The MAK Collection for Occupational Health and Safety

Dimethylformamide

MAK Value Documentation, addendum – Translation of the German version from 2016

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Keywords: N,N-dimethylformamide; liver; carcinogenicity; peak limitation; developmental toxicity; MAK value; maximum workplace concentration;

Citation Note: Hartwig A, MAK Commission. Dimethylformamide. MAK Value Documentation, addendum – Translation of the German version from 2016. MAK Collect Occup Health Saf [Original edition. Weinheim: Wiley-VCH; 2017 Jan;2(1):7-20]. Corrected republication without content-related editing. Düsseldorf: German Medical Science; 2026. https://doi.org/10.34865/mb6812e6017_w

Republished (online): 07 Aug 2026

Originally published by Wiley-VCH Verlag GmbH & Co. KGaA; https://doi.org/10.1002/3527600418.mb6812e6017

Addendum completed: 25 Feb 2015

Published (online): 26 Jan 2017

The commission established rules and measures to avoid conflicts of interest.

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Dimethylformamide

[68-12-2]

Supplement 2016

MAK value (2005)	**5 ml/m³ (ppm) ≙ 15 mg/m³**
Peak limitation (2011)	**Category II, excursion factor 2**
Absorption through the skin (1969)	**H**
Sensitization	**–**
Carcinogenicity (2015)	**Category 4**
Prenatal toxicity (1989)	**Pregnancy Risk Group B**
Germ cell mutagenicity	**–**
BAT value (2006)	**35 mg N-methylformamide plus N-hydroxymethyl-N-methylformamide/l urine**

For dimethylformamide, documentation is available from 1992 (documentation "Dimethylformamide" 1997, a translation of the 1992 German) and a supplement from 2006 (supplement "Dimethylformamide" 2010, a translation of the 2006 German), as well as a supplement for peak limitation from 2012 (supplement "N,N-Dimethylformamid" 2012, available in German only). The MAK value for dimethylformamide was re-evaluated in the supplement from 2006 (supplement "Dimethylformamide" 2010, a translation of the 2006 German). At the time, the prenatal toxicity of the substance was not re-evaluated. This has been carried out in this supplement. In addition, new long-term studies have been carried out which also make evaluation of the carcinogenic effects necessary.

Mechanism of Action

Dimethylformamide has toxic effects on the liver in humans and animals. Changes in liver parameters were observed in several investigations (supplement "Dimethyl-

formamide" 2010, a translation of the 2006 German). No evidence of genotoxic effects was found for dimethylformamide. The liver cell necrosis induced by dimethylformamide or its metabolites *N*-methylformamide and methyl isocyanate after long-term inhalation is the cause of the pronounced regenerative proliferation of hepatocytes which leads to carcinogenic effects in rats and mice. *N*-Methylformamide and methyl isocyanate are likewise strong hepatotoxins (see supplement "Dimethylformamide" 2010, a translation of the 2006 German; Ohbayashi et al. 2008, 2009).

Toxicokinetics and Metabolism

Relevant dermal absorption has been known for a long time from workplaces with exposure to dimethylformamide (see supplement "Dimethylformamide" 2010, a translation of the 2006 German) in addition to the adsorption by inhalation. After the exposure of volunteers in exposure chambers to dimethylformamide vapour, the amount of substance absorbed via the skin was between 13% and 36% of the total amount absorbed under resting conditions. With increasing temperature and humidity, absorption via the skin increases. The dermal absorption rate for undiluted liquid dimethylformamide in volunteers was 9.4 mg/cm^2 and hour (Mráz and Nohova 1992). After the exposure of volunteers to dimethylformamide vapour for 4 hours exclusively via the skin (90% of the body surface was uncovered) or via the lungs at rest, 40.4% of the total amount was absorbed via the skin and 59.6% by the lungs. This means that after whole-body exposure the amount absorbed via the skin is around the same as that absorbed by the lungs. The half-lives after dermal exposure were longer than after inhalation exposure (see supplement "Dimethylformamide" 2010, a translation of the 2006 German; Nomiyama et al. 2001).

Dimethylformamide in water was applied to pig skin for up to 24 hours in amounts of 0.2 ml/cm^2. Amounts of 9.1%, 2.6% and 1.2% of a 100%, 50% and 10% dimethylformamide solution penetrated the skin. Amounts of 5.0%, 0.8% and 0.2% of the 100%, 50% and 10% dimethylformamide solutions remained in the skin. The absorption rate was 0.872 mg/cm^2 and hour for undiluted dimethylformamide. The half-lives in the skin were 12.3, 4.0 and 1.24 hours for the 100%, 50% and 10% dimethylformamide solutions. The internal exposure to dimethylformamide can be extended beyond the duration of the external exposure by the reservoir effect, particularly in the case of mixtures in water with a high dimethylformamide content (Wang et al. 2009). The recommended highest dose that should be applied according to OECD Test Guideline 428 of 10 µl/cm^2 for liquids was greatly exceeded here, so that the percentage absorbed was greatly underestimated and for quantitative evaluations only the absorption rate can be used.

Animal Experiments and in vitro Studies

Subacute, subchronic and chronic toxicity

Inhalation

Groups of 5 male F344/DuCrj rats were exposed either for 6 hours a day, on 5 days a week, for 4 weeks by inhalation in whole-animal chambers to dimethylformamide concentrations of 0, 200 or 400 ml/m^3 or via the drinking water for 24 hours a day, on 7 days a week, for 4 weeks to 0, 800, 1600 or 3200 mg/l. Further groups were exposed both by inhalation to 200 ml/m^3 or 400 ml/m^3 and via the drinking water to 800, 1600 or 3200 mg/l (see Table 1). At the end of exposure the liver weights in nearly all groups of animals were significantly increased, with the exception of the 200 ml/m^3 group and the group of animals exposed by inhalation to 200 ml/m^3 and also via the drinking water to 800 mg/l. Centrilobular hepatocellular hypertrophy, the necrosis of liver cells, increased alanine aminotransferase activity, an increase in the number of PCNA (proliferating cell nuclear antigen)-positive hepatocytes and increased liver weights were found. The hypertrophic and necrotic effects increased in a dose-dependent manner only after oral or inhalation exposure alone. With combined exposure the effects reached a plateau. This presumably indicates that

Table 1 Exposure of F344/DuCrj rats to dimethylformamide by inhalation and with the drinking water (Ohbayashi et al. 2008)

Inhalation, 5 days/week, 6 hours/day (ml/m^3)	Drinking water, 7 days/week, 24 hours/day (mg/l)	Inhalation and drinking water, 5 days/week, 6 hours/day (mg/kg body weight and day)	Inhalation and drinking water, 7 days/week, 24 hours/day (mg/kg body weight and day)	Total amount (mg/kg body weight and day)
0	0	0	0	**0**
0	800	0	83	**83**
0	1600	0	144	**144**
0	3200	0	292	**292**
200	0	121	0	**121**
200	800	121	80	**201**
200	1600	121	143	**264**
200	3200	121	287	**408**
400	0	242	0	**242**
400	800	242	77	**319**
400	1600	242	150	**392**
400	3200	242	313	**555**

the metabolism of dimethylformamide into the strongly toxic metabolites *N*-methylformamide and methyl isocyanate becomes saturated. After combined exposure, the percentage of stained PCNA-positive hepatocytes, regarded as the proliferative index, was higher than after the addition of the effects of oral or inhalation exposure alone. These results show that the proliferative reaction of the hepatocytes after combined exposure can increase further, while the hypertrophic and necrotic reaction reaches a plateau (Ohbayashi et al. 2008). A NOAEC (no observed adverse effect concentration) cannot be derived from this study.

Groups of 50 male and 50 female F344/DuCrj(SPF) rats and groups of 50 male and 50 female Crj:BDF(SPF) mice were exposed in whole-animal chambers for 6 hours a day, on 5 days a week, for 2 years to dimethylformamide concentrations of 0, 200, 400 or 800 ml/m^3. Toxic effects on the liver were observed in all exposed animals. There was a dose-dependent, statistically significant decrease in the body weights of all exposed male rats, and in the female rats and male mice at 400 ml/m^3 and above, and in the female mice at 800 ml/m^3. A statistically significant increase was observed in the absolute and relative liver weights of all exposed mice, the relative liver weights of all exposed rats and the absolute liver weights of the rats of the 200 ml/m^3 and 800 ml/m^3 groups. Increased values for the activities of γ-glutamyltranspeptidase and alanine aminotransferase and for the total levels of bilirubin, cholesterol and phospholipids were obtained in all exposed rats. The activity of aspartate aminotransferase was increased in the male rats of the 400 ml/m^3 and 800 ml/m^3 groups and in the female animals of the 200 ml/m^3 and 800 ml/m^3 groups. The blood urea level was increased in all female rats and in the male rats of the 200 ml/m^3 and 800 ml/m^3 groups. In all exposed mice the activities of aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase and creatine phosphokinase and the total levels of cholesterol and protein were increased. The total level of bilirubin was increased in all female mice and in the male mice of the 800 ml/m^3 group. The level of blood urea was increased in the male mice of the 400 ml/m^3 and 800 ml/m^3 groups and in all exposed female mice. Liver changes, such as centrilobular hepatocellular hypertrophy, centrilobular necrosis, focal necrosis and eosinophilic liver foci were observed in mice in all exposure groups and increased with the concentration. In rats, in particular in the males, such liver changes were observed at 400 ml/m^3 and above (Senoh et al. 2004). A NOAEC cannot be derived from this study for either rats or mice, because first effects occurred in the liver even at the lowest exposure concentration of 200 ml/m^3 (see also Section "Carcinogenicity").

Reproductive and developmental toxicity

Fertility

In the supplement from 2006 (supplement "Dimethylformamide" 2010, a translation of the 2006 German), a generation study with continuous mating and adminis-

tration with the drinking water is described in which dimethylformamide doses of 800 mg/kg body weight and day and above led to the impairment of fertility in mice (supplement "Dimethylformamide" 2010, a translation of the 2006 German).

After continuous oral administration of 0, 500, 1000 or 2000 mg/kg body weight and day for 30 days, a decrease in body weights, and in sperm count and motility was observed in mice. The values of the follicle-stimulating hormone in serum were increased in all dose groups and the testosterone values in serum and the testes were decreased (Kennedy et al. 2012).

Developmental toxicity

Since the last supplement from 2006 (supplement "Dimethylformamide" 2010) no new studies of developmental toxicity have been carried out. The studies relevant to the evaluation from the documentation from 1992 (documentation "Dimethylformamide" 1997) and the supplement from 2006 (supplement "Dimethylformamide" 2010, a translation of the 2006 German) are summarized below.

Inhalation

The inhalation (whole-body exposure) of 172 ml/m^3 (Kimmerle and Machemer 1975) and 297 ml/m^3 (Keller and Lewis 1981; Lewis et al. 1992) led to reduced foetal weights in rats without evidence of maternal toxicity at 172 ml/m^3 and with maternal toxicity at 297 ml/m^3. In rabbits there was an increase in variations and the occurrence of umbilical hernias at 150 ml/m^3 with maternal toxicity, and at 450 ml/m^3 and above the incidence of malformations was increased (Hellwig et al. 1991). The studies showed that in rabbits embryotoxic and teratogenic effects occur only in concentration ranges which are also maternally toxic. The NOAEC for developmental toxicity after inhalation was given as 18 ml/m^3 (Kimmerle and Machemer 1975) and 31 ml/m^3 (Keller and Lewis 1981; Lewis et al. 1992) in rats, and 50 ml/m^3 in rabbits (Hellwig et al. 1991). The publication of Keller and Lewis (1981) is available only as a short summary. These results have been described in detail in the meantime in Lewis et al. (1992). The latter was not available when the NOAEC for developmental toxicity in the rat was derived (documentation "Dimethylformamide" 1997), so that there is now a higher NOAEC in the rat of 31 ml/m^3.

Oral administration

Gavage administration of dimethylformamide led to malformations also without evidence of maternal toxicity at the lowest tested doses of 44 and 182 mg/kg body weight and day, respectively, in rabbits and mice (Hellwig et al. 1991; Merkle and Zeller 1980). In the rat, foetal body weights were reduced at and above 100 mg/kg

body weight and day, skeletal variations accompanied by maternal toxicity, but no malformations, were observed at and above 200 mg/kg body weight and day, and malformations occurred at and above 503 mg/kg body weight and day. The NOAEL (no observed adverse effect level) for developmental toxicity and maternal toxicity in the rat after oral administration was 50 mg/kg body weight and day (Saillenfait et al. 1997).

Dermal application

After dermal application, vertebral anomalies without evidence of maternal toxicity were observed in rats at the lowest dose tested of 95 mg/kg body weight and day and above. In rabbits, malformations were seen in the foetuses at 400 mg/kg body weight and day and above with simultaneous maternal toxicity. The NOAEL for developmental toxicity and maternal toxicity after dermal application was 200 mg/kg body weight and day in the rabbit. A NOAEL for developmental toxicity cannot be derived for the rat (Hellwig et al. 1991).

Carcinogenicity

Groups of 50 male and 50 female F344/DuCrj(SPF) rats and groups of 50 male and 50 female Crj:BDF(SPF) mice were exposed for 6 hours a day, on 5 days a week, for 2 years to dimethylformamide concentrations of 0, 200, 400 or 800 ml/m^3 (see also Section "Subacute, subchronic and chronic toxicity"). A statistically significant increase in hepatocellular adenomas and hepatocellular carcinomas and preneoplasms in the liver (changed cell foci and spongiosis hepatis; see Bannasch 2003; Stroebel et al. 1995) were observed in the mice even at the low concentration of 200 ml/m^3, but in the rats only at 400 ml/m^3 and above (see Table 2). The statistical significance of the tumour incidences determined using Fisher's exact test was confirmed also with Peto's test (Peto et al. 1980). In the liver of exposed rats, several hepatocellular tumours were found per animal; in comparison, the control animals developed only single liver tumours. Also in the treated mice, several liver tumours per animal were found, distributed over the whole organ (Senoh et al. 2004).

In contrast, dimethylformamide was not found to have carcinogenic potential in a 2-year study with CD rats from 1994 and an 18-month study with CD mice after the inhalation of dimethylformamide concentrations of 0, 25, 100 or 400 ml/m^3. Increased tumour incidences were not observed. However, the authors mention in the text, without giving quantitative data, the that incidence of focal cystic degeneration in the liver (frequently used term for spongiosis hepatis, that is progressively increasing aggregates of sinusoidal cells; Bannasch 2003) of the male and female rats was increased after exposure to both 100 ml/m^3 and 400 ml/m^3. Other effects, such as focal necrosis, centrilobular hypertrophy and the formation of foci in the

Table 2 Studies of the carcinogenicity of dimethylformamide

Author:		Senoh et al. 2004				
Substance:		dimethylformamide (purity: 99.8%)				
Species:		**rat**, F344/DuCrj(SPF), 50 ♂, 50 ♀				
Administration route:		Inhalation				
Concentration:		0, 200, 400, 800 ml/m³				
Duration:		2 years, 5 days/week, 6 hours/day				
Toxicity:		200 ml/m³ and above: liver toxicity; body weights ↓, mortality ↑				
		Exposure concentration (ml/m³)				
		0	200	400	800	Peto's test
Survivors	♂	42/50 (84%)	38/50 (76%)	40/50 (80%)	37/50 (74%)	
	♀	42/49 (86%)	38/50 (76%)	38/50 (76%)	30/50 (60%)	
Liver:						
Preneoplasms						
clear cell foci	♂	11/50 (22%)	21/50 (42%)*	35/50 (70%)**	40/50 (80%)**	
	♀	3/49 (6%)	23/50 (46%)**	33/50 (66%)**	33/50 (66%)**	
eosinophilic cell foci	♂	13/50 (26%)	14/50 (28%)	34/50 (68%)**	40/50 (80%)**	
	♀	0/49 (0%)	4/50 (8%)	10/50 (20%)*	20/50 (40%)**	
basophilic cell foci	♂	24/50 (48%)	26/50 (52%)	29/50 (58%)	42/50 (84%)**	
	♀	23/49 (47%)	27/50 (54%)	15/50 (30%)	29/50 (58%)	
mixed cell foci	♂	0/50 (0%)	0/50 (0%)	1/50 (2%)	6/50 (12%)*	
	♀	0/49 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%)	
vacuolated cell foci	♂	6/50 (12%)	0/50 (0%)	7/50 (14%)	16/50 (32%)*	
	♀	0/49 (0%)	0/50 (0%)	1/50 (2%)	3/50 (6%)	
spongiosis hepatis	♂	4/50 (8%)	21/50 (42%)**	26/50 (52%)**	24/50 (48%)**	
	♀	0/49 (0%)	0/50 (0%)	0/50 (0%)	2/50 (4%)	
Tumours						
hepatocellular adenomas	♂	1/50 (2%)	3/50 (6%)	13/50 (26%)**	20/50 (40%)**	↑↑
	♀	1/49 (2%)	1/50 (2%)	6/50 (12%)*	16/50 (32%)**	↑↑
hepatocellular carcinomas	♂	0/50 (0%)	1/50 (2%)	0/50 (0%)	24/50 (48%)**	↑↑
	♀	0/49 (0%)	0/50 (0%)	0/50 (0%)	5/50 (10%)	↑↑

Table 2 (Continued)

hepatocellular tumours[a]	♂	1/50 (2%)	4/50 (8%)	13/50 (26%)**	33/50 (66%)**	↑↑
	♀	1/49 (2%)	1/50 (2%)	6/50 (12%)	19/50 (38%)**	↑↑

*p ≤ 0.05; **p ≤ 0.01, ↑p < 0.05, ↑↑p < 0.01 by Peto's test
[a] Hepatocellular tumours consist of adenomas and carcinomas,
Historical controls: incidences not known

Species:	**mouse**, DuCrj:BDF1(SPF), 50 ♂, 50 ♀				
Administration route:	Inhalation				
Concentration:	0, 200, 400, 800 ml/m^3				
Duration:	2 years, 5 days/week, 6 hours/day				
Toxicity:	200 ml/m^3 and above: liver toxicity; body weights ↓, mortality ↑				
	Exposure concentration (ml/m^3)				
	0	200	400	800	Peto's test
Survivors ♂	37/50 (74%)	33/50 (66%)	37/50 (74%)	40/50 (80%)	
♀	29/49 (59%)	30/50 (60%)	21/50 (42%)	22/49 (45%)	
Liver:					
Preneoplasms					
clear cell foci ♂	4/50 (8%)	21/50 (42%)**	13/49 (26%)**	17/50 (35%)**	
♀	3/49 (6%)	7/50 (14%)	4/50 (8%)	2/49 (4%)	
eosinophilic cell foci ♂	1/50 (2%)	38/50 (76%)**	41/49 (84%)**	42/50 (84%)**	
♀	1/49 (2%)	43/50 (86%)**	43/50 (86%)**	48/49 (98%)**	
Tumours					
hepatocellular ♂	6/50 (12%)	36/50 (72%)**	41/49 (84%)**	41/50 (82%)**	↑↑
adenomas ♀	1/49 (2%)	42/50 (84%)**	47/50 (94%)**	48/49 (98%)**	↑↑
hepatocellular ♂	2/50 (4%)	12/50 (24%)*	16/49 (32%)**	16/50 (32%)**	↑↑
carcinomas ♀	3/49 (6%)	25/50 (50%)**	32/50 (64%)**	35/49 (71%)**	↑↑
hepatoblastomas ♂	0/50 (0%)	13/50 (26%)**	7/49 (14%)	4/50 (8%)	
♀	0/49 (0%)	0/50 (0%)	4/50 (8%)	0/49 (0%)	
hepatocellular ♂	8/50 (16%)	42/50 (84%)**	46/49 (92%)**	44/50 (88%)**	↑↑
tumours[a] ♀	3/49 (6%)	45/50 (90%)**	49/50 (98%)**	49/49 (100%)**	↑↑

*p ≤ 0.05; **p ≤ 0.01, ↑p < 0.05, ↑↑p < 0.01 by Peto's test
[a] Hepatocellular tumours consist of adenomas, carcinomas and hepatoblastomas,
Historical controls: incidences not known

liver were observed in the mice even at the lowest concentration of 25 ml/m^3, but in the rats only after 100 ml/m^3 and above (see supplement "Dimethylformamide" 2010, a translation of the 2006 German; Malley et al. 1994).

An explanation for the inconsistent results might be the different strains of rats and mice used in the two studies (Senoh et al. 2004). The short exposure duration of 18 months in the mice in the study of Malley et al. (1994) may also have had an

Table 3 Carcinogenicity of dimethylformamide after inhalation, oral administration and combined inhalation and oral exposure

Author:	Ohbayashi et al. 2009								
Substance:	dimethylformamide (purity: >99.5%)								
Species:	**rat**, F344/DuCrlCrj, 50 ♂								
Administration route:	inhalation, drinking water, inhalation and drinking water								
Concentration:	0, 800 mg/l drinking water (44 mg/kg body weight and day), 1600 mg/l (82 mg/kg body weight and day) and additionally 0, 200 or 400 ml/m³								
Duration:	2 years, inhalation: 5 days/week, 6 hours/day; drinking water: ad libitum								
Toxicity:	liver toxicity in all treated animals								
	0 ml/m³ (0 mg/kg body weight and day)	800 mg/l (44 mg/kg body weight and day)	1600 mg/l (82 mg/kg body weight and day)	200 ml/m³ (121 mg/kg body weight and day)	200 ml/m³ and 800 mg/l (165 mg/kg body weight and day)[a]	200 ml/m³ and 1600 mg/l (205 mg/kg body weight and day)[a]	400 ml/m³ (242 mg/kg body weight and day)	400 ml/m³ and 800 mg/l (289 mg/kg body weight and day)[a]	400 ml/m³ and 1600 mg/l (338 mg/kg body weight and day)[a]
Survivors	41/50 (82%)	34/50 (68%)	40/50 (80%)	36/50 (72%)	36/50 (72%)	41/50 (82%)	37/50 (74%)	43/50 (86%)	38/50 (76%)
Liver tumours									
hepatocellular adenomas	1/50 (2%), [0]	6/50 (12%), [0]	8/50* (16%), [2]	15/50** (30%), [2]	28/50** (56%), [1]	45/50** (90%), [4]	26/50** (52%), [3]	43/50** (46%), [3]	46/50** (92%), [9]
hepatocellular carcinomas	0/50 (0%), [0]	0/50 (0%), [0]	4/50 (8%), [0]	1/50 (2%), [0]	6/50* (12%), [0]	14/50** (28%), [1]	2/50 (4%), [0]	12/50** (24%), [1]	14/50** (28%), [2]
hepatocellular adenomas and carcinomas	1/50 (2%), [0]	6/50 (12%), [2]	12/50** (24%), [2]	16/50** (32%), [2]	30/50** (60%), [1]	46/50** (92%), [5]	26/50** (52%), [3]	45/50** (90%), [4]	47/50** (94%), [9]
insufficiently differentiated carcinomas	0/50 (0%), [0]	0/50 (0%), [0]	1/50 (2%), [0]	0/50 (0%), [0]	5/50* (10%), [0]	5/50* (10%), [0]	2/50 (4%), [0]	9/50** (18%), [0]	9/50** (18%), [2]

*$p \leq 0.05$, **$p \leq 0.01$;
[a] dose estimated by the authors;
[ ] number of dead or moribund animals with hepatocellular tumours

influence on the results. However, the reduction in body weight in all exposed rats in the study of Senoh et al. (2004) is greater than 10%, which can be regarded as an indication that the MTD (maximum tolerable dose) was exceeded. Also the different methods of producing the dimethylformamide atmosphere in the exposure chambers has been suggested as an explanation for the different results of the two studies. In the study of Senoh et al. (2004), a dimethylformamide vapour–air mixture was produced by blowing clean air through liquid dimethylformamide in the air space of the solvent reservoir and then diluting the vapour phase with pure air (Senoh et al. 2003). It has been suggested that in the study of Senoh et al. (2004) additional dimethylformamide was present in the form of particle mass (Kennedy 2012). However, this assumption may not be correct, as the experimental configuration contained a drainage valve for any drops of liquid that may have been formed (Kano et al. 2002).

In another study, groups of 50 male F344/DuCrj(SPF) rats were treated for 6 hours a day, on 5 days a week, for 2 years, either orally with 0, 800 (44 mg/kg body weight and day) or 1600 mg/l drinking water (82 mg/kg body weight and day) or by inhalation with 0, 200 ml/m³ (121 mg/kg body weight and day) or 400 ml/m³ (242 mg/kg body weight and day). Further groups were exposed both by inhalation to 200 ml/m³ or 400 ml/m³ and orally to 800 or 1600 mg/l drinking water. The "combined" exposure was shown to induce a superadditive increase in the tumour incidences and tumour malignancy (see Table 3) (Ohbayashi et al. 2009). The incidences of the hepatocellular adenomas and carcinomas which were induced by the "combined" exposure, were higher than the sum of the incidences of hepatocellular adenomas and carcinomas after oral or inhalation exposure alone. In addition, several less differentiated carcinomas were induced by the "combined" exposure; these were not seen after only inhalation or oral exposure. A possible explanation for the superadditive effect after "combined" exposure is provided by the results of the study of Ohbayashi et al. (2008). This study revealed a pronounced proliferative index in the male rats. The increase in the index was greater than the sum of the two proliferative indices after only inhalation or oral exposure (see also Section "Subacute, subchronic and chronic toxicity").

Manifesto (MAK value/classification)

The effects on the liver are the critical effect.

MAK value and peak limitation. The MAK value was lowered in 2006 to 5 ml/m³ as a result of 2-year studies with rats with a NOAEC of 25 ml/m³ and mice with a LOAEC (lowest observed adverse effect concentration) of 25 ml/m³ and BMD (benchmark dose) and BMDL (benchmark dose lower confidence limit) values calculated from these of 14.7 and 7.8 ml/m³, respectively (see supplement "Dimethylformamide" 2010, a translation of the 2006 German). The first effects on

the liver occurred in mice at 25 ml/m³ and above and in rats at 100 ml/m³ and above. There are no new data available regarding this. The MAK value has therefore been retained. Even when this MAK value is observed, alcohol intolerance reactions in persons exposed to dimethylformamide cannot be excluded. To determine the amount of dimethylformamide absorbed by inhalation and through the skin, reference is made to the documentation of the BAT value. Peak Limitation Category II and excursion factor 2 (supplement "N,N-Dimethylformamid" 2012, available in German only) have likewise been retained.

Carcinogenicity and germ cell mutagenicity. Observations in humans and animal experiments have shown the liver to be the specific target organ, with increased liver-specific enzymes in serum and hepatocellular proliferation. After long-term inhalation exposure, dimethylformamide induced a statistically significant increase in the incidence of hepatocellular carcinomas in male rats of the high exposure group of 800 ml/m³ and in mice of all exposure groups of 200 ml/m³ and above. Numerous in vitro and in vivo studies have demonstrated that dimethylformamide does not have genotoxic or germ cell mutagenic effects (see supplement "Dimethylformamide" 2010 a translation of the 2006 German). The findings of the long-term study show that liver tumours do not occur until chronic toxic-regenerative changes have taken place. The tumours that were found are therefore to be seen as mainly the result of chronic damage. It can be concluded from this that exposure which does not lead to necrotic changes is not associated with an increased cancer risk. Due to this mechanism of action, dimethylformamide is classified in Category 4 for carcinogenic substances. Also with long-term exposure, the MAK value of 5 ml/m³ provides protection against toxic effects in the liver.

Prenatal toxicity. Since 1989, dimethylformamide has been classified in Pregnancy Risk Group B.

The inhalation of 172 ml/m³ led to reduced foetal weights and an increase in variations in rats (Kimmerle and Machemer 1975) while in rabbits concentrations of 150 ml/m³ led to the occurrence of umbilical hernias (Hellwig et al. 1991). Gavage administration of dimethylformamide led to malformations even without evidence of maternal toxicity at the lowest tested dose of 44 mg/kg body weight and day and above in rabbits (Merkle and Zeller 1980) and 182 mg/kg body weight and day and above in the mouse (Hellwig et al. 1991). In the rat, reduced foetal weights were observed at and above 100 mg/kg body weight and day with simultaneous maternal toxicity (Saillenfait et al. 1997). The NOAEC for developmental toxicity after inhalation was found to be 31 and 50 ml/m³, respectively, for the rat (Keller and Lewis 1981; Lewis et al. 1992) and rabbit (Hellwig et al. 1991). The given NOAECs are therefore 6 and 10 times higher than the MAK value of 5 ml/m³. After oral administration, the NOAEL for developmental toxicity in the rat was found to be 50 mg/kg body weight and day; for the rabbit and mouse, merely a LOAEL (lowest observed adverse effect level) of 44 and 182 mg/kg body weight and day, respectively, can be derived. The following toxicokinetic data are taken into consideration

for the extrapolation of the NOAEL for the rat and the LOAELs for the rabbit or mouse to a concentration in workplace air: the corresponding species-specific correction values for the rat, rabbit and mouse (1:4, 1:2.4, 1:7), the assumed oral absorption (100%), the body weight (70 kg) and respiratory volume (10 m^3) of the person and the determined 90% absorption by inhalation (supplement "Dimethylformamide" 2010, a translation of the 2006 German). The concentrations calculated are 32 ml/m^3 (97 mg/m^3), 47 ml/m^3 (142 mg/m^3) and 67 ml/m^3 (202 mg/m^3), respectively, which are 6, 10 and 13 times higher than the MAK value of 5 ml/m^3 (15 mg/m^3).

After dermal application, vertebral anomalies were observed in rats without any evidence of maternal toxicity at the lowest tested dose of 95 mg/kg body weight and day and above (Hellwig et al. 1991). In rabbits, foetal malformations were found at 400 mg/kg body weight and day and above with simultaneous maternal toxicity. The NOAEL after dermal application was 200 mg/kg body weight and day in rabbits. A NOAEL cannot be derived for the rat (Hellwig et al. 1991). The dermal absorption in rats and rabbits is unknown. The absorption rate of undiluted dimethylformamide is 0.872 mg/cm^2 and hour for porcine skin; for humans the flux was found to be 10 times higher. The LOAEL of 95 mg/kg body weight corresponds to a dose of 0.38 mg/cm^2 (body weight 200 g, exposed area 50 cm^2), it can therefore be assumed that the absorption of dimethylformamide in this experiment was 100%. For the rabbit, the corresponding dose at the LOAEL of 400 mg/kg body weight (body weight 2.5 kg, exposed area 66 cm^2) is 15 mg/cm^2. Here, the dermal absorption in the 6 hours of exposure may have been incomplete. Extrapolation of the rabbit dose to a concentration in air is therefore not possible. After dermal application, the calculated LOAEC for developmental toxicity in the rat is 12 times higher (61 ml/m^3) than the MAK value of 5 ml/m^3 (15 mg/m^3) (other parameters as above).

As malformations occurred in rabbits and mice at the LOAEL after oral administration and the margins between the NOAEL and LOAEL for developmental toxicity in the rat, rabbit and mouse and the MAK value of 5 ml/m^3 after inhalation, oral administration or dermal application are not sufficiently large, the classification of dimethylformamide in Pregnancy Risk Group B has been retained.

Sensitization. Dimethylformamide is not designated with "Sa/Sh" (for substances which cause sensitization of the airways or skin).

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completed 25.02.2015