
Doses: 100, 500, 1000 ppm in the drinking water (ca. 9.1, 45.5, 90.9 mg/kg/d)

Result: A dose-related increase of relative liver weights was observed. In liver and kidneys increased amounts of reduced glutathione and increased activity of microsomal UDP Glucuronosyl Transferase and of Ethoxycumarine O-Demethylase were seen. Cytochrom P-450 and NADPH-Cytochrom C-Reductase activity in the liver were not influenced by the treatment.

04-MAR-2003 (129)

Species: rat **Sex:**
Route of administration: drinking water
Exposure period: 14 or 49 days
Frequency of treatment: continuously in the drinking water
Doses: 102, 497, 1000 ppm in the drinking water (ca. 9.3, 45.2, 90.9 mg/kg/d)

Result: At the two lowest doses no changes in behavior were described. Dose-related changes in cerebral and glial enzyme activity were seen.

04-MAR-2003 (130)

Species: rat **Sex:** male/female
Strain: Sprague-Dawley
Route of administration: gavage
Exposure period: 28 days
Frequency of treatment: 5 d/w
Post exposure period: none
Doses: 250, 500, 1000 and 2000 µl/kg (about 238, 475, 950, 1900 mg/kg)

Control Group: other: aqua bidest.
NOAEL: 238 mg/kg bw
LOAEL: 475 mg/kg bw

Method: other
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: 10 male and 10 female Sprague-Dawley rats/group were 45 days of age when the study started. DMF was administered by gavage 5 days/week. DMF solutions in aqua bidest were prepared daily. A concurrent vehicle control group run in parallel. Food consumption was measured daily, body weight was determined twice weekly and clinical symptoms as well as mortality were examined daily. Clinical chemistry and hematology were investigated 10 days before the start of the study and in all surviving rats during the study, directly before the last substance administration. Urinalysis were performed after study day 21 or 22 on all surviving rats. At the end of the study surviving animals were sacrificed after a 16 h fasting-period and macroscopically examined. Body weight and organ weights of heart, liver, kidneys, spleen, thyroid, adrenals, testes, uterus and ovary were determined. Histopathology was performed on heart, lung, thyroid, stomach, duodenum, jejunum, ileum, mesenteric lymphnodes, liver, pancreas, spleen, kidneys, adrenals, urinary bladder, testes and ovaries and brain. Statistical calculations (t-Test; x²-Test) were done for clinical, pathological and clinical chemistry data as well as for data from hematology and urinalysis.

Result: At the highest dose group all animals died, mostly during the first 5 days of substance application. The animals in the highest dose group showed reduced state of health and reduced food consumption and body weight gain already after the first treatment.

At 950 mg DMF/kg the general state of health was reduced (in male animals already beginning in study week 1, in female animals at the end of study week 3) and the animals showed a significantly reduced food consumption (up to 36% reduced in the males and up to 40% reduced in the females) and significantly reduced body weight when compared to the controls (at the end of the study for male animals 28% lower, and for female animals 21 % lower than control).

4 male animals (on study days 7, 8, 14 and 19) and one female animal (after 15 substance applications) died.

Hepatic damage was represented by changes in clinical chemistry values (increased total bilirubin, increased enzyme values, i.e. GPT, AP) and disturbances in kidney function were represented by elevated urea (in 2 of 9 female animals) and creatinine values (in all animals of the 950 mg/kg dose group). Histologically an acute to subacute hemorrhagic liver dystrophy with necrosis was found in the animals of this and the highest dose group.

Relative liver weights were increased in both sexes and relative kidney weights were increased in the male animals at 950 mg/kg.

At 238 and 475 mg/kg reduced food consumption in the male animals and at 475 mg/kg significantly reduced body weight when compared to the control animals (14.6% lower than controls) were seen. In both sexes increased relative liver weights and in the males increased relative kidney weights were observed, however without histopathological correlates.

Reliability:

(2) valid with restrictions

Flag:

Critical study for SIDS endpoint

04-MAR-2003

(131)

Species:	rat	Sex: male
Strain:	other: albino	
Route of administration:	gavage	
Exposure period:	2 weeks	
Frequency of treatment:	9 applications	
Post exposure period:	none or 11 days	
Doses:	450 mg/kg/d	
Control Group:	yes	
Method:	other: no data	
GLP:	no	

Test substance: other TS: N,N-dimethylformamide technical, no further data

Result: Administration of the test substance (as a 10% aqueous solution) to a group of 6 rats resulted in transitory discomfort, reduced body weight gain, and increased water consumption in the dosed group. No deaths occurred. Three animals/group were sacrificed immediately after termination of dosing. Necropsy of these animals revealed histological evidence of a mild liver injury. The remaining animals were sacrificed after a rest period of 11 days; these rats exhibited no pathological lesions. During the recovery period, the rate of body weight gain was parallel to that of control animals, but at a level that was 40 g lower.

16-AUG-2000

(105) (132) (133)

Species: rat **Sex:**
Route of administration: dermal
Exposure period: 28 days
Frequency of treatment: daily or intermittently (1920 mg/kg)
Doses: 960, 1920 mg/kg

Result: After 4, 8, 14 and 28 days functional, biochemical and pathomorphological changes were described for the liver and the lipid metabolism. After intermittent exposure to 1920 mg/kg these changes should have been more distinct.

04-MAR-2003

(134)

Species: rat **Sex:**
Route of administration: dermal
Exposure period: 30 days
Doses: 215, 430, 960, 4800 mg/kg
NOAEL: = 215 mg/kg

Result: Dose-related changes in GOT, GPT, alkaline Phosphatase, Cholinesterase, GGT and in the lipid fraction in the serum and in the liver homogenate were described. The NOAEL was 215 mg/kg.

04-MAR-2003

(135)

Species: rat **Sex:**
Route of administration: dermal
Exposure period: 30 applications

Frequency of treatment: daily
Doses: 0.5 ml/kg (475 mg/kg)

Result: After the dermal treatment mentioned, the animals were treated once with 11.8 ml/kg (11.140 mg/kg corresponding to the dermal LD50). Thereafter all animals died within 48 hours. Due to this finding the authors deduce a cumulative effect and no adaptation, because the 30-day dermal pretreatment did not show any protective effect.

04-MAR-2003

(136)

Species: mouse **Sex:** male/female
Strain: B6C3F1
Route of administration: inhalation
Exposure period: 12 weeks
Frequency of treatment: 5 d/w; 6 h/d
Post exposure period: none
Doses: 150, 300, 600, 1200 ppm (ca. 0.45, 0.91, 1.82, 3.63 mg/l)
Control Group: other: air
NOAEL: 300 ppm
LOAEL: 600 ppm
Method: other
GLP: no data
Test substance: other TS: Dimethylformamide, no further data

Remark: Whole-body exposure to DMF vapor was tested in each 10 male and female mice/group. The animals were observed twice daily for mortality and overt signs of toxicity. Detailed clinical observations were obtained weekly and body weights biweekly. At sacrifice at least 5 mice per sex and group were investigated for clinical laboratory tests and hematology. Gross necropsy examinations were made on all animals, histopathology was done on selected tissues (lungs, heart, liver, thymus, spleen, pancreas, kidneys and testes). Dunnett's t-test was used for body weights and clinical pathology parameters in comparison to controls.

Result: At 1200 ppm 40% (8 animals, 5 males, 3 females) of the mice and at 600 ppm 10% (2 males) of the mice died or were sacrificed moribund. One male mouse was found dead at 150 ppm. Accidental deaths in single animals and single animals withdrawn from the study for various other reasons were evenly distributed amongst the five concentration levels. Discolored livers and/or alterations in consistency were the main findings at gross necropsy at both high concentrations. Microscopically 4/16 animals of the 600 ppm group and 4/10 mice of the 1200 ppm group showed areas of collapse (accd. to the authors residual of necrosis) or liver necrosis and one mouse of the 300 ppm group showed a large area of coagulative necrosis. Two mice of the highest concentration group that died 71 and 76 days after exposure started, exhibited hepatic single cell necrosis. Hepatic cytomegaly around central veins was seen in all exposed groups and the incidence and severity were dose-related. According to the authors the MTD was below 600 ppm.

25-OCT-2000

(110) (111)

Species: mouse **Sex:** male/female
Strain: B6C3F1
Route of administration: inhalation
Exposure period: 13 weeks
Frequency of treatment: 5 days/week, 6 hours/day
Post exposure period: none
Doses: 50, 100, 200, 400, 800 ppm (ca. 0.15, 0.30, 0.61, 1.21, 2.43 mg/l)
Control Group: yes, concurrent no treatment
NOAEL: ca. 400 ppm
LOAEL: ca. 800 ppm

Method: other: NTP study
Year: 1992
GLP: yes
Test substance: other TS: N,N-dimethylformamide, purity: > 99% according to Karl Fischer water analysis, nonaqueous amide functional group titration and two gas chromatographic systems.

Remark: 10 mice per sex and group were exposed by whole-body exposure to DMF vapors at concentrations of 0, 50, 100, 200, 400 and 800 ppm 6 h/day, 5 days/week for 13 weeks.

Mice were 46 days of age at the first exposure. Animals were observed twice daily for mortality and moribundity. Body weights were measured weekly and at necropsy. Moreover sperm morphology and vaginal cytology evaluations were performed on mice exposed to 0, 50, 200 and 800 ppm DMF. Epididymal sperm motility was evaluated at necropsy and vaginal cytology was done by vaginal lavage with saline during the 2 weeks just before necropsy.

At study termination mice were killed and complete necropsies performed. Examination for gross lesions was done and weights of liver, thymus, both kidneys, both testicles, heart and lungs were recorded. The target organ, i.e. the liver was microscopically examined in all dose groups and the following tissues were examined microscopically from all control and high dose group-animals: adrenals, brain, epididymis, seminal vesicles, prostate, testes, ovaries, uterus, esophagus, eyes (if grossly abnormal), femur with marrow, gallbladder, gross lesions and tissue masses with regional lymph nodes, heart, aorta, intestines, kidneys, larynx, liver, lungs, lymph nodes, mammary gland with adjacent skin, nasal cavity and turbinates, pancreas, parathyroid glands, pharynx (if grossly abnormal), pituitary, salivary glands, spleen, skeletal muscle, stomach, thymus, thyroid, trachea, urinary bladder and vagina.

Result:

The analytical concentrations in ppm, determined by infrared analysis during the study were 0, 50.2 +/- 1.69, 98.6 +/- 2.17, 198.1 +/- 5.34, 401.3 +/- 10.13 and 804.6 +/- 19.89 for the target concentrations of 0, 50, 100, 200, 400 and 800 ppm, respectively. (remark: the analytical values were hardly readable, so that there might be some wrong numbers quoted).

No substance-induced mortality was observed. 5 male mice died of undetermined causes during the study, 3 in the lowest exposure group and one, each at 100 and 200 ppm, thus suggesting that DMF exposure was not involved. All female mice survived until termination of the study. Body weight gains were slightly reduced (approximately 29% less than controls) in female mice exposed to 800 ppm.

Relative liver weights were increased in both sexes at all exposure concentrations without a clear dose-response relationship. Minimal to mild centrilobular hypertrophy was observed in all groups of male mice and in female mice exposed at 100 ppm and higher concentrations. In females there was a significant trend toward an increase in the estrous cycle length, however significantly prolonged estrus and diestrus was observed only in females exposed to 200 ppm. In summary, hepatocellular hypertrophy or increased liver weights occurred at all exposure concentrations and body weight gain was reduced in the females at the highest concentration tested.

Reliability: (2) valid with restrictions
reliable with restrictions
Flag: Critical study for SIDS endpoint
05-MAR-2003 (119)

Species: mouse **Sex:** male/female
Strain: other: Cr1:CD-1 (ICR)BR
Route of administration: inhalation
Exposure period: 18 months
Frequency of treatment: 5 d/w, 6 h/d
Post exposure period: none
Doses: 25, 100, 400 ppm (about 0.08, 0.30, 1.21 mg/l)
Control Group: yes
NOAEL: ca. 25 ppm
LOAEL: ca. 100 ppm

Method: other: no data
GLP: no data
Test substance: other TS: N,N-dimethylformamide, 99.9% pure, no further data

Remark: N,N-dimethylformamide was investigated in groups of 78 male and 78 female young adult mice. The mice were approx. 55 days of age at the beginning of the study. The animals were exposed by whole-body exposure to DMF vapors at concentrations of 0, 25, 100 and 400 ppm. The concurrent control (0 ppm) was exposed to dehumidified air alone. Examinations on body weight, organ weights, ophthalmoscopy, and a complete necropsy including microscopical examination were carried out.

Hematology was investigated at 3, 6, 12 and 18 months in each 10 male and 10 female animals/group. Estrous cycle evaluation was done in all female animals in the 0 and 400 ppm groups from test day 107 to test day 131. Cell proliferation in the liver was investigated after 2 weeks, 3 months and 12 months in five randomly selected animals per sex and group. Livers from animals in the 0 and 400 ppm groups were immunohistochemically evaluated.

Result:

Survival in treated male and female mice was similar to that in the concurrent control group (male animals: 56, 68, 60 and 59% for 0, 25, 100 and 400 ppm, respectively; female animals: 68, 57, 62 and 76%, respectively). There were no compound-related differences in hematology parameters and no significant differences with respect to estrous cycle evaluations or ophthalmoscopy.

In male animals exposed to 100 and 400 ppm, and in female mice at 400 ppm a significant increase in absolute and relative liver weights together with hepatocellular hypertrophy was observed. Microscopy revealed hepatic changes (minimal to mild hepatocellular hypertrophy) in all treated groups with the incidence being dose-related. Individual hepatocellular necrosis was seen in all groups with the incidence being greater in the DMF-treated groups.

Minimal to moderate Kupffer cell hyperplasia with accumulation of lipofuscin and hemosiderin was also observed in all groups again with the incidence being greater in the DMF-treated animals. A dose-related increase in mixed foci in the liver was seen in the males and a higher incidence of eosinophilic foci was seen in both sexes of the treated groups when compared to the concurrent control animals.

Cell labeling indices in the liver showed no compound-related effect at any exposure level. No compound-related lesions were observed in the nose or respiratory tract at any exposure level. The exposure of mice to DMF over a time period of 18 months was not oncogenic at concentrations up to 400 ppm.

A NOEC was not achieved in mice due to morphological changes seen in the liver at all three test concentrations.

However, according to the authors, the NOEC is expected to be close to 25 ppm due to the minimal changes observed at this concentration.

09-APR-2001

(122)

Species: mouse **Sex:** male/female
Strain: other: Swiss Webster CD-1
Route of administration: oral feed
Exposure period: 119 days
Frequency of treatment: continuously in the diet
Post exposure period: none
Doses: 160, 540, 1850 ppm in the diet (ca. 20, 67.5, 231.25 mg/kg)
Control Group: yes, concurrent no treatment
NOAEL: 160 ppm

Result: Mid and high dose levels led to hypertrophy of the liver (increased size of liver cells) and hepatomegaly. Other significant effects were not observed. The authors assume, that the liver hypertrophy is the result of a physiological adaptation to the metabolism of foreign substances. For other significant effects (body weight, biochemical parameters) a dose-relationship is missing. The finding of a retinopathy observed in all Groups (including the control group) is, according to the authors, most likely genetically determined.

05-MAR-2003

(126) (137)

Species: mouse **Sex:**
Route of administration: oral feed
Exposure period: 30 or 119 days
Frequency of treatment: continuously in the diet
Doses: 620, 1240 mg/kg in the diet (ca. 77.5, 155 mg/kg)

Result: Findings were anorexia and body weight loss.

05-MAR-2003

(138)

Species: mouse **Sex:**
Strain: other: desert mouse
Route of administration: drinking water
Exposure period: 6 - 200 days
Frequency of treatment: continuously in the drinking water
Doses: 10000, 17.000, 34.000 ppm in the drinking water (ca. 2000, 3400, 6800 mg/kg/d)

Result: The highest dose of 34000 ppm administered over a period of 6 days led to mortality (findings: livercell necrosis).
The cumulative LD50 was 3846 mg/kg bw.
The dose of 17000 ppm given over 80 days led also to mortality and livercell necrosis. The cumulative LD50 was 90206 mg/kg bw in this case.
10000 ppm given over 200 days led to livercell necrosis and to the death of 25% of the animals.
Over a time period of 30 days the dose of 10000 ppm did not cause changes in liver, kidneys of body weights.

05-MAR-2003

(139)

Species: rabbit **Sex:**
Route of administration: inhalation
Exposure period: 50 days
Frequency of treatment: daily; 8 h/d
Doses: 0.12 mg/l

Result: The authors describe microscopical and electron microscopical changes in the myocardium.

05-MAR-2003

(140)

Species: rabbit **Sex:** no data
Strain: no data
Route of administration: inhalation
Exposure period: 10 months
Frequency of treatment: daily; 6 h/d
Post exposure period: no data
Doses: 0.91 mg/l (300 ppm)
Control Group: yes, concurrent no treatment

Method: other: no data
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Result: No clinical evidence of liver or kidney damage.

05-MAR-2003

(118)

Species: rabbit **Sex:**
Route of administration: dermal
Exposure period: 25 days
Frequency of treatment: daily; 2 h/d
Doses: 1000 mg/kg

Result: After 5 to 8 days local hyperemia and slight infiltration as well as scaling were seen.

05-MAR-2003

(116)

Species: rabbit **Sex:** no data
Strain: other: no data
Route of administration: dermal
Exposure period: 2 weeks
Frequency of treatment: 9 applications
Post exposure period: 4, 11 days
Doses: 2000 mg/kg/d
Control Group: yes

Method: other: no data
GLP: no
Test substance: other TS: N,N-dimethylformamide technical, no further data

Result: Administration of the test substance to a group of 6 rabbits resulted in reduced body weights in the dosed group. Three animals were found dead 2 days after the 5th application, one died 2 days after the 9th application. The remaining 2 rabbits were sacrificed 4 and 11 days after the 9th application. Only 2 of the animals that died had sufficiently well preserved tissues for a histological appraisal; these animals exhibited histological evidence of liver injury. In the rabbit sacrificed 4 days after the last dosing, focal acute inflammatory lesions of the lungs and kidneys and chronic inflammatory lesions of the liver were found, however, according to the authors, this was not substance-related. The animal sacrificed 11 days after the last dosing exhibited only chronic nephritis.

16-AUG-2000

(105) (106)

Species: rabbit **Sex:** no data
Strain: no data
Route of administration: oral unspecified
Exposure period: max. 53 days
Frequency of treatment: up to 35 applications
Post exposure period: none
Doses: 475 mg/kg
Control Group: no

Method: other: no data
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: The investigations do not meet present standards (only 2 animals used).

After 14 or 35 administrations, the animals died after 23 and 53 days, respectively. Since the rabbits suffered under a purulent bronchopneumonia during the investigation, the relevance of the described findings (hematology) is questionable.

05-MAR-2003

(76)

Species: cat **Sex:** no data
Strain: no data
Route of administration: inhalation
Exposure period: 10 months or 10 weeks
Frequency of treatment: daily; 6 h/d
Doses: 0.91 mg/l (300 ppm; for 10 months), 3.03 mg/l (1000 ppm; for 10 weeks)
Control Group: yes, concurrent no treatment
Method: other: no data
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Result: There was no clinical evidence of liver or kidney damage in cats exposed to 300 ppm for 10 months. The inhalation of 1000 ppm for 10 weeks did not result in any clinical or histological evidence of liver injury.

05-MAR-2003

(118)

Species: cat **Sex:** no data
Strain: no data
Route of administration: oral unspecified
Exposure period: 28 days
Frequency of treatment: 8 applications
Post exposure period: no data
Doses: 475 mg/kg
Control Group: no
Method: other
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: The investigations do not meet today's standards (only 2 animals used). Reduced body weights and changes in hematological parameters were seen.

05-MAR-2003

(76)

Species: dog **Sex:**
Route of administration: inhalation
Exposure period: 28 days

Frequency of treatment: daily; 6 h/d
Doses: 0.063 mg/l

Result: GOT, GPT, bilirubin, urea and creatinine values
in the plasma were normal.

05-MAR-2003 (141)

Species: dog **Sex:** no data
Strain: no data
Route of administration: inhalation
Exposure period: 100 exposure days
Frequency of treatment: 6 hours / day
Post exposure period: no
Doses: 0,061 mg/l (20 ppm)
Control Group: yes

Method: other: no data
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Result: In the range of 0,0652 mg/l dogs survived more
than 100 exposure periods of 6 hours each and
showed no gross or microscopic pathology, but
showed a functional drop in systolic blood
pressure.

05-MAR-2003 (89) (142) (143) (144)

Species: dog **Sex:** no data
Strain: no data
Route of administration: inhalation
Exposure period: 3 weeks
Frequency of treatment: 6 hours/day, 5 days/week
Post exposure period: 4 weeks
Doses: 50 ppm (about 0.15 mg/L)
Control Group: other: dogs used served as their own
control during a preliminary control
period

Method: other
GLP: no
Test substance: other TS: Dimethylformamide, no further data

Remark: Two dogs were exposed to 50 ppm DMF over a
period of 3 weeks. Studies of the circulation
and heart sounds were made daily before and
after treatment and during the 4 week
observation period.

Result: Both dogs became abnormal (with respect to circulation findings) during the first week of treatment and remained abnormal throughout the treatment period. During the 4 weeks following treatment one of the two dogs recovered, the other showed only very little improvement. The results of these two dogs were comparable to those obtained in a former study, when four dogs were fed DMF over a period of 10 - 12 weeks at a dose of 25 mg/kg (for 10 weeks) and 50 mg/kg (for additional two weeks), respectively. Concerning heart sound studies, the animals did not show a significant number of abnormal readings during or following the treatment period. The general trend of the readings indicated a gradual increase of the heart muscle tonus.

22-AUG-2000 (121)

Species: dog **Sex:** male/female
Strain: Beagle
Route of administration: oral feed
Exposure period: 13 weeks
Frequency of treatment: continuously in the diet
Post exposure period: none
Doses: 40, 200, 1000 ppm in the diet
(corresponding to 1.4, 7.0, 34.8 mg/kg)
NOAEL: > 1000 ppm

Method: OECD Guide-line 409 "Subchronic Oral Toxicity-Non-rodent: 90-day Study"
Year: 1981
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: Neither clinical nor morphological signs of toxicity were observed.

01-SEP-1997 (145)

Species: dog **Sex:** no data
Strain: no data
Route of administration: oral feed
Exposure period: 10-12 weeks see under remarks
Frequency of treatment: daily, 5 d/week
Post exposure period: none
Doses: 25 mg/kg (for the first 10 weeks), 50 mg/kg (for an additional 2 weeks)

Control Group: other: the animals used in the experiment were their own controls during a preliminary control period, duration not further specified

Method: other

GLP: no

Test substance: other TS: Dimethylformamide, no further data

Remark: Four dogs were fed DMF for a period of 10 weeks (5 days a week) at a dose of 25 mg/kg. For an additional 2 weeks they received 50 mg/kg. During the control period and the treatment period the animals were examined twice daily for changes in the circulation and at definite intervals blood and urine samples were investigated.

Heart sound readings were made before and after exposure each day.

Result: According to the authors all four dogs became definitely abnormal during the first week of treatment, thereafter the dogs seemed to become acclimatised to the treatment.

Concerning the blood pressure one dog returned to normal, two other dogs showed a slight improvement during treatment but remained still abnormal and one dog, which showed poor condition already during the control period remained quite abnormal during treatment.

Doubling the daily dose of DMF for the last two weeks of treatment did not alter the trend of the blood pressure scores. Body weight and blood and urine analyses were normal throughout the experiment. With the exception of one dog showing some lymphatic infiltration in a few of the portal areas in the liver, there were no findings at necropsy.

Concerning the heart sound readings, two dogs (one which showed poor condition, see above) did not show any significant no. of heart sound readings during treatment, although the general trend of the readings indicated a depression of the muscle tonus. The two other dogs showed abnormal readings characteristic of an increased irritability of the heart muscle.

22-AUG-2000

(121)

Species: dog

Sex:

Route of administration: oral unspecified

Exposure period: 12 weeks

Frequency of treatment: 5 d/w
Doses: 25 mg/kg (weeks 1-9); 50 mg/kg (from week 10 onwards)

Result: With the exception of a drop in systolic blood pressure no other signs of toxic effects were observed.

05-MAR-2003

(146)

Species: guinea pig **Sex:** no data
Strain: no data
Route of administration: dermal
Exposure period: up to 8 days
Frequency of treatment: once daily
Post exposure period: no
Doses: 10 ml (ca. 9500 mg), ca. 13000 mg/kg
Control Group: yes

Method: other: no data

GLP: no data

Test substance: other TS: N,N-dimethylformamide, no further data

Remark: The treated animals died after 7-8 applications. Significantly decreased food consumption was recorded; convulsions were observed. Necropsy revealed hyperemia of the internal organs and damage of the liver and the spleen.

05-MAR-2003

(147)

Species: monkey **Sex:** male/female
Strain: other: Cynomolgus
Route of administration: inhalation
Exposure period: 2 weeks
Frequency of treatment: 6 h/d, 5 d/w
Post exposure period: no data
Doses: ca. 1.52 mg/l (500 ppm)
Control Group: no

Method: other: no data

GLP: no data

Test substance: other TS: N,N-dimethylformamide, no further data

Remark: Two adult monkeys were exposed. One monkey was exposed "head-only", the other was exposed "whole-body" to determine whether the toxic effects or the pharmacokinetic profile of the test substance were altered by the two exposure routes.

Plasma N,N-dimethylformamide (DMF) and N-methylformamide (NMF) were measured in blood collected at various time intervals after first and last exposure. The peak plasma DMF and the DMF AUC ((AUC=area under curve) values were markedly higher following whole-body exposure compared with values obtained after head- only exposure, strongly supporting the contribution of dermal gaseous absorption to the circulating DMF levels.

05-MAR-2003

(148)

Species: monkey **Sex:** male/female
Strain: other: Cynomolgus
Route of administration: inhalation
Exposure period: 13 weeks
Frequency of treatment: 5 d/w, 6 h/d
Post exposure period: additional 13 weeks with no exposure for additional 2 male monkeys/exposure group (see under remarks)
Doses: 30, 100, 500 ppm (about 0.09, 0.3, 1.5 mg/l)
Control Group: yes, concurrent no treatment
NOAEL: 500 ppm
Method: other: no data
GLP: yes
Test substance: other TS: N,N-Dimethylformamide, 100% purity

Remark: The study was performed to characterize the toxic effects of DMF in Cynomolgus monkeys following 13 weeks of inhalation exposure. The aim was to determine the target organ effects, concentration response, a NOAEL, to measure selected pharmacokinetic parameters, evaluate potential toxic effects on the male and female reproductive system, examine differences in response between sexes and to evaluate potential specimen differences in toxic responses (comparison with literature data) following exposure to DMF vapors. A total of 20 male and 12 adult female monkeys were required for this study. Three monkeys/sex/exposure group were exposed to the three concentrations of DMF (30, 100 or 500 ppm) or filtered room air (concurrent control). In addition, two males per exposure group were designated as the post-exposure group.

The post-exposure group was held for 13 additional weeks with no exposure and was then necropsied.

Result: The effects of the test substance were studied in groups of 5 male and 3 female monkeys (two males/group served as additional animals for the post-exposure period). There were no early deaths in this study and all animals were sacrificed on their scheduled day of necropsy. There were no treatment-related findings in the 13 week inhalation study except possible alterations in the menstrual cycle of DMF exposed females. The menstrual cycle of 1 low dose group female, 2 mid dose females and all high dose females were altered in length. According to the authors, the subchronic exposure of cynomolgus monkeys to DMF did not cause any adverse health effects (liver function, sperm production, and sperm motility appeared unaffected). With respect to the possible increase in menses length with exposure to DMF and its relevance, the experts conclusions were that while the data are suggestive of an effect, there is no confirmed evidence that DMF caused an effect on menstrual cycle because of the monkeys recent importation history and lack of preexposure data. these data were not completely evaluated at the time of publication.

Test substance: N,N-dimethylformamide; total contamination level was less than 0.5% of the DMF concentration (based upon FID raw peak area ratios)

Reliability: (2) valid with restrictions
reliable with restrictions

Flag: Critical study for SIDS endpoint
05-MAR-2003 (149)

Type: Sub-chronic
Species: monkey **Sex:** male/female
Strain: other: cynomolgus monkey
Route of administration: inhalation
Exposure period: 13 weeks
Frequency of treatment: 6 h/d; 5 days/week
Post exposure period: Two males were maintained for a further 13-wk observation period after exposure
Doses: 0, 30, 100, 500 ppm (0, 90, 300, 1500 mg/m³)
Control Group: yes

Remark: 3 animals/sex/group; 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 sign of toxicity and no effects on body weight gain, haematology, clinical chemistry, urinalysis, organ weights, or histopathological effects attributable to DMF (N,N-Dimethylformamide) in monkeys exposed to up to 500 ppm.

Reliability: (4) not assignable
second quotation

27-MAY-2003 (150)

Species: other: cat, rabbit, rat, mouse **Sex:**
Route of administration: inhalation
Exposure period: 21 days
Frequency of treatment: 5 d/w; 7 x 3 h/d followed by 8 x 5 h/d
Doses: 10 mg/l
Control Group: no

Method: other
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: Besides one cat, one rabbit, 4 rats and 10 mice were used in the present investigation that does not meet today's standards.
With the exception of changes in hematology in the cat no other overt findings were described.

05-MAR-2003 (76)

Species: other: cat, rabbit, rat, mouse **Sex:**
Route of administration: inhalation
Exposure period: 3 days
Frequency of treatment: 3 h/d
Post exposure period: 8 days
Doses: 12.5 mg/l (vapors generated by heating of 5 g of the test substance to 180 degrees C)
Control Group: no

Method: other
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: In an inhalation cage with a volume of 400 L, one cat, one rabbit, 4 rats and 10 mice were exposed to vapors generated by heating of 5g DMF up to 180° C. After 30 to 40 minutes the entire amount of the weighed liquid was evaporated. Vapor concentration was 12.5 mg/L. The cage temperature increased from 19 to 26° C. During exposure and in the following 8 days after exposure none of the animals used showed toxic effects. Urinalysis did not reveal any changes. The cat showed a slight increase in hemoglobin concomitant with a slight and transient increase in the number of erythrocytes. One mouse died 3 days after the last exposure, necropsy was macroscopically without any finding.

05-MAR-2003

(76)

Species: other: cat, rabbit, rat, mouse **Sex:**
Route of administration: inhalation
Exposure period: 3 days
Frequency of treatment: 1.+ 2. day: 6 h; 3. day: 7.5 h.
Post exposure period: at least 5 days
Doses: 1. day: 18 mg/l, 2. day: 20 mg/l, 3. day: 30 mg/l
Control Group: no

Method: other
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: DMF was heated up to 90-100° C and a current of air (200 L/h) was conducted over the heated test substance. The generated DMF enriched air was conducted into a glass cage where one cat, one rabbit, 4 rats and 10 mice were exposed. The cat showed lacrimation after the first exposure period. Later purulent rhinitis, leucocytosis and purulent conjunctivitis were observed in the cat. The animal died 5 days after the last exposure. In rats and the mice no overt signs of toxicity were observed during exposure. Two days after the second exposure one rat and 4 mice died and after the third exposure another mouse died.

At necropsy slight congestion of lung and spleen and a moderate fatty infiltration were seen.

05-MAR-2003

(76)

Species: other: cat, rabbit, rat, mouse **Sex:**
Route of administration: inhalation
Exposure period: 1 - 3 days
Frequency of treatment: 5 - 6 h/d
Post exposure period: 8 days
Doses: 75, 125, 150 mg/l
Control Group: no

Method: other
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: DMF was heated up to 100° C in a water-bath and the generated vapor was conducted via a current of air (400 L/h) into a cage where one cat, one rabbit, 4 rats and 10 mice were exposed. Substance concentration in the cage was 75 mg/L on the first, 125 mg/L on the second and 150 mg/L on the third day. The animals were exposed partly only at one exposure day, partly at all three exposure days. After single exposure for some hours most of the rats and mice showed tonic-clonic convulsions or signs of narcosis, about half of the animals died. After the third exposure cat and rabbit showed overt findings (salivation, accelerated breathing, strong excitation, redness of the ears). The animals died during exposure or some hours later. With the exception of fatty infiltration in the liver of the cat and broncho-pneumonic foci in the lungs of the rabbit, no other pathological findings were observed at necropsy.

05-MAR-2003

(76)

Species: other: cat, rat **Sex:**
Route of administration: inhalation
Exposure period: up to 120 days
Frequency of treatment: 8 h/d; on working days
Doses: 100, 230, 450 ppm (ca. 0.3, 0.7, 1.36 mg/l)

Result: The highest dose (450 ppm) led to mortality in 2 cats after 28 and 48 hours and in 6/16 rats within 56 days.

At the lowest dose of 100 ppm after a time period of 120 days body weight loss and livercell necrosis were seen in rats and cats. According to other descriptions of the investigations (Massmann W., Zbl. Arbeitsmedizin 6, 1956) as well as due to the insufficient performance of the experiment the relevance of the results is questionable.

05-MAR-2003

(151) (152)

Species: other: cat, rat **Sex:** no data
Route of administration: inhalation
Exposure period: 2 months
Frequency of treatment: 6 h/d
Doses: 1000 ppm (ca. 3.03 mg/ l)
Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4
Remark: No toxic effects on liver or kidney were observed in both species.

05-MAR-2003

(153)

Species: other: rabbit, guinea pig, rat, **Sex:**
mouse, dog
Strain: no data
Route of administration: inhalation
Exposure period: 58 days
Frequency of treatment: 5 d/w; 6 h/d
Post exposure period: none
Doses: 23, 426 ppm (ca. 0.07, 1.3 mg/l)
Control Group: yes
Method: other
GLP: no
Test substance: other TS: N,N-dimethylformamide, no further data
Remark: Dose levels used were: 23 ppm (the first 5.5 hours per exposure); 426 ppm (about 1.3 mg/L, for an additional half an hour at the end of each exposure).
The samples of DMF used in the present study were obtained from a plant, the material represented the material in use in the plant. Animals used in this experiment consisted of 10 male and 10 female rats, 10 female mice, 10 male guinea pigs, 2 male and 2 female rabbits and 4 male dogs.

Equal numbers of control animals were used. Controls were exposed daily for 6 hours to a current of air.

Result: There were no clinical signs of toxicity and no effects on the body weights in all animals but dogs.

Body weight of the dogs was maintained but in 2 of 4 dogs cardiovascular effects developed. In all four dogs degenerative anatomical changes were found in the heart muscle.

Changes in the functional status of the liver were observed in rats, rabbits and dogs. Plasma cholesterol was increased in rats, rabbits and one dog. The dog also showed increased alkaline phosphatase activity and a slight increase in the activity of plasma cholinesterase. The fat content of the livers was slightly increased in rats. Liver weights were increased in all but guinea pigs, but only the livers of mice were significantly heavier than controls. Hematological investigations revealed changes only in three dogs that showed a significant increase in thickness and number of the red blood cells.

There were pathology findings in a number of organs, however the major effect of DMF inhalation was on the heart, liver, pancreas, kidneys, adrenals and thymus.

05-MAR-2003

(154) (155)

Species: rodent **Sex:**
Route of administration: inhalation
Exposure period: 18 weeks
Frequency of treatment: 6 d/w; 6 h/d
Doses: 0.022 mg/l

Result: Besides the rats, rabbits were also investigated.

The rats showed changes in the liver, whereas the rabbits did not.

At a concentration of 317 mg/m³ (6 h/d, 6 d/week) the rabbits showed changes in the liver function and morphology.

05-MAR-2003

(156)

5.5 Genetic Toxicity 'in Vitro'

Type: Ames test
System of testing: Salmonella typhimurium
Metabolic activation: with and without

Result: negative

Test substance: other TS: N,N-dimethylformamide, no further data

Remark: These publications are summaries of several Ames tests.
Tester strains mentioned are: TA98, TA100, TA13535, TA1537, and TA1538 (deSerres and Ashby, 1981).
Only secondary literature; no further data.
05-MAR-2003 (157) (158) (159) (160)

Type: Ames test
System of testing: Salmonella typhimurium TA 98, TA 100
Metabolic activation: with
Result: ambiguous

Test substance: other TS: N,N-dimethylformamide, no further data

Remark: In the present investigation a fluctuation test with metabolic activation through primary hepatocytes was used.
Toxicity was observed at $\geq 50 \mu\text{g/ml}$.
According to the authors, it is possible that release of histidine from damaged hepatocytes could lead to artefacts.
06-MAR-2003 (161)

Type: other: SOS-Chromotest
Result: negative
06-MAR-2003 (158)

Type: Cytogenetic assay
System of testing: human lymphocytes
Result: positive

Remark: Concentration-related increase of chromosome aberrations at $10\text{E-}7$ to $10\text{E-}2$ molar concentration over 4 hours.
06-MAR-2003 (162)

Type: other: Cell transformation assay
System of testing: BHK-cells, SHE-cells

Remark: In a total of 8 studies the cell transforming activity of DMF was tested.

The investigation with BHK-cells (up to 500 µg/ml) led to a negative result. With SHE-cells three positive and 4 negative results were obtained.

06-MAR-2003

(87) (163)

System of testing: Escherichia coli, Saccharomyces cerevisiae, Schizosaccharomyces pombe

Result: negative

Remark: Different endpoints were investigated in the above mentioned test systems.

06-MAR-2003

(164)

Type: other: UMU-Test
System of testing: Salmonella typhimurium
Result: negative

06-MAR-2003

(164)

Type: other: aneuploidy-test
System of testing: Saccharomyces cerevisiae D6
Metabolic activation: with and without
Result: positive

Remark: result: positive (+/- S-9) at concentrations > 25 µg/ml.

06-MAR-2003

(165)

Type: DNA damage and repair assay
System of testing: Saccharomyces cerevisiae
Metabolic activation: with and without
Result: positive

Remark: result: positive (+/- S-9) at concentrations > 500 µg/ml.

06-MAR-2003

(166)

Type: other: Host-mediated assay
System of testing: Salmonella typhimurium TA 98, TA 1538

Remark: A dose-related increase of histidine-auxotroph revertants of Salmonella typhimurium strains TA 98 and TA 1538 which were incubated with mouse-blood (0.5 - 2 h after i.p. injection of DMF) was observed by the authors.

The mice were treated with each 0.5 ml of 1, 10, 25 and 30% (corresponding to 0.17, 1.7, 4.25 and 5.1 g DMF/kg) DMF-solutions in aqua dest., respectively.

At the two highest concentrations animals died, thus the number of animals used had to be increased to get a minimum of 3 animals. Blood samples were pooled.

The most overt effects were seen 1 h after the injection; after 2 and 4 h no effects were observed.

06-MAR-2003

(167)

Type: Sister chromatid exchange assay
System of testing: CHO-cells
Concentration: 0.00625-0.1% (about 0.0625 - 1 mg/ml)
Metabolic activation: with and without
Result: negative

Method: other: modified procedures developed by Perry, P. and Evans, H.J.: Nature 258, 121-125, (1975) and Stetka, D.G. and Wolff, S.: Mutat. Res. 41, 343-350, (1976)

GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Remark: Assay was conducted in duplicate in the presence and in the absence of an Aroclor-induced rat liver metabolic activation system (S-9 mix). Positive and negative controls were also tested in duplicate.
Test substance was dissolved and diluted in DMSO to form a series of concentrations (diluted 1:100 in culture medium).
The final concentration of DMSO was 1% which is not cytotoxic.
Before the assay was performed cytotoxicity measurements were done to obtain an indication of cytotoxicity and cell cycle effects. The cells were exposed to a series of five 1:5 dilutions of the test substance and the positive and negative controls. The highest concentration of DMF was 0.1%.
Positive controls were ethyl methanesulfonate (induction of SCEs in the absence of S-9 mix) and dimethylnitrosamine (induction of SCEs with S-9 mix). Negative control was DMSO.

In the assays without metabolic activation the cells were grown in the dark for 21.5 h at 37°C in the presence of the added test substance. In the assays with metabolic activation the cell cultures were exposed to the test substance in the S-9 mix for 2 h. After exposure the cells were washed and BrdU was added and the cultures incubated in the dark for 21.5 h. After 2.5 h in colchicine the cells were harvested and prepared for staining. 50 cells were scored for each concentration of the test substance and for the controls. The mean number of SCEs/chromosome were determined.

Result: DMF did not increase SCE frequencies at concentrations of 0.00625 - 0.1% in the presence and the absence of S-9 mix.
Reliability: (2) valid with restrictions
reliable with restrictions
Flag: Critical study for SIDS endpoint
25-OCT-2000 (168)

Type: Cytogenetic assay
System of testing: CHO-cells
Result: negative

Test substance: other TS: N,N-dimethylformamide, no further data

Remark: Only secondary literature; no further data.
06-MAR-2003 (169)

Type: Unscheduled DNA synthesis
System of testing: human diploid fibroblasts
Concentration: up to 9,220 µg/ml (about up to 9220 mg/l)
Metabolic activation: with and without
Result: negative

Method: other: no data
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Remark: To establish the range of concentrations of test compound to be used in the DNA repair assay a preliminary toxicity test was performed. The compound was dissolved directly in culture medium and 10 µl samples added to duplicate cell suspension. After incubation for 3 h at 37°C cultures were fixed and stained and examined for evidence of cellular damage.

No toxicity was observed even at the highest concentration of 9.633 mg/ml which was selected as the highest in a series of concentrations of DMF. In the DNA repair assay the prepared cell cultures were divided into 2 groups and 100 µl of S-9 mix added to one of them. S-9 mix was prepared from liver homogenate of Aroclor pretreated male CD rats. Solutions of hydroxyurea (250 mM) in sterile distilled water and 6-[3H]-thymidine were added to each culture. DMF was dissolved in DMSO and dilutions were made to give the required concentrations (no data given). Triplicate wells with and without S-9 mix received 10 µl samples of the DMF solution. 10 µl samples of DMSO were added to negative control cultures. The positive control compounds were 4-nitroquinoline-N-oxide (1.25 µg/ml) for s-9 free cultures and 2-aminoanthracene (3 µg/ml) for S-9 supplemented cultures.

After incubation for 3 h at 37°C, rinsing and drying the cells were processed for autoradiography and stained. Stained autoradiographs were examined. 50 nuclei were examined for each culture.

Result: There was no indication of any increase in the number of silver grains per nucleus at any concentration of DMF.

The positive control substances induced significant response in unscheduled DNA synthesis in the cells.

Test substance: N,N-dimethylformamide; purity >99%

Reliability: (2) valid with restrictions
reliable with restrictions

Flag: Critical study for SIDS endpoint

06-MAR-2003

(170)

Type: Unscheduled DNA synthesis

System of testing: primary hepatocytes from rodents, humane fibroblasts, WE-38-cells, HeLa-cells

Result: negative

Test substance: other TS: N,N-dimethylformamide, no further data

Remark: Only secondary literature; no further data.

06-MAR-2003

(164) (171) (172) (173) (174) (175)

Type: Mouse lymphoma assay
System of testing: L5178Y TK +/-mouse lymphoma cells
Concentration: no data
Metabolic activation: no data
Result: negative

Method: other: no data
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Remark: Only secondary literature; no further data.
06-MAR-2003 (176) (177)

Type: Mouse lymphoma assay
System of testing: Mouse-lymphoma-cells
Result: positive

Remark: result: the result was assessed as weakly positive (- S-9).
Differentiation between small and big colonies was not described.
06-MAR-2003 (178)

Type: Mitotic recombination in Saccharomyces cerevisiae
System of testing: Saccharomyces cerevisiae
Concentration: 0,0001 -0,3 mg/l
Metabolic activation: without
Result: negative

Method: other: no data
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data
03-SEP-1997 (179)

Type: other: SV40 gene amplification
System of testing: SV40-transformed embryonal CO631 hamster cells
Concentration: 0.001 - 5 mg/l
Metabolic activation: without
Result: negative

Method: other: no data
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data
04-SEP-1997 (180) (179)

Type: Bacterial gene mutation assay
System of testing: Escherichia coli WP2uvrA
Concentration: no data
Metabolic activation: with
Result: negative

Method: other: no data
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

06-MAR-2003 (181)

Type: other: mutations in plants
System of testing: Arabidopsis thaliana
Concentration: no data
Metabolic activation: no data
Result: negative

Method: other: no data
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Result: DMF had no effect on the frequency of recessive Chlorophyll and embryonic lethal mutations in Arabidopsis. In the same system DMF altered the mutagenic activity of known mutagens.

06-MAR-2003 (182) (183)

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538
Concentration: 600, 1200, 1800, 2400, 5000 ug/plate
Metabolic activation: with and without
Result: positive

Method: other: no data
GLP: no
Test substance: other TS

Remark: Ames test with and without metabolic activation with S-9 mix prepared from rat liver homogenate. According to the authors, the test substance was weakly mutagenic.

Test substance: N,N-dimethylformamide tar still residue; no data on purity of the compound

20-AUG-1997 (184)

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538

Concentration: 2000, 4000, 6000, 8000, 10000 ug/plate
Metabolic activation: with and without
Result: negative

Method: other: no data
GLP: no
Test substance: other TS: N,N-dimethylformamide, no further data

Remark: Ames test with and without metabolic activation with S-9 mix prepared from rat liver homogenate. Negative or solvent control: distilled water Positive control in the assay with metabolic activation: p-aminoanthracene; moreover a control plate without S-9 mix run in parallel. Positive control in the assay without metabolic activation: N-Methyl-N'-Nitro-N-Nitrosoguanidine (for TA 1535 and TA 100), 9-Aminoacridine (for TA 1537), 2-Nitrofluorene (for TA 1538 and TA 98). Plates were incubated for 48 hours.

25-OCT-2000 (185)

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538
Concentration: 100, 200, 300, 400, 480, 500 (+S-9); 80, 160, 240, 320, 400, 480 (-S-9) ug/plate
Metabolic activation: with and without
Result: negative

Method: other: no data
GLP: no
Test substance: other TS: N,N-dimethylformamide, no further data

Remark: Ames test with and without metabolic activation with S-9 mix prepared from rat liver homogenate.
Test substance: N,N-dimethylformamide tar still residue; no data on purity of the compound

05-MAR-2003 (186)

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538
Concentration: 9400, 24000, 47000, 94000, 190000, 470000 ug/plate
Metabolic activation: with and without
Result: negative

Method: other: standard plate incorporation assay, (Ames, 1975)

Year: 1975
GLP: no
Test substance: other TS: N,N-dimethylformamide, no further data

Remark: Ames test with and without metabolic activation with S-9 mix prepared from liver homogenate of Aroclor pretreated male Sprague-Dawley rats. Plates are incubated at 37°C for 48 hours. Cytotoxicity of the test sample as measured in strain TA1535 is the basis for selecting concentrations to be used in the present test. Concentrations of test sample that give less than 50% of control survival are normally not selected for the assay. Evaluation criteria: a chemical was classified as non-mutagenic if the reversion frequency was less than 2 times the spontaneous frequency. No statistical analysis was performed. However, in the present assay 470000 µg/plate was chosen because this experiment was done to aid in evaluating a recent Utah Biological Testing Service report, that concluded that DMF is mutagenic in 4 of the Ames strains of Salmonella typhimurium. 470000 µg/plate led to toxicity as indicated by sparse background lawn. A negative control run in parallel in the assay with and without metabolic activation. Positive control in the assay with metabolic activation was 2-Aminoanthracene tested in concentrations of 5, 10 and 100 µg/plate. Positive controls in the assay without metabolic activation were: N-Methyl-N'-nitro-N-nitrosoguanidine at 2 µg/plate (TA1535, TA100); 9-Aminoacridine at 50 µg/plate (TA1537); 2-Nitrofluorene at 25 µg/plate (TA1538 and TA98). Positive and negative controls did work well in the present investigation.

Result: DMF is not mutagenic even at concentrations that are cytotoxic. (Cytotoxicity occurred at 190000 and 470000 µg/plate without metabolic activation and at 470000 µg/plate with metabolic activation.)

Reliability: (2) valid with restrictions
reliable with restrictions

Flag: Critical study for SIDS endpoint
05-MAR-2003 (187)

Type: other: RL1-assay

System of testing: rat liver cells (RL1-cells)
Concentration: 75, 150, 300 mg/l
Metabolic activation: no data
Result: negative

Method: other: according to Dean, B.J. and Hodson-Walker: "An in vitro chromosome assay using cultured rat liver cells", Mutat. Res.; no further data
Year: 1979
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Remark: No chromosomal damage was observed in metaphase analysis after incubation of the cells with the test substance for 24 h.

Test substance: N,N-dimethylformamide; no data on purity of the compound

04-SEP-1997

(188)

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1535, TA1538
Concentration: 100, 500, 1000, 10000, 50000 ug/plate
Metabolic activation: with and without
Result: negative

Method: other: according to Ames, B.N.: Proc. Natl. Acad. Sci. 70, 2281-2285
Year: 1973
GLP: no
Test substance: other TS: N,N-dimethylformamide, no further data

Remark: Ames test with and without metabolic activation with S-9 mix prepared from liver homogenate of Aroclor pretreated male CD-rats.
Negative control: DMSO
Positive control: 2-acetylaminofluorene and vinyl chloride

Result: No mutagenic effect was seen in strains TA 98 and TA 1538.
With strains TA 100 and TA 1535 slight increase in the numbers of mutants per plate were seen in the presence of the S-9 mix. However, according to the authors these increases showed no dose-response relationship over a 500 fold range of test substance concentrations up to 50 mg per plate, neither in the number of mutants nor in indications of toxicity.

Test substance: N,N-dimethylformamide; no data on purity of the compound
10-APR-2001 (189)

Type: other: cell transformation
System of testing: Hamster Embryo cells
Concentration: no data
Metabolic activation: no data
Result: negative

Method: other: no data
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Remark: The test substance did not induce morphological transformation in Syrian hamster embryo cells (Pienta et al., 1977). No transformation was observed in hamster embryocells after transplacental exposure by i.p. injection (Quarles et al., 1979). Only secondary literature; no further data.
06-MAR-2003 (190) (191)

Type: Cytogenetic assay
System of testing: Human lymphocytes
Result: negative

Test substance: other TS: N,N-dimethylformamide, no further data

Remark: Only secondary literature, no further data.
06-MAR-2003 (157)

Type: Ames test
System of testing: Salmonella typhimurium TA 98, TA100, TA1535, TA1537, TA1538
Concentration: 47, 4700, 94000 and 470000 µg/plate
Metabolic activation: with and without
Result: negative

Method: other: no data
GLP: no
Test substance: other TS: N,N-Dimethylformamide, neat material 100 wght%, no further data

Remark: Ames test (overlay plate test) with and without metabolic activation with S-9 mix prepared from liver homogenate of Aroclor pretreated male Sprague-Dawley rats.

Negative control in the assay with non-activation and in the assay with activation was DMSO. Positive control in the assay with non-activation:
Methylnitrosoguanidine (TA1535 and TA100);
Quinacrine mustard (TA1537); 2-Nitrifluorene (TA98, TA1538).
Positive control in the assay with activation:
2-Anthramine (TA1535); 8-Aminoquinoline (TA1537);
2-Aminofluorene (TA98, TA100, TA153

12-SEP-2000 (192)

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538
Concentration: 47, 4700, 94000, 470000 µg/plate
Metabolic activation: with and without
Result: negative

Method: other: no data
GLP: no
Test substance: other TS: Dow Corning 790 Building Sealant Natural Stone , a mixture containing 1 wght.% N,N-Dimethylformamide, no further data

Remark: Ames test (overlay plate test) with uncured and cured test material tested with and without metabolic activation with S-9 mix prepared from liver homogenate of Aroclor pretreated male Sprague-Dawley rats.
Negative control in the assay with non-activation and in the assay with activation was DMSO.
Positive control in the assay with non-activation: Methylnitrosoguanidine (TA1535 and TA100); Quinacrine mustard (TA1537); 2-Nitrifluorene (TA98, TA1538).
Positive control in the assay with activation: 2-Anthramine (TA1535); 8-Aminoquinoline (TA1537); 2-Aminofluorene (TA98, TA100, TA1538

05-MAR-2003 (193)

Type: other: Chromosome Aberration/Sister Chromatid Exchange Assay
System of testing: CHO cells
Concentration: 1.67, 3.33, 6.67 µl/ml (about 1.6, 3.2, 6.3 mg/ml)
Metabolic activation: with and without
Result: negative

Method: other
GLP: no data
Test substance: other TS: N,N-Dimethylformamide, no further data

Remark: In this assay the frequencies of chromosome aberrations and sister chromatid exchanges induced in CHO cells were determined. CHO cells grown in the dark for one cell cycle and supplemented with BrdU were treated for 1 h with various concentrations of DMF in the presence or absence of S9 fraction (S-9 mix was prepared from Aroclor-induced rat liver homogenates). After treatment the cells were washed and allowed to recover for \geq 12 h. After the colcemid block the cells were prepared for staining. Some preparations from each treatment were stained with Giemsa stain for the determination of the frequencies of chromosome aberrations. For determination of the frequencies of sister chromatid exchanges preparations were first stained with Hoechst 33258 and stained with Giemsa solution in order to obtain sister chromatid differentiation. 25 to 50 cells were scored for the frequencies of sister chromatid exchanges. 50 to 100 cells were scored for aberrations for each point, i.e. gaps, breaks and exchanges. Two controls, one with S-9 and one without S-9 mix treated with the solvent DMSO were included in the test.

Result: DMF was found to be negative in both tests, in the presence or absence of S-9 mix during treatment.

Reliability: (2) valid with restrictions
reliable with restrictions

Flag: Critical study for SIDS endpoint

06-MAR-2003

(194)

Type: Mouse lymphoma assay
System of testing: L5178Y mouse lymphoma cell
Concentration: no data
Result: negative

Reliability: (4) not assignable
second quotation

27-MAY-2003

(195)

5.6 Genetic Toxicity 'in Vivo'

Type: Cytogenetic assay
Species: rat **Sex:** male/female
Strain: other: CD
Route of admin.: inhalation
Exposure period: 1 or 5 days (7 h/d)
Doses: 10, 400 ppm (ca. 0.03, 1.21 mg/l)

Method: other
GLP: no data
Test substance: other TS: N,N-Dimethylformamide, of 99% purity, no further data

Result: Result: questionable negative
The frequencies of chromosomal aberrations were not increased in rat bone marrow cells at 6 h and 48 h sample times, except in the 24 h sample time males following a single exposure. According to the authors this effect was almost entirely due to a single rat, which may have been abnormal.

14-SEP-2000

(196) (197)

Type: Dominant lethal assay
Species: mouse **Sex:** male
Strain: NMRI
Route of admin.: i.p.
Exposure period: single dose
Doses: 400 µl/kg (ca. 380 mg/kg)
Result: negative

Method: other: according to WHO: "evaluation and testing of drugs for mutagenicity: Principles and Problems", WHO, Technical Report Series, no. 482

Year: 1971

GLP: no

Test substance: other TS: N,N-dimethylformamide, no further data

Remark: In two studies DMF was administered once by i.p. injection as an aqueous solution at 0.1 ml/animal at a dose of 380 mg/kg to 20 male NMRI mice. The animals were about 12-14 weeks of age and the mean body weight was about 31 g in the first and about 28.5 g in the second study. Positive control was 2,3,5-Tris-ethyleneimino-benzoquinone-1,4 at a dose of 0.125 mg/kg in the first and at a dose of 0.056 mg/kg in the second study.

Negative (untreated) control groups run in parallel. Twenty male mice each were used for the positive and the negative control group. About 20 h after substance application, the male mice were mated with 3 untreated virgin female mice (1:3) for the duration of 7 days. Then the females were removed and replaced with three new untreated virgin females. This mating procedure continued for 7 consecutive weeks.

Female animals were sacrificed 18 days after the first day of mating with the male rat, resulting in a gestation period of 10-17 days.

All animals were observed daily for clinical symptoms. Body weight of the male mice was determined before treatment, after treatment and weekly thereafter. All male mice were killed at the end of the last mating period (week eight) and macroscopically examined.

For the female animals the conception rate was calculated for each mating interval (derived from pregnant animals in relation to mated females). Moreover implantation sites/female animal were recorded and mean number of implantation sites/dam were calculated.

Implantation sites were further distinguished as live and dead fetuses and deciduoma (early resorption sites still macroscopically discernible) and early resorptions discernible only by the staining method according to Salewski. The mutagenicity index (= percentage of dead implantation sites) per mating interval was derived from the number of dead fetuses plus deciduoma plus early resorptions divided by the number of implantation sites multiplied with 100.

Result:

In the first study no substance-related effect on conception and number of live implantations was observed. In the second week of mating a significantly increased number of dead implantations (mutagenicity index) was observed in the females mated with DMF treated males when compared to untreated controls. However, according to the authors the mutagenicity index was still in the range of normal values that occurred also in the concurrent untreated control group. Whereas in the positive control a significant decrease in the mean number of implantation sites and a significant increase in the percentage of dead implantation sites (mutagenicity index) was observed during the

first three mating intervals.
In the second study again no substance-related effect on conception and number of live implantation sites was seen but there was a statistically (mathematically) significant increase in the number of dead implantations in the 1st and 2nd week of mating in comparison to the untreated control.

However, according to the authors, this was not due to the test substance since this effect was also observed at other time points and occurred in untreated controls, too.

In the positive control a significant decrease in the mean number of implantation sites was observed in the first week of mating and a significant increase in the percentage of dead implantation sites (mutagenicity index) was observed in the first three mating intervals.

Reliability:

(2) valid with restrictions
reliable with restrictions

Flag:

Critical study for SIDS endpoint

06-MAR-2003

(198) (199)

Type:

Dominant lethal assay

Species:

rat

Sex: male

Strain:

other: CD

Route of admin.:

inhalation

Exposure period:

5 days, 7 h/d

Doses:

10, 400 ppm (ca. 0.03, 1.21 mg/l)

Method:

other: no data

GLP:

no data

Test substance:

other TS: N,N-dimethylformamide, no further data

Result:

negative

There were no effects attributable to the test substance on pregnancy frequency, numbers of corpora lutea or implantations or the frequency of early deaths.

Test substance:

N,N-dimethylformamide; purity >99%

04-SEP-1997

(196) (170)

Type:

Dominant lethal assay

Species:

rat

Sex: male

Strain:

other: Sprague-Dawley (CRCD)

Route of admin.:

inhalation

Exposure period:

5 days, 6 h/d

Doses:

30, 300 ppm (ca. 0.09, 0.91 mg/l)

Result:

negative

Method: other: no data
GLP: no
Test substance: other TS: N,N-dimethylformamide, no further data

Remark: In the present study a negative (untreated) control and a positive control group (Triethylenemelamine saline solution at a dose of 0.5 mg/kg and a volume of 1 ml/kg administered once i.p. two hours prior to mating) run in parallel to the DMF-vapor-treated groups.
Each group (two DMF-exposed) and the control groups contained 10 proven fertile male rats. Over a six week post-treatment period the mutagenic potential of DMF was evaluated. Males used were about 8 weeks and females about 6 weeks of age.
The fertility of each male was determined during a two week pre-treatment mating period. At least two hours after the last exposure, two untreated virgin females were placed into each male's cage for 7 days.
Then the females were removed and replaced with two new untreated virgin females. This mating procedure continued for six consecutive weeks. Females were sacrificed 18 days after the first day of caging with the male, resulting in a gestation period of 11-18 days. Uterine implantation data were recorded (number of implantation sites, early resorptions distinguishable as deciduoma, late resorptions and viable fetuses).
During the mating intervals all animals were observed daily for clinical signs and mortality and body weight of the male animals was determined weekly.
At completion of the study the males were sacrificed and necropsy was performed. The following tissues of 5males/group were preserved: seminal vesicles, epididymides, testes, prostate and from all males any abnormal lesions or tissue masses.
Histopathological examination was carried out on seminal vesicles, epididymides, testes and prostate.

Result: All male animals survived until termination of the study.
During treatment and during the six week post-treatment mating period all animals were unremarkable.

Mean body weights for males exposed to 30 and 300 ppm DMF were slightly lower than the negative control already during pre-treatment. This trend persisted during treatment and post-treatment. Body weight gain during the post-treatment mating period was slightly lower than negative control for the males exposed to 300 ppm DMF. Pregnancy rates and implantation efficiency values of females mated to males exposed to DMF were considered comparable to the negative control throughout the post-treatment period. In contrast, pregnancy rates for the females mated to males of the positive control were lower than the negative control at mating weeks 2,3 and 4, only at week 4 this difference was statistically significant. Implantation efficiency values were significantly lower at weeks 2-6. Early fetal death data were significantly increased during the entire post-treatment mating period. Fetal death data for the DMF-treated groups were slightly higher than negative control at week 2 for both treated groups and week 5 for the 30 ppm and week 6 for the 300 ppm group. According to the authors, at each interval the increase in fetal deaths was, in part, attributable to a single female that had uterine implants comprised entirely of early fetal deaths. These increases were not considered indicative of a dominant lethal mutagenic response since the second female of the pair mated with the DMF-treated male had high numbers of uterine implants which in most cases were all viable fetal swellings. Histopathology of male reproductive organs revealed no alterations to treatment. Thus, pre-mating DMF-exposure of the rats for 5 consecutive days did not result in mutagenic effects in the test system.

Test substance: N,N-dimethylformamide; no data on purity of the compound

Reliability: (2) valid with restrictions
reliable with restrictions

Flag: Critical study for SIDS endpoint

06-MAR-2003

(82)

Type: Dominant lethal assay

Species: mouse

Sex: male

Strain: other: albino

Route of admin.: dermal

Exposure period: single dose

Doses: 1500, 3000, 5000 mg/kg

Method: other: no data
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Remark: negative
Test substance: N,N-dimethylformamide; no data on purity of the compound

04-SEP-1997 (200)

Type: Dominant lethal assay
Species: rat **Sex:** male
Route of admin.: inhalation
Exposure period: 5 days; 6-7 h/d
Doses: 400 ppm (ca. 1.21 mg/l)

Result: result: negative
No chromosomal aberrations were seen in the rats. The investigations performed with respect to possible effects on spermcell morphology was also negative.

06-MAR-2003 (201)

Type: Drosophila SLRL test
Species: Drosophila melanogaster **Sex:**
Doses: no data

Method: other: no data
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Remark: Only secondary literature; no further data.
Result: negative

06-MAR-2003 (202) (203) (204) (205) (206)

Type: Drosophila SLRL test
Species: Drosophila melanogaster **Sex:** male
Route of admin.: inhalation
Exposure period: 2.25 hours
Doses: 400 ppm

Method: other: no data
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Result: negative
tester strains:
males: Oregon-K (wild-type), Mueller-5
(bascbalancer X-chromosome);
females: Mueller-5

Test substance: N,N-dimethylformamide; purity >99%
06-MAR-2003 (201) (196) (170)

Type: Micronucleus assay
Species: mouse **Sex:** male
Strain: Balb/c
Route of admin.: i.p.
Doses: 0.2, 20 and 2000 mg/kg
Result: negative

Method: other: according to the methodology of Schmid
W.: Chem. Mutagens, Vol. 4, 31-53, (1976)
GLP: no data
Test substance: other TS: N,N-Dimethylformamide, no further data

Remark: Young (8-12 weeks old) male Balb/c mice (5 per
treatment group) were injected i.p. with 0.2, 20
and 2000 mg DMF/kg.
Positive controls received 100 mg/kg
cyclophosphamide. A negative control (not
further specified) run in parallel
Preparations of bone marrow cells were made 30 h
aftertreatment.

Result: There was no increase in cells with micronuclei
in the DMF-treated animals, whereas the positive
control showed a clear increase.

Reliability: (2) valid with restrictions
reliable with restrictions

Flag: Critical study for SIDS endpoint
14-SEP-2000 (207)

Type: Micronucleus assay
Species: mouse **Sex:** male
Strain: ICR
Route of admin.: i.p.
Doses: 0.425, 0.85 and 1.70 ml/kg (about 404, 808, 1615
mg/kg)
Result: negative

Method: other: modification of the method of Schmid w.:
Chem. Mutagens, Vol. 4, 31-53, (1976)
GLP: no data

Test substance: other TS: N,N-Dimethylformamide, no further data

Remark: DMF dissolved in DMSO was administered i.p. once at 5 ml/kg to male ICR mice (weight of 18-30 g). Groups of 8 animals each were administered 50, 25 or 12.5% of the LD50, i.e. 1.70, 0.85 or 0.425 ml/kg. The negative control received 5 ml/kg of DMSO and the positive control animals were given 1,500 mg/kg of trimethylphosphate in DMSO at 5ml/kg.

Femoral bone marrow smears were made from 4 animals each per group at 30 h and at 48 h according to the method of Schmid W. (1976). For each animal scored, 1000 polychromatophilic erythrocytes were examined for the presence of micronuclei. The ratio of polychromatophilic erythrocytes to normochromatic erythrocytes was determined for the first four animals in each group. Since there was no significant difference in the value obtained at 30 h from that at 48 h, the results have been pooled.

Result: Under the conditions of the present test, DMF was not mutagenic.

Reliability: (2) valid with restrictions
reliable with restrictions

Flag: Critical study for SIDS endpoint

06-MAR-2003

(208)

Type: Micronucleus assay

Species: mouse

Sex: male

Route of admin.: i.p.

Exposure period: once, or daily repeatedly 1 mg/kg

Doses: 0.1 - 20 mg/kg

Result: result: ambiguous

The positive results described could not be assessed since low doses were chosen and information was missing with respect to the experimental procedure.

06-MAR-2003

(209)

Type: Sister chromatid exchange assay

Species: mouse

Sex: male

Doses: up to 60 % of the LD50

Result: result: negative

No effects on sister chromatid exchange-rate in the liver and the bone marrow.

06-MAR-2003

(210)

Type: other: sperm abnormality test
Species: mouse **Sex:** male
Strain: B6C3F1
Route of admin.: inhalation
Exposure period: 5 days, 7 h/d
Doses: 10, 400 ppm (ca. 0.03, 1.21 mg/l)
Method: other: no data
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Result: negative
Test substance: N,N-dimethylformamide; purity >99%
04-SEP-1997 (196) (170)

Type: other: spermcell morphology
Species: **Sex:** male
Route of admin.: i.p.
Doses: up to 2000 mg/kg

Result: result: negative, no effects
06-MAR-2003 (157) (211)

5.7 Carcinogenicity

Species: rat **Sex:**
Strain: other: BD-rats
Route of administration: drinking water
Exposure period: 250 - 500 days
Frequency of treatment: daily
Post exposure period: up to a total experimental period of 750 days
Doses: 75, 150 mg/kg (total dose up to 38000 mg/kg)

Method: other
GLP: no
Test substance: other TS: N,N-Dimethylformamide, no further data

Result: The daily treatment of 15 and 5 rats with 75 and 150 mg/kg, respectively caused no increased tumor incidence during the observation period. Even a weekly s.c. injection of 200 or 400 mg/kg bw to each 12 rats (up to a total doses of 8 to 20 g/kg bw) caused no

increased tumor incidence.
Single i.p. injection at concomitant partial
hepatectomy did not cause liver tumors nor any
preneoplastic foci.

06-MAR-2003

(212) (78)

Species: rat **Sex:** female
Strain: Wistar
Route of administration: gavage
Post exposure period: no data
Doses: 0.1 ml/dose (ca. 95 mg/dose), ca. 400
mg/kg

Method: other: no data
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Remark: This investigation was part of a study on the
carcinogenic action of aflatoxin; the test
substance (DMF) was used as vehicle. Nineteen
weanling rats were given the test substance and
served as vehicle control group. One rat
died on the 3rd day of the study, the remaining
rats died or were sacrificed between the 13th
and 34th month of the study. No macroscopic
hepatic tumors or nodular lesions of the liver
were observed in this group. According to the
authors, hepatoma or other changes were observed
in animals treated with aflatoxin but not in
controls.

Test substance: N,N-dimethylformamide; no data on purity of the
compound

06-MAR-2003

(213)

Species: rat **Sex:** male/female
Strain: other: randomly bred Medical Research
Council (MRC) rats
Route of administration: i.p.
Exposure period: 10 weeks
Frequency of treatment: once a week
Post exposure period: 103 weeks
Doses: 1 ml/animal (ca. 950 mg/animal), ca. 4000
mg/kg
Control Group: yes, concurrent no treatment

Method: other: no data
GLP: no
Test substance: other TS: N,N-dimethylformamide, no further data

Result: The study design is insufficient and inadequately described. In 9/18 males and 11/19 females multiple tumors (adenocarcinoma, sarcoma, leiomyoma, carcinoma of the rectum, pheochromocytoma of the adrenal medulla, embryonalcell like tumors of the testis and numerous benign tumors) irregular and partial livercell necrosis and ulceration of the intestinal mucosa occurred. An untreated control group with 14 male and 14 female animals run in parallel. The DMF-treated animals served as solvent-control group for a group of animals treated with aflatoxine dissolved in DMF. In both groups comparable tumor incidences occurred. The validity of the investigation is limited due to assessments of the performing institute itself (Clayson D.B.; 1977) and assessments of external sites. The tumor incidences given in the publications are varying.

06-MAR-2003

(214) (215) (216) (217)

Species: Syrian hamster **Sex:** male/female
Strain: other
Route of administration: i.p.
Exposure period: 6 - 8.5 months
Frequency of treatment: once a week
Doses: 0.1 ml of a 50 % solution

Method: other
GLP: no
Test substance: other TS: N,N-Dimethylformamide, no further data
Result: The treatment did not cause tumors in 10 Syrian hamsters.

06-MAR-2003

(218) (219)

Species: rat **Sex:** male/female
Strain: other: Cr1:CD BR
Route of administration: inhalation
Exposure period: 2 years
Frequency of treatment: 5 d/w; 6 h/d
Post exposure period: none
Doses: 25, 100, 400 ppm (about 0.08, 0.3, 1.2 mg/l)
Control Group: yes
Method: other: no data
GLP: no data

Test substance: other TS: N,N-dimethylformamide, 99.9% pure, no further data

Remark: 87 male and female rats were used per group. The rats were approx. 47 days of age at the beginning of the study. They were exposed to DMF vapors by whole body exposure at dose levels of 0, 25, 100 and 400 ppm for two years. The concurrent control group animals (0 ppm) were exposed to dehumidified air alone. Clinical pathology was investigated at 3, 6, 12, 18 and 24 months in each 10 male and 10 female animals/group. At 12 months interim sacrifice of 10 male and 10 female animals per group took place, thus again 10 rats per sex and group had to be selected for the 18 and 24 months examinations. After 2 weeks, 3 months and 12 months of testing cell proliferation in the liver was evaluated in 5 randomly selected rats per sex and group. An immunohistochemical evaluation was done on livers from animals of the 0 ppm and 400 ppm groups. Estrous cycle evaluation was done in all female animals of the control and the high dose group from test day 107 through test day 131. Moreover, examinations on body weight, organ weights, ophthalmoscopy, urinalysis and a complete necropsy including microscopical examinations were carried out.

Result: There were no compound-related differences in the survival of the animals in the present study (for male rats survival was 27, 34, 40 and 44% for 0, 25, 100 and 400 ppm, respectively. For female rats survival was 35, 23, 19 and 39%, respectively). Ophthalmologic examinations, hematology and urinalysis revealed no compound-related effects in the rats. Moreover, no compound-related effects were seen on the estrous cycles of rats exposed up to 400 ppm DMF. Body weight and body weight gain were reduced in both sexes of the 400 ppm group and in the male animals of the 100 ppm group. Serum sorbitol dehydrogenase activity was increased in the animals of the 100 and 400 ppm groups. These animals also showed increased mean relative liver weights and centrilobular hepatocellular hypertrophy as well as an increased centrilobular accumulation of

lipofuscin/hemosiderin. At 400 ppm there was also an increased incidence of hepatocellular single cell necrosis.

The incidence of clear cell foci was increased in 100 ppm males and in both sexes of the highest dose group. An increased incidence of eosinophilic foci was seen in the 400 ppm females. Cell-labeling indices for hepatocytes were not statistically significant different between control and 400 ppm rats, however, rates were slightly higher for 400 ppm males at 2 weeks and 3 months but not at 12 months.

An increased incidence of endometrial stromal polyp of the uterus (14.8%) occurred in the females of the 400 ppm group.

According to the authors endometrial stromal polyps are the most common uterine neoplasm in rats. Moreover, the incidence showed no clear dose-response relation-ship and was in the range of historical control incidences for the respective laboratory (2.0-15.0%) Thus, the authors concluded, that the increased incidence is probably a chance variation rather than a compound-related effect.

There were no compound-related lesions noted in the nose or respiratory tract for any exposure concentration. The incidences of hepatic tumors and testicular tumors in rats exposed up to 400 ppm DMF were similar to control values.

Exposure to DMF for 2 years did not cause a compound-related increase of tumors in rats. According to the authors the NOEC in rats is 25 ppm.

Reliability: (2) valid with restrictions
reliable with restrictions
Flag: Critical study for SIDS endpoint

07-MAR-2003

(122)

Species: mouse **Sex:** male/female
Strain: other: Crl:CD-1 (ICR)BR
Route of administration: inhalation
Exposure period: 18 months
Frequency of treatment: 5 d/w; 6 h/d
Post exposure period: none
Doses: 25, 100, 400 ppm (about 0.08, 0.30, 1.21 mg/l)
Control Group: yes
Method: other: no data

GLP: no data
Test substance: other TS: N,N-dimethylformamide, 99.9% pure no further data

Remark: The carcinogenic effect of the test substance was investigated in groups of 78 male and 78 female young adult mice. The mice were approx. 55 days of age at the beginning of the study. The animals were exposed by whole-body exposure to DMF vapors at concentrations of 0, 25, 100 and 400 ppm. The concurrent control (0 ppm) was exposed to dehumidified air alone. Examinations on body weight, organ weights, ophthalmoscopy, and a complete necropsy including microscopical examination were carried out. Hematology was investigated at 3, 6, 12 and 18 months in each 10 male and 10 female animals/group. Estrous cycle evaluation was done in all female animals in the 0 and 400 ppm groups from test day 107 to test day 131. Cell proliferation in the liver was investigated after 2 weeks, 3 months and 12 months in five randomly selected animals per sex and group. Livers from animals in the 0 and 400 ppm groups were immunohistochemically evaluated.

Result: Survival in treated male and female mice was similar to that in the concurrent control group (male animals: 56, 68, 60 and 59% for 0, 25, 100 and 400 ppm, respectively; female animals: 68, 57, 62 and 76%, respectively). There were no compound-related differences in hematology parameters and no significant differences with respect to estrous cycle evaluations or ophthalmoscopy. In male animals exposed to 100 and 400 ppm, and in female mice at 400 ppm a significant increase in absolute and relative liver weights together with hepatocellular hypertrophy was observed. Microscopy revealed hepatic changes (minimal to mild hepatocellular hypertrophy) in all treated groups with the incidence being dose-related. Individual hepatocellular necrosis was seen in all groups with the incidence being greater in the DMF-treated groups. Minimal to moderate Kupffer cell hyperplasia with accumulation of lipofuscin and hemosiderin was also observed in all groups again with the incidence being greater in the DMF-treated animals. A dose-related increase in mixed foci in the liver was seen in the males and a higher

incidence of eosinophilic foci was seen in both sexes of the treated groups when compared to the concurrent control animals.

Cell labeling indices in the liver showed no compound-related effect at any exposure level. No compound-related lesions were observed in the nose or respiratory tract at any exposure level. The incidence of hepatic and testicular tumors was similar to control for all exposure concentrations.

The exposure of mice to DMF over a time period of 18 months was not oncogenic at concentrations up to 400 ppm.

According to the authors, a NOEC (no-observable-effect level) was not achieved in mice due to morphological changes seen in the liver at all three test concentrations, nevertheless, they expected the NOEC to be close to 25 ppm due to the minimal changes observed at this concentration.

However, due the findings at 25 ppm (slightly (for the males significantly) increased incidence of hepatocellular hypertrophy, dose-related and statistically significantly increased incidence of hepatic single cell necrosis in both sexes, and dose-related (for the males significantly) increased incidence of hepatic kupffer cell hyperplasia and pigment accumulation) that occurred in most cases in a dose-related manner, a clear NOAEC could not be determined and consequently, the LOAEC for mice was considered to be 25 ppm.

Reliability:

(2) valid with restrictions
reliable with restrictions

Flag:

Critical study for SIDS endpoint

07-MAR-2003

(122)

Remark:

Two communications inform about DMF used as inactive solvent-control in former carcinogenicity studies. In the study of Craddock (1971) DMF dissolved in saline was administered at a dose of 500 mg/kg by i.p. injection to six albino rats of the Porton strain. 30 minutes after this treating, doses of 6, 9, 12, 30, 33 and 36 mg Dimethylnitrosamine (DMN)/kg were administered to the rats (one rat/dose). With respect to further examinations, special attention was paid to the liver.

According to the author, none of the animals treated with DMF before receiving varying doses of DMN developed liver nodules or liver tumors. In the study of van Duuren et al. (1971) 30 female ICR/Ha Swiss mice were given weekly s.c. injections of DMF dissolved in 0.05 ml of a vehicle (not readable). Concurrent untreated, vehicle-treated and positive control (chloromethyl methyl ether) mice run in parallel. Duration of the test and median survival time were 75 weeks for the DMF-treated mice. No tumors were observed.

06-MAR-2003

(220) (221) (222) (223)

5.8.1 Toxicity to Fertility

Type: One generation study
Species: rat
Sex: male/female
Strain: other: CD
Route of administration: dermal
Exposure Period: up to 164 days
Frequency of treatment: daily
Premating Exposure Period
 male: 0, 28, or 56 days
 female: 0, 28, or 56 days
Duration of test: 164 days
Doses: 500, 1000, 2000 mg/kg/d
Control Group: yes

Method: other: no data
 GLP: no
Test substance: other TS: N,N-dimethylformamide, no further data

Remark: The reproductive effect of the test substance was investigated in 11 groups of 10 male and 20 female rats, each. The study period was divided into several stages: pre mating 1 (days 0-28), pre mating 2 (days 29-56), first mating (days 57-72), first gestation (days 73-94), first lactation (days 95-116), rest period (days 117-127), second mating (days 128-143), second gestation (days 144-164). Two control groups were given a placebo throughout the study. Three groups (sequence I) were treated on days 0-28 with the test substance at the different dose levels and received a placebo on the remaining days.

Females of 3 groups (sequence II) received the test substance during mating and gestation (days 57-94 and 128-164) and were given a placebo on the remaining days; males of these groups were given a placebo. The last 3 groups (sequence III) were given the test substance throughout the study.

F1a litters were delivered naturally, F1b litter were delivered by caesarian section on gestational day 20 (day 164 of the study).

Result:

Body weight gains and final body weights were reduced in males of sequence I and III given 1000 and 2000 mg/kg/d and in females of sequence II and III given 2000 mg/kg/d.

Mortality was increased among the sequence III females given 1000 and 2000 mg/kg/d; death was attributed to chronic respiratory infection. There were no abnormal behavioural reactions among parental animals during the investigation. Gross and histopathological examination of 10 males and 10 females of the control groups and 2000 mg/kg/d groups of each treatment sequence revealed no difference between test and control animals. Reproductive ability was not affected by the test substance.

Fewer pups were delivered and retained during the lactation period by females of sequence II and III given 2000 mg/kg/d. Pup survival was reduced in sequence II and III groups given 1000 or 2000 mg/kg/d. Litter size and pup survival of the other groups were similar to control.

Administration of 2000 mg/kg/d in sequences I, II, and III resulted in a reduction in the numbers of viable pups per litter in the F1b litters delivered by caesarian section.

Generally, these decreases were the result of reduced numbers of corpora lutea and implantation sites per female in those groups. Treatment with 500 or 1000 mg/kg/d did not affect ovulation, implantation, or fetal survival. Fetal body weights remained unaffected. Examination of fetal external development and the internal development of the control, and 2000 mg/kg/d levels revealed no differences between test and control groups which could be attributed to the test substance. An increase in the percent of fetuses with incompletely or non-ossified sternum sections was observed among the pups obtained from

females of the 2000 mg/kg/d groups.
However, according to the authors, the values obtained were not out of the normally expected range experienced at the laboratory and were not attributed to the test substance.

26-SEP-2000

(224)

Type: other: reproductive toxicity using the continuous breeding protocol

Species: mouse

Sex: male/female

Strain: CD-1

Route of administration: drinking water

Exposure Period: see under RM Task 1-4

Frequency of treatment: continuously in the drinking water

Premating Exposure Period

male: 7 days (Task 2)

female: 7 days (Task 2)

Duration of test: up to the F2 generation

Doses: 1000, 4000, 7000 ppm (ca. 219, 820 and 1455 mg/kg/d)

Control Group: yes, concurrent vehicle

NOAEL Parental: < 1000 ppm

NOAEL F1 Offspring: 1000 ppm

NOAEL F2 Offspring: < 1000 ppm

Method: other: continuous breeding protocol (NTP)

Year: 1992

GLP: yes

Test substance: other TS: N,N-dimethylformamide, purity > 99%

Remark: DMF was evaluated for reproductive toxicity using the continuous breeding protocol.
Task 1: range finding study; at 8 weeks of age 48 males and 48 females were randomly assigned to six treatment groups (8/sex/group). During a 2-week exposure period, animals were housed singly. Animals received 0, 2500, 5000, 7500, 10,000 and 15,000 ppm DMF in deionized filtered tap water. Feed and water consumption and body weight were measured weekly. Animals were killed at the end of week 2.
Task 2: F0 cohabitation and lactation phase; at 11 weeks of age 100 male and 100 female animals were randomly assigned (body weight-dependent) to four dose groups. The control group consisted of 40 males and 40 females, the substance-treated groups consisted of 20 males and 20

females each. On the basis of the results of Task 1 doses selected were 0, 1000, 4000 and 7000 ppm DMF. Exposure of males and females takes place for one week before cohabitation (animals were housed individually), during 14 weeks of cohabitation (animals were housed in breeding pairs), and for up to 14 weeks after separation. After separation of the breeding pairs at week 16 of exposure, the F0 females were allowed to deliver and rear the final litter until PND 21.

Data collection: Body weights and feed and water consumption were recorded during treatment weeks 1, 8 and 16.

During the F0 cohabitation the following data were recorded: litter interval, number, sex, weight of pups/litter, number of litters per breeding pair and the postnatal day 0 dam body weight.

On postnatal day 0, 4, 7, 14 and 21 of the lactation phase, pups were sexed, counted and weighed

Task 3: crossover mating trial of control and high dose animals (a) control males x control females, b) high dose males x control females and c) high dose females x control males); starting at week 23 of exposure, the respective animals will be cohabited for one week, during this time exposure will be discontinued. The breeding pairs will then be separated and dosing will be reinstated as in Task 2.

Data collection: Upon delivery of each litter, lethality, gestation length, sex, number, weight of pups and dam weight were determined. All newborn litters were killed humanely following evaluation. After all litters had been delivered, vaginal smears were collected from F0 females for 12 days.

At week 29 all F0 animals were weighed and necropsied after CO2 asphyxiation. Liver and paired kidney with attached adrenal were weighed for both sexes; for males right testis, right epididymis, prostate and seminal vesicles with coagulating glands and for females right ovary with attached oviducts were weighed. All tissues were preserved for histological examinations.

Sperm evaluation (motility, concentration and morphology) from the right testis and epididymis and homogenization resistant spermatid count

were performed with the left testis. Histopathology was done on all livers, kidneys and adrenals, right testis and epididymis, prostate, seminal vesicles, ovary and any gross lesions observed.

Task 4: assessment of effects on fertility of the F1 generation using the control, low-, mid- and high-dose groups. On PND 21 randomly selected F1-pups from each dose group were weaned and housed in same-sex pairs by dose. At 74+/- 10 days of age, males and females of control- and substance-treated groups were cohabited avoiding sibling breeding pairs for about 1 week. Due to reduced survival in some of the dosed groups, especially in the 7000 ppm group, 20 nonsibling pairs were not available, so 15 pairs were cohabited, some of which were siblings. Necropsy took place at 119 +/- 10 days of age.

Data collection: litter data were collected as described for F0 adults in Task 3. After delivery of the F2 litters vaginal smears were collected for 12 days from F1 females.

Body weight and feed and water consumption were recorded at 74+/-10, 84 +/-10 and 112 +/-10 days of age during F1 fertility assessment. Maternal body weight was recorded upon discovery of an F2 litter.

At necropsy F1 animals were weighed and data collected as described for F0 animals.

Histopathology was conducted on the same organs as for the F0 animals with the exception of the seminal vesicles.

Since craniofacial malformations were observed in some F1 pups selected F2 litters were preserved on postnatal day 1 and evaluated for whole body skeletal malformations and soft tissue malformations of the head.

Selected adult F1 animals were evaluated for skeletal malformations.

Result:

Male and female mice were exposed at doses of 1000, 4000 and 7000 ppm. Average doses in 1000 ppm males ranged from 182+/-6.9 mg/kg bw/d on week 1 to 187.9+/-27.7 mg/kg bw/d on week 27. Females consumed 256+/-38 to 193+/-11.1 mg/kg bw/d for the same period. Doses for 4000 ppm ranged 545+/-29 to 845 +/-39 mg/kg bw/d in F0 males and females. At 7000 ppm 1026+/-42 to 1578+/-104 mg/kg bw/d were consumed.

For F1 animals (week 12 - 16) average doses ranged from 213+/-16 to 315+/-13 mg/kg bw/d at 1000 ppm, 1006+/-30 to 1172+/-36 mg/kg bw/d at 4000 ppm and from 1684+/-113 to 2160+/-72 mg/kg bw/d at 7000 ppm. In general, females consumed more DMF per kg body weight than did males, most likely due to pregnancy. No dose-related clinical signs or increased incidence of mortality were observed for the F0 animals. At all dose levels in F0 mice, there was increased liver weight for males and increased absolute and relative liver weights and increased relative kidney plus adrenal weights in females. Moreover at necropsy body weight was significantly depressed in the females of the 7000 ppm group. Although liver histopathology was only examined in DMF-treated mice exhibiting gross hepatic lesions (2/10 high dose males and 2/10 mid-dose females), all those examined exhibited centrilobular hepatic hypertrophy. Reproductive toxicity was observed in the F0 generation, primarily at the mid- and high dose levels. At 4000 and 7000 ppm, fertility and fecundity were reduced; F1 pup postnatal survival at 4000 and 7000 ppm was reduced during the pre- and post- weaning periods, and F1 pup body weight was reduced at the mid and high doses. Surviving F1 pups in the mid- and high-dose groups exhibited craniofacial malformations. The proportion of litters with one or more pups with an abnormal appearance was 10.5%, 90.0% and 77.8% for the 1000, 4000 and 7000 ppm groups, respectively, compared to 7.9% for the control group. Because of decreased fertility, increased prenatal death and postnatal cannibalism in the high dose group a slight reduction in the percentage of litters with malformed pups was seen in comparison to the mid-dose group. At F0 necropsy, sperm parameters, and estrous cycle length were not adversely affected, with the exception of a decreased number of females in the high dose group having normal cycles and of a slight decrease in sperm concentration at the low and the high dose. However, microscopic evaluation of the reproductive organs revealed no histopathology due to DMF treatment.

The crossover mating trial was not able to determine the gender responsible for the decrease in fertility observed in the continuous breeding phase of the study. However, females treated with 7000 ppm produced somewhat smaller litters compared to control pairs or the treated males and pup weights were lower from treated females compared to those sired by treated males. These data suggest that the female was the sex affected by DMF exposure. In addition, 7000 ppm females mated to control males produced pups with malformations similar to those observed in Task 2. Further examinations of pups from 7000 ppm task 3 females revealed abnormal ossification of the cranial plates and abnormal or incomplete formation of the sternbrae.

The selected males and females of the F1 generation for inclusion in the reproductive performance evaluation of the F1 generation showed reduced body weights in the mid- and high-dose group (from PND 74 to necropsy). In the F1 mating trial, the mating index was reduced at 7000 ppm, while the pregnancy index, litter size and proportion of pups born alive/litter were reduced at 4000 and 7000 ppm. Live pup weight was reduced at all doses.

Malformations of F2 pups were similar to those observed for F1 litters of F0 pairs. The proportion of externally malformed pups was 0, 27.7, 60 and 75% in the control, low-, mid- and high- dose groups.

The F1 animals of all DMF-treated groups had an increase in liver weight in males and females associated with centrilobular hepatocellular hypertrophy. F1 estrous cycles were significantly longer in the 7000 ppm females compared to the control females. Evaluation of F1 reproductive tissues revealed some significant reproductive effects for males but not for females. Relative prostate weight was decreased at all doses as was absolute prostate weight in males of the mid- and high-dose group and epididymidal spermatozoa concentration was decreased at the high dose.

At necropsy, F1 animals from each DMF dose group and the control group (5 females/5 males, each) selected for skeletal evaluation exhibited malformations persistent from birth at 4000 ppm and above.

In summary, the MTD for generalized toxicity was 1000 ppm for both the F0 and F1 generation. According to the authors, the NOAEL for generalized toxicity could not be determined for either the F0 or F1 generation. Significant reproductive and developmental toxicity was observed at 4000 ppm for the F0 and F1 generation in the presence of some general toxicity.

Reliability: (2) valid with restrictions
reliable with restrictions
Flag: Critical study for SIDS endpoint
27-MAY-2003 (225) (226)

5.8.2 Developmental Toxicity/Teratogenicity

Species: rat **Sex:** female
Strain: Sprague-Dawley
Route of administration: inhalation
Exposure period: day 4-8 of gestation
Frequency of treatment: 6 h/d
Duration of test: until day 20 of gestation
Doses: ca. 0.67, 1.58 mg/l (220, 520 ppm)
Control Group: yes, concurrent no treatment

Method: other: BASF-test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: The teratogenic effects of the test substance were investigated in a total of 55 rats (18, 17, and 18 rats in the high dose, low dose, and air-control group, respectively). All animals were sacrificed on day 20 of gestation. In the high dose group, body weight gain of the dams was significantly reduced; this concentration had embryolethal and embryotoxic effects. No teratogenic effect was detected; the number and type of malformations corresponded to those in the air control group and the changes which are known to occur spontaneously in Sprague-Dawley rats. In the low dose group, a slight decrease in maternal body weight gain was observed. Fetal weights and lengths were significantly decreased. However, the number and type of the retardations and variations corresponded to those in the control group; thus, the reduction in weight and size of the fetuses could not be

assessed as the expression of fetotoxicity.
Test substance: N,N-dimethylformamide; purity >=99.9%
07-MAR-2003 (227) (228) (229) (230) (231)

Species: rat **Sex:** female
Strain: Sprague-Dawley
Route of administration: inhalation
Exposure period: day 0-1, 4-8, 11-15, or 18-19 of gestation
Frequency of treatment: 6 h/d
Duration of test: until day 21 post partum
Doses: ca. 0.87 mg/l (287 ppm)
Control Group: yes, concurrent no treatment

Method: other: BASF-test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: According to TSCATS: OTS 0521155, Doc. ID. 86-890000649, exposure was carried out on gestational days 0-3, 6-10, 13-18.

Result: The prenatal, perinatal and postnatal toxicity of the test substance was investigated. A total of 30 rats was exposed to vapours of the test substance, control rats inhaled normal air. On day 20 of gestation, 20/30 treated rats were sacrificed and the fetuses were excised for examination.
The remaining rats were allowed to litter naturally; these rats and their offspring were sacrificed on day 21 post partum. Exposure to the test substance resulted in a decreased body weight gain. A fetotoxic effect was detected: mean fetal weights were decreased, the number of retardations and variations was increased in the treated group. No teratogenic effect was observed; the number and type of malformation found in the treated group fetuses was similar to control.
There were no adverse effects on the behaviour of the animals during delivery. Mean weight gain of the offspring of treated dams, viability index and lactation index were unaffected. Absolute and relative organ weights were not significantly different from control. Necropsy of the offspring revealed no pathological changes of the internal organs.

Test substance: N,N-dimethylformamide; purity >=99.9%
07-MAR-2003 (232) (233) (234) (235)

Species: rat **Sex:** female
Strain: Long-Evans
Route of administration: inhalation
Exposure period: day 6 to day 15 of pregnancy
Frequency of treatment: 6 h/day
Duration of test: until day 20 of gestation
Doses: 18; 172 ppm (ca. 0.055; 0.52 mg/l)
Control Group: yes, concurrent vehicle
NOAEL Maternal Toxicity: ca. 172 ppm
NOAEL Teratogenicity: ca. 172 ppm

Method: other: according to standardized methods of Lorke D.: Naunyn-Schmiedeberg's Arch. exp. Pathol. Pharmakol, 246, 147, (1963) and Lorke D.: Naunyn-Schmiedeberg's Arch. exp. Pathol. Pharmakol., 250, 360, (1965)

GLP: no

Test substance: other TS: N,N-Dimethylformamide, no further data

Remark: Female rats weighed 200-250 g and were 2.5 - 3.5 month old at the beginning of the study. After mating (2 females :1 male, overnight; vaginal smears were prepared and the day sperm were observed was designated day 0 of gestation) the females were housed singly and were exposed in groups of 22-23 animals to analytical measured concentrations of 17.8 +/- 5.5 ppm DMF and to 172.3 +/- 36.7 ppm DMF for 6 h/day on 10 consecutive days (gestation day 6 to 15). DMF was dissolved in polyethylene glycol 400. The vehicle control animals inhaled 20 mm³/l air. Cesarean sections were performed on gestation day 20. The average weight of the fetuses/litter was determined and all fetuses were examined for external deformities. Approx. 1/3 of all fetuses/litter were examined for visceral deformities using the 'Wilson Technique' (1965) modified by Machemer and Stenger (1971). The remaining fetuses were exenterated and abdominal and thoracal organs were evaluated. The fetuses were stained according to Dawson (1926) for skeletal examinations.

Result: All animals survived until cesarian section. The conception rate was not influenced by DMF exposure (85%, 100% and 100% were pregnant in the control, the 18 ppm and the 172 ppm group, respectively). The inhalation of DMF up to about 172 ppm in the present study was not toxic to pregnant rats nor

occurred teratogenic effects in the fetuses. The only finding observed in the fetuses was a significantly lower mean body weight of the fetuses from the 172 ppm group in comparison to the controls. However, evaluation of the skeletons showed a normal age-dependent development.

Isolated deformities of the skeleton occurred in all test groups including the control. According to the authors frequency and type were within the normal range for this strain of rats.

In the present study fetotoxicity was found at 172 ppm DMF, thus the NOAEC for fetotoxicity was 18 ppm.

Reliability: (2) valid with restrictions
reliable with restrictions
Flag: Critical study for SIDS endpoint
11-SEP-2001 (236)

Species: rat **Sex:** no data
Strain: no data
Route of administration: inhalation
Exposure period: days 1-19 of gestation
Frequency of treatment: 4 h/d
Doses: 5x10E-5, 6x10E-4 mg/l
Control Group: yes, concurrent no treatment

Method: other: no data
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Remark: No maternal effect was observed, but fetal growth was reduced at the lower dose and growth retardation and postimplantation embryonic death were seen at the higher dose. The number of the postnatal deaths was increased in the higher dose group.
No further data or effects available.
07-MAR-2003 (237)

Species: rat **Sex:** female
Strain: other: Crl:CD (Sprague-Dawley)
Route of administration: inhalation
Exposure period: days 6 - 15 of gestation
Frequency of treatment: 6 h/d
Duration of test: 21 days
Doses: 30, 300 ppm (ca. 0.09, 0.91 mg/l)
Control Group: yes, concurrent no treatment
NOAEL Maternal Toxicity: ca. .09 mg/l
NOAEL Teratogenicity: > .91 mg/l

Method: other: no data
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Remark: Female rats, 12 to 14 weeks of age were mated 1:1 with male rats of the same strain. Groups of 21 mated rats were exposed to 30 or 300 ppm DMF by whole body exposure from day 6 to day 15 of gestation for 6 h/day. DMF was generated by passing a stream of dry air through bubblers containing DMF. Analytical determined concentrations were 31.2 +/- 4.6 ppm and 297 +/- 22 ppm. Control rats were exposed to air only. Dams were weighed on days 0, 6 through 15 and 21 of gestation. Clinical signs were recorded daily. Caesarian section took place on day 21 of gestation. The animals were investigated by a gross pathologic examination. Corpora lutea were counted and fetuses were removed from the uterus, the number of live, dead and resorbed fetuses were recorded. The fetuses were individually weighed, sexed and examined for malformations. Approx. 2/3 of the fetuses per litter were examined for visceral alterations, after evisceration they were stained for skeletal examinations. Approx. 1/3 of the fetuses were fixed in Bouin's solution and examined for neural and visceral defects using the technique of Wilson (1965).

Result: The teratogenic effects of the test substance were investigated in groups of 21 rats. All female rats survived the testing period. There were no substance-related effects on the dams of the 30 ppm group. In the 300 ppm group the dams showed a significantly lower weight gain during the treatment period (gestation day 6-15) when compared to the control group (39 g in comparison to 50 g). Weight gain from day 6 through 21 was not significantly different but approx. 10% lower than that in the concurrent control group. At necropsy, there were no substance-related findings. With respect to reproductive effects, there was no effect on pregnancy rates but in the 30 ppm group a significantly lower mean number of implantations and fetuses was seen in comparison

to the control group (12.7 versus 14.2 mean implantations/female or 12.0 versus 13.7 live fetuses/female respectively). The number of corpora lutea/female was slightly lower in the 30 ppm group than that of the controls (14.6 versus 15.3). These findings were not seen in the 300 ppm females. The number of resorptions was unaltered by DMF exposure, but the number of dams with 2 or more resorptions (early and late) was highest in the 30 ppm group.

According to the authors the reduction in the number of fetuses at 30 ppm is regarded as an unexplainable, but not DMF-related decrease in ovulation and implantation rates.

The number of females with one or more resorptions was within the ranges seen in control females.

A reduction in mean fetal weight, but not length was observed in fetuses from dams of the 300 ppm groups (5.3 g versus 5.5 g in the control). This was not seen at 30 ppm.

Soft tissue and skeletal malformations were comparable between the control and the DMF-treated groups. Isolated findings of gross external malformations were seen in two fetuses of the 30 ppm group and in two fetuses out of one litter in the 300 ppm group.

Thus, in the present study maternal and fetal toxicity were seen at 300 ppm.

The NOAEL was determined to be 30 ppm.

According to the authors, these findings suggested that the test substance was not teratogenic even at a maternal toxic dose level.

07-MAR-2003

(238) (239)

Species:	rat	Sex: female
Strain:	Sprague-Dawley	
Route of administration:	inhalation	
Exposure period:	on days 6-15 of gestation	
Frequency of treatment:	6 h/day	
Duration of test:	until day 21 of gestation	
Doses:	30, 300 ppm (ca. 0.09, 0.91 mg/l)	
Control Group:	yes	
NOAEL Maternal Toxicity:	ca. .09 mg/l	
NOAEL Teratogenicity:	ca. .91 mg/l	

Method: other: according to FDA: "Guidelines for Reproduction Studies for Safety Evaluation of Drugs for Human Use", Segment II

Year: 1966
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Remark: The test substance was administered to groups of 21 pregnant rats. The female rats were 12 to 14 weeks of age at the beginning of the study. Overnight mating (1:1) was done and vaginal smears were prepared. When sperm and/or vaginal plug were observed the day was defined as day 0 of gestation. Two control groups were used: one chamber-air exposed (negative control) and one group given 250 mg/kg/d of acetylsalicylic acid (ASA) suspended in 0.5% Methocel by gavage (positive control) on gestation days 6-15. Females were sacrificed on gestation day 21. Fetuses were evaluated for external, soft tissue and skeletal malformations.

Result: All 21 female rats each of the negative and the two DMF-treated groups survived the testing period. In the positive control group two animals died, one on day 11 and one on day 6 of gestation. According to the authors, these deaths were not related to ASA administration but assumed to be due to dosing accidents because of the lung lesions observed in these animals.

There were no substance-related effects on the dams of the 30 ppm group. In the 300 ppm group the dams showed a significantly lower weight gain during the treatment period (gestation day 6-15) when compared to the control group (39 g in comparison to 50 g). From day 15 through 21 of gestation the animals recovered and weight gain was comparable to that of the concurrent negative control group.

At necropsy, there were no substance-related findings.

With respect to reproductive effects, there was no effect on pregnancy rates (100%, 94.7%, 100% and 100% in the negative control, the positive control and the 30 ppm and 300 ppm DMF group, respectively) but in the 30 ppm group a significantly lower mean number of implantations and fetuses was seen in comparison to the negative control group (12.7 versus 14.2 mean implantations/female and 12.0 versus 13.7 live fetuses/female, respectively).

The number of corpora lutea/female was slightly lower in the 30 ppm group than that of the negative controls (14.6 versus 15.3). These findings were not seen in the 300 ppm females. The mean number of resorptions was unaltered by DMF exposure (0.5, 0.8 and 0.5 in the negative control, the 30 and the 300 ppm DMF group, respectively), but the number of dams with 2 or more resorptions (early and late) was highest in the 30 ppm group (1/21 in the negative control, 4/21 in the 30 ppm DMF and 2/21 in the 300 ppm DMF group, respectively).

According to the authors the reduction in the number of fetuses at 30 ppm is regarded as an unexplainable, but not DMF-related decrease in ovulation and implantation rates.

The number of females with one or more resorptions was within the ranges seen in control females.

The statistically significantly decrease in implantation efficiency in the 30 ppm group in comparison to the negative control (87.3% versus 92.5%) was, according to the authors, in part attributable to a single female in this group that had an unusually low number of implants and high number of corpora lutea.

A reduction in mean fetal weight, but not length was observed in fetuses from dams of the 300 ppm groups (5.3 g versus 5.5 g in the negative control). This was not seen at 30 ppm.

The incidence of fetuses with ossification variations was significantly higher in the 300 ppm DMF group when compared to the negative control (75.0% versus 60.2%), however the incidence of litters containing fetuses with ossification variations was comparable to the negative control group. Soft tissue and skeletal malformations were comparable between the negative control and the DMF-treated groups. Isolated and not dose-related findings of soft tissue malformations were seen in one fetus of the 30 ppm group (diaphragmatic hernia) and in two fetuses out of one litter in the 300 ppm group (vacuoles in the lens of the eye).

Positive control females gained less body weight during the dosing and post-treatment period when compared to negative control values and had fewer fetuses and higher incidence of resorptions. The fetuses were smaller, had a higher number of ossification variations and an

increased incidence of external, soft tissue and skeletal malformations. A dose of 250 mg/kg/d of ASA was considered to be embryotoxic and teratogenic.

Thus, in the present study maternal and fetal toxicity were seen at 300 ppm.

The NOAEC for maternal toxicity and fetotoxicity was determined to be 30 ppm.

According to the authors, these findings suggested that the test substance was not embryotoxic or teratogenic at 30 ppm and non-teratogenic even at a maternal toxic dose level of 300 ppm DMF.

Reliability: (2) valid with restrictions
reliable with restrictions

Flag: Critical study for SIDS endpoint

11-MAR-2003

(82)

Species: rabbit **Sex:** female
Strain: Himalayan
Route of administration: inhalation
Exposure period: day 7 - 19 post insemination
Frequency of treatment: 6 h/d
Duration of test: until day 29 post insemination
Doses: 50, 150, 450 ppm (ca. 0.15; 0.45; 1.36 mg/l)
Control Group: yes, concurrent no treatment
NOAEL Maternal Toxicity: ca. .15 mg/l
NOAEL Teratogenicity: ca. .15 mg/l

Method: OECD Guide-line 414 "Teratogenicity"

Year: 1981

GLP: yes

Test substance: as prescribed by 1.1 - 1.4

Remark: 15 female Himalayan rabbits per group were used. At the start of the study (i.e. day 0 = day of artificial insemination), the animals weighed about 2.7 kg and were about 32-41 weeks old. Animals of the negative concurrent control were exposed to air, for the DMF-treated groups concentrations of 50, 150 and 450 ppm were chosen. The animals were treated with DMF vapor by whole-body exposure on day 7 through day 19 post insemination. During exposure food and water were withdrawn. Post-treatment period lasted from day 20 p.i. until the day the animals were sacrificed (29 p.i.).

The analytically determined concentrations were calculated to the mean of the overall concentration and were 51 ppm, 148 ppm and 452 ppm, respectively.

Result:

With respect to survival of the treated animals, one animal of the mid dose group was sacrificed on day 27 p.i. due to abortion. In the control group one animal with rhinitis was sacrificed on day 7 p.i. and one animal died on day 16 p.i.. Necropsy findings for these animals were of incidental nature.

Maternal toxicity was observed at 150 ppm (static weight during exposure) and at 450 ppm (body weight loss of about 34.4 g between days 7 and 10 p.i. and static weight until day 19 p.i.). No clinical symptoms or autopsy findings that could be related to treatment were seen. No effects on uterine weights or reproduction data were observed. Embryo-/fetotoxicity (significantly reduced fetal body weights, i.e. mean fetal body weight was 37.7 g in comparison to 43.7 g in the concurrent control group) was observed at the highest concentration which was maternal toxic. In this group, the incidence of malformations (especially hernia umbilicalis in 7 out of 86 fetuses in 4 out of 15 litters) and variations (mainly skeletal, i.e. skull bones and sternbrae) was significantly increased. A slight increase was found for external variations (i.e. pseudoankylosis in 6 out of 86 fetuses in 2 of 15 litters).

Total malformations occurred at a fetal incidence of 15 and a litter incidence of 9 at 450 ppm in comparison to a fetal incidence of 3 and a litter incidence of 2 in the concurrent control. Fetal and litter incidences for total variations at 450 ppm were 77 and 15, respectively in comparison to 29 and 11 in the concurrent control.

One hernia umbilicalis among 75 fetuses was observed in the 150 ppm group, the number of skeletal variations was also increased in this group but without being statistical significant. At the lowest concentration (50 ppm) neither dams nor fetuses showed any adverse effect.

Thus, maternal toxicity was seen at 150 and 450 ppm and clear signs of embryo-/fetotoxicity including indications of teratogenicity were seen at the highest concentration tested.

According to the authors, the NOEL for maternal toxic effects and fetotoxic effects was 50 ppm.

Reliability: (1) valid without restriction reliable without restrictions

Flag: Critical study for SIDS endpoint
11-MAR-2003 (240) (241)

Species: rat **Sex:** female
Strain: Sprague-Dawley
Route of administration: gavage
Exposure period: days 6 - 15 of gestation
Frequency of treatment: daily
Duration of test: until day 20 of gestation
Doses: 176, 533 and 1600 µl/kg (about 167, 506, 1520 mg/kg)
Control Group: yes, concurrent no treatment
NOAEL Maternal Toxicity: ca. 167 mg/kg bw
NOAEL Teratogenicity: ca. 167 mg/kg bw

Method: other: in accordance with the FDA guidelines (Guidelines for reproduction studies for safety evaluation of drugs for human use, Food and Drug Administration, Washington 1966)

Year: 1966
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: DMF was dissolved in distilled water and administered by gavage (to a volume of 5 ml/kg body weight) to 19-23 pregnant females/group from day 6 to day 15 of gestation. Each treated group had an untreated control of 18-23 pregnant females. The female rats were impregnated overnight by untreated males of the same strain and of proven fertility. When sperm were detected next morning in the vaginal smear, the day was defined as day 0 of gestation. Caesarian section was carried out on day 20 of gestation. Body weight was determined three times a week, clinical signs and mortality were checked each day. At sacrifice all animals were examined for gross pathological changes and uterine contents were investigated. All fetuses were examined for external changes (malformations, variations, retardations) and 2/3 of the fetuses in each litter were examined for skeletal - and 1/3 of the fetuses of each litter were examined for soft tissue malformations, variations and retardations. For the assessment of the

skeletal system fetuses were treated by a modified Dawson method (1926). Assessment of the organs of the fetuses was performed according to the Wilson method (1965).

Result:

With the exception of one animal in the high dose group, that died on day 10 p.c., all animals survived until termination of the study. Maternal toxicity occurred at 1520 and 506 mg DMF/kg shown by a dose-dependent decrease in body weight gain. At 1520 mg/kg a clear stagnation of body weight gain during the time of test substance application (day 6-15 of gestation) was observed.

Embryo lethality occurred at 1520 mg DMF/kg. About 63% of the implants were resorbed, thus the number of live fetuses (85 in comparison to 265 live fetuses of the concurrent control) was distinctly reduced. Mean placental weight was significantly reduced and live fetuses of this group had significantly reduced mean body weight and showed an increased incidence of skeletal retardations. At this dose teratogenicity occurred. About 12 %, i.e. 10 fetuses of the 85 live fetuses had one or more malformations in the form of anasarca (9 fetuses), aplasia of the tail (2 fetuses) and micrognathia (1 fetus) as well as malformations of the vertebral column (mainly aplasia), ribs and sternum.

At the dose of 506 mg/kg embryo lethality occurred; about 11% of the implants died mainly in the early part of pregnancy.

Signs of embryo-/fetotoxicity were seen in the form of significantly reduced mean fetal body weight and reduced mean placental weight as well as an increased incidence of skeletal and organ retardations and/or variations. The oral administration of 506 mg DMF/kg also led to teratogenicity in about 9.47% (25 of 264 fetuses) of the live fetuses in the form of anasarca (1 fetus), aplasia of the tail (2 fetuses) and atresia ani (1 fetus), cleft palate (1 fetus) and open eyelid (1 fetus) as well as malformations of the vertebral column (split or aplastic vertebrae).

At the dose of 167 mg/kg neither maternal toxicity nor clear embryo-/fetotoxicity or teratogenicity occurred. The only finding was slightly but significantly and dose-related reduced mean placental weight

(0.50 g versus 0.52 g in the concurrent control), however the number of live fetuses and fetal weights of the low dose were comparable to the respective concurrent control or even higher.

Thus, the NOAEL for maternal toxicity and embryo-/fetotoxicity was determined to be 167 mg/kg bw.

Reliability: (2) valid with restrictions
reliable with restrictions
Flag: Critical study for SIDS endpoint
11-MAR-2003 (242) (241)

Species: rat **Sex:** female
Strain: Sprague-Dawley
Route of administration: gavage
Exposure period: day 10-14 of gestation
Frequency of treatment: daily
Duration of test: until day 20 of gestation or day 46 post partum
Doses: 750 mg/kg/d
Control Group: other: Aqua deionized

Method: other: no data
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Result: maternal toxicity: no data
In the present combined teratogenicity and reproduction toxicity study no data were given with respect to maternal toxicity. The fetuses, examined on day 20 of pregnancy, did not show malformations but reduced fetal body weights and delayed skeletal maturation/ossification as well as an increased incidence of synostosis of the sternebrae. The pups evaluated 46 days post partum showed also delayed body weight gain and delayed ossification of some parts of the skull as well as irregular ossification of the sternum. Effects on behavior and brain weight were not observed.

07-MAR-2003 (243) (244)

Species: rat **Sex:** female
Strain: other: ChR-CD
Route of administration: gavage
Exposure period: on day 6, 12, or 18 of gestation
Frequency of treatment: single dose
Duration of test: until day 20 of gestation
Doses: 40, 200, 1000 mg/kg/d

Control Group: yes, concurrent vehicle

Method: other: no data
GLP: no

Test substance: other TS: N,N-dimethylformamide technical, no further data

Result: The possible teratogenic and abortifacient effects of the test substance were studied in 15 rats, 6 of which were administered the vehicle only (control). The remaining 9 rats were given the test substance on day 6, 12, or 18 of gestation at dose levels of 40, 200, or 1000 mg/kg/d, so that only 1 rat/dose level/application time was used. According to the authors, the test substance had no significant abortifacient or teratogenic effect at any dose level or time of dosing.

Test substance: N,N-dimethylformamide; technical grade
15-AUG-2000 (245) (246) (247) (248)

Species: rat **Sex:** female
Strain: Sprague-Dawley
Route of administration: gavage
Exposure period: gestation day (GD) 6-20
Frequency of treatment: daily
Duration of test: until GD 21
Doses: 50, 100, 200, 300 mg/kg
Control Group: yes, concurrent vehicle
NOAEL Maternal Toxicity: ca. 50 mg/kg bw
NOAEL Teratogenicity: ca. 300 mg/kg bw

Method: other: no data
GLP: no data

Test substance: other TS: N,N-dimethylformamide of 99.9% purity assessed by GC purchased from Prolabo, Paris

Remark: In the present study developmental toxicity and placental and milk transfer of DMF in rats were evaluated. For further information on placental and milk transfer see chapter 5.11 'other relevant information'.
Groups of 22-24 time-mated rats (mating procedure one male:2-3 females housed overnight; the day sperm were detected in the vaginal smear was considered to be day 0 of gestation) received daily doses of 50-300 mg DMF/kg by gavage. Dosing volume was 2ml/kg. Doses were adjusted every 3 days throughout the treatment period from GD 6-20.

Concurrent vehicle (distilled water) control group consisted of 24 females. All females were observed daily for clinical signs of toxicity. Food consumption was measured at 3-day intervals starting on GD 6. Maternal body weights were recorded on GD 0, 6, 9, 12, 15, 18, and 21. Animals were killed on GD 21. Uterus was removed, weighed and uterine contents were examined with respect to number of implantation sites, resorptions, live and dead fetuses. To detect very early resorptions, uteri were stained with ammonium sulfid. Live fetuses were weighed, sexed and examined for external anomalies. Half of the fetuses of each litter were preserved in Bouin's solution and examined for visceral changes, the other half were processed for skeletal staining for skeletal examination.

Result:

Maternal toxicity: All females survived to the end of the study. Maternal weight gain was significantly reduced from GD 6-12 at 100 mg/kg and from GD 6-15 and 18-21 at 200 mg/kg and throughout treatment at 300 mg/kg. A significant dose-related decrease in maternal weight gain and in corrected weight gain was seen between GD 6-21 at doses of 100-300 mg/kg. Food consumption was also significantly and dose-related reduced at 100-300 mg/kg.

Fetal toxicity: fetal body weight/litter was significantly and dose-related reduced in the 100-300 mg/kg dose groups.

The incidence of two skeletal variations (unossified or incompletely ossified supraoccipital and sternebrae) was statistically significant increased in fetuses from the 200 and 300 mg/kg dose groups. Thus the total number with skeletal variations was significantly increased at 200 and 300 mg DMF/kg, however, even in the 50 and 100 mg/kg groups a slight (not statistically significant) but dose-related increase in the total number with skeletal variations was seen (number of fetuses (litters): 21(11), 34(13), 48(16), 81(19), 125(20) in the control, the 50, 100, 200 and 300 mg/kg group, respectively).

There was no significant increase in the incidence of total malformations.

According to the authors, the maternal and developmental NOAEL was 50 mg/kg. However, since there were slight indications for some embryo-/fetotoxicity even at 50 mg/kg bw, the LOAEL for embryo-/fetotoxicity should be set at this dose level.

Reliability: (2) valid with restrictions
reliable with restrictions
Flag: Critical study for SIDS endpoint
11-SEP-2001 (249)

Species: mouse **Sex:** female
Route of administration: gavage
Exposure period: single exposure
Frequency of treatment: treatment on the individual days of pregnancy (6.-15. day)
Doses: 1378 mg/kg

Method: other
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: maternal toxicity: not observed
A maternal toxic effect could not be caused on the treatment days during pregnancy. Slight embryo-/fetotoxic effects were seen on days 8 to 11 and 14 of pregnancy. No teratogenicity occurred.
07-MAR-2003 (81) (250)

Species: mouse **Sex:** female
Strain: NMRI
Route of administration: gavage
Exposure period: days 6 - 15 of gestation
Frequency of treatment: daily
Duration of test: until day 18 of gestation
Doses: 193 and 580 µl/kg bw (about 183 and 551 mg/kg bw)
Control Group: yes, concurrent no treatment
NOAEL Maternal Toxicity: ca. 551 mg/kg bw
NOAEL Teratogenicity: ca. 183 mg/kg bw

Method: other: in accordance with the FDA guidelines (Guidelines for reproduction studies for safety evaluation of drugs for human use, Food and Drug Administration, Washington 1966)
Year: 1966
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: DMF was dissolved in distilled water and administered by gavage (to a volume of 0.2 ml/animal at concentrations of 20-30% aqueous solutions) to 24 pregnant females/group from day 6 to day 15 of gestation. Each treated group had an untreated control group of 23 pregnant females. The female mice were impregnated in the morning (during two hours) by untreated males of the same strain and of proven fertility. When a vaginal plug was observed after these two hours, the females were regarded to be impregnated and the day was defined as day 0 of gestation. Cesarean section was carried out on day 18 of gestation. Body weight was determined three times a week, clinical signs and mortality were checked each day. At sacrifice all animals were examined for gross pathological findings and uterine contents were investigated. All fetuses were examined for external changes (malformations, variations, retardations) and 2/3 of the fetuses of each litter were examined for skeletal - and 1/3 of the fetuses of each litter were examined for soft tissue malformations, variations and retardations. For the assessment of the skeletal system fetuses were treated by a modified Dawson method (1926). Assessment of the organs of the fetuses was performed according to the Wilson method (1965).

Result: At both doses tested no clinical findings nor any mortalities were observed that could be related to the test substance administration. In the low dose and the respective control group, one animal of each group showed abortion. Body weight and body weight gain in the treated animals were comparable to the control animals. With respect to fetal findings (embryo-/fetotoxicity) there was a statistically significant decrease in mean fetal weights (for males and females and for both sexes combined) at the highest dose group in comparison to the concurrent control and also a decrease in fetal weights (statistically significant for males and females but without being statistically significantly different when both sexes were combined) in the low dose group in comparison to the respective control group. Fetal length was significantly reduced in the fetuses of both treated groups and the number

of runts was concomitantly increased. A dose-response relationship was not seen for these findings.

The number of retardations and variations was increased in both substance-treated groups. In the high dose group 17 of 241 fetuses (7.05%) showed malformations (e.g. cleft palate, exencephalies, hydrocephalus internus, aplasia of the presphenoid). At 183 mg/kg bw 4 of 245 fetuses (1.63%) were malformed (three cleft palates, one aplasia of presphenoid and one fused rib). In the concurrent control groups 2 of 229 and 1 of 210 fetuses (i.e. 0.87% and 0.48%), respectively had cleft palate (a very common malformation in mice). Thus, in the absence of maternal toxicity embryo-/fetotoxicity together with clear signs of teratogenicity were seen at the high and embryo-/fetotoxicity without teratogenicity were seen in the low dose.

Reliability: (2) valid with restrictions
reliable with restrictions

Flag: Critical study for SIDS endpoint

11-MAR-2003 (242) (241)

Species: rabbit **Sex:** female

Strain: other: Chbb: HM (Russian) = Himalayan rabbit

Route of administration: gavage

Exposure period: day 6-18 post insemination

Frequency of treatment: daily

Duration of test: until day 28 post insemination

Doses: 46.4, 68.1, 200 µl/kg (ca. 44.1, 65, 190 mg/kg/d)

Control Group: yes, concurrent no treatment

NOAEL Maternal Toxicity: ca. 65 mg/kg bw

NOAEL Teratogenicity: ca. 44.1 mg/kg bw

Method: other: according to FDA Guidelines for reproduction studies for safety evaluation of drugs for human use. Food and Drug Administration, Washington

Year: 1966

GLP: no

Test substance: other TS: N,N-dimethylformamide, no further data

Remark: The effects of the test substance on embryonal development were investigated in a total of 65 rabbits; 24, 12, 18, and 11 animals were used for untreated control, low dose, mid dose,

and high dose group, respectively. The animals were 20 to 47 weeks of age. The day of artificial insemination was defined as day 0 of gestation. The doses applied corresponded to ca. 1/45, 1/30, and 1/10 of the approximate 50% lethal dose (ALD50).

DMF was dissolved in aqua bidest and was administered by gavage at a volume of 10 ml/kg from day 6-18 post insemination. The does were sacrificed on day 28 p.i. and were investigated by gross pathological examination.

During the study clinical signs of toxicity, mortality and food consumption were recorded daily. Body weight was determined three times/week and on days 0, 6, 12, 18 and 28 p.i.. At the day of cesarian section the uterine content was examined with respect to the number of implantation sites, resorptions (very early resorptions were examined by ammonium sulfid staining), number of live and dead fetuses and the number of corpora lutea was counted. Sex, length and weight of live fetuses and the respective placental weight were determined. All fetuses were examined for external malformations and for skeletal examination they were X-rayed in two levels (dorsoventral and lateral). The heads of all fetuses were fixed in Bouin's solution and investigated according to the technique of Wilson (1965).

Result:

All animals survived until termination of the study.

In the high dose group, maternal toxicity was observed. Body weight was significantly reduced at the end of the treatment period and also on day 28 p.i., body weight gain was significantly reduced (animals even lost weight) during the entire treatment period that was also true for food consumption. 3 dams aborted, one on day 21, one on day 24 and one on day 28 p.i.. At necropsy the liver of 1 dam was of a clay-like color. Fertility index, number of corpora lutea, number of implantations and the ratio of live/dead fetuses were unaffected. Placental weights and fetal weights as well as fetal length were significantly decreased. The incidence of malformed fetuses observed in 7 litters was increased (16/45 = 35.5%); hydrocephalus internus (6 fetuses), exophthalmia (2 fetuses), ectopia visceralis (3 fetuses),

hernia umbilicalis (7 fetuses) and cleft palate (1 fetus) were observed. Three fetuses showed multiple malformations.

In the mid dose group, no clinical signs of toxicity were observed. A transiently reduced food consumption was noted during the treatment period, however, this had no effect on body weight or body weight gain. Gross necropsy revealed a clay-like colored liver in 1 dam. Mean number of implantation and percentage of live fetuses was decreased, however a dose-response relationship was missing for this finding. Fetal parameters, number and type of variations and retardations were unchanged. Three malformed fetuses in two litters were found. This incidence was not statistically different from control, however, the type of malformation (hydrocephalus internus) indicated a substance-related effect.

In the low dose group, no deaths or clinical signs of toxicity were noted except a transient reduction of food consumption during the treatment period without any effect on body weight or body weight gain. No substance related pathological findings were recorded, gestational and fetal parameters were unaffected.

One fetus with malformation (hydrocephalus internus) was found, however, this incidence was in the range of control.

These results suggested that the NOAELs were 68.1 µl/kg/d (65 mg/kg/d) for maternal toxicity and between 46.4 µl/kg/d (44.1 mg/kg/d) and 68.1 µl/kg/d (65 mg/kg/d) for fetotoxicity. When taking into account that a dose-response relationship was missing for the findings of decreased mean number of implantations and percentage of of live fetuses in the mid dose, the NOAEL for embryo-/fetotoxicity could be set at 65 mg/kg bw.

Clear signs of teratogenicity occurred at the high dose of 190 mg/kg. The three malformed fetuses at the mid dose indicated also a substance-related effect.

Test substance:

Reliability:

Flag:

11-MAR-2003

N,N-dimethylformamide, purity 99.97 %

(2) valid with restrictions

reliable with restrictions

Critical study for SIDS endpoint

(251) (252)

Species: rat **Sex:** female
Strain: Sprague-Dawley
Route of administration: dermal
Exposure period: day 6-10 and 13-15 of gestation
Frequency of treatment: daily
Duration of test: until day 20 of gestation
Doses: ca. 95, 475, 950 mg/kg/d (100, 500, 1000 ul/kg/d)
Control Group: yes

Method: other: BASF-Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: The prenatal toxicity was investigated in a total of 75 pregnant Sprague-Dawley rats; 22, 21, and 22 animals were applied 100, 500, and 1000 ul of the neat test substance, respectively, 10 rats were applied 1000 ul of bidistilled water (control). On day 20 of gestation, all animals were sacrificed. No signs of toxicity were observed in the treated dams; only one dam of the 1000 ul group showed inflammatory reactions of the skin. On necropsy, no dose-related changes in maternal or fetal parameters were observed. However, the length of fetuses of the high-dose group was significantly decreased. Malformations (mainly splitting of the thoracic vertebrae and wavy ribs) were found in 7/268, 7/253, and 14/258 the low, mid, and high dose group while no malformations were found in controls. According to the authors, the anomalies were in the range of control.

07-MAR-2003

(253) (254)

Species: rat **Sex:**
Route of administration: dermal
Exposure period: days 6 - 15 or 1 - 20 of gestation
Doses: 240, 950, 1900 mg/kg/d (0.25, 1, 2 ml/kg/d)

Result: The dermal application was performed under occlusive conditions. Embryotoxic and some teratogenic effects were observed. Effects occurred at dose levels of 1 and 2 ml/kg. At 0.25 ml/kg no effects were recorded.

07-MAR-2003

(255)

Species: rat **Sex:** no data
Strain: Sprague-Dawley
Route of administration: dermal
Exposure period: day 9, 10+11, 11+12, 12+13, or 11-13 of gestation
Frequency of treatment: 1 or 2 doses
Doses: 600-2400 mg/kg/d
Control Group: other: application of water

Method: other: no data

GLP: no data

Test substance: other TS

Remark: Groups of three to nine rats were examined. DMF caused an increase in the rate of embryonic death at a dose that also resulted in maternal mortality. Subcutaneous haemorrhages were observed in the fetuses exposed during days 12 and 13 or 11-13. However, according to the authors, this finding was not considered to be toxicologically significant.

Test substance: N,N-dimethylformamide; commercial grade with less than 2% impurities

04-SEP-1997

(256) (257) (258)

Species: rat **Sex:** female
Strain: other: Charles River-CD (Sprague-Dawley origin)
Route of administration: dermal
Exposure period: day 9, 10-11, 11-12, or 12-13 of gestation
Frequency of treatment: 1 or 2 doses
Duration of test: until day 20 of gestation
Doses: 0.15 ml/application (ca. 140 mg/application), ca. 560 mg/kg bw
Control Group: yes

Method: other: no data

GLP: no

Test substance: other TS: N,N-dimethylformamide, no further data

Remark: Probably, these results are part of a study published by Stula, E.F. and Krauss, W.C. (Toxicol. Appl. Pharmacol. 41, 35-55 (1977); cited in: IARC Monographs, 47, (1989))

Result: The effects of the test substance on embryonic development after dermal application in middle stage of gestation were investigated in groups of 8 rats.

An amount of 0.15 ml (ca. 140 mg) was applied on day 9, 10+11, 11+12, or 12+13 of gestation; controls were applied 0.15 ml water on days 11 and 12 of gestation.

No gross fetal abnormalities were observed and no apparent skeletal abnormalities were found in alizarin stained fetuses. In the group treated at days 10+11, one dead pup was found; however, this was not statistically different from control and not contributed to the test substance. According to the authors, these results suggested that a total dose of 0.3 ml was not embryotoxic, teratogenic or maternal toxic.

04-SEP-1997

(259) (260) (261) (262) (248) (263)

Species: rat **Sex:** female
Strain: other: Charles River-CD
Route of administration: dermal
Exposure period: days 11-13 of gestation
Frequency of treatment: daily, 6 times a day
Duration of test: until day 20 of gestation
Doses: 6x0.05 ml, 6x0.1 ml; total dose 0.9, 1.8 ml (ca. 900, 1700 mg), ca. 1200, 2400 mg/kg bw
Control Group: yes
Method: other: no data
GLP: no
Test substance: other TS: N,N-dimethylformamide, no further data
Remark: Probably, these results are part of a study published by Stula, E.F. and Krauss, W.C. (Toxicol. Appl. Pharmacol. 41, 35-55 (1977); cited in: IARC Monographs, 47, (1989))
Result: The effects of the test substance on embryonic development after dermal application in middle stage of gestation were investigated. Ten and nine rats were given 0.05 and 0.1 ml, respectively, 6 times a day for 3 consecutive days (total dose: 0.9 and 1.8 ml, respectively). Two pregnant and one non-pregnant low dose group rat and one pregnant high dose group rats died due to exposure. Fetal resorption rate was higher in the low dose group than in the high dose group. Three and one abnormal pup was found in the low and high dose group (respectively). The abnormalities were cranial hemorrhages (low dose) and paleness and small size (high dose group).

According to the authors, these results suggested that a total dose of 0.9 or 1.8 ml of the test substance was markedly embryotoxic and maternal toxic, but not teratogenic.

04-SEP-1997

(261) (262) (248) (263)

Species: rat **Sex:** female
Strain: other: ChR-CD
Route of administration: dermal
Exposure period: on day 12 and 13 of gestation
Duration of test: until day 20 of gestation
Doses: total dose: 0.3, 0.6, 1.2 ml (ca. 300, 600, 1200 mg)
Control Group: yes

Method: other: no data
GLP: no
Test substance: other TS: N,N-dimethylformamide, no further data

Result: The effects of the test substance following application to the clipped back skin on embryonic development were investigated in groups of 7-8 rats. On day 20 of gestation, the dams were sacrificed, uteri and contents were examined. According to the authors, the test substance appeared to be slightly embryotoxic at all dose levels tested but the embryotoxicity was not dose-related. The only gross evidence of embryotoxicity was subcutaneous hemorrhages which was observed in all treated groups but not in control. Ressorption rates were not affected by the test substance; no deformed pups were observed. No further data.

04-SEP-1997

(248) (264)

Species: rat **Sex:** female
Strain: other: Charles River
Route of administration: dermal
Exposure period: day 6-15 of gestation
Frequency of treatment: daily
Duration of test: until day 20 of gestation
Doses: 500, 1000, 2000 mg/kg/d
Control Group: yes, concurrent no treatment
NOAEL Maternal Toxicity: > 2000 mg/kg bw
NOAEL Teratogenicity: > 2000 mg/kg bw

Method: other: no data
GLP: no

Test substance: other TS: N,N-dimethylformamide, no further data

Remark: The teratogenic effect of the test substance was investigated in groups of 21-22 rats. After confirmation of pregnancy by sperm-positive results of vaginal examinations at the Charles River Breeding Lab. (= day 0 of gestation), the rats were delivered to the investigating Laboratory. DMF was applied to the shaved backs of pregnant rats daily during days 6 to 15 of gestation. Body weight data reported were mean group body weights at day 6, 6, 12, 15 and day 20 of gestation. Signs of toxicity and mortality were recorded daily. At sacrifice of the dams on day 20 of gestation the uterine contents were investigated. Fetal swellings, implantation sites and resorptions were counted. The number of viable fetuses was determined. Live fetuses were weighed. The fetuses were examined for external anomalies, then they were examined for either skeletal (according to the method of Hurley, 1965) or internal development (according to the method of Wilson, 1965). When possible, equal number of fetuses of each sex from each litter were examined by each method. Statistical evaluation of the data recorded was not mentioned or described in the report.

Result: No mortality or abnormal behaviour was observed in the control or treated groups. The body weight gains were not altered in treated rats. Administration of the test substance did not affect fetal survival. The numbers of implantations and resorption sites, corpora lutea, and viable fetuses were similar to control. Fetal body weight and external development was not affected. One fetus of the high dose group (2000 mg/kg) was observed with an umbilical hernia and cyclopia, no abnormalities were seen in the low and mid dose groups. Thus, these results are not considered indicative of a teratogenic response. Evaluations of fetal skeletal development revealed an increase in non-ossified or incompletely ossified sternum sections in the treated groups.

According to the authors, these classifications were measures of the extent of skeletal calcification at the time of sacrifice rather than evidence of teratogenicity.

25-SEP-2000

(265)

Species: rat **Sex:** female
Strain: other: ChR-CD
Route of administration: dermal
Exposure period: on day 10 and 11 of gestation
Frequency of treatment: no data
Duration of test: until day 20 of gestation
Doses: 0.3, 0.6, 1.2 ml (about 285, 570 , 1140 mg) total dose; about 950 mg/kg, 1900 mg/kg and 3800 mg/kg when assumed that a rat has a weight of 300 g
Control Group: yes
Method: other: no data
Year: 1967
GLP: no
Test substance: other TS: Dimethylformamaide , no further data

Remark: On day 10 and 11 of pregnancy DMF was applied to the clipped back of 7-8 pregnant rats/group at total doses of 0.3, 0.6 and 1.2 ml. At day 20 of gestation the females were sacrificed and uteri and contents investigated.

Result: DMF was embryotoxic at the highest dose level (total dose of 1.2 ml) evidenced by high resorption rate (26% compared to 3.2% of the control group) and consequently smaller number of live pups/dam. However, DMF was not toxic to the dams and produced no abnormal, i.e. malformed pups.

29-AUG-2000

(266)

Species: rabbit **Sex:** female
Strain: Himalayan
Route of administration: dermal
Exposure period: day 6-18 post insemination
Frequency of treatment: daily
Duration of test: until day 29 post insemination
Doses: 100, 200, 400 mg/kg/d
Control Group: yes
NOAEL Maternal Toxicity: ca. 200 mg/kg bw
NOAEL Teratogenicity: ca. 200 mg/kg bw

Method: OECD Guide-line 414 "Teratogenicity"
Year: 1981

GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Remark: The teratogenic effects of the test substance were studied in groups of 15 rabbits. Rabbits were between 49 and 56 weeks old and had a mean weight of 2.572 kg (calculated from the means of the groups) on the day of artificial insemination, which was designated as day 0 of gestation.

The test substance was administered directly (i.e. undiluted) on the shaved dorsal skin daily for 6 hours from day 6 to 18 post insemination. Depending on the dose, DMF was applied to an area of about 9, 28 or 66 cm² (for the low, mid and high dose, respectively). The amount of DMF to be administered at each dose level per kg body weight was 0.105 ml, 0.211 ml and 0.421 ml for the low, mid and high dose group, respectively. The skin area was changed daily during the application period to avoid irritation. The test material was applied semi-occlusively using a cover of a porous dressing in four layers and gauze and a porous bandage. After the 6 hours the patches and bandages were removed. Control animals received a volume of 0.421 ml 0.9% saline solution/kg bw in the same manner. During the application period (6 hours/day) the animals were placed in a hood. On day 29 post insemination the does were sacrificed and macroscopically examined for pathological changes. Uterus, uterine contents and fetuses were investigated. All fetuses were eviscerated, the organs examined macroscopically and the sex determined. For skeletal examination the fetuses were X-rayed, the heads were fixed in Bouin's solution and after fixations processed and evaluated according to the method of Wilson (1965).

Result: All animals survived until termination of the study.

Conception rate varied between 93.33 and 100%. The repeated dermal application caused a dose dependent skin irritation in all DMF-treated groups. At the end of the treatment period, days 16 and 18 of gestation, a slight statistical significant decrease in body weight was observed at 400 mg/kg/d (5.5 and 5.6% decrease in relation to the control animals).

However, according to the authors, this finding was without biological relevance. One doe of the 400 mg/kg group showed abortion on day 21 post insemination.

No further signs of maternal toxicity were noted.

No embryotoxic effects were found at 100 and 200 mg/kg/d; since there were no effects in the 200 mg/kg group the findings observed at the lowest dose (one fetus out of 80 live fetuses with a sternal anomaly, three fetuses with gall bladder agenesis and one of the latter with a hypertrophic-dilatative cardiac-aortic malformation) were attributed to spontaneous pathology.

There were no differences between the groups concerning the variations and retardations. However, one dead fetus was found at 400 mg/kg/d and several malformations were observed, i.e two fetuses in two litters showed umbilical hernia, a distinct increase of skeletal anomalies in the form of sternal malformations was seen in 15 fetuses in seven litters and 5 fetuses in 2 litters had gall bladder agenesis. Thus 21 fetuses out of 9 litters (31% fetuses/litter versus 0.0% in the concurrent control) showed anomalies at 400 mg/kg/d. With the exception of the anomalies of the sternum, the other findings mentioned above for the 400 mg/kg group can be seen in the strain of rabbits used in this experiment, thus they were regarded to be independent of the compound administered. Under the conditions of the present study and according to the authors, disregarding the skin reactions, the NOEL for maternal toxicity and embryo-/fetotoxicity including teratogenicity was 200 mg/kg bw/d.

Test substance: N,N-Dimethylformamide, purity: 99.99%

Reliability: (1) valid without restriction
reliable without restrictions

Flag: Critical study for SIDS endpoint

11-MAR-2003

(267) (241)

Species: rabbit **Sex:** no data
Strain: New Zealand white
Route of administration: dermal
Exposure period: on days 8 - 16 of gestation
Frequency of treatment: daily
Doses: 200 mg/kg/d
Control Group: other: application of water

Method: other: no data
GLP: no data
Test substance: other TS

Result: Groups of 4-5 rabbits were used. No adverse effect was observed. Only secondary literature, no further data.

Test substance: N,N-dimethylformamide; commercial grade with less than 2% impurities

04-SEP-1997

(256) (257) (258)

Species: rat **Sex:** female
Strain: Long-Evans
Route of administration: i.p.
Exposure period: on day 7 or 11 of gestation
Frequency of treatment: single dose
Duration of test: until day 21 of gestation
Doses: ca. 475-1900 mg/kg (0.5-2 ml/kg)
Control Group: no data specified

Method: other: no data
GLP: no
Test substance: other TS: N,N-dimethylformamide, no further data

Result: The animals were sacrificed on day 21 of gestation, the uteri were excised and the litters were examined. There were no substance-related effects detected. No further data.

07-MAR-2003

(268)

Species: mouse **Sex:** female
Strain: NMRI
Route of administration: i.p.
Exposure period: days 11 - 15 of gestation
Frequency of treatment: daily
Doses: 0.4, 1.0 ml/kg (ca. 380, 950 mg/kg)
Control Group: yes, historical

Method: other
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: maternal toxicity: 380 mg/kg (reduced body weight gain) In the present study DMF and carbon tetrachloride were investigated. The study does not meet today's standards. At the high dose the dams showed delayed body weight gain and mortality. At necropsy the dams showed changes in the liver that were less

pronounced in DMF-treated animals than in carbon tetrachloride-treated animals. Two of the surviving dams of the high dose showed abortion. In this group 8/36 fetuses showed malformations (7 fetuses with exencephaly and 1 with cleft palate). At the low dose 2/82 showed exencephaly. A control group did not run in parallel; the results were compared to the data of historical controls.

07-MAR-2003

(95) (96)

Species: mouse **Sex:** no data
Strain: NMRI
Route of administration: i.p.
Exposure period: days 6-15 of gestation
Frequency of treatment: no data
Duration of test: no data
Doses: 1.24 ml (ca. 1120 mg)
Control Group: no data specified

Method: other: no data
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Remark: No teratogenic effect was observed with dimethylformamide while monomethylformamide at a dose of 0,1 ml/kg induced a high incidence of fetal death and malformations.

07-MAR-2003

(269)

Species: mouse **Sex:** no data
Strain: other: AB-Jena-Halle and C57BL
Route of administration: i.p.
Exposure period: on days 3, 7, 9, or 1-14 of gestation
Frequency of treatment: single or repeated daily dose
Duration of test: no data
Doses: 170 - 2100 mg/kg/application
Control Group: no data specified

Method: other: no data
GLP: no data
Test substance: other TS: N,N-dimethylformamide, no further data

Remark: Groups of 12 - 30 mice were given i.p. injections of 170 - 2100 mg/kg bw DMF on either one or several days of gestation, and the fetuses were examined for growth, morphology and viability. Single injections of 2100 mg/kg bw into Jena-Halle strain on day 3, 7 or 9 of gestation were reported to be embryotoxic.

Treatment of this strain with 600 or 1080 mg/kg bw and of C57BL mice with 1080 mg/kg bw on days 1 - 14 of gestation induced a high incidence of malformations in both strains. Defects included deficient ossification of the occipital and parietal bones, and open eyes.

07-MAR-2003

(270)

Species: rat **Sex:** female
Strain: other: no data
Route of administration: other: gavage or inhalation
Exposure period: days 1-19 of gestation (inhalation, gavage); days 4 and 10 of gestation (inhalation)
Frequency of treatment: daily; inhalation: 4 h/d
Duration of test: until day 19 of gestation
Doses: gavage: 1/20 LD50; inhalation: ca. 1 +/- 0.7 mg/l; no further data
Control Group: no data specified
Method: other: no data
GLP: no
Test substance: other TS: N,N-dimethylformamide, no further data

Result: The embryotropic action of the test substance after daily gastric intubation of 1/20 LD50 during the entire pregnancy, daily 4-hour inhalation during the entire pregnancy, or 4-hour inhalation during critical periods of embryogenesis (on the 4th and 10th day of gestation) was investigated. The animals were sacrificed on day 19 of gestation. According to the authors, no statistically significant changes were observed on rats treated orally. During inhalation exposure, embryotropic action of the test substance was observed in rats treated during the whole period of pregnancy. The animals exhibited a significant decrease in the number of live embryos when compared to control. There were no differences in the number of corpora lutea and implantation sites; thus, according to the authors, it was concluded that the test substance affected fetal development. Administration of the test substance on day 4 and 10 of gestation did not result in reliably detected disturbances of the characteristic indicators of embryotropic action.

This publication is a translation of a Russian study presented by Silant'eva, I.V. et al., Institute of Labor Hygiene and Occupational Diseases, Academy of Medical Sciences of the USSR, Moscow

07-MAR-2003

(271)

5.8.3 Toxicity to Reproduction, Other Studies

5.9 Specific Investigations

5.10 Exposure Experience

Remark: Stomach ache, nausea, vomiting, and convulsions have been reported in dimethylformamide exposures. In many cases dimethylformamide was taken up by percutaneous absorption as well as by inhalation and mixed exposures were common. Thus, it is difficult to predict the effects of inhaled dimethylformamide alone.

25-APR-1994 (272) (273) (274) (275) (276) (277)

Remark: In several hundred workers handling dimethylformamide over years no ill health effects or abnormal liver function tests were observed. Possible skin absorption was restricted by a skin protection program and air concentration was maintained on average below 5 ppm.

30-MAR-1994 (278)

Remark: Casuistics described testis cancer in tannery workers exposed to a number of chemicals including dimethylformamide. Available data however, were not sufficient for an adequate confirmation.

30-MAR-1994 (279)

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

30-MAR-1994 (280)

- Remark:** Several cases of acute accidental intoxications with inhalational and dermal uptake at the workplace with dimethylformamide have been reported. Main ill health effects were gastrointestinal disturbance with dizziness, nausea and vomiting, lack of appetite, sleepiness, alcohol intolerance and skin irritations. Also disturbance of liver function and morphologic changes in the liver were reported.
- 19-APR-1994 (272) (281) (282) (283) (275) (284)
- Remark:** After exposure to dimethylformamide at the workplace eye irritation, headache, lack of appetite and gastrointestinal disturbance have been reported; in some cases also hepatomegalia, disturbance of liver function and hematological changes were observed.
- 06-APR-1994 (285) (286)
- Remark:** In a questionnaire study (only few details given) miscarriages were reported in 14 % of the women of a group of women exposed to ca. 100 mg/m³ dimethylformamide, compared to 10 % in a control group.
- 26-AUG-2002 (287)
- Remark:** Disturbance of the menstruation in 26 of 70 women exposed for about 1 year to dimethylformamide concentrations of 30 - 150 mg/m³ has been reported.
- 06-APR-1994 (288)
- Remark:** Miscarriages in 3 of 9 women exposed to dimethylformamide and other chemicals have been reported.
- 06-APR-1994 (289)
- Remark:** Influence of dimethylformamide on the stratum corneum and the barrier function of the skin was demonstrated in human volunteers.
- 06-APR-1994 (290)

Remark: Three cases of testicular germ-cell tumour occurred during 1981-83 among 153 white men engaged in a jet aircraft repair shops and led to a survey of two other shops. Four case of testicular germ-cell tumours (approx. one expected) among 680 white male workers diagnosed during 1970-83 were found in a shop comparable to the initial one. No case were found among 446 workers of the second shop. Of the seven cases, five were seminomas and two were embryonal-cell carcinomas.
All seven had a long work histories in aircraft repair.
Exposure to a solvent mixture containing 80 % DMF (20 % unspecified) was certain in three cases and probable in another three cases.

Reliability: (2) valid with restrictions acceptable study meets basic scientific principles

Flag: Critical study for SIDS endpoint

08-AUG-2002 (291)

Remark: Three cases of embryonal-cell carcinomas of the testis were described in workers of a leather tannery. Besides DMF a wide range of dyes and solvents were used in leather tanning. No measurements were available. A further screening in the tannery showed no additional cases in fifty-one of 83 workers employed in the plant between 1975 and 1989.

Reliability: (2) valid with restrictions
basic data given, acceptable restrictions

Flag: Critical study for SIDS endpoint

27-MAY-2003 (292)

Remark: Case-control studies of cancers of the buccal cavity and pharynx (n=39), liver (n=6), prostate (N=43), testis (n=11) and malignant melanoma of the skin (n=39) among worker with potential exposure to DMF and ACN were conducted, approximately 8700 workers per year. Cancers occurring during 1956 to 1985 were identified. Potential exposure to DMF was classified as low or moderate from job title/work area combinations. Mean DMF concentrations ranged from less than 1.0 ppm to about 10 ppm.

Odds ratios for ever exposed were 0.9 (n=15) [0.4-2.3] for buccal cavity and pharynx cancers, 1.7 (n=16) [0.5-5.5] for malignant melanoma, 1.5 (n=17) [0.7-3.3] for prostate cancer and 1.0 (n=3) [0.2-4.4] for testicular cancer. Two liver cancer cases and one control gave a odds ratio of 6.1 [0.4-72.0].

Reliability: (2) valid with restrictions acceptable study meets basic scientific principles

Flag: Critical study for SIDS endpoint

08-AUG-2002 (293)

Remark: Cancer incidence was studied among 2530 actively employed workers with potential exposure to DMF during 1950-70 and 1329 employees with exposure to DMF and ACN at an acrylic fibre manufacturing plant. Cancer incidence rates for the company (1956-84) and US rates (1973-77) were used to calculate expected numbers. For all workers exposed to DMF (alone or with ACN), the standardized incidence ration (SIR) based on company rates was 1.1 [0.9-1.4] (88 cases). One case of testicular cancer was found among the 3859 workers exposed to DMF (alone or with ACN), with 1.7 expected based on company rates. The SIR for cancer of the buccal cavity and pharynx was 3.4 [1.7-6.2] (11 cases) among workers exposed to DMF, based on company rates. No such excess for any cancer was found among 1329 workers exposed to both DMF and ACN. There was no relationship between cancer of the buccal cavity and pharynx and intensity or duration of exposure: low exposure, SIR 4.2 (5 cases, 1.2 expected); moderate exposure, SIR 3.0 (6 cases, 2.0 expected). 'Low' exposure was defined as workplace levels consistently below 10 ppm, while moderate exposure was defined as workplace levels sometimes above 10 ppm.

Reliability: (2) valid with restrictions acceptable study meets basic scientific principles

Flag: Critical study for SIDS endpoint

08-AUG-2002 (294) (295)

- Remark:** Mortality rates in 1950-82 in workers with potential exposure to DMF at an acrylic fibre manufacturing plant (active and pensioned employees) based on company rates were for all workers exposed to DMF only 0.9 [38 obs./40.1 exp.] for all cancers combined, 2.5 [2 obs./0.8 exp.] for buccal cavity and pharynx and 1.4 [19 obs./13.5 exp.] for lung cancer. No other cancer excesses were reported.
- Reliability:** (2) valid with restrictions
acceptable study meets basic scientific principles
- Flag:** Critical study for SIDS endpoint
08-AUG-2002 (296)
- Remark:** Investigation of interaction of ethanol and organic solvents. Ethanol intolerance was reported in dimethylformamide exposed workers.
26-AUG-2002 (297) (298) (299)
- Remark:** Within 24 hours after diemthylformamide exposure and shortly after ethanol intake the following adverse reactions were observed: flush, dizziness, vomiting, feeling of chest tightness, sometimes dyspnea and palpitation. Symptoms lasted for up to two hours.
26-AUG-2002 (300) (301) (302) (283) (303)
- Remark:** Abnormal liver function tests were observed in workers with ethanol intake of 50 - 70 g/day and exposure to dimethylformamide concentrations of 45 - 66 mg/m³. However, these workers were also exposed to other solvents.
26-AUG-2002 (304)
- Remark:** Chromosomal aberrations in peripheral blood lymphocytes of 20 workers exposed to amines and DMF investigated. Mean DMF concentrations at the workplace the year before sampling were 12.3 mg/m³. The frequency of chromosomal gaps and breaks was 1.4 % in the exposed group compared with 0.4 % in 18 controls

- (value in controls was low compared to other studies).
- Reliability:** (2) valid with restrictions
valid with restrictions
- Flag:** Critical study for SIDS endpoint
- 08-AUG-2002 (305)
- Remark:** Mutagenicity: cytogenetic analyses of human lymphocytes, dose 100 nmol/l. No further data given.
- 26-AUG-2002 (306)
- Remark:** Skin and eye irritation study in humans. At a dose of 100 ppm/24h slight effect. No further data given.
- 26-AUG-2002 (307)
- Remark:** In the context of nine investigations in polyacrylonitrile plants some of the patients complained about nervousness and sleep disturbance, others about facial flushing. Despite the low vapor pressure of dimethylformamide, the investigations showed that dimethylformamide causes effects in exposed workers, especially in workers suffering from stomach and liver diseases (ulcus, gastritis, alcoholism).
- 26-AUG-2002 (308)
- Remark:** Stomach ache, nausea, vomiting, epigastric cramps were reported in dimethylformamide exposed subjects. Because of the rapid skin absorption of dimethylformamide no clear relation of dimethylformamide air concentration to the observed effects was eligible.
- 26-AUG-2002 (309)
- Remark:** Dimethylformamide is rated as moderate hazardous by inhalation, but present a distinct hazard by skin absorption.
- 26-AUG-2002 (310)
- Remark:** Target organs of dimethylformamide toxicity are: liver, kidney, skin, and cardiovascular system.
- 26-AUG-2002 (311)

Remark: Dimethylformamide passes through the intact skin and the is absorpted by the lungs.
26-AUG-2002 (312)

Remark: In humans dimethylformamide is metabolized to methylformamide and formamide, and for the most part excreted via the urine. Dimethylformamide reaches an average blood concentration of 2.8 mg/l at an air concentration of 21 ppm for 4 hours. Repeated daily exposure to this concentration did not result in an accumulation of dimethylformamide or its metabolites in the blood.
26-AUG-2002 (313)

Remark: 80 healthy men were exposed to dimethylformamide vapor for 6 hours daily for five days. Monomethylformamide was rapidly excreted via the urine. The highest urine-concentration was observed several hours after end of exposure.
26-AUG-2002 (314)

Remark: Metabolism of dimethylformamide was examined in two groups of workers. Both groups showed that the major amount was excreted within 24 hours. Main metabolite in the urine was N-methylformamide.
26-AUG-2002 (315)

Remark: Facial flushing and other symptoms were observed in 19 of 102 workers exposed to dimethylformamide. 26 of 34 episodes were observed after alcohol ingestion. A inhibition of the acetaldehyde metabolism is possible, by probably by N-methylformamide.
26-AUG-2002 (302)

Remark: Review of the available data of the influence on human health, metabolism, and biological indicators was performed. The determination of a substance or its metabolites in the urine is used for assessment of workplace exposure, e.g. for dimethylformamide.
26-AUG-2002 (316)

Remark: Report of peculiarities and mechanisms of abnormal pregnancies in women working under

unfavourable conditions.
Included in the report were illnesses most frequently resulting in complications in women employed in the chemical and electrical industry.

26-AUG-2002

(317)

Remark:

In a case-control study all inhabitants of Fulton County aged 20 - 54 coming down with testicular cancer between 1984 - 1987 were compared to a control group, suffering other types of cancer. A total of 10 testicular cancer cases were identified. 5 were employed in the leather producing or leather processing industry.

26-AUG-2002

(318)

Remark:

In eight textile plants air concentrations of dust, vapour and gases were measured at selected workplaces. In the group of the organic solvents dimethylformamide came close or exceeded the exposure limit value.

26-AUG-2002

(319)

Remark:

Letter to the editor: studies suggested a link between testicular cancer and dimethylformamide exposure. Since mutagenicity studies of dimethylformamide containing lacquers in animals and populations in industrial areas did not show a relationship between exposure and tumors, it is concluded that dimethylformamide only acts as solvent enhancing absorption of soluble carcinogens by the skin.

26-AUG-2002

(320)

Remark:

The relationship between formation of mercapto uric acid and dimethylformamide exposure and dimethylformamide induced liver toxicity was investigated in animals and humans exposed to dimethylformamide vapour concentrations of 30 or 60 mg/m³ for 3 hours. It was concluded, that the risk of humans exposed to dimethylformamide is higher compared to exposed animals.

26-AUG-2002

(321)

Remark:

Prolonged susceptibility to alcohol-induced flushing for months after former exposure to

- Reliability:** DMF was reported in a 30-year old man.
(2) valid with restrictions
acceptable study meets basic scientific principles
- Flag:** Critical study for SIDS endpoint
08-AUG-2002 (322)
- Remark:** Reports of 30 occupational dimethylformamide intoxications were compared to published clinical and experimental data. The following effects were observed: burns of skin and eyes, inhibition of ZNS, abdominal pain, gastric disturbances, alcohol intolerance, and liver damage. Below the workplace limit value for dimethylformamide of 30 mg/m³ in France alcohol intolerance, abdominal pain, and increased gamma glutamyl transferase values in the blood were observed. Most of the occupational dimethylformamide intoxications resulted from prolonged and/or repeated skin contact.
26-AUG-2002 (323)
- Remark:** 208 workers exposed to up to 9 ppm DMF (116 workers exposed to DMF alone and 96 workers exposed to DMF and toluene) showed a good and linear correlation between amounts of DMF and N-hydroxymethyl-N-methylformamide in the urine at the end of an 8-h shift and the atmospheric concentration of DMF.
- Reliability:** (1) valid without restriction
method and performance conform to standard
- Flag:** Critical study for SIDS endpoint
08-AUG-2002 (324)
- Remark:** Percutaneous absorption in vivo from DMF liquid and vapour was examined in human volunteers. Absorption rate by dipping one hand into undiluted DMF for up to 20 min and by application of 2 mmol DMF over an area of 100 cm² on the forearm was 9 mg/cm²/h. Percutaneous uptake of DMF vapour of 50 mg/m³ for 4 h, while wearing light clothing and breathing fresh air through masks. The percutaneous uptake of DMF increased with increasing ambient temperature and humidity and contributed some 13-36 % of the urinary N-hydroxymethyl-N-methylformamide excreted during combined inhalation and

- percutaneous exposure to the same conc. of DMF vapour.
- Reliability:** (1) valid without restriction
method and performance conform to standard
- Flag:** Critical study for SIDS endpoint
08-AUG-2002 (325)
- Remark:** Ten volunteers were exposed to DMF conc. of 10, 30 and 60 mg/m³ for 8 h and four volunteers were exposed to 30 mg/m³ for 8 h on five consecutive days. The uptake from the respiratory tract was 90 % and the various urinary metabolites examined accounted for 49 % of the retained dose and the various urinary metabolites examined accounted for 49 % of the retained dose. The half-lives of excretion and the urinary recoveries of the metabolites were: DMF, 2h (0.3% of dose); N-hydroxymethyl-N-methylformamide, 4 h (2 %); N-hydroxymethylformamide, 7 h (13 %); and the mercapturic acid conjugate, N-acetyl-S-(N-methylcarbamoyl)cysteine, 23 h (13 %).
- Reliability:** (1) valid without restriction
method and performance conform to standard
- Flag:** Critical study for SIDS endpoint
08-AUG-2002 (326)
- Remark:** In a group of 318 workers no significant alterations of haemtological and clinical chemistry parameters were found compared to controls (N=143). Subjective symptoms like nausea and abdominal pain and alcohol intolerance showed a dose-dependent increase. Most of the workers were exposed to DMF concentrations up to 7 ppm (mean), some to a mixture of DMF (up to 2.1 ppm) and toluene (up to 4.2 ppm).
- Reliability:** (2) valid with restrictions
acceptable study meets basic scientific principles
- Flag:** Critical study for SIDS endpoint
08-AUG-2002 (327)
- Remark:** Chronic hepatotoxicity was investigated in dimethylformamide exposed workers. 100 workers from five different synthetic leather plants were subjected to a physical examination, a questionnaire and biochemical analysis. Results showed a relation of the clinical effects lack of appetite, nausea,

vomiting, dizziness, and chest tightness and exposure. Biochemical tests showed a relation of the retention rate for Indocyanine Green with increasing dimethylformamide exposure. It was concluded that chronic exposure to dimethylformamide of 10 ppm probably causes an increased Indocyanine retention rate and possibly liver damage.

26-AUG-2002

(328)

Remark:

DMF kann am Arbeitsplatz inhalatorisch oder perkutan aufgenommen werden. Nach Aufnahme von 2047 - 4386 Mikrogramm/kg DMF (bei einer Luftkonzentration von 60 mg/m³ ueber 8 Stunden) in einer experimentellen Untersuchung an 10 Probanden wurden 16,1 - 47,8 % als N-(Hydroxymethyl)-N-methylformamid (HMMF), 8,3 - 23,9 % als Formamid und 9,7 - 22,8 % als N-Acetyl-S-(N-methylcarbamoyl)cystein (AMCC) innerhalb von 72 Std. im Urin ausgeschieden. AMCC und HMMF konnten auch bei DMF-exponierten Arbeitern nachgewiesen werden.

18-APR-1994

(329)

Remark:

Seit den 50-er Jahren sind in Fallberichten und einigen epidemiologischen Studien nach inhalatorischer und perkutaner Stoffaufnahme beim gewerblichen Umgang mit DMF neben Herz-Kreislauf-Stoerungen und Stoerungen des Nervensystems vor allem gastrointestinale Beschwerden verschiedenster Art beschrieben.

18-APR-1994

(330) (331) (332) (333) (334)

Remark:

A cluster of toxic liver disease in a fabric-coating factory using DMF as a solvent under poor ventilation and without appropriate skin protection appeared. Overall, 36 of 58 workers had elevated either ASAT or ALAT values. Among 46 workers the following symptoms were reported: anorexia, abdominal pain or nausea by 31 workers; headaches and dizziness by 18 workers; alcohol intolerance (facial flushing and palpitations) by 11 workers. Liver biopsies of workers exposed to several organic solvents, mainly DMF, showed focal hepatocellular necrosis and microvesicular steatosis.

Reliability:

(2) valid with restrictions
acceptable study meets basic scientific principles

Flag: 08-AUG-2002	Critical study for SIDS endpoint (335) (336)
Remark: 19-APR-1994	Increased amylase values in serum with suspected pancreatitis and dimethylformamide exposure have been reported. (272)
Remark: 19-APR-1994	Even low dimethylformamide concentrations (below 20 ppm) have caused temporary disturbance of the liver function. Coexposure to other chemicals may have taken place or unusual plant conditions may have been responsible for the exposures. (332) (337)
Remark: 27-AUG-2002	In plants with workplace concentrations below 10 - 20 ppm no dimethylformamide related ill health effects were observed. (305) (338) (339) (340) (341) (342)
Remark: 27-AUG-2002	Concomittant uptake of dimethylformamide and alcohol showed an interference. Inhibition of acetaldehyde metabolism by dimethylformamide and inhibition of dimethylation of dimethylformamide by alcohol is suggested. (343)
Remark: 27-AUG-2002	Two epidemiological studies with dimethylformamide concentrations most of the time below 10 ppm for several years in 28 and 11 workers did not show abnormal liver values. However, alcohol intolerance was observed. (344) (345)
Remark: 27-AUG-2002	Liquid dimethylformamide irritates skin and mucous membranes. Prolonged exposure cause so called "Waschfrauenhände" with edema and afterwards scaling. (332)
Remark: 27-AUG-2002	After exposure to liquid dimethylformamide skin sensitization, ecema and vitiligo has been reported. (346)
Remark:	Case report of 30-year-old man who had a 6-year history of episodic flushing of the face, upper chest and upper arms after

29-MAR-2001	alcohol ingestion and DMF exposure.	(322)
Remark:	Even low dimethylformamide concentrations (below 20 m/m ³) have caused temporary disturbance of liver function.	
27-AUG-2002		(347) (332)
Remark:	100 dimethylformamide workers were compared with 100 matched controls. Mean dimethylformamide exposure was 22 mg/m ³ (range 8-58 mg/m ³). Exposed subjects and their matched controls were evaluated clinically and a questionnaire was used for the registrations and the comparison of subjective complaints. A laboratory assessment was performed, including transaminase and gamma-glutamyl transpeptidase. Among symptoms studied, headache, dyspepsia and digestive impairment of hepatic type could be specifically associated with chronic dimethylformamide exposure and increased levels of gamma-glutamyl transpeptidase demonstrated minimal hepato-cellular damage, even without ethanol dietary intake. No chronic sickness was diagnosed and the disturbances observed are better considered as indicators of malaise and discomfort due to a toxic effect of dimethylformamide. Dermal flushing as an ethanol intolerance reaction was often registered.	
25-APR-1994		(301)
Remark:	A significant correlation between DMF exposure (25 - 60 ppm) and elevated serum ALAT and serum CPK in 183 out of 204 employees of a synthetic leather factory was shown. HBsAg-positive subjects were more susceptible than HBsAg-negative. High DMF concentrations were also correlated to symptoms like dizziness, anorexia, nausea and epigastric pain.	
Reliability:	(2) valid with restrictions acceptable study meets basic scientific principles	
Flag:	Critical study for SIDS endpoint	
08-AUG-2002		(348)
Remark:	Investigation showed in a group of 20 dimethylformamide exposed subjects	

- (median 45 mg/m³, maximal value 4,080 mg/m³) a significantly increased aberration rate of 4.3 % compared 1.7 % in a group of 19 controls. It is stated that the signs of mutagenicity in humans were in contrast to experience in animals. As possible explanation an interaction with alcohol intake in dietary doses is discussed.
- 27-AUG-2002 (349)
- Remark:** Chromosomal aberrations in peripheral lymphocytes were reported in about 40 workers exposed to several solvents including DMF. Blood samples were taken at exposure levels of 180 and 150 mg/m³ (average). The frequencies of chromosomal aberrations were 3.82 % and 2.74 %. At exposure of 50, 40, and 35 mg/m³ DMF gave lower aberration frequencies of 1.59 %, 1.58 % and 1.49 %. Aberration frequencies in two control groups were 1.61 % and 1.10 %.
- Reliability:** (2) valid with restrictions
acceptable study meets basic scientific principles
- Flag:** Critical study for SIDS endpoint
- 08-AUG-2002 (350) (351)
- Remark:** SCE rates in peripheral lymphocytes from 22 DMF-exposed women were studied in comparison to 22 controls. SCE rates were significantly higher in the high- and medium exposure groups than in the controls, but not in the low-exposure group (high: mean 5.8 ppm, medium: mean 0.7 ppm, low: mean 0.3 ppm).
- Reliability:** (2) valid with restrictions
basic data given, restrictions
- Flag:** Critical study for SIDS endpoint
- 08-AUG-2002 (352)
- Remark:** Cohort-incidence-study in 80 subjects employed in a tannery between 1975 - 1987. Three observed cases of testicular cancer were compared to the New York State cancer registry. SIR was significantly increased (40.5). A relative risk of 5.8 % for employees in the tannery industry was estimated.
- 27-AUG-2002 (353)
- Remark:** Case report on abdominal colic in workers in dye manufacturing plant.
- 27-MAR-1997 (354)

Remark: 38 DMF-exposed workers of a synthetic skin manufacturing factory showed high prevalence of digestive symptoms such as dyspepsia, abdominal pain, nausea, dry throat; and moderate alterations in the liver cytolysis indexes, with exposures values of DMF below the TLV. All alcohol consumers of the sample showed symptoms of alcohol intolerance, although social drinkers.

27-MAR-1997

(355)

Remark: Biomonitoring of workers exposed to DMF was carried out by determination of the urinary metabolites, N-methylformamide (MF, mainly from N-hydroxymethylformamide) and N-acetyl-S-(n-methylcarbamoyl)cysteine (AMCC). The urinary levels of MF increased rapidly at the start of the work shift, and decreased almost to zero within 24 h after the beginning of the last exposure. AMCC levels remained constant over the consecutive works days and increased after the cessation of exposure, with the peak conc. being observed 16-40 h after the cessation of exposure. AMCC levels at the beginning of the next morning shift were closely correlated with personal exposure levels of DMF in air.

Reliability:

(1) valid without restriction
method and performance conform to standard
Critical study for SIDS endpoint

Flag:

09-AUG-2002

(356)

Remark: DMF exposure was monitored in a synthetic leather factory; at the same time, urinary DMF and its metabolites were measured. Environmental exposure to DMF ranged between 10 and 25 mg/m³. The unmodified solvent found in urine collect at the end of the exposure was significantly related to the environmental conc. of DMF; its urinary conc. were found to range between 0.1 and 1 mg/l. Higher conc. of NMF (mean 23.3 mg/l) and formamide (24.7 mg/l) were measured at the end of workshifts. AMCC conc. were 40.4 mg/l at the end of the week and 10.3 mg/l on Monday.

Reliability:

(1) valid without restriction method and
performance conform to standard
Critical study for SIDS endpoint

Flag:

09-AUG-2002

(357)

Remark: In fibre-producing factory with skin contact to DMF the DMF-conc. in the air and via biomonitoring was evaluated. The DMF air conc. was 19 mg/m³ (mean). NMF in urine was 1.9 - 121.9 mg/l (mean 16.2 mg/l). In 36 cases the BAT value (15 mg/l NMF in urine) was exceeded.

27-MAR-1997

(358)

Remark: Case report on a patient who was resuscitated after a suicide attempt with a product containing DMF as solvent. DMF serum conc. were high compared with values published on occupational exposure. The patient showed only transient increase in liver enzymes. The patient was treated with N-acetylcysteine to prevent hepatotoxicity from DMF.

27-MAR-1997

(359)

Remark: A cross-sectional study of the prevalence of chronic liver function alterations was performed in 75 workers employed in a synthetic leather factory, exposed to DMF air conc. below threshold limit values (30 mg/m³). Biological monitoring among workers were 6.4 mg/l (6.1 mg/g creat.) before and 13.6 mg/l (13.4 mg/g creat.) after shift. The worker survey showed a high percentage of disulfiram-like symptoms (50%) and liver function abnormalities (22.7%), compared to a demographically similar group of unexposed workers. Enzymes level were significantly higher in the exposed workers than in controls.

Reliability: (2) valid with restrictions acceptable study, meets basic scientific principles

30-NOV-1999

(360)

Remark: Clinical serum and urine parameters and genotoxicological endpoints such as chromosome aberration (CA), sister chromatid exchange (SCE), high frequency sister chromatid exchange (HFC), cell cycle kinetics, and UV-induced unscheduled DNA synthesis (UDS) were followed up three times during a 20-month period in peripheral lymphocytes (PBL) of 26 workers (13 maintainers and 13 fiber production)

occupationally exposed to acrylonitrile (ACN) and/or dimethylformamide (DMF) in a viscose rayon plant, 26 matched controls, and six industrial controls. Six of the 26 exposed subjects were hospitalized because of liver dysfunction that had developed due inhalative DMF exposure. Average peak ACN and DMF conc. were over the maximum conc. limits at the time of both investigations. Urine ACN and monomethylformamide (MMF) excretions of the exposed subjects were almost doubled after work shifts. An increase in lymphocyte count, and severe alterations in the liver function were observed in the exposed subjects. In PBLs the proliferative rate index (PRI) was already increased in month 0 compared with the controls. In each study, significant increases in CA and SCE frequencies, as well as increases in UDS were found in PBLs of the exposed subjects. The frequencies of chromatid breaks and acentric fragments further increased in month 7 and remained constantly elevated in month 20. Increased yields of both chromatid and chromosome-type exchange aberrations first appeared in month 20, when HFCs were 2.72 times more frequent in fiber producers than in maintainers.

Reliability:

(2) valid with restrictions acceptable
study, meets basic scientific principles
Critical study for SIDS endpoint

Flag:

10-JUL-2001

(361)

Remark:

In a factory producing synthetic fibers the hepatotoxic effects of DMF were investigated in 126 male employees, especially with regard to the combination effects of DMF exposure and ethyl alcohol consumption. The DMF conc. in the air ranged from <0.1 to 37.9 ppm (median 1.2 ppm).

Concentrations of the DMFmetaboite NMF in urine were 0.02-44.6 mg/g creat. (preshift) and 0.4-62.3 mg/g creat.(postshift). A comparison of the liver function values (y-GT, AST, and ALT) found in the exposed persons and in the control group yielded statistically significant higher values in the exposed groups for y-GT and AST. Complaints occurred after drinking alcohol in 71.5 % of the exposed persons and 3.8 % of the controls.

Reliability:

(2) valid with restrictions acceptable

30-NOV-1999 study, meets basic scientific principles (362)

Remark: Sister chromatid exchange (SCE) frequency in peripheral lymphocytes was examined in 85 workers exposed to epichlorhydrin (ECH) and dimethylformamide (DMF) in epoxy resin, synthetic leather, and printed circuit board manufacturing plants. Median time weighed average (TWA) ranged between non detectable (ND) to 3.9 ppm for ECH and 0.9 to 23.5 for DMF. In analysis, smoking was significantly associated with increased SCE frequency. Workers with high ECH exposure al had significantly higher SCE frequencies than those with low or no ECH exposure. DMF exposure was not associated with SCE frequency.

Reliability: (2) valid with restrictions acceptable
Flag: study, meets basic scientific principles
Critical study for SIDS endpoint

10-JUL-2001 (363)

Remark: In order to investigate the importance of premature (early) centromere division (PCD) in cancer risk assessment, thr frequency of PCDs in peripheral blood lymphocytes (PBL) of 212 humans occupationally exposed to clastogenic agents, such as acrylonitrile and/or DMF, benzene, cytostatic drugs, ethylene oxide, mixed exposure in rubber industry, mixed organic solvents including CCl4, hot oil-mists, bitumen, and polychlorinated biphenyls (PCB) and 188 controls were studied. PCD yields are significantly higher in populations exposed to mixed chemicals, crude oils and cytostatic drugs, compared with controls. PCDs involving more than three chromosomes are also more frequent in ethylene oxide- and oil-mist exposed groups than in others. For the acrylonitrile and/or DMF exposed no significant difference from the industrial control was found.

Reliability: (2) valid with restrictions acceptable
Flag: study, meets basic scientific principles
Critical study for SIDS endpoint

29-MAR-2001 (364)

Remark: Case report of vesicular and intensively prurigious eczema on the hands of a 19-year-

old woman handling several chemicals. Results of patch tests showed a positive reaction to DMF 0.1 and 1.0 % in pet. DMF 0.1% in pet. was negative in 20 controls.

Reliability: (1) valid without restriction method and performance conform to standard

Flag: Critical study for SIDS endpoint

09-AUG-2002 (365)

Remark: Case report of painful edema of the hands in a worker using DMF for degreasing.

Reliability: (2) valid with restrictions basic data given, restrictions

Flag: Critical study for SIDS endpoint

09-AUG-2002 (366)

Remark: Dose-response relationship of observed abnormal liver function among DMF-exposed workers and the interactions among DMF, other chemical exposures, HBV infection, and potential confounders on liver abnormalities were examined.

The average DMF exposure conc. was 11.6 ppm; 65 of 176 workers had high (>10 ppm) exposure 37 had middle (>5 ppm, <=10 ppm) exposure, and 74 had low (<=5 ppm) exposure. Compared with the workers having low DMF exposure, the HBV, drinking, body mass index, sex, duration of employment, epichlorhydrin, and toluene exposure adjusted odds ratios for abnormal LFTs were 1.62 (CI 0.61-4.28) for workers with middle DMF exposure and 2.93 (CI 1.27-6.8) for those with high DMF exposure, and there was a significant dose response DMF exposure and the prevalence of abnormal LFTs (P=0.006).

There were significant associations between abnormal LFTs and HBV carriers and between abnormal LFTs and increased BMI.

27-JUL-2001 (367)

Remark: A cluster of toxic liver disease among workers exposed to DMF was reported. Thirty-five out of 45 exposed production workers showed elevated liver enzyme values, compared to one in a control group of 12 workers.

Reliability: (2) valid with restrictions acceptable study meets basic scientific principles

Flag: Critical study for SIDS endpoint

08-AUG-2002 (368)

Remark: The correlation between dimethylformamide air monitoring measurements and biological measurements of a suitable metabolite of DMF in a cohort of operatives in a polyurethane production unit was assessed. This was done with a view to assessing how much the inhalation route contributed to total DMF exposure, mainly for control purposes. We investigated the relationship between personal air sample measurements of DMF and biological measurements of N-methylformamide (NMF) in nine adult subjects, recruited across the shifts, with varying levels of exposure to DMF. Personal exposure monitoring was carried out with a low-flow-rate Model 222-4 SKC pump, while post-shift urine samples were obtained for further analysis. Operatives were asked to abstain from consuming alcohol for 24 h before the designated shift, as advised by the laboratory responsible for the analysis of urine samples. A very strong statistical association between air sample measurements of DMF and NMF in the urine of the sample population ($R(2) = 0.95$, $P < 0.0001$) was found.

21-NOV-2002

(369)

Remark: A 19-year-old man suffered hepatic dysfunction after 5 months of exposure to N,N-dimethylformamide (DMF) at his job in the synthetic resins industry. Laboratory data revealed elevated levels of AST (578 IU/l), ALT (1193 IU/l), and gamma-GTP (107 IU/l), no viral infection with HAV, HBV, or HCV, and no history or evidence of hepatic injury, although he did have a slight abdominal abnormality and swelling which was detected by palpation. His urinary N-methylformamide level, as a biological exposure index of DMF, was 42.8 mg/l, indicating 10-30 ppm of DMF exposure. After 2 months he was reinstated in two workplaces, the former where he worked in the morning and the other in the afternoon where environmental DMF concentrations were less than those in the former workplace. On the 18th day after his reinstatement, his liver function became exasperated again. After the

second period of medication and one month of rest from work, he had fully recovered and was reinstated, but to a workshop without DMF exposure.

21-NOV-2002

(370)

Remark:

The main metabolite of N,N-dimethylformamide formed in both man and animals is N-hydroxymethyl-N-methylformamide. Demethylation leads to N-methylformamide (NMF) and formamide and also to a small extent to hydroxy-methylformamide. A biomonitoring study with the aim of evaluating the correlation between the excretion of N-methylformamide (mainly from N-hydroxymethylformamide) and levels of exposure to N,N-dimethylformamide among occupationally exposed people was conducted. The mean time-weighted average (TWA) exposure was about half (13.5 mg/m³) of the current threshold limit value, the range of the values varying from 0.4 to 75.2 mg/m³. A linear equation existed between urinary NMF concentration and DMF concentration in the environment. The findings show that the urinary NMF concentration can be used as an appropriate biological exposure index. For occupationally exposed subjects, a urinary NMF concentration corresponding to the time-weighted average of the threshold limit value of 39.9 mg/l (37.2 mg/g creatinine) and a 95% lower confidence limit (biological threshold) of 23.4 mg/l (22.2 mg/g creatinine) was suggested.

21-NOV-2002

(371)

Remark:

Monitoring of workplace air and biological monitoring of 23 workers exposed to N,N-dimethylformamide (DMF) in the polyacrylic fibre industry was carried out on 4 consecutive days. The main focus of the investigation was to study the relationship between external and internal exposure, the suitability of the metabolites of DMF for biological monitoring and their toxicokinetic behaviour in humans. Air samples were collected using personal air samplers. The limit of detection (LOD) for DMF using an analytical method recommended by the Deutsche Forschungsgemeinschaft (DFG) was 0.1 ppm. The urinary metabolites,

N-hydroxymethyl-N-methylformamide (HMMF), N-methylformamide (NMF), and N-acetyl-S-(N-methylcarbamoyl)-cysteine (AMCC), were determined in one analytical run by gas chromatography with thermionic sensitive detection (GC/TSD). The total sum of HMMF and NMF was determined in the form of NMF. The LOD was 1.0 mg/l for NMF and 0.5 mg/l for AMCC. The external exposure to DMF vapour varied greatly depending on the workplace (median 1.74 ppm, range < 0.1-159.77 ppm). Urinary NMF concentrations were highest in post-shift samples. They also covered a wide range (< 1.0-108.7 mg/l). This variation was probably the result of different concentrations of DMF in the air at different workplaces, dermal absorption and differences in the protective measures implemented by each individual (gloves, gas masks etc.). The urinary NMF concentrations had decreased almost to zero by the beginning of the next shift. The median half-time for NMF was determined to be 5.1 h. The concentrations of AMCC in urine were determined to be in the range from < 0.5 to 204.9 mg/l. Unlike the concentrations of NMF, the AMCC concentrations did not decrease during the intervals between the shifts. For the exposure situation investigated in our study, a steady state was found between the external exposure to DMF and the levels of AMCC excreted in urine about 2 days after the beginning of exposure. AMCC is therefore excreted more slowly than NMF. The half-time for AMCC is more than 16 h.

Linear regression analysis for external exposure and urinary excretion of metabolites was carried out for a sub-group of 12 workers. External exposure to 10 ppm DMF in air (the current German MAK value) corresponds to an average NMF concentration of about 27.9 mg/l in post-shift urine from the same day and an average AMCC concentration of 69.2 mg/l in pre-shift urine from the following day. NMF in urine samples therefore represents an index of daily exposure to DMF, while AMCC represents an index of the average exposure over the preceding working days. AMCC is considered to be better suited for

21-NOV-2002
(371)

biomonitoring purposes because (1) it has a longer half-time than NMF and (2) its formation in humans is more closely related to DMF toxicity.

Remark:

21-NOV-2002 (373)

Case report of a solvent-induced (dimethylformamide and other solvents, including methylethyl ketone and toluene) hepatitis in a male construction worker.

Remark:

A biomonitoring study with the aim of evaluating the correlation between the excretion of N-methylformamide (NMF) (mainly from N-hydroxy- N-methylformamide) and N-acetyl- S-(N-methylcarbamoyl) cysteine (AMCC), and levels of exposure to N, N-dimethylformamide (DMF) among occupationally exposed subjects was conducted. Exposure levels were determined by personal sampling: breathing zone air samples were collected by means of passive samplers. DMF collected by the charcoal in personal samplers was analysed after extraction with methanol by a gas chromatograph. For the purpose of biological monitoring the levels of NMF and AMCC were measured in pre-shift and post-shift samples. Determinations were carried out by, respectively, gas chromatography and high performance liquid chromatography (HPLC). The mean time-weighted average (TWA) exposure was approximately half (13.5 mg/m³) of the current threshold limit value, the range of the values was from 0.4 to 75.2 mg/m³. Environmental DMF concentrations exhibited a significant correlation with the specific mercapturic acid (AMCC) collected at the end of the working week (AMCC Friday morning mg/l=1.384xDMF (mg/m³)+8.708; r(2)=0.47; P<0.008]; hence urinary AMCC represents an index of the average exposure during several preceding working days, making it possible to calculate the approximate relationship between DMF uptake and excretion of this metabolite. A significant correlation was found also between the daily excretion of NMF and the corresponding levels of DMF in air.

The equation of the regression line was:
NMF (mg/g creatinine)=0.936xDMF
(mg/m(3))+7.306; r(2)=0.522 (P<0.0001).
21-NOV-2002 (374)

5.11 Additional Remarks

Type: adsorption
Remark: DMF in liquid or vapour form is readily absorbed through the skin, after inhalation or after oral exposure (humans).
10-MAR-2003 (375)

Type: adsorption
Remark: In humans DMF is rapidly metabolized and excreted in the urine in the form of N-hydroxymethyl-N-methylformamide and, to a small extent, N-methylformamide, N-hydroxymethyl- formamide and unmetabolized DMF.
26-AUG-1997 (376)

Type: Biochemical or cellular interactions
Remark: DMF inhibited intercellular communication (as measured by metabolic cooperation) between Chinese hamster V79 hpert +/-cells.
10-MAR-2003 (377)

Type: Biochemical or cellular interactions
Remark: The influence of DMF on ethanol oxidation might be explained, at least partially, by its inhibitory effect on the activity of alcohol dehydrogenase in vivo and in vitro.
10-MAR-2003 (378)

Type: Biochemical or cellular interactions
Remark: Exposure of rats (male, SD) for 4 h to air containing 0 (0), 0,215 (66), 0,411 (126), 0,917 (281) and 1,024 mg/l (314 ppm) DMF resulted in increased alanine amino transferase, glutamate dehydrogenase and sorbitol dehydrogenase levels

in blood collected 24 h after cessation of exposure at concentrations of 0,411 mg/l (126 ppm) or higher. When rats were exposed for 6 h/d, for 2 or 4 days, to atmospheres containing 0,411 mg/l (LOEL of the former experiment), it appeared that a single 4 h exposure generally induced a more marked increase of enzyme activities than 2 or 4 daily repeated 6 h-exposures.

01-SEP-1997

(379)

Type: Biochemical or cellular interactions

Remark: Two groups of weanling female Wistar rats were treated once with DMF alone (500 mg/kg, i.p.) or with DMF (500 mg/kg i.p.) in combination with N-nitrosodimethylamine to examine whether DMF (DMF is known to decrease the rate of N-nitrosodimethylamine metabolism) had any influence on the hepatocarcinogenicity of N-nitrosodimethylamine. The rats were kept until they became moribund, and were killed. None of the test groups developed liver nodules or liver tumours.

26-AUG-1997

(380)

Type: Biochemical or cellular interactions

Remark: DMF enhanced the mutagenicity of tryptophan-pyrollysate mutagens in the Ames test.

26-AUG-1997

(381)

Type: Cytotoxicity

Remark: In vitro Dimethylformamide had an effect on the differentiation pattern of cells.

01-SEP-1997

(73)

Type: Cytotoxicity

Remark: The authors assume that decrease in cellular glutathione-content is possibly the reason for the influence of cell differentiation in vitro.

10-AUG-2000

(382)

Type: Cytotoxicity

Remark: In in vivo investigations no disturbances of the cell differentiation is observed.

26-AUG-1997 (383)

Type: Cytotoxicity

Remark: Liver necrosis was seen in mice inhaled 0,489 - 3,91 mg/l (150 - 1200 ppm; 450 - 3600 mg/m³) DMF. Exposure period was not mentioned.

01-SEP-1997 (384)

Type: Cytotoxicity

Remark: Toxicity was observed in guinea pigs after several daily intragastric administrations of 10 ml undiluted DMF. Without any further specification which effects were observed.

10-MAR-2003 (385)

Type: Distribution

Remark: DMF has been shown to cross the placenta exposure of rats by inhalation.

26-AUG-1997 (386)

Type: Excretion

Remark: When ¹⁴C-DMF was administered to mice, 83 % of the dose was recovered in urine within 24 h. Of this amount, 56 % was excreted as N-hydroxymethyl-N-methylformamide and 5 % as unmetabolized DMF; 3 % of the dose administered was excreted as N-(hydroxymethyl)-formamide or formamide and 18 % as unidentified metabolites.

26-AUG-1997 (387)

Type: Metabolism

Remark: The initially expected main metabolite mono-N-methylformamide develops only in minor quantity.

17-JUL-1997 (73)

Type: Metabolism

Remark: An intermediary developing carbamoylating metabolite could be responsible for the cytotoxic effects (e.g. on hepatocytes). The authors postulate a relatively higher proportion of this metabolite in humans. However, as limiting point, it should be taken into account that different ways of administration between humans and mice make it difficult to compare the data of humans and animals.

31-AUG-2000 (161) (388) (389)

Type: Metabolism

Remark: According to the authors it may be possible that an intermediary electro-affine metabolite develops, which could be responsible for the hepato(cyto)toxic effects of the test substance.

26-AUG-1997 (390) (391)

Type: Metabolism

Remark: In the urine of a test person the adduct N-acetal-S- (N-methyl-carbamoyl) cysteine resulting from the glutathione decomposition was found.

26-AUG-1997 (392)

Type: Metabolism

Remark: In the urine of exposed rodents N-acetyl-S- (N-methyl-carbamoyl) cysteine was also found.

26-AUG-1997 (391)

Type: Metabolism

Remark: Dimethylformamide is almost readily resorbed after oral, dermal and inhalative administration/exposure and is metabolised in the liver. The main metabolite found in the urine is N-hydroxymethyl-N-methylformamide.

10-MAR-2003 (383) (393)

Type:	Metabolism
Remark:	<p>Comparative studies with respect to the metabolism of DMF after inhalation by female rabbits and rats were performed to elucidate the higher sensitivity of rabbit in comparison to rats with respect to embryotoxic and teratogenic effects after oral administration of DMF.</p> <p>Both animal species were exposed once for 6 h with 19 ppm (about 0.06 mg/L) and 205 ppm (about 0.62 mg/L), respectively or 5 times for 6 h with 200 ppm (about 0.6 mg/L). Blood and urine were investigated. The metabolites were N-methylformamide and formamide in both species. After acute exposure at 200 ppm the decomposition happened somewhat slower in rabbits than in rats. Other species differences in the metabolism were not observed.</p>
10-MAR-2003	(394) (395) (396)
Type:	Metabolism
Remark:	<p>The main metabolic pathway of DMF in rodents involves hydroxylation of the methyl group to form N-hydroxymethyl-N-methylformamide.</p>
10-MAR-2003	(387)
Type:	Metabolism
Remark:	<p>Accumulation of acetaldehyde in blood has been demonstrated in rats which were given ethanol 18 hours after exposure to DMF.</p>
26-AUG-1997	(397)
Type:	Metabolism
Remark:	<p>One of the most widely reported symptoms of DMF exposure is alcohol intolerance (the antabus effect). Disturbance of alcohol metabolism seems to be the most sensitive sign of effects of DMF.</p>
10-MAR-2003	(398)
Type:	Metabolism
Remark:	<p>A greatly delayed excretion of</p>

monomethylformamide in urine, due to delayed biotransformation of DMF after combined exposure to ethanol and DMF, has been demonstrated in experimental animals, human volunteers and persons occupationally exposed.

10-MAR-2003

(399) (400)

Type: Metabolism

Remark: The authors studied the biotransformation of DMF in vivo in male and female SD rats after i.p. treatment, and in vitro in various rat organs and tissues. Their results demonstrated that NMF was the main metabolite in rat in vivo. Formamide was a quantitatively less important urinary metabolite. In male and female rats the liver was the main organ of biotransformation. The total amount of metabolites of DMF excreted in urine was identical in both sexes, but females excreted more unchanged DMF than the males.

26-AUG-1997

(401)

Type: Metabolism

Remark: DMF can be bioactivated to methyl isocyanate, a reactive species associated with hepatotoxicity.

26-AUG-1997

(402) (403)

Type: Metabolism

Remark: The authors examined the hepatotoxic potential in mice. The results suggested that 2 metabolic pathways of N-alkylformamides can be distinguished: hydroxylation of the -carbon of the N-alkyl group and oxidation of the formyl moiety; the former pathway presumably constitutes a detoxification route, and the latter may well be associated with hepatotoxicity, and affords a glutathione conjugate, S-(N-methylcarbamoyl) glutathione, eventually excreted in the urine as mercapturate (N-acetyl-S-(N-methyl-carbomoyl) cysteine = AMCC). AMCC is supposed to be indicative of bioactivation of DMF toward a reactive species associated with hepatotoxicity.

01-SEP-1997

(404)

Type: Metabolism

Remark: The metabolism of DMF (without further specification on the test substance) was assayed in vitro in liver homogenates of untreated and phenobarbital treated rats. The amount of amide demethylated was determined by measuring the micromols of formaldehyde liberated after correcting for any formaldehyde in liver and in substrate blanks. In vitro demethylation of DMF had been demonstrated in rat liver homogenates and a 50% increase in the demethylation of DMF occurred in the livers from rats treated with phenobarbital. Thus, the metabolism of DMF can be enhanced by treatment with chemicals which induce microsomal enzymes such as phenobarbital.

16-AUG-2000

(405)

Type: Metabolism

Remark: Monomethylformamide (MMF) has been identified as the principal metabolite of DMF when it was administered s.c. to rats. According to the authors, the metabolite in sufficient dosage can cause teratogenic effects in rats but DMF has not been shown to be teratogenic. In the present paper experiments are shortly described that were conducted to identify the major metabolite of DMF, to measure its concentration in blood and urine after a single s.c. dose in rats, and to confirm the presence of this metabolite in the urine of workmen handling DMF. In the pooled urine of 24 male rats (collected from Monday to Friday) that were treated subcutaneously with a dose of 300 mg DMF on Monday and on Wednesday, the principal compound in the urine analysed by gas chromatography was identified as MMF by its retention time. A series of rats were treated s.c. with a single injection of 0.6 ml of a 50% solution of DMF or MMF and sacrificed at intervals over a period of 64 hours to measure blood concentration of MMF. During each interval the urine was also collected for analysis. Evidence for metabolic transformation of DMF was found in blood within one-half hour, the concentration increased slowly and about 24 hours elapsed before a

maximum was reached.
When DMF is administered to rats about 75% of the dose was excreted in the urine as MMF and DMF. Although some DMF has been found in the expired air and the feces, the DMF unaccounted for may be completely demethylated to formamide.
In the urine samples of workmen handling DMF, MMF and not DMF was identified by its relative retention time analysed by gas chromatography.

21-AUG-2000

(406)

Type: Metabolism

Remark: Metabolism of DMF in humans and three species of rodents (mouse, rat, hamster) was compared in terms of N-acetal-S-(N-methylcarbamoyl)cysteine (AMCC). The animals were treated with DMF (in saline) by single i.p. injections (7, 50, 500 mg/kg bw), whereas humans were exposed to DMF vapors at 30 or 60 mg/l for 8 hours. Urine was collected and investigated. The results suggest that the metabolic pathway leading to AMCC is much more important in humans than in rodents.

31-AUG-2000

(407)

Type: Metabolism

Result: N,N-dimethylformamide is readily absorbed after oral intake, dermal exposure or inhalation. Absorbed N,N-dimethylformamide is rapidly and uniformly distributed in the organism. Metabolization takes place mainly in the liver by microsomal enzymes. N-hydroxymethyl-N-methylformamide is the main metabolite of N,N-dimethylformamide in animals and human beings and it is excreted with the urine. Mono-N-methylformamide which was once considered to be the main metabolite of N,N-dimethylformamide is found only in low levels in the urine. It could be shown that mono-N-methylformamide was mainly an artefact formed on the gas chromatographic column. Moreover it was shown, that intermediary metabolism produces to a lower extent via a second pathway glutathion adducts and its degradation products. As carbamoylating species, which reacts with glutathione methyl isocyanate

was postulated but not proven. The cysteine adduct N-acetyl-S-(N-methylcarbamoyl)cysteine is also found in urine at levels of 1% to 5% of the dose in urine of laboratory animals (mice, rat, hamsters) treated parenterally and at 10% to 23% of the dose in persons who had inhaled the substance.

Formation and excretion of the cysteine adduct (N-acetyl-S-(N-methylcarbamoyl)cysteine) in the urine of persons inhaling N,N-dimethylformamide takes place with a half-time of 23 hours. Moreover, investigations in animals had shown that at least after administration in single high doses, N,N-dimethylformamide can inhibit its own metabolism (saturated metabolism). Metabolic interaction occurs between N,N-dimethylformamide and ethanol. Ethanol and probably the ethanol metabolite, acetaldehyde inhibit the breakdown of N,N-dimethylformamide. Conversely, N,N-dimethylformamide inhibits the metabolism of ethanol and acetaldehyde. Thus, increased N,N-dimethylformamide levels in the blood were found after the administration of alcohol and increased alcohol or acetaldehyde levels for up to 24 hours were reported after exposure to N,N-dimethylformamide.

Flag: Critical study for SIDS endpoint

10-MAR-2003 (408)

Type: Metabolism

Remark: The publication describes investigations of female Sprague-Dawley rats exposed for 4 h to 2250 ppm or 565 ppm DMF (about 6.82 mg/l or 1.71 mg/l). Concentrations of DMF and the biotransformation product monomethylformamide (MMF) were measured in blood and some tissues at different times after the end of exposure (groups of 4 rats were killed 0, 3, 6, 20 and 48 h after the end of exposure). Both DMF and MMF were distributed fairly uniformly over the different tissues, though blood and kidneys usually had the highest concentrations. MMF concentrations 0 and 3 h after the end of the high exposure were generally lower than MMF concentrations at the same time after the low exposure. Thus, the results suggest that DMF

	biotransformation to MMF is delayed after the high exposure.
Flag:	Critical study for SIDS endpoint
23-APR-2001	(409)
Type:	Metabolism
Remark:	<p>The toxicity of DMF has been associated with its metabolism to S-(N-methylcarbamoyl)glutathione (SMG).</p> <p>The major urinary metabolite of DMF is N-(hydroxymethyl)-N-methylformamide (HMMF). HMMF undergoes oxidation in the formyl moiety, possibly via the intermediacy of its hydrolysis product N-methylformamide (NMF), and the reactive intermediate generated reacts with glutathione to yield SMG.</p> <p>In experiments to elucidate enzymatic details of the metabolism of DMF it turned out that the affinity of DMF for the metabolising enzyme (cytochrome P 450 2E1) in rat liver microsomes is considerably higher than that of NMF or of HMMF. The respective values observed with human microsomes are very similar.</p> <p>With deuterated isotopomers investigations were performed on the kinetic deuterium isotope effect (KDIE) on DMF metabolism that was determined by incubations with rat microsomes in three ways.</p> <p>It could be shown that DMF inhibited the oxidation of NMF or HMMF to SMG. DMF competed with the P450 2E1 substrate NMF for the enzyme active site. The results obtained suggest that a) hepatic P 450 2E1 is an important catalyst of the metabolism of DMF, b) DMF inhibits its own metabolic toxification and c) there is a marked KDIE on the metabolic oxidation of DMF.</p>
Flag:	Critical study for SIDS endpoint
10-MAR-2003	(410)
Type:	Metabolism
Remark:	<p>Male rats (Cr1:CD BR) and male mice (B6C3F1 (Cr1:BR)) were used for the present study for whole body exposure to 10, 250 and 500 ppm DMF (about 0.03, 0.76 and 1.5 mg/l).</p> <p>Exposure routines were single 1-, 3-, or 6-hour</p>

exposures and ten 6-hour exposures (5d/week). AUC values were determined for DMF and "NMF" (NMF determination represents the sum of DMF-OH and NMF in plasma due to quantitative conversion of DMF-OH to NMF during the GLC analytic procedure).

For each sampling interval 4 rats and 4 mice were used for blood and/or urine collection. The DMF AUC values increased 8- and 29-fold for rats and mice, respectively, following single 6-h exposures to 250 and 500 ppm DMF. These data were indicative of saturation of DMF metabolism. Peak NMF plasma concentrations for rats and mice, following single 6-h exposures did not increase as DMF exposure concentrations increased from 250 to 500 ppm. In addition, the NMF plasma levels in rats following a single 6-h 500 ppm DMF exposure did not decay by 24 hours post exposure. These NMF plasma data also indicate saturation of DMF metabolism.

Multiple exposure to 500 ppm DMF resulted in a 3- and 4-fold reduction in DMF AUC values for rats and mice, respectively, compared to AUC values after a single 6-h 500 ppm exposure.

This together with elevated peak plasma levels for NMF indicate enhanced metabolism of DMF resulting from multiple 500 ppm DMF exposures. Based on prior metabolism studies with DMF and NMF and the present data, the authors propose two major pathways for DMF metabolism.

One pathway is formation of DMF-OH which is then excreted in the urine. A previous metabolism study from Scailteur and Lauwreys, 1984) with DMF-OH confirmed its unchanged excretion into urine which represented approx. 60% of the dose and conversion of DMF-OH to NMF was not indicated.

The second pathway is conversion of DMF to NMF and subsequent metabolism of NMF to a variety of Metabolites including cysteine conjugate.

Involved in this pathway is a proposed reactive intermediate that may be responsible for the observed hepatotoxicity.

Flag: Critical study for SIDS endpoint

10-MAR-2003 (411)

Type: Metabolism

Remark: Male and female cynomolgus monkeys were treated

by whole-body inhalation with concentrations of 30, 100 and 500 ppm DMF (about 0.091, 0.30 and 1.5 mg/l) for 6 h/d and 5 d/week over a 13 week period.

Serial blood samples (from 2 monkeys/sex/group) were taken at the end of the first day of exposure and following 15, 29, 57 and 85 days of testing.

AUC values were determined for DMF and "NMF" (NMF plus DMF-OH). Urine samples were collected and assays for DMF, NMF and DMF-OH.

DMF AUC values increased 19- to 37-fold in male and 35- to 54-fold in female monkeys as the inhalation concentrations increased 5-fold (100 to 500 ppm). These data are consistent with saturation of DMF metabolism as inhaled DMF concentrations increased from 100 to 500 ppm. Estimated plasma half-lives ranged from 1 - 2 hours to 4 - 15 hours for DMF and "NMF", respectively. DMF was rapidly converted to "NMF" following 30 ppm exposures, with "NMF" plasma concentrations higher than DMF plasma concentrations at the 0.5 h timepoint.

DMF-OH was always the main urinary metabolite (56 - 95 %) regardless of exposure levels or time on study.

Flag: Critical study for SIDS endpoint

23-APR-2001

(412)

Type: Toxicokinetics

Remark: The toxicokinetics of N,N-dimethylformamide and N-methylcarbamoyl thioesters ('SMG') formed from DMF in male Sprague-Dawley rats were investigated. For this purpose dermal and inhalative uptake rates of DMF vapours were determined using systems for head-only and body-only exposures, that allowed also the determination of the urinary excretion of unchanged DMF.

A physiological toxicokinetic model of DMF was developed using the determined uptake clearances and partition coefficients. Moreover an analytical method was developed for the determination of 'SMG' in blood plasma of rats. Steady state exposures of rats to DMF vapour at different concentrations were performed to obtain a quantitative relation between concentrations of DMF in atmosphere and concentrations of 'SMG' in blood plasma.

It could be shown that a linear relation between concentration of DMF vapour up to 84 ppm and concentration of 'SMG' in blood plasma occurred in rats exposed at steady state to DMF. Moreover, the 'SMG' concentrations determined in blood plasma of rats exposed at steady state to DMF vapours of 25 and 84 ppm were in the range which produced toxic effects in studies performed in vitro.

Flag: Critical study for SIDS endpoint

10-MAR-2003
(413)

Type: other

Remark: Effects of DMF on H⁺ extrusion and cytosolic pH (pHi) of mouse hepatoma cells (Hepa 1C1C7) were investigated. The data suggest that suppression of acidification rate by DMF is likely due to decreased metabolic acid production. It is possible that alteration in H⁺ production and transport contribute to the hepatotoxicity of DMF and its effects on cellular differentiation.

10-AUG-2000 (414)

Type: other

Remark: Groups of 10 male rats were administered a single i.p. injection of DMF (10, 100, 500 or 1500 mg/kg) or were exposed for 4 h to DMF vapours (0.23, 0.45, 0.91, 1.36 and 2.73 mg/l, respectively (75, 150, 300, 450 or 900 ppm)) under dynamic conditions. Concurrent vehicle control animals received the vehicle, i.e. physiological saline solution or were exposed to air only. 24, 48 or 72 h after i.p. injection or after the end of the inhalation exposure blood was taken from the animals and assayed for the activities of SDH and GLDH. After 500 mg/kg DMF both enzymes peaked at 48 h and the levels increased 72 h after the injection of 1500 mg/kg DMF. Maximum elevations were dose- and time-dependent. After inhalation of DMF, concentrations of 0.45-1.36 mg/l led to moderate elevations of enzyme activities, the maxima of which occurred at 24 h and were concentration-dependent. At the highest concentration tested (2.73 mg/l)

enzyme activities peaked at 48 h. Enzyme activities were more pronounced (i.p.) and/or were obtained at lower levels (inhalation) with SDH than with GLDH. This suggests that SDH is a more sensitive indicator of DMF-induced liver damage than GLDH.

29-AUG-2000

(415)

Type: other: bacterial gene mutation assay

Result: DMF enhanced the mutagenicity of tryptophan-pyrollysate in *Salmonella typhimurium* (TA98) in the presence of an exogenous metabolic activation.

10-MAR-2003

(416)

Type: other: developmental toxicity in a limb bud organ culture

Remark: N,N-dimethylformamide and its major metabolites were investigated for their developmental toxicity in the mouse limb bud assay. Neither N,N-dimethylformamide nor the predominant urinary metabolite N-hydroxymethyl-N-methylformamide exhibited developmental activity in the present investigation, whereas the metabolites resulting from the glutathione binding pathway, i.e. S-(N-methylcarbamoyl)glutathione, S-(N-methylcarbamoyl)cysteine and N-acetyl-S-(N-methylcarbamoyl)cysteine showed potent developmental activity on growth (300 µg/ml) and development (100 µg/ml) of day 12 old mouse limb buds after 24 hours as well as 6 days in culture. The three compounds appear to be equipotent on a molar basis. Limb bud defects were not observed in in vivo studies, where typical malformations were seen in the form of vertebral, rib and tail defects and hernia of brain and omphalos. The defects reported in the present investigation indicate that certain differentiating tissues are specifically sensitive to the effective substances (glutathione adducts). Since the present in vitro experiments were designated to distinguish between effective and non-effective metabolites in this regard and were not bound to generate in vivo-like or -comparable effects.

In former experiments (Mraz et al. 1989) a higher portion of a N,N-dimethylformamide dose in humans was found to be metabolized to N-acetyl-S-(N-methylcarbamoyl)cysteine (14.5% after inhalation exposure versus only less than 5.2% in rodents after i.v. injection. According to the authors, this seems to be indicative of a higher human susceptibility, but may also be a consequence of the different dose and route. The data of the present investigation indicate that glutathione adduct formation is the causative pathway for the developmental toxicity of N,N-dimethylformamide.

Flag: Critical study for SIDS endpoint

10-MAR-2003 (417)

Type: other: embryo neural retina cell model

Result: In a chick embryo neural retina cell culture model, a number of developmental toxicants were investigated. Exposure period was 24 hours. This model undergoes processes of cell-cell recognition and interaction, growth, and differentiation over a 7-day culture period. Each of these developmental events is measured separately as formation of multicellular aggregates, protein content and glutamine synthetase activity. The LOECs for DMF affecting aggregation and differentiation was > 50 g/l (> 68,5 mM) and 6,26 g/l (8,56 mM) affecting growth. This assay showed a 80 % concordance with mammalian data.

01-SEP-1997 (418)

Type: other: epidemiological studies (human)

Remark: These studies report on evaluation of health effects, especially on cancer following occupational exposure to N,N-dimethylformamide.

04-SEP-1997 (419) (420) (82) (421)

Type: other: evaluation of ocular irritancy potential

Remark: In an 'evaluation of ocular irritancy potential: sources of intralaboratory variability and effect of dosage volume' DMF was tested together with six other compounds that were all

previously tested for ocular irritancy using standard Haskell Laboratory procedures.

22-AUG-2000 (422)

Type: other: human excretion

Remark: N-methylformamide, formed from N-hydroxymethyl-N-methylformamide during gas chromatographic analysis, has been measured in the urine of exposed workers. Urinary measurements showed a dose-relationship to airborne levels of DMF after exposure by inhalation.

26-AUG-1997 (423)

Type: other: inhalative toxicity

Remark: A single 8 hour inhalation exposure of cats, rabbits, guinea pigs and rats to a DMF saturated vapour-air mixture showed no effects.

04-SEP-1997 (424)

Type: other: mouse sensory irritation (Alarie Test)

Remark: DMF was tested as a negative control for sensory (upper airway) irritation potential in male Swiss Albino Charles River CD-1 mice by head only exposure for 10 minutes exposure periods. DMF concentrations used ranging from 0 to 2110 ppm (6.4 mg/L). The test was performed according to the method of Alarie. Saturated vapors of DMF produced minimal irritation and the RD50 (concentration of a material required to produce a 50% respiration rate decrease) was determined > 2000 ppm DMF. The maximum respiration decrease induced was 30% slowing.

21-AUG-2000 (425)

Type: other: odor threshold

Remark: The odor threshold has been reported to be 300 mg/m³ (0,3 mg/l; 100 ppm).

01-SEP-1997 (426)

Type: other: placental and milk transfer of DMF in pregnant rats

Remark: Placental transfer: a single oral dose of 100 mg/kg radiolabelled DMF in distilled water (dose led to slight maternal and fetal toxicity in a parallel conducted developmental study, see chapter 5.9) was given by gavage to 5-6 pregnant rats on GD 12 or GD 18. Animals were fasted 16 h prior to dosing. Excreta, blood and organs (kidneys, liver, ovaries, stomach, intestine and uterus) as well as placenta/embryo/fetal units (pooled per litter) were investigated for radioactivity. It was shown in the study that the radiocarbon associated with a single oral dose of 100 mg/kg DMF and/or its metabolites readily traversed the placenta and distributed within embryonic/fetal tissues on GD 12 and GD 18.

Regardless of the stage of pregnancy, concentrations of radioactivity were comparable or slightly higher in the embryo or fetus than in the placenta. Peak conc. of radioactivity were equal in GD 12 embryos and GD 18 fetuses, indicating that the placenta was freely and equally permeable to DMF and/or its metabolites. No evidence of accumulation of radioactivity in any maternal or embryonic/fetal tissues was observed.

Milk transfer: Lactating female rats (n=16) received a single oral dose of 100 mg/kg radiolabelled DMF on day 14 p.p.. 1, 2, 4 and 24 h after dosing (n=4 maternal animals/time point) were anesthetized and milk samples were collected. Maternal blood samples were collected from abdominal aorta following the milk collection.

Radioactivity conc. in the milk were similar to those in the plasma throughout the 24 h period. About 82-86% of the total radioactivity was unchanged DMF, however metabolites (N-Hydroxymethyl-N-methylformamide, HMMF and N-Methylformamide, NMF) were also transferred into the milk.

10-MAR-2003

(427)

Type: other: retention

Remark: At air concentrations between 1,1 and 24,2 mg DMF/m³, lung retention in humans has been calculated to be 64 % to 83 %.

26-AUG-1997

(428)

Type: other: review

04-SEP-1997 (429) (73) (430) (431) (432) (433) (434) (435) (436)
(437) (82) (438) (439) (440)

Type: other: review

31-AUG-2000

(441)

Type: other: review

31-AUG-2000

(442)

Type: other: review

10-MAR-2003

(443)

Type: other: review

Remark: Short presentation of data on toxicology and biological monitoring of DMF.

29-SEP-2000

(444)

Type: other: review on reproductive and developmental effects

Remark: In a review, NIOSH has reviewed the literature on the reproductive and developmental effects of DMF. DMF is known to have induced malformations in the offspring of mice and rabbits (NIOSH, 1990).

26-AUG-1997

(445) (446)

Type: other: summary of range finding toxicological data

Remark: acute oral: 3000 mg DMF/kg were administered as a 10% solution in water to two rats. The animals survived but showed slight initial weight loss. According to literature values the LD50 in rats is cited with 7000 mg/kg and in rabbits with 5000 mg/kg. eye irritation-rabbit: 100% DMF, unwashed led to moderate pain, irritation and possibly some permanent corneal damage. 100% DMF, washed led to very slight pain, irritation and possible permanent corneal damage. 10% DMF unwashed and washed led to very slight pain and

irritation for a few hours but not to corneal injury.
skin irritation-rabbit: 5 applications of 100% DMF on the intact skin of the belly led to moderate hyperemia and death in 6 days. 10 applications of 100% DMF on the intact skin of the ear led to very slight hyperemia. 10 applications of 10% DMF on the intact skin of the belly led to very slight scaliness. 10 applications of 10% DMF on the intact skin of the ear remained without any findings.
skin absorption-rabbit: DMF is readily enough absorbed through the intact skin.
inhalation(saturated atmosphere)-rat: after 7 hours of exposure of 3 rats no death occurred. There was only very slight initial loss of weight. chronic vapor studies: according to the authors results of inhalation experiments on dogs reported to them by another laboratory indicated that DMF has an appreciable chronic toxicity.

23-AUG-2000

(447)

Type:

other: time kill study in fish

Remark:

Nopco 140, a mixture containing about 15 - 30% Dimethylformamide (active ingredients Hexachloro dimethyl sulfone 17%, Methylene bis-thiocyanate 6%; inert ingredients 77%) had shown to be biologically unstable at use concentrations. In a time-kill study it could be shown that the mixture lost its toxicity for fish upon aging. Fishes were observed for 96 hours, there were no changes in the death of fish past 24 hours. Moreover in the TSCAT the following LC50 values for Nopco 140 are given: LC50 values for 96 hours in *Lepomis macrochirus* are 0.135 mg/L and 0.23 mg/L in *Oncorhynchus mykiss*.

24-AUG-2000

(448)

Remark:

Ethanol and Dimethylformamide decomposition is mutually inhibited. After previous administration of one of both substances either increased Dimethylformamide or increased Ethanol/Acetaldehyde-blood levels were seen.

10-MAR-2003

(87)

- Remark:** Investigations with respect to hepatotoxicity after i.p. administration.
- 10-MAR-2003 (449) (450)
- Remark:** Investigations with respect to antineoplastic effects.
- 10-MAR-2003 (451)
- Remark:** Measurements of DMF in blood and exhaled air of humans for assessing exposure.
- 10-MAR-2003 (452)
- Remark:** In this validation study with 40 chemicals the authors investigated two computer-based techniques, COMPACT and HazardExpert to evaluate their performance individually and in combination for toxicity prediction against human and rodent carcinogenicity data. The aims were to continue the validation of COMPACT for predicting carcinogenicity, widening the range of CYP450 interactions calculated; and to assess the predictive value of HazardExpert with the same chemical. COMPACT is based on the analysis of the electronic and molecular structure of a chemical; HazardExpert identifies structural alerts associated with carcinogenicity, mutagenicity, teratogenicity, irritancy, neurotoxicity and immunotoxicity. The authors resumed that DMF is shown to be CYP4502E specific in COMPACT, but that there is no evidence for ROS (reactive oxygen species) toxicity. Consequently, it is unlikely that DMF is carcinogenic. Furthermore DMF is not a direct-acting electrophile. HazardExpert does not predict any toxic effects for DMF.
- 10-MAR-2003 (453)
- Remark:** To assess the suitability of DMF as solvents for the Ames test the authors examined its toxicity for the bacteria alone and in combination with model compounds. DMF is toxic for bacteria at levels of 500 µl per plate and higher.
- 10-MAR-2003 (454)
- 10-MAR-2003 (455)

Remark: DMF was tested in fertilized *Cyprinus carpio* eggs in test concentrations of 400 - 6400 mg/l for 7 days. Fertilized *Rana nigromaculata* eggs were tested with the same concentrations for 8 days. The NOEC in the *C. carpio* test was 800 mg/l the LOEC was 1600 mg/l. For *R. nigromaculata* the NOEC was 3200 mg/l and the LOEC was 6400 mg/l.

10-MAR-2003

(456)

Remark: Comparison of the toxicity of DMF and Dimethylacetamide. DMF is more toxic than DMAC by oral and skin administration. Oral administration of DMF (without further details on animals, test substance specification, doses and exposure conditions used) led to mortality in 9 out of 10 animals. The dermal administration of 1 cc. DMF had shown a fatality of 75% after six treatments (again further experimental information is not given). In a summary table the following values were given without further details on study designs: oral, rat ALD 2250 mg/kg liver, kidney, lung damage oral, rat subacute 10 applications of 450 mg/kg: no deaths in 6 animals, marked weight loss, milder liver and kidney damage oral, guinea pig ALD 3400 mg/kg skin absorption, rabbits ALD 5000 mg/kg liver damage, lung edema skin absorption, subacute 10 applications of 1000 mg/kg: no deaths in 6 animals, moderate weight loss skin irritation and sensitization, 100% led to strong temporary irritation (30 min to several hours); not a sensitizer inhalation, rat 92.8 mg/L (30600 ppm) lethal; 78.9 mg/L (26000 ppm) non-lethal inhalation, dog 6 exposure of 0.03 - 0.079 mg/L (11-26 ppm) for 6 hours: no effect
Some of the data are also cited in: Greim H.: Occupational Toxicants, Critical Data Evaluation for MAK Values and Classification of Carcinogens, 8, Deutsche Forschungsgemeinschaft, 1992

10-MAR-2003

(457)

Remark: 100% pure DMF was used for single and multiple whole-body inhalation exposure in male Crl:CD BR rats and male B6C3F1 male mice. For the single one-hour, the single three-hour and the single

six-hour exposure as well as for multiple exposure three dose levels of 10, 250 and 500 ppm (about 0.03, 0.76, 1.52 mg/L) were chosen. Each 4 male rats and 4 male mice were investigated at these dose levels for the one- and the three-hour exposure. From these animals blood was collected 0.5 hours after exposure. For the six-hour exposure each 32 male rats and male mice were used at the three dose levels. From selected animals of the six-hour exposure blood and urine were collected at various time points until 24 hours after exposure.

Each 32 male rats and mice were exposed 10 times for six hours/day, on 5 days a week for 2 weeks to the above mentioned dose levels of DMF. Each 6 male rats and mice served as a control. From selected control and treated animals blood and urine samples were collected at various time points until 24 hours after exposure. To assess cell proliferation and morphological changes the following organs: liver, testes, kidney, nasal tissues, trachea, lung and prostate were taken 24 hours after exposure from selected animals that supplied the 24-hour blood and the 12- and 24-hour urine samples. The animals selected for examination of cell proliferation were implanted an osmotic pump after five days of exposure that were loaded with [3H] thymidine. The animals were exposed to DMF for an additional 5 days.

Result:

The DMF area under the plasma concentration curve (AUC) values increased 8- and 29-fold for rats and mice, following single 6-hour exposures to 250 and 500 ppm DMF. These data are indicative of saturation of DMF metabolism. Multiple exposure to 500 ppm resulted in a 3- and 4-fold reduction in DMF AUC values for rats and mice, respectively, compared to AUC values following a single six-hour 500 ppm DMF exposure. DMF plasma half-life was also reduced 2-fold for both species tested following multiple 500 ppm exposures compared to single 500 ppm exposures. These data are indicative for enhanced metabolism of DMF resulting from multiple 500 ppm exposures.

Urinary analysis of all samples revealed N-(hydroxymethyl)-N-methylformamide (DMF-OH) represented over 90% of the summed DMF, DMF-OH and N,-methylformamide (NMF) quantities.

Under the conditions of the present study, repeated DMF exposures did not significantly elevate cellular proliferation indexes in livers of rats and mice. However, in mice a slight concentration related increase in cell proliferation occurred in mouse liver, but according to the authors the changes were not statistically different from control possibly due in part to the small sample group size (n=4). Although lung tissue had not previously been identified as being affected by DMF exposure, a statistically significant elevation of cellular proliferation index was seen in rat lungs after multiple DMF exposures in this study.

10-MAR-2003

(458)

Remark:

Male and female cynomolgus monkeys were exposed by whole-body inhalation to 30, 100 and 500 ppm (about 0.09, 0.3, 1.52 mg/L) DMF of > 99% purity for six hours/day, five days/week for 13 weeks. Two male and two female monkeys at each exposure level were used for pharmacokinetic investigations.

Serial blood samples were drawn at the end of the first day of exposure and following day 15, 29, 57 and 85 on study (i.e. end of 2, 4, 8 and 12 weeks of exposure). AUC values were determined for DMF and N-methylformamide (NMF). From the same monkeys that provided blood samples, urine samples were collected at the above mentioned time points and assayed for DMF, NMF and N-(hydroxymethyl)-N-methylformamide (DMF-OH). Since blood samples were drawn 0.5, 1, 2, 4, 6, 8, 12 and 24 hours following termination of exposure, the first exposure day was followed by two non-exposure days to enable drawing the 24 hour blood sample. Additional timepoints of 36 and 48 hours were added to the week 8 and 12 blood collections.

Result:

Disproportionate increases in AUC values for DMF were seen during the entire duration of the study from 100 to 500 ppm. Metabolic conversion of DMF to NMF was not saturated following 500 ppm DMF exposures as indicated by increased peak plasma NMF levels between 100 and 500 ppm exposures to DMF. No discernible effect on DMF or NMF pharmacokinetic profiles for either sex within each exposure were seen from day 15

through day 85 of the study. Enhanced conversion of DMF to NMF between day 1 and day 15 was indicated by elevated NMF plasma concentrations. NMF plasma half-lives were often at least 5-fold longer than companion DMF plasma half-lives. NMF plasma half-lives were typically longer following 500 ppm DMF exposures.

DMF-OH was excreted in the urine in greater relative abundance than DMF or NMF. DMF-OH represented over 60% of the sum of DMF, NMF and DMF-OH excretion products. These data suggest that a substantial amount of DMF-OH was present in circulating plasma but was converted to NMF during plasma analysis.

Following 13 weeks of exposure to DMF there was no evidence of any toxicity (including liver toxicity) at dose levels of 30, 100 and 500 ppm. When comparing the data of the present study with the data of rats and mice exposed to 250 and 500 ppm DMF by inhalation for 2 weeks there is, according to the authors an indication that DMF toxicity in rodents overestimates human risk to DMF inhalation exposures.

10-MAR-2003

(459)

Remark:

Pregnant rats were treated multiple times by topical administration on gestation days 11, 12 and 13. Total doses administered were 0.9 and 1.8 ml, respectively. Urine was collected and analyzed. (Comment: Due to the fact, that the TSCAT/Microfiche was not readable in most parts, no further information can be given.)

10-MAR-2003

(460)

6.1 Analytical Methods

6.2 Detection and Identification

7.1 Function

7.2 Effects on Organisms to be Controlled

7.3 Organisms to be Protected

7.4 User

7.5 Resistance

8.1 Methods Handling and Storing

8.2 Fire Guidance

8.3 Emergency Measures

8.4 Possib. of Rendering Subst. Harmless

8.5 Waste Management

8.6 Side-effects Detection

8.7 Substance Registered as Dangerous for Ground Water

8.8 Reactivity Towards Container Material

- (1) BASF AG, Safety data sheet DIMETHYLFORMAMIDE, 06.11.2001
- (2) Commission Directive 2001/59EC, 6 August 2001 (28th adapti to the technical progress of 67/548/EEC)
- (3) TRGS 903 (Technical guidance for hazardous substances - Technische Regeln für Gefahrstoffe) (Germany) of 04/2001
- (4) TRGS 900 (Technical guidance for hazardous substances - Technische Regeln für Gefahrstoffe) (Germany) of 09/2001
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- (6) National Chemical Inventories, 2002 Issue 2
- (7) Bipp H., Kieczka H., Formamides, in: Ullmann's Encyclopedia of Industrial Chemistry, Fifth Edition, Vol. A 12, pp. 1-12, VCH Verlagsgesellschaft, Weinheim, 1989
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- (10) BASF AG, Safety Data Sheet Dimethylformamide (28.01.2000)
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10.1 End Point Summary

10.2 Hazard Summary

10.3 Risk Assessment

Memo : Hazard Assessment Experience with Human Exposure

Remark : [5.11] Experience with Human Exposure

Percutaneous absorption of liquid and DMF vapor was shown in human volunteers. A good and linear correlation of DMF concentrations in the air of the workplace and N-hydroxymethyl-N-methylformamide in the urine at the end of an 8-h shift was found. Workers with high DMF workplace exposure concentrations reported headaches, dizziness, anorexia, nausea, abdominal pain, and alcohol intolerance (facial flushing and palpitations). Clinical investigations showed elevated liver enzyme values (ASAT, ALAT, and CPK). Case reports of testicular cancer in aircraft repair and leather tannery facilities were reported. Mortality and cancer incidence studies and nested case-control studies of testicular cancer at several other anatomical sites however showed no convincing evidence. Validity of increased rates chromosomal aberration and SCE rates reported in workers is questioned by some methodological shortcomings of these studies.

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