The MAK Collection for Occupational Health and Safety

N,N-Dimethylacetamide

MAK Value Documentation, addendum – Translation of the German version from 2018

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N,N-Dimethylacetamide

MAK Value Documentation

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Abstract

The German Commission for the investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated the maximum concentration at the workplace (MAK value) and the Pregnancy Risk Group of *N,N*-dimethylacetamide [127-19-5].

N,N-Dimethylacetamide causes focal cystic degenerations, peliosis, hemosiderin/lipofuscin accumulation and apoptosis in the liver of rats and male mice after chronic whole body inhalation at 100 ml/m³. The NOAEC in both species is 25 ml/m³. Elastane fibre workers with exposure to *N,N*-dimethylacetamide show hepatocellular injury. The data at the workplace is not adequate to derive a MAK value. The former MAK value of 10 ml/m³ was derived from the NOAEC of 25 ml/m³ in rats and mice. The MAK value is now lowered to 5 ml/m³ which takes into account the increased respiratory volume at the workplace because the blood:air partition coefficient of *N,N*-dimethylacetamide is > 5 (see List of MAK and BAT Values, Sections I b and I c). Since a systemic effect is critical, Peak Limitation Category II is retained. The default excursion factor of 2 is retained as well, as the mechanism of action and the half-life in blood are not known.

In rats and rabbits, *N,N*-dimethylacetamide induces via inhalation at 450 or 570 ml/m³, respectively, and above, specific teratogenic effects, cardiovascular and skeletal malformations. The NOAEC for teratogenicity in rats and rabbits are 300 or 200 ml/m³, respectively. The lowest NOAEC for developmental toxicity in rats and rabbits are 100 and 57 ml/m³, respectively. Considering the increased respiratory volume at the workplace, the NOAEC for rabbits is only six times the MAK value. However, taking into account that the NOAEC could be higher than 57 ml/m³ and the observed effects, reduced fetal body weight and increased incidence of skeletal variations, are considered marginal, the difference to the MAK value is sufficient. Therefore, damage to the embryo or foetus is unlikely when the MAK value is observed and *N,N*-dimethylacetamide remains assigned to Pregnancy Risk Group C. Skin contact should be avoided as *N,N*-dimethylacetamide is designated with an "H".

Keywords

N,N-dimethylacetamide; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; reproductive toxicity; fertility; developmental toxicity; peak limitation; prenatal toxicity; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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2004

N,N-Dimethylacetamide

[127-19-5]

Supplement 2018

MAK value (2017)	**5 ml/m³ (ppm) ≙ 18 mg/m³**
Peak limitation (2002)	**Category II, excursion factor 2**
Absorption through the skin (1969)	**H**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (1990)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value (2000)	**30 mg *N*-methylacetamide/g creatinine**
Vapour pressure at 25 °C	2.67 hPa (SRC 2013)
log K_{OW}[1)]	–0.77 (SRC 2013)
1 ml/m³ (ppm) ≙ 3.615 mg/m³	**1 mg/m³ ≙ 0.277 ml/m³ (ppm)**

For *N,N*-dimethylacetamide, documentation is available from 1998 (documentation "N,N-Dimethylacetamid" 1998, available in German only) and a supplement on peak limitation from 2002 (supplement "N,N-Dimethylacetamid" 2002, available in German only).

In 2016, the Commission began using a revised approach for assessing substances with a MAK value based on systemic effects and derived from inhalation studies with animals or studies with volunteers at rest; this new approach takes into account that the respiratory volume at the workplace is higher than under experimental conditions. However, this does not apply to gases or vapours with a blood:air partition coefficient < 5 (see List of MAK and BAT Values, Sections I b and I c). According to the formula of Buist et al. (2012) the blood:air partition coefficient of *N,N*-dimethylacetamide is 26 037. This supplement evaluates whether the MAK value for *N,N*-dimethylacetamide needs to be re-assessed as a result of the higher respiratory volume at the workplace.

1) octanol/water partition coefficient

New data have been taken from the REACH registration dossier (ECHA 2016 a), the report of the Committee for Risk Assessment (RAC) (ECHA 2014) and the SIDS (Screening Information Dataset) Initial Assessment Report of the OECD (Organisation for Economic Co-operation and Development) (OECD 2001).

Due to its reproductive toxicity, *N,N*-dimethylacetamide was included as a substance of very high concern in the list of candidates for authorization in 2011 (ECHA 2016 b).

Toxicokinetics and Metabolism

Absorption, distribution, elimination

N,N-Dimethylacetamide is readily absorbed after inhalation, ingestion and skin contact (OECD 2001). The substance can be absorbed through the skin both in liquid form and from the gaseous phase. After absorption, *N,N*-dimethylacetamide is metabolized for the most part in the liver and is rapidly eliminated mainly with the urine (documentation "N,N-Dimethylacetamid" 1998, available in German only).

In animal studies (up to 70%) and also in humans, the main metabolite found in the urine was *N*-methylacetamide. Already in the documentation of 1998 attention was drawn to the fact that, in analogy to the findings with dimethylformamide, this is most likely an artefact from sample preparation; under analytical conditions the original metabolite *N*-hydroxymethyl-*N*-methylacetamide loses the hydroxymethyl residue (documentation "N,N-Dimethylacetamid" 1998, available in German only).

In the workplace study described below, the authors also draw attention to the fact that at the high temperatures of 250 °C during gas chromatography, *N*-hydroxymethyl-*N*-methylacetamide is transformed into *N*-methylacetamide. For this reason, the main metabolite in the urine is probably *N*-hydroxymethyl-*N*-methylacetamide (Perbellini et al. 2003).

Twelve healthy male volunteers (average age 25.2 years, range: 21 to 43 years) were exposed to an *N,N*-dimethylacetamide concentration of 6.1 ml/m^3 in vapour form twice for 4 hours at an interval of at least 96 hours, either dermally via the gaseous phase in a chamber (whole body, 90% of the skin uncovered, breathing mask with fresh air) or at rest via inhalation only using a breathing mask. The 36-hour urine and samples taken 48 and 72 hours after exposure were analysed. The biological half-life of *N*-methylacetamide was 9 hours after dermal exposure and 5.6 hours after inhalation. The mean dermal absorption was estimated to be 40.4% of the total uptake of *N,N*-dimethylacetamide vapour. The mean amount of *N*-methylacetamide in urine calculated for exposure to 10 ml *N,N*-dimethylacetamide/m^3 on 5 consecutive workdays (8 hours/day) was 33.7 (18.6–70.0) mg/g creatinine after inhalation and dermal absorption (Nomiyama et al. 2000).

In a workplace study at an Italian factory producing synthetic acrylic fibres, 223 workers exposed to *N,N*-dimethylacetamide were investigated. At the end of their workshift, urine samples were obtained from the workers. The highest urine concentrations of unchanged *N,N*-dimethylacetamide and *N*-methylacetamide were found in the workers engaged in starting up the machines. The *N*-methylacetamide concentrations in the urine were between 1.5 and 173.6 mg/g creatinine (median

value 20.5 mg/g creatinine). Of the 223 urine samples 46 (19%) were found to have more than 30 mg *N*-methylacetamide/g creatinine. The concentrations of *N,N*-dimethylacetamide in the workplace air were determined at different times of the year, in different parts of the working area and under all working conditions (no other details). The analyses revealed very low average levels of *N,N*-dimethylacetamide (no details), which were never higher than 1.5 ml/m³. For short periods of less than five minutes, levels of between 5 and 10 ml/m³ were sometimes reached (no other details; Perbellini et al. 2003). Due to the assumed skin contact, it is not possible to establish a correlation between the concentration of the substance in workplace air and the elimination of *N*-methylacetamide in urine (Bader 2016).

Metabolism

As already mentioned above, the main metabolite in the urine is probably *N*-hydroxymethyl-*N*-methylacetamide. In addition, a metabolite not identified up to the documentation from 1998, *S*-acetamidomethyl-*L*-acetylcysteine, was found in the urine. This is presumably formed from *N*-methylacetamide (Perbellini et al. 2003). The proposed metabolism in humans is shown in Figure 1.

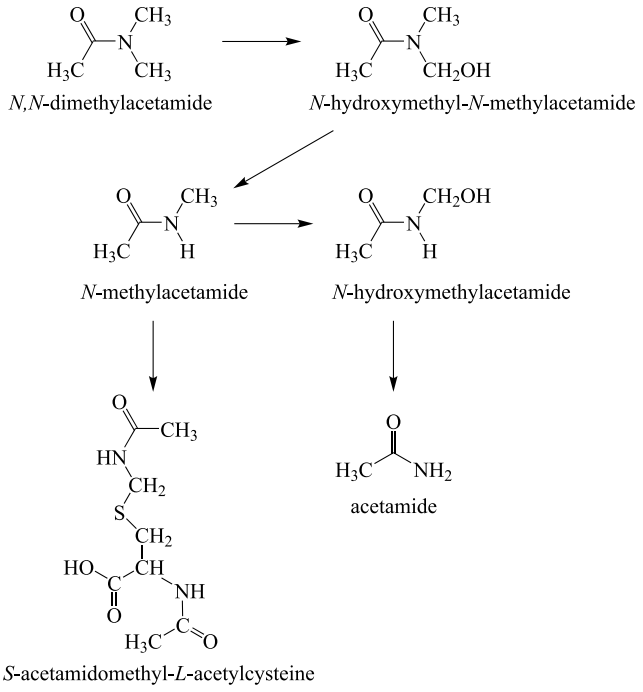

Figure 1 Proposed metabolism of *N,N*-dimethylacetamide in humans (Perbellini et al. 2003)

First of all, *N,N*-dimethylacetamide is enzymatically hydroxylated at one of the *N*-methyl groups, which results in *N*-hydroxymethyl-*N*-methylacetamide. This is easily degraded to *N*-methylacetamide. As a result of the enzymatic *N*-methyl oxidation, *N*-hydroxymethylacetamide is formed, from which acetamide results. An alternative pathway starting with *N*-methylacetamide proceeds via reaction with glutathione, which results in the formation of *S*-acetamidomethyl-*L*-acetylcysteine.

Effects in Humans

Repeated exposure

In a workplace study in Korea involving the production of elastane fibres, 440 workers from ten companies at two production sites were investigated who started work between 1st January 2002 and 31st July 2004. *N,N*-Dimethylacetamide was used as solvent for the urethane oligomer mixture. Concentrations in the workplace air were not determined. The participants completed a preplacement health examination, which included serum hepatic function tests such as alanine transaminase (ALT), aspartate transaminase (AST), and gamma glutamyl transpeptidase (GGT) levels, and serological tests for viral hepatitis B and C. Information concerning alcohol intake, smoking, exercise, and current or past diseases was obtained. The new workers were monitored with follow-up hepatic function tests every 10 days for three months, and health checks were carried out every six months. The definition of *N,N*-dimethylacetamide-induced hepatic injury was based, with some modification, on the results of the "International Consensus Meeting on Acute Hepatic Injury" and a publication of Danan and Benichou (1993) about methods of assessing the causality of drug-induced liver injuries. Hepatic injury was classified as "hepatocellular" when the ALT activity was more than twice the upper limit of the normal range or when the ratio of serum ALT activity to serum alkaline phosphatase activity was ≥ 5. There had to be exposure to *N,N*-dimethylacetamide prior to the diagnosis, the half-life of ALT after the end of exposure had to be less than 30 days and viral hepatitis had to be excluded. In this way 28 cases of hepatocellular damage attributed to *N,N*-dimethylacetamide were found. The overall incidence of *N,N*-dimethylacetamide-induced hepatic injury in this study was 0.089/person-year. From January 2003 to July 2004, the *N*-methylacetamide concentrations in the workers' urine were analysed on a half-yearly basis and 967 urine samples were obtained. The incidence of hepatic injury in the high exposure group was about 7 to 10 times higher than in the low exposure group. Classification in low and high exposure groups was based on the geometric mean value of the *N*-methylacetamide concentrations in the workers' urine. *N*-Methylacetamide levels of 20 mg (model 1) and 30 mg (model 2) per g creatinine were used as the cut-off criteria for the low exposure group. The odds ratio for *N,N*-dimethylacetamide-induced liver damage was 3.70 (95% confidence interval (CI): 1.33–10.26; $p < 0.05$) for model 1 and 4.67 (95% CI: 1.66–13.15; $p < 0.01$) for model 2. No hepatic injury was found in the workers exposed for more than 7 months in either the high exposure group or the low exposure group. In the authors' opinion, this inverse relationship between the incidence of *N,N*-dimethylacetamide-induced liver damage and the work duration

reflects a kind of healthy survivor effect or tolerance to *N,N*-dimethylacetamide-induced liver damage. The median *N*-methylacetamide concentration in the urine of workers from the eight departments (number of workers in the departments not specified) with the 28 cases of *N,N*-dimethylacetamide-induced liver damage was 19.6 mg *N*-methylacetamide/g creatinine (503 urine samples, range 2.2 to 196.5). Analysis of the 464 urine samples from the other 11 departments yielded a median of 5.2 mg *N*-methylacetamide/g creatinine (range 0.1 to 79.2). The authors report that they could not directly determine the *N*-methylacetamide concentrations in the 28 workers with hepatocellular damage, as no agreement had been reached in this regard with the companies (Lee et al. 2006). Therefore, it was not possible to establish a correlation between liver damage and the *N*-methylacetamide level in urine. From the available data, therefore, no LOAEL (lowest observed adverse effect level) can be derived for the *N*-methylacetamide concentration. Absorption through the skin was not quantified.

In another workplace study conducted by the same research group, 1045 workers at two factories producing elastane in Korea were investigated who started work between 1st January 2001 and 31st July 2004. The procedure of the investigation was the same as that of the preceding study. Here also, concentrations in air were not determined. Of 58 suspected cases, 38 cases of *N,N*-dimethylacetamide-induced hepatic injury were identified, three of which were recurrences. The interval between the beginning of exposure and the identification of liver damage (latency period) was in most cases less than two months and never exceeded six months. In addition, the three recurrent cases of *N,N*-dimethylacetamide-induced liver damage had much shorter latency periods than their initial latency periods. At the time, when the urinalyses of *N*-methylacetamide were carried out at half-yearly intervals (1284 urine samples), that is between January 2003 and July 2004, 21 cases of a total of 38 cases of *N,N*-dimethylacetamide-induced liver damage were observed in the department (number of workers in the departments not specified) in which packaging, changing of spinnerets and visual inspection took place. The median urinary *N*-methylacetamide concentration in workers from the department with the 21 cases of *N,N*-dimethylacetamide-induced liver damage was 25.1 mg/g creatinine (228 urine samples, range 4.6 to 196.5; interquartile range 17.5 to 51.7). The median *N*-methylacetamide concentration of the 1056 urine samples from the other department was 11.8 mg/g creatinine (range 0.1 to 133.9; interquartile range 4.8 to 23.4) (Jung et al. 2007). The *N*-methylacetamide levels in the 21 workers with hepatocellular damage are not given, but only the average values from the department. A LOAEL for the *N*-methylacetamide concentration cannot be derived from these data. Absorption through the skin was also not quantified.

Animal Experiments and in vitro Studies

Subacute, subchronic and chronic toxicity

Inhalation

In the long-term inhalation studies similar to OECD Test Guideline 453 (combined chronic toxicity/carcinogenicity studies) with rats and mice already described in the documentation of 1998 (documentation "N,N-Dimethylacetamid" 1998, available in German only), the liver was found to be the target organ in both species. Male and female Crl:CD-BR rats (87/dose and sex) and male and female Crl:CD-1(ICR)BR mice (78/dose and sex) were exposed to *N,N*-dimethylacetamide concentrations of 0, 25, 100 or 350 ml/m^3 for 6 hours daily, on 5 days per week, over 24 or 18 months (whole-body, vapour). The histological examination of organs at the end of the study yielded the following results: in male **rats**, the incidence of focal cystic degeneration (control group: 17/65, 26%; 100 ml/m^3: 28/63, 44%; 350 ml/m^3: 31/62, 50%) and of peliosis (control group: 3/65, 5%; 100 ml/m^3: 7/63, 11%; 350 ml/m^3: 8/62, 13%; statistical significance only at 350 ml/m^3) in the liver was increased at concentrations of 100 ml/m^3 and above. In the male rats, the incidence of biliary hyperplasia (control group: 37/65, 57%; 350 ml/m^3: 49/62, 79%) and haemosiderin/lipofuscin accumulation in the Kupffer cells, especially in the centrilobular areas (control group: 1/65, 2%; 350 ml/m^3: 21/63, 34%), was increased at 350 ml/m^3 only. In the female rats, an increased incidence of haemosiderin/lipofuscin accumulation was observed at 100 ml/m^3 and above (control group: 2/62, 3%; 100 ml/m^3: 8/62, 13%; 350 ml/m^3: 13/62, 21%). The NOAEC (no observed adverse effect concentration) for liver toxicity was 25 ml/m^3. In the male **mice**, increased incidences of haemosiderin/lipofuscin accumulation (control group: 6/64, 9%; 100 ml/m^3: 17/64, 27%; 350 ml/m^3: 30/65, 46%) and single hepatocellular necrosis (= apoptosis; control group: 9/64, 14%; 100 ml/m^3: 12/64, 19%; 350 ml/m^3: 16/65, 25%) were found at concentrations of 100 ml/m^3 and above. Only the incidence of hepatic single cell necrosis (control group: 1/63, 2%; 350 ml/m^3: 10/65, 15%) was increased in the female mice at 350 ml/m^3. The NOAEC for liver toxicity was 25 ml/m^3 in male mice and 100 ml/m^3 in female mice (DuPont 1994; Malley et al. 1995).

Reproductive and developmental toxicity

Fertility

The results of fertility studies with *N,N*-dimethylacetamide are shown in Table 1.

In a study of male and female fertility in Crl:CD(SD)BR rats with whole-body inhalation exposure, no impaired fertility was found at the highest concentration tested of 300 ml/m^3. Reduced body weights and increased relative liver weights were observed in the parent animals at 300 ml/m^3. The NOAEC for male and female fertility was 300 ml/m^3, and the NOAEC for parental toxicity 100 ml/m^3 (Ferenz and Kennedy 1986; documentation "N,N-Dimethylacetamid" 1998, available in German only).

Table 1 Results of fertility studies with *N,N*-dimethylacetamide

Species	Exposure	Findings	References
rat, Crl:CD(SD)BR, 10 ♂ and 20 ♀	**10 weeks before mating (5 days/week), 7–8 weeks during mating, gestation and lactation (7 days/week), but pregnant ♀ not exposed between GD 21 and PND 4,** 0, 30, 100, 300 ml/m³, vapour, at 300 ml/m³: exposed ♂ mated with untreated ♀ and vice versa, whole-body, 6 hours/day, purity: 99.9%, examination: PND 1, 4, 14, 21	**100 ml/m³: NOAEC parental toxicity;** **300 ml/m³**: parents: body weights ↓, relative liver weights ↑; offspring PND 21: body weights ↓, relative liver weights ↑; **300 ml/m³: NOAEC ♂ and ♀ fertility;** no abnormal findings in parents: body weights, survival, clinical signs, fertility, mating, gestation duration, number, appearance and survival of offspring, weights of reproductive organs; no histological examination of reproductive organs	Ferenz and Kennedy 1986; documentation "N,N-Dimethylacetamid" 1998, available in German only
rat, Sprague Dawley, 12 ♂	**43 days before mating and during mating (in total 69 exposure days),** only ♂ treated, ♀ untreated, 0, 40, 120, 400 ml/m³, analysed value: 0, 40, 116, 386 ml/m³, vapour, whole-body, 6 hours/day, 5 days/week, purity: 99.8%, examination: ♂ after final exposure, ♀ GD 20	**116 ml/m³: NOAEC paternal toxicity;** **116 ml/m³: and above:** ♂ parents: relative liver weights ↑ (116 ml/m³: 12%, 400 ml/m³: 22%); **368 ml/m³: NOAEC ♂ fertility;** no effects on copulation and mating efficiency, body weights of parents, number of live foetuses, foetal weights, number of resorptions, nidation and corpora lutea, histological examination of liver, kidneys, testes of ♂ parents	Wang et al. 1989; documentation "N,N-Dimethylacetamid" 1998, available in German only

GD: gestation day; NOAEC: no observed adverse effect concentration; PND: postnatal day

In a study with whole-body inhalation exposure of Sprague Dawley rats, a NOAEC for male fertility of 368 ml/m^3 was obtained, the highest concentration tested. In the male parents exposed to 368 ml/m^3, the relative liver weights were increased by more than 20%. The NOAEC for parental toxicity was therefore 116 ml/m^3 (Wang et al. 1989; documentation "N,N-Dimethylacetamid" 1998, available in German only).

A number of studies (Caujolle et al. 1970; Thiersch 1962, 1971) are not included in the evaluation, as a direct effect on the foetuses cannot be excluded with intraperitoneal administration. In addition, a dose was not given for the painting of the tail. The description of the method and the presentation of the results are inadequately documented.

A one-generation study with rats (Monsanto 1973) already cited in the documentation of 1998 (documentation "N,N-Dimethylacetamid" 1998, available in German only) was carried out in 1973 by the contract laboratories Industrial Biotest (IBT). In the studies of IBT carried out at this time, irregularities in the conduct of studies and in the documentation of the results were found (OECD 2005), so that the quality of the study cannot be guaranteed and therefore the study cannot be used for the evaluation.

In 14-day inhalation studies, *N,N*-dimethylacetamide produced testicular damage in rats and mice at concentrations of 300 ml/m^3 and above. The NOAEC was 100 ml/m^3 (Kelly et al. 1984; Valentine et al. 1997). A study carried out according to OECD Test Guideline 453 with whole-body inhalation exposure for 24 months revealed an increase in testicular damage in male rats at 350 ml/m^3; this was considered by the authors to be a secondary effect of the observed nephropathy. In mice, on the other hand, no testicular damage was observed up to the highest concentration tested of 350 ml/m^3 after whole-body inhalation exposure for 18 months (DuPont 1994; Malley et al. 1995; documentation "N,N-Dimethylacetamid" 1998, available in German only).

In dominant lethal tests, *N,N*-dimethylacetamide was not found to cause an increase in dominant lethal mutations in rats after single inhalation exposures (20 and 700 ml/m^3), or in mice after single intraperitoneal injections (640 mg/kg body weight), single dermal applications (1500 and 3000 mg/kg body weight) or inhalation exposure for 5 days (7 hours/day, 20 and 700 ml/m^3) (documentation "N,N-Dimethylacetamid" 1998, available in German only).

Developmental toxicity

Studies of the prenatal, or prenatal and postnatal developmental toxicity of the substance are shown in Table 2.

Table 2 Studies with prenatal, or prenatal and postnatal exposure to *N,N*-dimethylacetamide

Species	Exposure	Findings	References
Inhalation			
rat, Crl:CD(SD) IGS, 10 ♀	**GD 6–19**, 0, 100, 300, 450, 600 ml/m³, vapour, whole-body, 6 hours/day, purity: > 99.9%, examination: GD 20, similar to OECD Test Guideline 414	**100 ml/m³: NOAEC developmental and maternal toxicity**; **300 ml/m³: NOAEC teratogenicity (cardiovascular and skeletal malformations)**; **300 ml/m³ and above**: dams: relative liver weights ↑ (13%, not absolute liver weights), liver: hepatocellular swelling; foetuses: body weights ↓; **450 ml/m³**: dams: body weights (GD 20) ↓; foetuses: overall incidence of visceral malformations and individual malformations (ventricular septal defects) ↑, overall incidence of skeletal malformations and incidence of individual malformations (fused cervical vertebral arches) ↑; **600 ml/m³**: foetuses: number of live ♂ foetuses ↓, incidence of visceral malformations (persistent truncus arteriosus, malpositioned subclavian branch and retro-oesophageal subclavian artery) and skeletal malformations (fused exoccipital bones) ↑	Okuda et al. 2006
rat, Crl:CD, 25 ♀	**GD 6–15**, 0, 30, 100, 300 ml/m³ (0, 110, 360, 3110 mg/m³), analysed value: 0, 32, 100, 282 ml/m³, vapour, whole-body, 6 hours/day, purity: 99.9%, examination: GD 21, similar to OECD Test Guideline 414	**100 ml/m³: NOAEC developmental and maternal toxicity**; **282 ml/m³**: dams: body weight gains ↓; foetuses: body weights ↓; no unusual changes: number of corpora lutea/dam, implantations/litter, resorptions/litter, live foetuses/litter, incidences of external, visceral and skeletal variations and malformations	Solomon et al. 1991; documentation "N,N-Dimethylacetamid" 1998, available in German only)

Tab. 2 (continued)

Species	Exposure	Findings	References
rabbit, Himalayan, 15 ♀, satellite group: 5 ♀ (0, 570 ml/m³)	**GD 7–19**, 0, 57, 200, 570 ml/m³ (0, 200, 700, 2000 mg/m³), vapour, whole-body, 6 hours/day, purity: > 99.9%, examination: GD 29, OECD Test Guideline 414	**57 ml/m³: NOAEC developmental toxicity**; **57 ml/m³ and above**: foetuses: body weights ↓ (average litter weight: no statistically significant change); placenta weights ↓ (no statistically significant change in average placenta weight/litter); **200 ml/m³: NOAEC teratogenicity**; **200 ml/m³ and above**: foetuses: incidence of additional ribs (variation) related to foetuses per litter ↑ (see Table 3); **570 ml/m³**: foetuses: incidence of fused sternebrae (variation) related to foetuses per litter ↑, overall incidence of variations related to foetuses per litter ↑, incidence of visceral malformations ↑ (heart and great vessels, statistically not significant), incidence of skeletal malformations ↑; **570 ml/m³: NOAEC maternal toxicity**	Klimisch and Hellwig 2000; BG Chemie 1989
Ingestion			
rat, Crl:CD(SD) BR, 25 ♀	**GD 7–21**, 0, 20, 65, 150, 400 mg/kg body weight and day, gavage, vehicle: water, purity: at least 99.9%, examination: GD 22, OECD Test Guideline 414	**65 mg/kg body weight**: **NOAEL developmental and maternal toxicity**; **150 mg/kg body weight and above**: dams: body weight gains ↓; foetuses: body weights ↓ (150 mg/kg body weight: 4%; 400 mg/kg body weight: 34%; ECHA 2014), in one foetus malformations (atresia of nasal openings, malformation of heart and vessels, cleft palate, macroglossia, micrognatia, synotia; this dose represents the lower limit of the dose/effect relationship for malformations); **400 mg/kg body weight**: dams: food consumption ↓, absolute and relative kidney weights ↑, relative liver weights ↑; foetuses: number of resorptions ↑, number of malformations (synotia, anasarca, micrognatia, naris atresia, defects of the heart and great vessels, distension of the lateral cerebral ventricle, fused ribs, absent vertebrae, hemivertebrae) ↑, number of variations ↑; original study only available in textual form, without tables	DuPont 1997; documentation "N,N-Dimethylacetamid" 1998, available in German only; ECHA 2014

Tab. 2 (continued)

Species	Exposure	Findings	References
rat, COBS CD, 25 ♀	**GD 6–19**, 0, 65, 160, 400 mg/kg body weight and day, gavage, vehicle: water, purity: 99.7%, examination: GD 20, similar to OECD Test Guideline 414	**160 mg/kg body weight: NOAEL developmental toxicity, teratogenicity and maternal toxicity**; **400 mg/kg body weight**: dams: body weight gains ↓; foetuses: body weights ↓, number of postimplantations ↑, total number of malformations ↑, number of cardiac and vascular malformations ↑, variations ↑ (reduced ossification, non-ossified sternebrae)	Johannsen et al. 1987; documentation "N,N-Dimethylacetamid" 1998, available in German only
rat, Sprague Dawley, 18–24 ♀	**GD 6–15**, 0, 106, 323, 960 mg/kg body weight and day, gavage, vehicle: water, purity: technical grade, examination: GD 20 similar to OECD Test Guideline 414	**106 mg/kg body weight: NOAEL developmental toxicity, teratogenicity and maternal toxicity**; **323 mg/kg body weight**: dams: body weight gains ↓, vaginal bleeding, placenta weights ↓; foetuses: body weights ↓, teratogenicity (external malformations: 6/91 foetuses with anasarca, 2 with tail aplasia, 1 with atresia ani; controls 0/94; visceral malformation: incidence of 18/91, controls: 2/94, split/aplastic vertebrae, hydroureter); **960 mg/kg body weight**: foetuses: mortality 100%; original study not available	ECHA 2014
mouse, NMRI, at least 19–24 ♀	**GD 6–15**, 0, 240, 400, 1200 mg/kg body weight and day, gavage, vehicle: water, purity: not specified, examination: GD 18	**240 mg/kg body weight**: foetuses: body weights ↓, absolute weight of placenta ↓; **400 mg/kg body weight: NOAEL maternal toxicity**; **1200 mg/kg body weight**: dams: body weight gains ↓, diarrhoea; foetuses: number of implantations ↓, percentage of foetuses with malformations ↑; original study not available	ECHA 2014

Tab. 2 (continued)

Species	Exposure	Findings	References
mouse, NMRI, number not specified	**GD 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15**, 0, 1200, 3000 mg/kg body weight and day, GD 9: additional 400, 600 mg/kg body weight and day, GD 10, 11, 12: additional 600 mg/kg body weight and day, gavage, purity: technical grade, examination: GD 18	**GD 6**: **1200 mg/kg body weight:** foetuses: no effects; **3000 mg/kg body weight**: foetuses: embryolethality, foetotoxicity, teratogenicity; **GD 7**: **1200 mg/kg body weight**: foetuses: slight foetotoxicity; **3000 mg/kg body weight**: foetuses: foetotoxicity, teratogenicity; **GD 8**: **1200 mg/kg body weight**: foetuses: strong teratogenicity; **3000 mg/kg body weight**: foetuses: embryolethality, foetotoxicity, teratogenicity; **GD 9**: **400 mg/kg body weight**: foetuses: no effects; **600 mg/kg body weight**: foetuses: foetotoxicity, teratogenicity; **1200 mg/kg body weight**: foetuses: foetotoxicity, teratogenicity; **3000 mg/kg body weight**: foetuses: embryolethality, foetotoxicity, teratogenicity; **GD 10**: **600 mg/kg body weight**: foetuses: weak foetotoxicity; **1200 mg/kg body weight**: foetuses: foetotoxicity, teratogenicity; **3000 mg/kg body weight**: foetuses: embryolethality, foetotoxicity, teratogenicity; **GD 11**: **600 mg/kg body weight**: foetuses: no effects; **1200 mg/kg body weight**: foetuses: foetotoxicity; **3000 mg/kg body weight**: foetuses: foetotoxicity, teratogenicity;	ECHA 2014

Tab. 2 (continued)

Species	Exposure	Findings	References
		GD 12: **600 mg/kg body weight**: foetuses: no effects; **1200 mg/kg body weight**: foetuses: doubtful foetotoxicity and teratogenicity; **3000 mg/kg body weight**: foetuses: foetotoxicity, teratogenicity; **GD 13**: **1200 mg/kg body weight**: foetuses: no effects; **3000 mg/kg body weight**: foetuses: embryolethality, slight foetotoxicity; **GD 14**: **1200 mg/kg body weight**: foetuses: no effects; **3000 mg/kg body weight**: foetuses: doubtful embryolethality and foetotoxicity; **GD 15**: **1200 mg/kg body weight**: foetuses: no effects; **3000 mg/kg body weight**: foetuses: weak foetotoxicity; no maternal toxicity; original study not available	
rabbit, Himalayan, 10–12 ♀	**GD 6–18**, 0, 94, 282, 470 mg/kg body weight and day, gavage, vehicle: water, purity: technical grade, examination: GD 28	**no NOAEL maternal toxicity**; **94 mg/kg body weight**: **NOAEL developmental toxicity**; **94 mg/kg body weight and above**: dams: body weight gains ↓, food consumption ↓; **282 mg/kg body weight and above**: foetuses: number of resorptions ↑, number of live foetuses/litter ↓, body weights ↓, number of cleft palates ↑ (4 foetuses, statistically not significant, but substance-related; 1 foetus with fused ribs and microphthalmia, number of examined foetuses not specified); **470 mg/kg body weight**: dams: mortality 2/12; foetuses: resorptions 100%	Merkle and Zeller1980; documentation "N,N-Dimethylacetamid" 1998, available in German only

Tab. 2 (continued)

Species	Exposure	Findings	References
Dermal application			
rat, ChR-CD, 6–8 ♀	**GD 9, GD 10–11, GD 11–12, GD 12–13,** 1st study: 0, 600, 1200 mg/kg body weight and day, 2nd study: 0, 600, 1200, 2400 mg/kg body weight and day (only 10–11), as undiluted liquid, open application, purity: > 98%, examination: GD 20	**600 mg/kg body weight and above** foetuses: embryo mortality slightly ↑ (effect less pronounced when applied on GD 12–13 than on GD 10–11); **1200 mg/kg body weight**: 1st study: GD 10–11: foetuses: 3/34 encephalcoele, 2nd study: GD 10–11: dams: stagnation in body weight gains; foetuses: subcutaneous haemorrhage	Stula 1979; Stula and Krauss 1977; documentation "N,N-Dimethylacetamid" 1998, available in German only
rabbit, New Zealand, 5 ♀, controls: 4 ♀	**GD 8–16,** 0, 200 mg/kg body weight and day, as undiluted liquid, open application, purity: > 98%, investigated: GD 30	no unusual findings in foetuses or dams	Stula 1979; Stula and Krauss 1977
Subcutaneous injection			
rat, CD and BD IX, 2–5 ♀	**GD 13, 14 or 15,** GD 13: 600, 800, 1000 mg/kg body weight, GD 14, 15: 1000 mg/kg body weight, subcutaneous, no other details	**GD 13**: **600 mg/kg body weight and above**: number of foetuses with malformations ↑, foetotoxicity (no other details); **GD 14**: **1000 mg/kg body weight**: number of foetuses with malformations ↑, foetotoxicity (no other details); **GD 15**: no unusual findings; no controls, no details of maternal toxicity	von Kreybig et al. 1969

Tab. 2 (continued)

Species	Exposure	Findings	References
Prenatal and postnatal exposure			
rat, Crl:CD(SD) BR, 10 ♂ and 20 ♀	**10 weeks before mating (5 days/week), 7–8 weeks during mating, gestation and lactation (7 days/week), but pregnant ♀ not exposed between GD 21 and PND 4,** 0, 30, 100, 300 ml/m³, vapour, at 300 ml/m³: exposed ♂ mated with untreated ♀ and vice versa, whole-body, 6 hours/day, purity: 99.9%, examination: PND 1, 4, 14, 21	**100 ml/m³: NOAEC parental toxicity;** **300 ml/m³**: parents: body weights ↓, relative liver weights ↑; offspring PND 21: body weights ↓, relative liver weights ↑; **300 ml/m³: NOAEC foetotoxicity;** no unusual findings in parents: body weights, survival, symptoms, fertility, mating, duration of gestation, number, appearance and survival of offspring, weight of reproductive organs; no histological examination of reproductive organs	see also Section "Fertility"; Ferenz and Kennedy 1986; documentation "N,N-Dimethylacetamid" 1998, available in German only

GD: gestation day; NOAEC: no observed adverse effect concentration; NOAEL: no observed adverse effect level; PND: postnatal day

Inhalation

In Crl:CD(SD)IGS rats, after whole-body inhalation exposure to *N,N*-dimethylacetamide vapour between gestation days 6 and 19, reduced body weights were found in the foetuses and increased relative liver weights and hepatocellular swelling in the dams at concentrations of 300 ml/m^3 and above. In the foetuses, *N,N*-dimethylacetamide led to increased incidences of visceral malformations such as ventricular septal defects at concentrations of 450 ml/m^3 and above. In addition, skeletal malformations occurred at 450 ml/m^3 in the form of fused cervical vertebral arches, and fused exoccipital bones at 600 ml/m^3. The NOAEC for developmental toxicity and maternal toxicity was 100 ml/m^3. The NOAEC for teratogenicity was 300 ml/m^3 (Okuda et al. 2006).

In Crl:CD rats, after whole-body inhalation exposure to *N,N*-dimethylacetamide vapour between gestation days 6 and 15, reduced body weights were found in the foetuses and delayed body weight gains in the dams at the highest concentration tested of 282 ml/m^3. The NOAEC for developmental toxicity and maternal toxicity was 100 ml/m^3 (Solomon et al. 1991; documentation "N,N-Dimethylacetamid" 1998, available in German only).

In a study with Himalayan rabbits carried out according to OECD Test Guideline 414 with whole-body inhalation exposure between gestation days 7 and 19, *N,N*-dimethylacetamide vapour led to an increased incidence of additional ribs (variation) on foetus and litter-basis at concentrations of 200 ml/m^3 and above. The NOAEC for developmental toxicity was 57 ml/m^3, the NOAEC for teratogenicity (skeletal and visceral malformations) 200 ml/m^3 and the NOAEC for maternal toxicity was 570 ml/m^3, the highest concentration tested (Klimisch and Hellwig 2000; BG Chemie 1989). For Himalayan rabbits (CHBB:HM, SPF), historical control data from between 1968 and 1999 are available from the laboratories of Boehringer Ingelheim in Biberach. The incidence of additional lumbar ribs was 40 in 7616 (0.5%) foetuses (Viertel and Trieb 2003); this is less than that found in the historical controls of the testing laboratory (0.9%) (see Table 3; Klimisch and Hellwig 2000).

Table 3 Additional ribs (skeletal variation) in rabbits after inhalation exposure to *N,N*-dimethylacetamide (Klimisch and Hellwig 2000)

Exposure (ml/m^3)	Controls	57	200	570	Historical controls
foetal incidence (in percent)	0 (0%)	1 (1.2%)	10 (11%)**	29 (37%)**	2 (0.9%)
litter incidence (in percent)	0 (0%)	1 (7.7%)	6 (43%)*	10 (71%)**	2 (4.5%)

*$p < 0.05$; ** $p < 0.01$ (Fisher's exact test)

Oral administration

In a study with Crl:CD(SD)B rats available only in text form without tables, reduced foetal body weights and one malformed foetus and reduced body weight gains in the dams were found after gavage doses of 150 mg/kg body weight and day administered from gestation days 7 to 21. At 400 mg/kg body weight and day, the total number of malformations and variations was increased. Therefore, the dose of 150 mg/kg body weight and day represents the lower limit of the dose–response relationship for malformations. The NOAEL (no observed adverse effect level) for developmental and maternal toxicity was 65 mg/kg body weight and day (DuPont 1997; documentation "N,N-Dimethylacetamid" 1998, available in German only).

In COBS-CD rats treated by gavage from gestation days 6 to 19, at 400 mg/kg body weight and day an increased number of postimplantation losses and an increased total number of malformations were observed, particularly heart and vessel malformations, as well as variations, especially reduced ossifications and non-ossified sternebrae. At this dose level, the body weight gains in the dams were reduced. The NOAEL for developmental toxicity, that is teratogenicity and maternal toxicity was 160 mg/kg body weight and day (Johannsen et al. 1987; documentation "N,N-Dimethylacetamid" 1998, available in German only).

In an unpublished study, the original of which is not available, with Sprague Dawley rats, gavage doses of 323 mg/kg body weight and day administered from gestation days 6 to 15 led to reduced body weights and slightly increased incidences of external and visceral malformations in the foetuses. At this dose level and above, the body weight gains in the dams were reduced. The NOAEL for developmental toxicity and maternal toxicity was 106 mg/kg body weight and day (ECHA 2014).

In two unpublished studies in NMRI mice, likewise not available in the original, with gavage administration from days 6 to 15 of gestation, decreased foetal body weights and reduced absolute placenta weights were found at the lowest dose tested of 240 mg/kg body weight and day and above. The highest sensitivity to teratogenic effects was seen on gestation day 9 with effects on body weights occurring at 600 mg/kg (ECHA 2014).

In Himalayan rabbits, administration of the substance by gavage from gestation days 6 to 18 led to an increased number of resorptions, a reduced number of live foetuses and an increase in the number of cleft palates that was not statistically significant at 282 mg/kg body weight and day and above. At 94 mg/kg body weight and day and above, body weight gains and food consumption were reduced in the dams. The NOAEL for developmental toxicity was 94 mg/kg body weight and day. A NOAEL for maternal toxicity could not be derived (Merkle and Zeller 1980; documentation "N,N-Dimethylacetamid" 1998, available in German only).

Dermal application

Neither of the two studies with dermal application are used for the evaluation, as the study with ChR-CD rats (Stula 1979; Stula and Krauss 1977; documentation "N,N-Dimethylacetamid" 1998, available in German only) involved only two-day exposures during gestation and in the study with New Zealand White rabbits (Stula 1979; Stula and Krauss 1977) only one dose was tested and the data were inadequately documented.

Subcutaneous injection

Single subcutaneous injections in rats on gestation day 13 produced malformations and foetotoxic effects at 600 mg/kg body weight and above. Administration on gestation day 15 did not produce these effects (von Kreybig et al. 1969). No control animals were used and no data were given for maternal toxicity.

Prenatal and postnatal exposure

In a study of male and female fertility in Crl:CD(SD)BR rats with prenatal and postnatal whole-body inhalation exposure, no substance-related effects were found in the offspring up to postnatal day 4 at the highest concentration tested of 300 ml/m^3. The NOAEC for parental toxicity was 100 ml/m^3 and the NOAEC for foetotoxicity 300 ml/m^3, the highest concentration tested (see also Section "Fertility"; Ferenz and Kennedy 1986; documentation "N,N-Dimethylacetamid" 1998, available in German only).

Manifesto (MAK value/classification)

The critical effects are histological changes in the liver of male rats, such as focal cystic degeneration and peliosis, and in mice haemosiderin/lipofuscin accumulation and apoptosis after inhalation exposure. In both species, the females are less sensitive.

Liver damage occurred also in workers employed in elastane fibre production after exposure to *N,N*-dimethylacetamide.

MAK value. In two workplace studies in Korea, the concentrations in air were not determined and the effects of direct skin contact were not quantified (Jung et al. 2007; Lee et al. 2006). They are therefore not suitable for the derivation of a MAK value. The studies are also not suitable for the derivation of a biological limit value, as the elimination of *N*-methylacetamide by the workers with hepatocellular damage was not directly determined.

In 24-month or 18-month inhalation studies similar to OECD Test Guideline 453 (combined chronic toxicity/carcinogenicity studies), with whole-body exposure of rats or mice to *N,N*-dimethylacetamide vapour, histological changes in the liver occurred in the male animals at concentrations of 100 ml/m^3 and above. The NOAEC was in each case 25 ml/m^3.

On the basis of the NOAEC of 25 ml/m^3 obtained in the long-term inhalation studies and taking into consideration the extrapolation of animal study data to humans (1:2) and the higher respiratory volume of humans at the workplace compared with animals at rest (1:2) as well as the preferred value approach, the MAK value has been lowered to 5 ml/m^3.

The results of studies with humans have shown that after exposure to 1.9 ml/m^3 (geometric 12-hour mean value, corresponding as an 8-hour mean value to about 3 ml/m^3) and short-term exposure to up to about 6.7 ml/m^3, no clinico-chemically determinable hepatotoxicity occurs (Spies et al. 1995). The results therefore do not contradict the MAK value of 5 ml/m^3.

In the documentation of 1998 (documentation "N,N-Dimethylacetamid" 1998, available in German only), it is mentioned that the irritation in the respiratory tract described in other inhalation studies at 100 ml/m³ was not confirmed in the long-term study. The lungs, nose (4 cross-sections including paranasal tissue), trachea and larynx/pharynx were examined histologically in rats and mice of the control group and the high concentration group of 350 ml/m³ and no unusual findings were observed (DuPont 1994; Malley et al. 1995). Therefore, the MAK value of 5 ml/m³ is also sufficient to protect against possible local irritation.

A concentration of 10 ml/m³ in the air corresponds to about 30 mg *N*-methylacetamide/g creatinine after an 8-hour exposure of volunteers without increased physical activity (Nomiyama et al. 2000). Assuming the uptake due to increased respiratory activity to be twice as high, it may be concluded from this that a level of 30 mg *N*-methylacetamide/g creatinine is to be expected at the MAK value of 5 ml/m³; the BAT value is thus observed.

Peak limitation. As the MAK value of *N,N*-dimethylacetamide is derived on the basis of systemic effects, the substance remains assigned to Peak Limitation Category II. The oxidative conversion of *N,N*-dimethylacetamide to *N*-hydroxymethylacetamide or *N*-methylacetamide is, in analogy to dimethylformamide, considered important for hepatotoxicity (Palmen et al. 1993). The supplement on peak limitation from 2002 proposes that the central nervous effects described in the workers exposed to *N,N*-dimethylacetamide may be attributed to metabolites, although this has not been confirmed (supplement "N,N-Dimethylacetamid" 2002, available in German only). There are still no exact details available for the mechanisms of action and the half-lives. The default excursion factor 2 has therefore been retained.

Prenatal toxicity. In 1990, *N,N*-dimethylacetamide was classified in Pregnancy Risk Group C, and in 1998 assignment to Group C was confirmed, as long as skin contact is avoided (documentation "N,N-Dimethylacetamid" 1998, available in German only).

Table 4 gives the NOAECs or the NOAELs of studies relevant for the assessment, their toxicokinetic extrapolation factors and the resulting differences to the MAK value of 5 ml/m³ (18 mg/m³), taking, where necessary, the increased respiratory volume into account. After oral administration, *N,N*-dimethylacetamide is readily absorbed (no other details; OECD 2001). For this reason an oral absorption of 100% is assumed in rats and rabbits.

With the exception of the gavage study in rats and the inhalation study in rabbits, the differences between the MAK value and the calculated NOAECs for developmental toxicity and foetotoxicity from the studies with inhalation exposure and oral administration are sufficiently large. In the gavage study with rats, 150 mg/kg body weight and day was found to be the lower limit of the dose–response relationship for malformations (DuPont 1997). At this dose there is a difference of 15 to the MAK value, which is likewise considered to be sufficiently large. Moreover, if the marginal effects starting at 150 mg/kg body weight and day are taken into account, the NOAEL might be higher than 65 mg/kg body weight and day. In addition, it has to be borne in mind that bolus administration was used and that an adequate margin to the NOAEC was obtained from the inhalation study with rats relevant

Table 4 Relevant NOAECs/NOAELs in rats and rabbits, toxicokinetic extrapolation of the NOAELs to a concentration in air and the resulting differences to the MAK value of 5 ml/m³ (≙ 18 mg/m³)

References	Species, exposure	NOAEC/NOAEL: end point	Toxicokinetic extrapolation[a] (mg/m³)	Difference to MAK value of 18 mg/m³ or 5 ml/m³
	rat			
Okuda et al. 2006; Solomon et al. 1991	prenatal, inhalation	100 ml/m³: developmental toxicity (body weights ↓)		10[b]
Okuda et al. 2006	prenatal, inhalation	300 ml/m³: teratogenicity (cardiovascular and skeletal malformations)		30[b]
Ferenz and Kennedy 1986	prenatal and postnatal, inhalation	300 ml/m³: foetotoxicity		30[b]
DuPont 1997	prenatal, gavage	65 mg/kg body weight and day: developmental toxicity (body weights ↓)	114	6
		150 mg/kg body weight and day: lower limit of the dose–response relationship for malformations	263	15
Johannsen et al. 1987	prenatal, gavage	160 mg/kg body weight and day: developmental toxicity (body weights ↓, postimplantations ↑, skeletal variations ↑) and teratogenicity (heart and vessel malformations)	280	16
	rabbit			
Klimisch and Hellwig 2000	prenatal, inhalation	57 ml/m³: developmental toxicity (body weights ↓, skeletal variations ↑)		6[b]
		200 ml/m³: teratogenicity (skeletal and visceral malformations)		20[b]
Merkle and Zeller 1980	prenatal, gavage	94 mg/kg body weight and day: developmental toxicity (resorptions ↑, live foetuses ↓, body weights ↓) and incipient teratogenicity (cleft palates)	274	15

[a] NOAEL × 1:4 (rat) or 1:2.4 (rabbits) × 70 kg / 10 m³ × 1.0 (oral absorption in animals) / 1.0 (inhalation absorption in humans)
[b] The increased respiratory volume (1:2) has been taken into account.

for the workplace. In the inhalation study with rabbits, the NOAEC and the LOAEC for additional ribs were 57 and 200 ml/m^3, respectively, without maternal toxicity (Klimisch and Hellwig 2000), which means that the NOAEC could in this case also be greater. Therefore, the difference to the MAK value would be greater than 6. In addition, the additional ribs are a skeletal variation indicating merely an incipient marginal effect. For these reasons, assignment to Pregnancy Risk Group C has been confirmed.

N,N-Dimethylacetamide passes easily through the skin. For this reason, in 1990, the additional note that skin contact should be avoided was included (documentation "N,N-Dimethylacetamid" 1998, available in German only). Quantitative data for dermal penetration from animal studies are not available. In humans, the dermal absorption of *N,N*-dimethylacetamide in vapour form is about 40% (Nomiyama et al. 2000). For this reason, the importance of avoiding skin contact is emphasized and attention is additionally drawn to the high level of dermal absorption from the gaseous phase.

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