SCOEL/SUM/121
September 2006

Recommendation from the Scientific Committee
for Occupational Exposure Limits
on N,N-Dimethylformamide

8 hour TWA	:	5 ppm (15 mg/m^3)
STEL (15 mins)	:	10 ppm (30 mg/m^3)
Additional classification:		"skin"
BLV	:	15 mg N-methylformamide/l urine (post-shift)

Substance:

N,N-Dimethylformamide $OHC–N(CH_3)_2$

Synonyms	:	DMF, Formic acid dimethyl amide, Formyl dimethylamide, N,N-Dimethyl formic acid amide
EINECS Nº	:	200-679-5
EEC Nº	:	616-001-00-X
CAS Nº	:	68-12-2
MWt	:	73.09

Conversion factor (20ºC, 101kPa) : 3.038 mg/m^3 = 1 ppm

Classification :	Repr. Cat. 2 ;	R61; May cause harm to the unborn child
	Xn,	R20/21; Harmful by inhalation and in contact with skin
	Xi	R36, Irritating to eyes

The toxicity of N,N-dimethylformamide (dimethylformamide, DMF) was assessed recently by different organisations. This documentation is based on the Concise International Chemical Assessment Document (WHO, 2001), the SIDS Initial Assessment Report (OECD, 2003), the IARC Monographs (IARC, 1989, 1999), the IPCS Environmental Health Criteria (WHO, 1991), documentations from BUA (BUA, 1994) and from the German MAK Commission (DFG, 1997).

Occurrence/use:

Dimethylformamide is a colourless, high-boiling, strongly polar, hygroscopic liquid with a faint amine odour. It is a flammable liquid with an acrid odour and infinitely miscible with water and with many lipophilic solvents.

It has a MPt of -60.5°C, a BPt of 153°C and a flash point of 58°C. It has a vapour pressure of about 3.53 hPa at 20°C, and it is explosive in the range 2.2 - 16 % in air (BUA, 1994).

Dimethylformamide is predominately used as a solvent in the synthesis of fine chemicals, in polyacrylonitrile fibre production, polyurethane coating and in the electronics industry. The remaining use is split into various applications like varnishing, surface coating, polyamide coating, absorbents, cleaners, and extractants. In addition, dimethylformamide is used as a solvent in crop protection agents. In the year 2000 the total production volume in the EU was in the range of 50,000 to 100, 000 t/a (OECD, 2003).

Health Significance:

Metabolism and Toxicokinetics

Dimethylformamide is readily absorbed following oral, dermal, or inhalation exposure (WHO, 2001). Due to the possibility of significant dermal uptake of dimethylformamide through the skin (e.g. Chang *et al*., 2004; Nomiyama *et al*., 2001), air monitoring is not sufficient for the prevention of health effects from occupational exposure. Biological monitoring is therefore essential. Following absorption, dimethylformamide is uniformly distributed, metabolized primarily in the liver, and rapidly excreted as metabolites in urine (WHO, 2001).

The major pathway of dimethylformamide (DMF) involves the monooxidation of methyl moieties with cytochrome P450, resulting in *N*-(hydroxymethyl)-*N*-methylformamide (HMMF), which is the major urinary metabolite in humans and animals. HMMF in turn can hydrolyse to *N*-methylformamide (NMF). In turn, enzymatic *N*-methyl oxidation of NMF can produce *N*-(hydroxymethyl)formamide (HMF), which further hydrolyses to formamide. An alternative pathway for the metabolism of NMF is oxidation of the formyl group followed by conjugation with glutathione, resulting in *N*-acetyl-*S*-(*N*-methylcarbamoyl) cysteine (AMCC), which has been identified as a secondary urinary metabolite in rodents and humans. A reactive intermediate, the structure of which has not yet been determined (possibly methyl isocyanate or a phosphate derivative), is formed in this pathway; while direct supporting experimental evidence was not identified, this intermediate is suggested to be the putatively toxic metabolite. Available data indicate that a greater proportion of dimethylformamide may be metabolized by the toxic pathway in humans than in experimental animals (WHO, 2001).

Ten volunteers who absorbed between 28 and 60 µmol dimethylformamide/kg body weight during an 8-hr exposure to dimethylformamide in the air at 60 mg/m^3 (20 ppm) excreted in the urine within 72 hr between 16.1 and 48.7 % of the dose as N-(hydroxymethyl)-N-methylformamide (HMMF), between 8.3 and 23.9 % as formamide, and between 9.7 and 22.8 % as N-acetyl-S-(N-methylcarbamoyl) cysteine (AMCC). In mice, rats, or hamsters the portion of the doses given i.p. (0.1, 0.7, or 7.0 mmol/kg body weight) which were metabolized

to HMMF increased with increasing dose from 8.4 up to 47.3 %. The excretion of formamide decreased with increasing dose and ranged from 7.9 to 37.5 %. Only 1.1 to 5.2 % was excreted as AMCC. The results suggest that there is a quantitative difference between humans and rodents in the metabolic pathway of dimethylformamide to AMCC. It is argued that the hepatotoxic potential of dimethylformamide may be linked to the extent of its metabolic conversion to AMCC (Mráz *et al*., 1989).

The biological half-life of urinary NMF after the 4 h dermal (whole-body) exposure of 13 male volunteers was given as 4.75±1.63 h. After 4 h respiratory exposure, the urinary half-life of NMF was 2.42±0.63 h (Nomiyama *et al*., 2001). There is metabolic interaction between dimethylformamide and alcohol (WHO, 2001). Ethanol and probably the metabolite acetaldehyde inhibit the metabolism of dimethylformamide and conversely, dimethylformamide inhibits the metabolism of ethanol and acetaldehyde (OECD, 2003).

Effects on experimental animals

Acute Toxicity, Irritation, Sensitisation

Following oral, dermal, inhalation, or parenteral administration, the acute toxicity of dimethylformamide in a number of species is low. Lethal doses are generally in the g/kg body weight range for oral, dermal, and parenteral routes and in the g/m^3 range for inhalation exposure. Clinical signs following acute exposure include general depression, anaesthesia, loss of appetite, loss of body weight, tremors, laboured breathing, convulsions, haemorrhage at nose and mouth, liver injury, and coma preceding death. Where protocols included histopathological examination, damage was observed primarily in the liver (WHO, 1991). In the rat, oral LD_{50}s range from 3,000 to 7,170 mg/kg body weight, dermal LD_{50}s range from 5,000 to >11,520 mg/kg body weight, and inhalation LC_{50}s range from 9,432 to 15,000 mg/m^3 (WHO, 1991).

Dimethylformamide was irritating to the eyes of rabbits but not irritating to the skin of rabbits and rats (OECD, 2003).

Dimethylformamide did not show a sensitising potential when used in a local lymph node assay (OECD, 2003).

Subchronic and Chronic Toxicity

In a 13-week feeding study with Charles River CD rats, the **NOAEL** was 200 ppm dimethylformamide in the diet (about 12 mg/kg body weight and day). Relative liver weights were slightly increased at 1000 ppm (60 mg/kg body weight and day). 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 also

observed. At 5000 ppm (300 mg/kg body weight and day) both sexes showed depressed body weight gain and reduced food consumption. Slight anemia, leucocytosis, 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 (OECD, 2003).

F344 rats and BDF_1 mice of both sexes were exposed by inhalation (6 h/d, 5 d/wk) to 100, 200, 400, 800 or 1,600 ppm dimethylformamide for 2 weeks, and 50, 100, 200, 400 or 800 ppm for 13 weeks. Three male and 7 female rats died during the 2-wk exposure to 1,600 ppm dimethylformamide, but no death of the exposed rats or mice occurred under any other exposure conditions. Massive, focal and single cell necroses were observed in the liver of the exposed rats ($\geq$200 ppm) and mice ($\geq$100 ppm). The massive necrosis associated with the centrilobular fibrosis occurred at the highest exposure concentration. The single cell necrosis was associated with fragmentation of the nucleoli as well as an increased mitotic figure. The 13-week exposures of rats and mice to dimethylformamide were characterized by increases in absolute liver weights (mice $\geq$50 ppm) and relative liver weights (male mice $\geq$100 ppm; male rats $\geq$50 ppm), by the incidence of centrilobular hepatocellular hypertrophy (male rats $\geq$200 ppm; male mice $\geq$50 ppm), as well as by increased serum levels of AST, ALT, LDH, total cholesterol and phospholipids. Lower confidence limits of the benchmark dose yielding the response with a 10 % extra risk (BMDL10) were determined for the relative liver weight and the incidence of hepatocellular hypertrophy of the 13-wk exposed animals. The $BMDL_{10}$ resulted in 1 ppm for the increased relative liver weight of male rats and mice and 17 ppm for the hepatocellular hypertrophy of male mice (Senoh *et al*., 2003). The LOEC of this study is 50 ppm.

Male and female F344 rats and $B6C3F_1$ mice (10/sex/group) were exposed to dimethylformamide by whole-body inhalation exposure at 0, 50, 100, 200, 400, or 800 ppm, 6 h/day, 5 days/week, for 13 weeks. A concentration-dependent depression in body weight occurred in rats of both sexes at 400 and 800 ppm. In contrast, all weight changes in both sexes of mice were within 10% of controls. No rats died, while 5 mice died from causes non-related to exposure. Relative liver weights were significantly increased at all dimethylformamide concentrations in both sexes and both species. Activities of serum sorbitol dehydrogenase (SDH) were statistically increased in male and female rats (200 – 800 ppm). Alanine aminotransferase (ALT) and isocitrate dehydrogenase (ICD) activities were statistically increased in both sexes of rats exposed to 800 ppm dimethylformamide. Cholesterol (CHOL) levels were statistically increased in male and female rats at all concentrations (50 – 800 ppm). Levels of total bile acids (TBA) were statistically increased in both sexes of rats (400 – 800 ppm). Centrilobular hepatocellular necrosis (minimal to moderate) was seen in rats of both sexes exposed at 400 and 800 ppm, with the lesions more severe in females. Centrilobular hepatocellular hypertrophy (minimal to mild) was found in

all groups of dimethylformamide-exposed male mice, and in female mice exposed at 100 – 800 ppm. For male and female rats, the no-observed-adverse-effect concentration (NOAEC) for microscopic liver injury was 200 ppm, although liver enzymes and liver weights were increased at all exposure concentrations (50 – 800 ppm). For female mice the NOAEC for microscopic liver lesions was 50 ppm, however increased liver weights were observed at this concentration. A NOAEC could not be defined in male mice, as centrilobular hepatocellular hypertrophy and incresaed liver weights were observed at all exposure concentrations (50 – 800 ppm) (Lynch *et al.*, 2003). A technical report on this study has been published by the National Toxicology Program (NTP, 1992). The LOEC is 50 ppm based on increased relative liver weights.

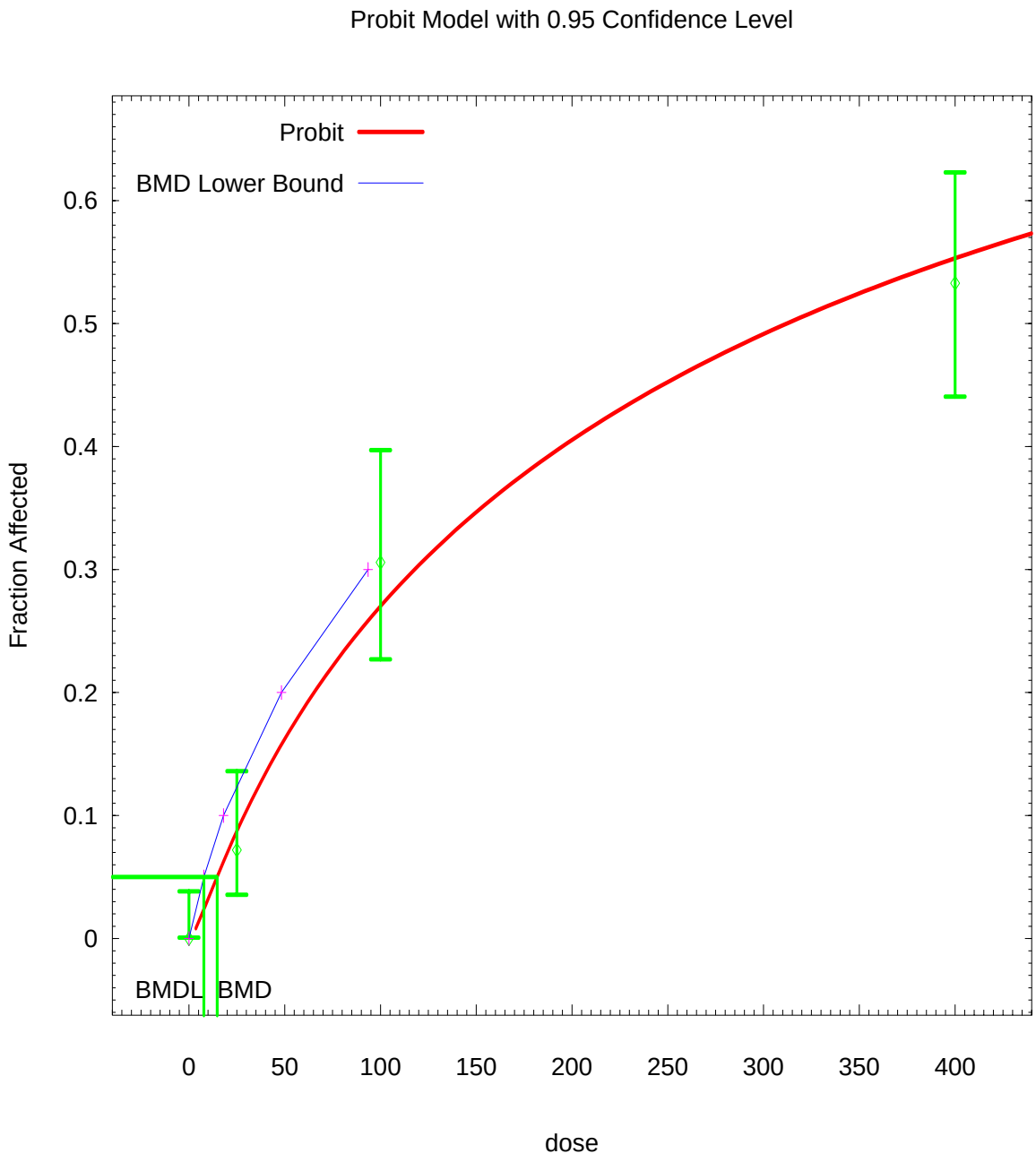
Male and female rats and mice were exposed to 0, 25, 100, or 400 ppm dimethylformamide for 6 h per day on 5 days per week for 18 months (mice) or 2 years (rats). Body weights of rats exposed to 100 ppm (males only) and 400 ppm were reduced. Compound-related morphological changes were observed only in the liver. In rats, exposure to 100 and 400 ppm produced increased relative liver weights, centrilobular hepatocellular hypertrophy, lipofuscin/hemosiderin accumulation in Kupffer cells, and centrilobular single cell necrosis (400 ppm only). In mice, increased liver weights (100 ppm males, 400 ppm both sexes), centrilobular hepatocellular hypertrophy, accumulation of lipofuscin/hemosiderin in Kupffer cells, and centrilobular single cell necrosis were observed in all exposure groups. These observations occurred in a dose-response fashion and were minimal at 25 ppm. No increase in hepatic cell proliferation was seen in mice or female rats. Slightly higher proliferation was seen in male rats exposed to 400 ppm at 2 weeks and 3 months but not at 12 months (Malley *et al*., 1994). In this study 25 ppm is a NOAEC for rats and a LOAEC for mice. A Benchmark dose calculation was performed using the morphological observations in mouse liver (see Table 1). The most relevant endpoint used for calculation was "centrilobular hepatocellular hypertrophy". Data from male and female mice were combined as theses data did not show a great variability. The Benchmark dose calculation was performed with the US EPA software Version 1.3.2 using a log-Probit model with a benchmark response of 5% extra risk. A BDML was calculated with 7.8 ppm, the BMD with 14.7 ppm. Fit of the model was not optimal (AIC 388; chi^2 1.35), however, modelling using the endpoints "single cell necrosis or "Kupffer cell hyperplasia/pigment accumulation" was much more problematic due to high background values. The endpoint "foci alteration" was not used since this endpoint is not the most sensitive one.

Table 1 Incidence of compound-related morphological observations in mice exposed to dimethylformamide for 18 months (Malley *et al*., 1994)

Endpoint	Sex	dimethylformamide (ppm)			
		0	25	100	400
Number of livers examined	male	60	62	60	59
	female	61	63	61	63
	male + female	121	125	121	122
Centrilobular hepatocellular hypertrophy	male	0 (0 %)	5[1)] (8 %)*	25 (41 %)*	31 (52 %)*
	female	0 (0 %)	4 (6 %)	12 (19 %)*	34 (54 %)*
	male + female	0 (0 %)	9 (7,2 %)	37 (31 %)	65 (53 %)
Single cell necrosis	male	14 (24 %)	37 (59 %)*	41 (68 %)*	51 (87 %)*
	female	18 (29 %)	28 (44 %)*	43 (70 %)*	48 (76 %)*
Kupffer cell hyperplasia/ pigment accumulation	male	13 (22 %)	32 (52 %)*	36 (6 %)*	51 (86 %)*
	female	31 (51 %)	36 (57 %)	43 (71 %)*	61 (96 %)*
Mixed foci alteration	male	0 (0 %)	2 (3 %)	8 (13 %*)	11 (19 %)*
	female	0 (0 %)	0 (0 %)	2 (3 %)	2 (3 %)

* statistically significant at $p<0.05$

[1)] The incidence numbers of livers affected were calculated/assumed from the incidences (%) given in the publication



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Cynomolgus monkeys showed no measurable adverse effects following inhalation of 500 ppm dimethylformamide for 6 h per day on 5 days per week for two weeks (Hurtt *et al*., 1991).

In a 13-week inhalation study, groups of three cynomolgus monkeys per sex and group received whole-body exposures to 0, 30, 100, or 500 ppm dimethylformamide for 6 h per day on 5 days per week. Based on extensive monitoring of the monkeys' clinical condition, semen quantity and quality, clinical and histopathological evaluations, haematological parameters and serum chemistry including transaminases, the NOAEL for cynomolgus monkeys is 500 ppm (Hurtt *et al*., 1992). Since effects on the liver have been reported in workers exposed to dimethylformamide concentrations of 10 to 20 ppm and above, the results on cynomolgus monkeys are not considered relevant for man and are not used for OEL setting.

Genotoxicity

Dimethylformamide has been tested extensively in a broad range of in-vitro and in-vivo genotoxicity tests. Results have been consistently negative in well controlled studies (OECD, 2003; IARC, 1999).

Carcinogenicity

Dimethylformamide was adequately tested for carcinogenicity by inhalation in one study. Male and female CD rats and CD-1 mice were exposed to 0, 25, 100, or 400 ppm dimethylformamide for 6 h per day on 5 days per week for 18 months (mice) or 2 years (rats). In this study 25 ppm is a NOAEC for rats and a LOAEC for mice (see above). No increases in tumours were found (Malley *et al*., 1994). Based on this study together with the information from epidemiologic studies, dimethylformamide was classified by IARC as "not classifiable as to its carcinogenicty" to humans (Group 3) (IARC, 1999).

Reproductive Toxicity

Fertility

Using the Reproductive Assessment by Continuous Breeding Protocols, chronic exposure of CD-1 mice to dimethylformamide in drinking water at 0, 1000, 4000, and 7000 ppm (approximately 200 to 1300 mg/kg body weight and day) reduced fertility by the first litter at 4000 ppm, reduced body weight in F0 females at 7000 ppm, and increased liver weights at all doses in both sexes. A crossover mating at 7000 ppm identified F0 females as the affected sex. F1 postnatal survival was reduced at 4000 ppm and higher. F1 mating reduced F2 litter size and live pup weight at 1000 ppm and above (ca. 200 mg/kg bw and day). At necropsy, body weight of F1 males and females was reduced starting at 4000 ppm. Dimethylformamide-

treated pups (both F1 and F2) and F1 adults had cranial and sternebral skeletal malformations. A NOAEL was not established (Fail *et al*., 1998).

Developmental toxicity

Inhalation exposure of Sprague-Dawley rats to 287 ppm dimethylformamide (only one concentration tested) on gestational days 0 – 1, 4 – 8, 11 – 15, and 18 – 19 or 0 – 3, 6 – 10, and 11 – 18 caused foetotoxicity and embryolethality (Hellwig *et al*., 1991). Groups of pregnant CD-rats were exposed by inhalation to either 0, 30, or 300 ppm dimethylformamide from gestation day 6 through 15. In the rats exposed to 300 ppm, both maternal weight gain during gestation and fetal weights were lower than those of the controls. Dimethylformamide did not produce malformations in the rat fetus. The NOAEL for both fetal and maternal toxicity in rats was 30 ppm (Lewis *et al*., 1992).
A clear teratogenic effect was shown in rabbits exposed on gestational days 6 through 19 to dimethylformamide at 450 ppm. Marginal effects were observed at 150 ppm in the presence of overt maternal toxicity. The NOAEL for maternal and developmental toxicity in the inhalation study with rabbits was 50 ppm (Hellwig *et al*., 1991).

Administration of dimethylformamide by gavage on gestation days 6 through 15 led to an increase in malformations in Sprague-Dawley rats and NMRI mice at doses starting from 500 mg/kg body weight and day in the absence of overt maternal toxicity. The LOAEL (reduced fetal body weights) was 182 mg/kg body weight in mice and 166 mg/kg body weight in rats; lower doses were not tested (Hellwig *et al*., 1991). Sprague-Dawley rats were given 0, 50, 100, 200, and 300 mg dimethylformamide/kg body weight and day by gavage on gestation days 6 through 20. Maternal toxicity was indicated by depressions in weight gain and food consumption at doses of 100 mg/kg body weight and above. Fetal toxicity was indicated by decreased fetal body weight at doses of 100 mg/kg body weight and above, and by increased incidences of two skeletal variations (absent or poorly ossified supraoccipital and sternebrae) at 200 and 300 mg/kg body weight. The NOAEL for maternal and developmental toxicity in the oral study with rats was 50 mg/kg body weight and day (Saillenfait *et al*., 1997).

Rats were dosed epicutaneously on gestation days 6 through 15 or on gestation days 1 through 20 at dose levels of up to 2 ml dimethylformamide/kg body weight per day. Body weight, weight gain and pregnancy rate were reduced in those rats receiving 2 ml dimethylformamide/kg body weight on days 6 to 15. A reduction in the number of live fetuses and in fetal weight, as well as an increase in postimplantation loss, were also observed at this dose level. Similar but more pronounced effects were observed in rats dosed on days 1 through 20 with 2 ml/kg body weight. The LOAEL was 1 ml/kg body weight (950 mg/kg body weight). No other dose-related effects were found in this study (Hansen and Meyer, 1990). After dermal administration of dimethylformamide, a dose-dependent increased

incidence of malformations was observed in rats at 94, 472 and 944 mg/kg body weight and day in the absence of overt maternal toxicity. The LOAEL for dermal administration of dimethylformamide to rats is 94 mg/kg body weight and day (Hellwig *et al*., 1991). In rabbits, dermal administration of dimethylformamide led to a clear teratogenic effect in the presence of slight maternal toxicity at 400 mg/kg body weight and day. The 200 mg/kg body weight and day dose appeared to be the NOAEL for rabbits after dermal application (Hellwig *et al*., 1991). [At 100 mg/kg body weight anomalies were observed in 3 fetuses of 2 litters. As no anomalies were observed at 200 mg/kg body weight, these results were not taken into consideration.]

Effects in Man

In workers exposed to dimethylformamide the liver has been shown to be the target organ associated with disorders of the digestive system. Symptoms include abdominal pain, anorexia, incoordination, and jaundice, as well as nausea, vomiting, and diarrhoea. Changes in both liver function with increases in hepatic enzymes in the serum (AST, ALT, γ-GT, and AP) and morphology have been observed. In addition, alcohol intolerance reactions, characterized by flushing of the face, dizziness, nausea, and tightness of the chest have been widely reported among dimethylformamide-exposed workers (DFG 1997; WHO, 2001).

Tables 2 and 3 summarizes effects of dimethylformamide exposure in workers in Asia and in Europe, respectively.

Studies performed in Asia

Table 2: Effects of dimethylformamide exposure in workers in Asia

Collective examined		DMF in the air [mean±SD (range)]	NMF in urine	Results	Reference
Case reports					
9	Workers in synthetic leather factory	0–5 ppm, personal sampling, TWA	0.4–19.56 mg/d	**No effects on serum biochemistry** (ALT, AST, AP, γ-GT); **Alcohol intolerance** (6/11 workers less tolerant to alcohol than before but no typical signs of alcohol intolerance)	Yonemoto and Suzuki, 1980 (Japan)
10	Workers	2.5–10.4 ppm (geometric means), personal sampling	24.7±5.4 mg/g creat.	**No effects on liver enzymes** (AST, ALT, AP)	Sakai *et al*., 1995 (Japan)
13	Workers	10.3–42.1 ppm (STEL, 15 min)	–	**Abdominal colic** (7/13); **Abnormal liver function** (3/13; not further specified); **Facial flushing** (3/13)	Yang *et al*., 1994 (Abstract) (Taiwan)

Collective examined		DMF in the air [mean±SD (range)]	NMF in urine	Results	Reference
Cohort studies					
143	Controls	–	–	Alcohol intolerance: 10/40 (25%)	Cai *et al.*, 1992 (China)
207	All workers in the production of polyurethane plastics	4.5 ppm, stationary sampling, 8-h TWA	–	**Group of all exposed workers:** **Symptoms** (eye irritation, dimmed vision, nasal irritation, sore throat, unusual taste, dizziness, nausea, vomiting, tightness in the chest, shortage of breath, abdominal pain, dry mouth, proneness to stumbling while walking, rough skin, frequent cough) **Liver enzymes** (AST, ALT, γ-GT) only in singular cases above normal range	
59	laboratory B	0.2 ppm	–	0.1–1.9 ppm: No increased alcohol intolerance: 1/7 (14%)	
23	laboratory A	0.4 ppm	–		
17	shoe-sole production	0.7 ppm	–		
65	polyurethane production	**3.9 ppm**	–	**2.0–4.9 ppm**: **Increased alcohol intolerance**: 5/7 (71%)*	
43	synthetic leather production	**9.1 ppm**	–	**>5 ppm: Increased alcohol intolerance**: **5–9.9 ppm**: 4/5 (80%)* **≥10 ppm**: 6/7 (86%)**	
176	All workers	**11.6±13.8** (0.1–86.6) ppm, area and personal sampling (n=45)	–		Luo *et al.*, 2001 (Taiwan)
74	Workers in synthetic leather and resin factory	2.9±1.1 (0.5–5) ppm	–	Abnormal liver function (AST, ALT, γ-GT) (18%)	
37		**6.4±0.7** (5.98.2) ppm	–	**Abnormal liver function (27%);** adjusted OR 1.62 (0.61–4.28) compared to low DMF exposure group	
65		**24.6±15.6** (11.2–86.6) ppm	–	**Abnormal liver function (37%);** adjusted OR 2.93 (1.276.8) compared to low DMF exposure group, **Significant effect on individual liver enzymes (**AST, γ-GT**), Chronic liver diseases**	
76	Workers in synthetic leather factory with enhanced prevalence of liver injury in workers	<10 ppm	–	ALT (14±6 IU/L); 6.4% of the workers with alcohol consumption >24 g/d	Wang *et al.*, 1991 (China)
83		**10–40 ppm**	–	**ALT increased** (18±7 IU/L); **CPK increased** (indicator of muscle damage); **3.7% of the workers with alcohol consumption >24 g/d**	
24		**25–60 ppm**	–	**ALT increased** (25±6 IU/L); Incidence of abnormal ALT values sign. increase (>35 IU/l); **CPK increased**; **no workers with alcohol consumption >24 g/d**	

Abbreviations: AP: alkaline phosphatase; AST: aspartate aminotransferase [=(S)GOT]; ALAT: alanine aminotransferase [=(S)GPT]; BUN: blood urea nitrogen; CPK: creatinine phosphokinase; DMF: N,N-dimethylformamide; γ-GT: γ-glutamyltranspeptidase; LAP: leucin amino peptidase; LDH: lactate dehydrogenase; NAG: N-acetyl-α-D-glucosamidase; NMF: N-methylformamide; OCT: ornithine carmamyl transferase; SGOT, SGPT: liver transaminases

In a biological monitoring study with 9 workers in Japan exposed up to 5 ml/m^3, the daily amount of NMF excreted ranged from 0.4 to 19.56 mg. The values for AST, ALT, alkaline phosphatase and γ-GT were reported to be in the normal range. Among 11 workers of this section, six claimed that they were less tolerant to alcohol beverages than before (Yonemoto und Suzuki 1980).

In another biological monitoring study with 10 workers in Japan exposed up to 10.4 ml/m^3, corresponding to 24.7±5.4 mg NMF/g creatinine, the values for ALT, AST and alkaline phosphatase were also in the normal range (Sakai *et al.*, 1995).

An abstract reported that among 13 workers in Taiwan, 7 had abdominal colic sustained for more than three days, 3 had abnormal liver function and 3 had facial flushing. Levels of 10.3 ppm to 42.1 ppm dimethylformamide were detected for short-term exposures of 15 minutes in different departments (Yang *et al.*, 1994).

In Chinese workers exposed to a mean concentration of 4.5 ppm dimethylformamide, a dose-dependent increase in subjective symptoms, especially during work (e.g. dimmed vision and unusual taste), and digestive system-related symptoms (e.g. nausea and abdominal pain) were reported in the past 3-month period. The prevalence rate of alcohol intolerance complaints among male (assumedly) social drinkers was also elevated in relation to dimethylformamide exposure, being significant at concentrations of 3.9 ppm (range 2.0–4.9 ppm) and higher. Values for AST and ALT exceeded normal values only in two workers. Values for γ-GT did not exceed normal ranges in any worker (Cai *et al.*, 1992). This study indicate increased alcohol intolerance reactions in Chinese workers with dimethylformamide concentrations of 3.9 ppm and no effects on liver enzymes with concentrations up to 9 ppm. As no biological monitoring was performed, the internal dose due to additional dermal uptake of dimethylformamide cannot be estimated.

In Taiwanese workers exposed to 24.6±15.6 ppm dimethylformamide, an increased incidence of chronic liver disease and liver abnormalities (37%) as well as increased values for liver enzymes (AST, γ-GT) was observed compared to moderate (6.4±0.7 ppm) or low (2.9±1.1 ppm) exposed workers. The incidences for liver abnormalities were 27% and 22% for the mid and low exposure group (Luo *et al.*, 2001). As a non-exposed control group is missing, the effects observed in the mid and low exposure group cannot be evaluated.

In a further study with Chinese workers, increased ALT, reduced alcohol consumption and indications for muscle damage were observed in workers exposed to dimethylformamide in concentrations of more than 10 ppm (up to 60 ppm), compared to workers exposed to concentrations below 10 ppm (Wang *et al.*, 1991). Since a non-exposed control group is missing, the effects observed in workers exposed to dimethylformamide below 10 ppm cannot be evaluated.

Studies performed in Europe

Table 3: Effects of dimethylformamide exposure in workers in Europe

Collective examined		DMF in the air [mean±SD (range)]	NMF in urine	Results	Reference
Case reports					
102	Workers using DMF as a solvent	> 10 ppm (max. 200 ppm)	--	**Alcohol intolerance reactions**	Lyle *et al.*, 1979
		<10 ppm	<10 µg/l (94%)		
13	Workers in synthetic leather production	5–20 ppm	–	**Symptoms** (irritation of eyes and upper airways, digestive tract 11/13; nausea 8/13); **Hepatic pain** (4/13); **Alcohol intolerance** (8/13)	Tomasini *et al.*, 1983 (Italy)
Cohort studies					
126	All workers in acrylic fibre plant	**4.1**±7.4 (<0.1–37.9) ppm; personal air sampling 8-h TWA	**14.9**±18.7 (0.9–100) **mg/l**; **9.1**±11.4 (0.4–62.3) **mg/g creat.**	**All workers** **Synergistic effect with alcohol** (questionnaire), **Effects on liver enzymes** (AST, γ-GT)	Wrbitzky and Angerer, (1998); Wrbitzky, (1999) (Germany)
55	finishing	1.4±2.2 (<0.1–13.7) ppm	4.5±4.3 (0.6–19.9) mg/g creat.	**"Low exposure"** **Effects on liver index** (ALT, AST, γ-GT) in workers drinking alcohol	
12	dyeing	2.5±3.1 (0.1–9.8) ppm	6.7±5.4 (0.8–17.2) mg/g creat.	**"High exposure"** **No effects on liver index** (ALT, AST, γ-GT) in workers not drinking alcohol; **Reduced alcohol consumption** in workers drinking alcohol	
28	dry spinning	6.4±9.6 (0.8–36.9) ppm	11.6±13.1 (0.9–62.3) mg/g creat.		
30	wet spinning	7.3±10.2 (0.3–37.9) ppm	16.0±15.9 (0.4–54.0) mg/g creat.		
54	Controls	–	–		
28	Workers in acrylic fibre plant	**6** (4–8) ppm, no information on sampling method, 8-h TWA	22.3 mg/l	**No significant effects on liver enzymes** (ALT, AST, γ-GT, AP)	Catenacci *et al.*, 1984 (Italy)
26		1 (0.6–1.6) ppm	7 mg/l		
54	Controls (matched)	–	–		
22	Workers in acrylic fibre factory; co-exposure to acrylo-nitrile (ACN)	**4.5** (0.4–15.3) ppm, stationary sampling	**20 (20–63) mg/g creat.**	**No abnormal effects on serum biochemistry** (bilirubin, thymol, cholesterol, total protein, albumin, ALT, AST, AP, γ-GT, OCT, cholinesterase); **Signs of alcohol intolerance in some workers** (after peak exposure; no further	Lauwerys *et al.*, 1980 (Belgium)

Collective examined		DMF in the air [mean±SD (range)]	NMF in urine	Results	Reference
28	Controls (not matched)	–	–	information given)	
75	Workers in synthetic leather factory	**7**±0.7 (1.6–13) ppm **6**±0.6 (0.7–12) ppm, stationary sampling, 8-h TWA	[13.6±3.3 mg/l; 13.4±3.2 mg/g creat.][1)]	**Effect on liver enzymes** (ALT, AST, γ-GT, AP); **Abnormal liver function** (23% exposed workers, 4% controls); **Alcohol intolerance** (50% exposed workers) **Alcohol consumption of 20–40 g/day reduced**	Fiorito *et al.*, 1997 (Italy)
75	Controls (matched)	–	–		
100	Workers in synthetic leather production	**7** (2.6–19) ppm, personal sampling, TWA	–	**Symptoms** (headache, nausea, loss of concentration, dizziness, eye irritation, gastritis, hepatic insufficiency); **Abnormal values of liver enzymes** (γ-GT significant; AST and AST not significant); **Alcohol intolerance** (39/100; intolerance after ingestion of wine some hours after work); **Alcohol consumption reduced**	Cirla *et al.*, (1984) (Italy)
100	Controls (carefully matched)	–	–		

Abbreviations: see Table 2

1) analytical method underestimates exposure compared to Wrbitzky and Angerer (1998)

Facial flushing and other symptoms were reported by 19 of a group of 102 men who worked with dimethylformamide. Twenty-six of the 34 episodes occurred after the workers had consumed alcoholic drinks, and twenty-eight episodes were reported after dimethylformamide in the air exceeded 20 ppm. During this time, the maximum concentration recorded was up to 200 ppm. However, the three highest recorded concentrations of dimethylformamide in air did not coincide with reports of facial flushing (Lyle *et al.,* 1979).

In a study of 13 workers exposed to dimethylformamide and other solvents in a factory producing synthetic leather, concentrations of dimethylformamide varied between 14 und 60 mg/m^3 (5 – 20 ml/m^3). Eleven workers complained of irritation of their eyes and upper airways, 8 reported nausea, 8 more alcohol intolerance and 4 hepatic pain (Tomasini *et al.,* 1983).

Thirty cases of dimethylformamide poisoning have been reported after occupational exposure. Some of the symptoms (alcohol intolerance, abdominal pain and increased levels of γ-GT) could be observed at dimethylformamide concentrations below 10 ppm, even when skin contamination had been avoided. However, most cases were consequences of prolonged and/or repeated skin contaminations. The authors conclude that the OEL of 10 ppm does not prevent all dimethylformamide effects (Garnier *et al.,* 1992).

In a recent cross-sectional study in Germany, 126 workers were exposed to mean dimethylformamide concentrations of 4.1±7.4 ppm. Mean concentrations in different work

areas were 1.4±2.2 ppm (finishing), 2.5±3.1 ppm (dyeing), 6.4±9.6 ppm (dry spinning), and 7.3±10.2 ppm (wet spinning) corresponding to NMF excretion in urine of 4.5±4.3 mg/g creatinine, 6.7±5.4 mg/g creatinine, 11.6±13.1 mg/g creatinine, and 16.0±15.9 mg/g creatinine. The anamnestic data of 123 exposed workers indicated significant effects on flush symptoms (69.9 %; control 3.8 %), complaints after alcohol consumption (71.5 %; control 3.8 %) and less alcohol consumption since employment in the factory (14.7 %; control 0 %). Flush symptoms were reported in the group with higher levels of dimethylformamide exposure (66.2 %) as well as in the group with lower levels of exposure (70.9 %). In the dimethylformamide-exposed group, 22 (17.8 %) persons stated previous liver diseases, including increased liver function values, as opposed to only 7 (13.2 %) in the control group. Of these 22 dimethylformamide-exposed persons, 14 worked in the areas of higher exposure and 7 in areas of lower exposure. The results of laboratory investigations yielded statistically significant values in the exposed groups for γ-GT and AST. To test dose-dependent effects on the liver, the total collective was divided into groups with no exposure to dimethylformamide (controls), lower exposure, and higher exposure. Based on the information given by Wrbitzky and Angerer (1998) the lower exposure group comprised the workers of "finishing" and the higher exposure group the workers of "dyeing", "dry spinning", and "wet spinning". In addition, the total collective was divided according to the alcohol consumption (no alcohol; <50 g alcohol/d; >50 g alcohol/d). The liver index (AST, ALT and γ-GT, combined) was increased significantly with increasing alcohol consumption; additional dimethylformamide exposure further increased the liver index to a small extent.

23 of the 70 workers of the “higher exposure group” did not consume alcohol and did not show a significant increase in the liver index (Wrbitzky, 1999). Exposure of this higher group was up to 7.3±10.2 ppm ppm (16.0±15.9 mg/g creatinine) (Wrbitzky and Angerer, 1998). Due to the high number of workers drinking alcohol during shift (61.8 %) and due to the high amount of daily alcohol intake (on average 50 g/day), the results with workers who consumed alcohol are not considered for OEL setting. In addition, the reported alcohol intolerance reactions cannot be used for OEL setting as these data are anamnestic and no information is given under which past exposure conditions these reactions were elicited.

In a further experiment conducted at the end of the working shift with 17 workers included in the study by Wrbitzky (1999), intake of 0.66 l beer (about 33 g alcohol) did not elicit intolerance reactions. The group consisted of 3 workers with no alcohol consumption, 4 workers with a consumption of 0.5 l beer/day (about 25 g alcohol/d) and 10 workers with a consumption of 1 to 3 l beer/day ($\underline{\geq}$ 50 g alcohol/day). The mean NMF concentration in urine was 19±25.9 mg/l urine (Angerer and Drexler 2005; personal communication).

54 Workers from two departments of an acrylic fibre plant were exposed to 1 or 6 ppm dimethylformamide for more that 5 years. No significant effects on ALT, AST, γ-GT or alkaline phosphatase could be detected compared to 54 matched controls (Cattenacci *et al.*,

1984). The authors did not mention alcohol intolerance reactions. This short communication indicates no increased liver values at 6 ppm (maximum 8 ppm) dimethylformamide, corresponding to 22 mg NMF/l urine.

A study was carried out on 22 workers exposed to dimethylformamide in an acrylic fibre factory and on 28 control workers. No information was available whether the controls were matched. Only one exposed worker reported to be a moderate consumer of alcoholic beverages of more than 3 glasses of beer per day. The integrated exposure to dimethylformamide varied between 92.6 mg x h/m^3 on Tuesday (about 15.4 mg/m^3 or 5 ppm for a 6-h shift) and 50.2 mg x h/m^3 on Thursday (about 8.3 mg/m^3 or 2.7 ppm). The corresponding excretion of NMF in urine was 63.0 mg/g creatinine (Tuesday) and 20.5 mg/g creatinine (Thursday). Plasma analysis (e.g. AST, ALT, AP, γ-GT) performed on Friday morning revealed no significant difference between exposed and control workers. The authors conclude that if concentrations of NMF in urine samples collected at the end of the workshift do not exceed 40 to 50 mg/g creatinine (correlating to 13 mg/m^3 or 4.3 ppm) the exposure is probably safe with regard to the acute and long-term action of dimethylformamide on liver function (Lauwerys *et al.*, 1980**)**. However, as only stationary airborne concentrations were measured, the individual exposure to dimethylformamide in the air may have been higher. Furthermore, plasma analysis was performed on Friday morning which indicates that 20.5 mg NMF/g creatinine measured on Thursday has no effect on liver enzymes on Friday morning. That the relatively high exposure on Tuesday may have had an effect on liver enzymes cannot be ruled out. The authors further indicate that the exposure conditions documented in the study may still be associated with signs of alcohol intolerance in some workers.

In a cross-sectional study in Italy, 74 workers exposed to median dimethylformamide concentrations of 18.7 mg/m^3 (6 ppm) in production (10 stationary air samples) and 21.5 mg/m^3 (7 ppm) in washing (22 stationary air samples) were examined. Biological monitoring was performed in 22 workers, resulting in post-shift values of 13.6±3.3 mg NMF/l urine or 13.4±3.2 mg NMF/g creatinine and in a maximum value of 126 mg/g creatinine. The wide range indicated that occasional overexposure was possible. Skin absorption of dimethylformamide was assumed to occur not only accidentally but also potentially through gloves and unprotected skin. 40% of workers reported disulfiram-like symptoms in combination with alcohol consumption such as face flushing, palpitations, headache, dizziness, body flushing and tremors, 50% of the workers showed gastrointestinal symptoms like stomach pain, nausea, loss of appetite. Serum analysis revealed that the mean values of liver function indices (ALT, AST, γ-GT, AP) were significantly higher in the exposed group compared to controls, as was the percentage of workers with abnormal liver function. 22.7% of the workers had abnormal transaminase values compared to 4% in controls. Co-variance analysis (ANCOVA) revealed that enzyme levels were significantly higher in exposed workers than in controls after data were corrected for age, alcohol consumption, body mass

index, and cholesterol levels. Most of the workers (52 of 75) consumed little (<20 g/day) or no alcohol (Fiorito *et al.*, 1997). This study shows a high percentage of alcohol intolerance reactions, gastrointestinal symptoms and abnormal liver functions in workers exposed to median dimethylformamide concentrations of 6 to 7 ppm, corresponding to about 13.5 mg NMF/l urine. The limitations of this study as indicated by the authors are that only a few exposure measurements in the air were performed, and biological monitoring was done in only 30% of the workers. Furthermore, only stationary measurement of dimethylformamide in the air was performed and the method for analysing NMF in urine gave values much lower than those obtained with other methods e.g. that used by Wrbitzky and Angerer (1998). Therefore, higher exposure values have to be assumed.

In another study in Italy 100 dimethylformamide-exposed workers from the mixing and spreading department were compared with 100 matched controls. Subjects from the drying and finishing stages, who were irregularly or slightly exposed, were rejected. Subjects with a work history of possible high accidental exposure in the past or who had undertaken activities involving high exposure were not considered. The control group was selected by a careful pair-matching; the customary alcohol intake was particularly considered in exposed and control workers. Dimethylformamide exposure in the air was measured by personal sampling and revealed a mean concentration of 7 ml/m^3 with a range from 3 to 19 ml/m^3. The mean duration of exposure was 5 years (range 1 to 15 years). Among symptoms studied, headache, dyspepsia and digestive impairment of hepatic type could be specifically associated with chronic dimethylformamide exposure. 32/100 exposed workers reduced alcohol drinking or stopped drinking at all. There was a high incidence of disulfiram-ethanol-reactions in the exposed group where 39 subjects experienced this syndrome after alcohol ingestion on one or more occasions. In all episodes an ingestion of small amounts of wine some hours after work was followed by symptoms like flushing of the skin, dizziness, nausea, sometimes tightness of the chest and perspiration. γ-GT was the only biochemical test with a statistically significant increase of abnormal values in 25 exposed workers compared to 10 controls. 5 of the 25 exposed workers with abnormal γ-GT were non-drinkers (20%), 11 moderate drinkers (44%) and 9 heavy drinkers (36%). In the 10 control persons with abnormal γ-GT, 1 was a non-drinker (10%), 3 moderate drinkers (20%) and 6 heavy drinkers (60%). The authors therefore conclude that not only alcohol but also dimethylformamide has an influence on γ-GT. The incidences of abnormal values of AST and ALT were slightly but not statistically significantly increased in exposed workers compared to controls. However, a comparison, if normal values of AST and ALT were increased compared to controls was not performed. The authors think that absorption of dimethylformamide through the skin contributed to personal exposure even under normal working conditions (Cirla *et al.*, 1984). The study indicated alcohol intolerance reactions and effects on the liver (γ-GT) at mean concentrations of 7 ppm with a maximum of 19 ppm. Final conclusions about increased transaminase values are not

possible. Furthermore, contribution of dermal absorption to the internal exposure cannot be evaluated as no biological monitoring was performed.

Summary of the effects in man

Effects on the liver

The results show no increases in serum hepatic enzymes at mean concentrations of 7 ppm (Catenacci *et al*., 1984; Lauwerys *et al*., 1980; Yonemoto and Suzuki, 1980) or up to 10 ppm (Cai *et al*., 1992; Sakai *et al*., 1995). Workers without alcohol consumption showed no significant increase in liver enzymes up to 7.3±10.2 ppm (Wrbitzy and Angerer 1998; Wrbitzky 1999). In these studies, an excretion of NMF in urine was measured as 16±16 mg/g creatinine (Wrbitzky and Angerer 1998), 22.3 mg/l urine (Catenacci *et al*., 1984), 22 mg/g creatinine (Lauwerys *et al*., 1980), and 24.7±5.4 mg/g creatinine (Sakai *et al*., 1995).

On the other hand there are results indicating effects at concentrations of about 7 ppm and below. The data from Wrbitzky (1999) indicate an increase in γ-GT (indicating alcohol consumption) and AST (indicating dimethylformamide exposure) in the group of all workers exposed to 4.1±7.4 ppm dimethylformamide. Differentiation of the workers by alcohol consumption and dimethylformamide exposure indicated a synergistic effect of dimethylformamide on the liver index (AST, ALT and γ-GT combined) in combination with alcohol consumption. Two studies on workers of synthetic leather factories in Italy reported increased serum levels of hepatic enzymes at exposure concentrations of 7 ppm (maximum 13 and 19 ppm) (Cirla *et al*., 1984; Fiorito *et al*., 1997). The effects may have been results of high dermal exposure to dimethylformamide.

Alcohol intolerance reactions

The most prominent effects are alcohol intolerance reactions, characterized by flushing of the face, dizziness, nausea, and tightness of the chest, which have been widely reported among dimethylformamide-exposed workers. Intolerance reactions are usually reported to occur after work (Lauwerys *et al*., 1980) even when only small amounts of wine were consumed (Cirla *et al*., 1984). The reason for such alcohol intolerance reactions (disulfiram type) is assumed to be the inhibitory effect of dimethylformamide on alcohol and aldehyde dehydrogenase, resulting in an accumulation of acetaldehyde. Acetaldehyde accumulation suppresses macrophage function in vitro, leading to a suppression of TNF-alpha release, which plays a role in modifying acute hepatic inflammation in rats (Nakamura *et al*., 2004). Differences in alcohol sensitivity are well known (Chan, 1986) based on genetic polymorphisms of the enzymes alcohol dehydrogenase and aldehyde dehydrogenase (see Quertemont, 2004). In European populations about 5% and in Asian populations up to 90% of the people belong to this sensitive group. Due to this difference in sensitivity, studies performed in Europe are

evaluated separately from studies performed in Asia. In a cohort of workers in China, increased incidences of alcohol intolerance reactions have been reported with mean dimethylformamide concentrations of 3.9 ppm (minimum 2 ppm) (Cai *et al.*, 1992). In cohorts of workers in Europe intolerance reactions were reported at mean or median dimethylformamide concentrations at 7 ppm or lower (Cirla *et al.*, 1984; Lauwerys *et al.*, 1980; Wrbitzky, 1999). However, intolerance reaction were reported if they ever occurred. Such effects can therefore not be correlated to the exposure conditions measured. In addition, there are indications that alcohol intolerance reactions occurred after repeated or long-term dermal contact to dimethylformamide (Garnier *et al.*, 1992) or after cleaning with high peak concentrations of dimethylformamide (Lauwerys *et al.*, 1980). The database available does not provide sufficient information to quantify the conditions under which intolerance reactions are elicited; derivation of an OEL based on this endpoint is not possible.

Genotoxicity

Reports of chromosomal damage in workers exposed to dimethylformamide either failed to take into account smoking as a bias factor or were incompletely documented (IARC, 1999).

In 85 male workers in epoxy resin, synthetic leather, and printed circuit board manufacturing plants, exposure to dimethylformamide was not associated with SCE frequency (Cheng *et al.*, 1999).

A cytogenetic study with 26 workers occupationally exposed to dimethylformamide (max. 8 ppm) and high concentrations of acrylonitrile (max. 17.6 mg/m^3) and 26 matched control subjects revealed significant increases in CA, SCE and UDS (Major *et al.*, 1998). Due to the high co-exposure to acrylonitrile, the relevance of dimethylformamide for the cytogenetic effects remains questionable.

Carcinogenicity

Case reports of testicular cancer in aircraft repair and leather tannery facilities suggested possible association with dimethylformamide. Further research has failed to confirm this relationship. A screening effort at a leather tannery, where a cancer cluster had been noted, indentified no additional cases. Mortality and cancer incidence studies and nested case-control investigations of testicular cancer and cancer at several other anatomical sites were conducted at several facilities; no convincing association with exposure to dimethylformamide was noted. The data were evaluated by IARC as "inadequate evidence" in humans for the carcinogenicity of dimethylformamide (IARC, 1999).

Reproductive toxicity

In 12 dimethylformamide-exposed workers in a synthetic leather factory, both conventional microscopy and computer-assisted semen analysis showed that sperm motility was significantly reduced compared to 8 matched controls. Motility parameters were related to urinary NMF in a dose-response manner but were not related to airborne dimethylformamide concentration. The authors conclude that the responsible toxicant for the alterations of sperm function could be the active NMF metabolite instead of dimethylformamide, but this conclusion warrants a further complete investigation (Chang *et al.*, 2004).

Biological monitoring

Dimethylformamide is extensively absorbed through the skin, its metabolism and kinetics are well known, and urinary metabolites exist that can be accurately measured. As a result, biological monitoring has been extensively used in the assessment of the absorbed amounts in occupationally exposed populations. The metabolite most often analysed is *N*-methylformamide (NMF) which represents an index of daily exposure. Further research focuses on the metabolite *N*-acetyl-*S*-(*N*-methylcarbamoyl)cysteine (AMCC) which has a longer half-time (about 23 h) than NMF and whose formation in humans is more closely related to dimethylformamide toxicity. AMCC could be used for monitoring industrial exposure over several workdays, by its measurement in urine samples collected at the end of the working week.

Recent studies on biological monitoring are summarized in Table 4. Only such studies are listed in which a correlation equation was calculated from dimethylformamide exposure in the air and NMF or AMCC excretion in urine. For comparison, the exposure concentration of dimethylformamide in the air was extrapolated to 10 ppm.

Extrapolated to a dimethylformamide concentration of 10 ppm (30 mg/m^3) in the air, the values of NMF in urine varied between 18.2 mg/l (Kawai *et al.*, 1992) to 61 mg/g creatinine (Sakai *et al.*, 1995). The variation may be due to different working conditions (exposure concentration, working load, use of protection equipment, amount of dermal exposure). Also alcohol consumption increases excretion of NMF (Kim *et al.*, 2004). Corresponding to 10 ppm, a biological limit value was set with 35 mg NMF/l urine (DFG, 2001). Based on the data available (table 4), 5 ppm would correspond to 9 to 25 mg NMF/l urine, in mean to about 15 mg NMF/l urine.

Data on monitoring AMCC obtained in different studies are inconsistent. Further information and research is needed before a well-founded biological limit value based on this metabolite can be set.

Table 4: Biomonitoring studies on dimethylformamide-exposed workers

Exposed group	DMF in the air	NMF in urine	AMCC in urine	Reference
Asia				
116 workers	**10 ppm**[1)] [1.8 ppm][2)]	**18.2 mg/l**[3)]	–	Kawai *et al*., 1992
345 workers	**10 ppm**[1)]	24.2 mg/g creat. [3)] 37.7 mg/l (inhalation only) **39.1 mg/g creat.** [3)] **45.3 mg/l** (dermal + inhal.)	–	Yang *et al*., 2000
59 workers	**10 ppm**[1)] [4.1 ppm] [2)]	**38.4 mg/l**[3)], **39.4 mg/g creat.**[3)]	–	Wang *et al*., 2004
144 workers	**10 ppm**[1)] [8.8 ppm] [2)]	**53.4 mg/l**[3)]	8.0 mg/l [3)] (sampling time not specified)	Kim *et al*., 2004
10 workers	**10 ppm**[1)] [2.5 - 10.4 ppm][2)]	**61.9 mg/g creat.**[3)]	55.3 mg/g creat. [3)] (end of shift) 82.7 mg/g creat. [3)] (next morning)	Sakai *et al*., 1995
Europe				
125 workers	**10 ppm**[1)] [4.1 ppm] [2)]	**24.3 mg/l**[3)]	–	Wrbitzky and Angerer 1998
23 workers	**10 ppm**[1)]	**27.9 mg/l**[3)]	69.2 mg/l [3)] (next morning)	Käfferlein *et al*., 2000
25 workers	**10 ppm**[1)] [4.5 ppm] [2)]	**35.4 mg/g creat.**[3)]	26.1 mg/l [3)] (end of shift), 31.9 mg/l [3)] (next morning)	Imbriani *et al*., 2002
26 workers	**10 ppm**[1)] [5.5 ppm] [2)]	**39.6 mg/l**[3)]	(no correlation possible)	Casal Lareo and Perbellini 1995

[1)] exposure concentration extrapolated

[2)] exposure concentration measured in the study

[3)] data extrapolated from the corresponding equation of the regression line

[4)] value taken from a relationship between dimethylformamide in the air and NMF in urine

Recommendation:

Dimethylformamide induces liver damage in man and in experimental animals. In a 2-year inhalation study, 25 ppm was the NOAEL for rats and the LOAEL for mice with minimal effects on the liver (Malley *et al.*, 1994). A benchmark dose calculation resulted in a BMDL of 7.8 and a BMD of 14.7 ppm for male and female mice combined. Developmental effects are observed at higher concentrations with NOAELs for maternal and developmental toxicity of 30 ppm in rats (Lewis *et al.*, 1992) and 50 ppm in rabbits (Hellwig *et al.*, 1991Irrespective of the data in animals, the effects in man are considered the best available basis for setting exposure limits. Most of the studies indicate no significant effects on liver enzymes up to 7 or 10 ppm corresponding to about 25 mg NMF/l urine. In workers without any alcohol consumption no increase in serum hepatic enzymes was observed at concentrations of 7±10 ppm, corresponding to 16±16 mg/g creatinine (about 24 mg NMF/l urine) (Wrbitzky, 1999). In combination with alcohol consumption, dimethylformamide exposure even of 7 ppm and below was reported to elicit intolerance reactions like highly visible facial flushing accompanied by other objective and subjective symptoms of discomfort. Since alcohol intolerance reactions have been reported when alcohol was consumed after the end of the work day (Cirla *et al*., 1984; Lyle *et al.*, 1979), this effect should be avoided. Sensitive individuals (about 5% of European populations and up to 90% of Asian populations) have a higher risk for alcohol intolerance reactions being reported even at concentrations of about 4 ppm. The database available, however, provides no reliable NOAEL for eliciting such alcohol intolerance reactions.

Based on the human data on liver enzymes, an OEL of 10 ppm (25 mg NMF/l urine) is considered protective provided that excessive dermal uptake and alcohol consumption are avoided. However, taking into account the results from the effects on the liver in a long-term toxicity study in mice, for which a BMDL of 7.8 ppm and BMD of 14.7 ppm was calculated, an OEL of 5 ppm is proposed. The OEL of 5 ppm also protects from developmental toxicity for which the NOEL was 50 ppm.

Dimethylformamide shows irritating properties in the eyes but not on the skin of laboratory animals. In experiments with volunteers exposed to 20 ppm dimethylformamide for 8 hours, no indications of irritation were observed. Therefore, an STEL of 10 ppm is considered to protect from local irritation.

Dermal uptake of dimethylformamide (liquid or gaseous) contributes significantly to systemic toxicity. A “skin” notation is considered necessary. Due to the significant dermal uptake of dimethylformamide, biological monitoring is highly recommended. A 8-h TWA of 5 ppm corresponds to a biological value (post-shift) of about 15 mg N-methylformamide/l urine.

At the levels recommended, no measurement difficulties are foreseen.

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