The MAK Collection for Occupational Health and Safety

Diethylamine

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

A. Hartwig[1,*], MAK Commission[2,*]

[1] *Chair of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Institute of Applied Biosciences, Department of Food Chemistry and Toxicology, Karlsruhe Institute of Technology (KIT), Adenauerring 20a, Building 50.41, 76131 Karlsruhe, Germany*

[2] *Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Kennedyallee 40, 53175 Bonn, Germany*

* *email: A. Hartwig (andrea.hartwig@kit.edu), MAK Commission (arbeitsstoffkommission@dfg.de)*

Keywords: diethylamine; MAK value; maximum workplace concentration; peak limitation; momentary value; ceiling limit value; skin absorption; irritation; olfactory epithelium

Citation Note: Hartwig A, MAK Commission. Diethylamine. MAK Value Documentation, addendum – Translation of the German version from 2016. MAK Collect Occup Health Saf [Original edition. Weinheim: Wiley-VCH; 2018 Apr;3(2):466-480]. Corrected republication without content-related editing. Düsseldorf: German Medical Science; 2025. https://doi.org/10.34865/mb10989e6018_w

Republished (online): 12 Dec 2025

Originally published by Wiley-VCH Verlag GmbH & Co. KGaA; https://doi.org/10.1002/3527600418.mb10989e6018

Addendum completed: 25 Feb 2015

Published (online): 24 Apr 2018

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

Diethylamine

MAK Value Documentation

A. Hartwig[1, *], MAK Commission[2, *]

DOI: 10.1002/3527600418.mb10989e6018

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) of diethylamine of 5 ml/m³, considering all toxicity endpoints. Available unpublished study reports and publications are described in detail. The critical effect of diethylamine is atrophy of the olfactory mucosa in rats and mice in a 2-year study. Since 2014 the Commission uses an empirical approach to set MAK values for substances with critical effects on the upper respiratory tract or the eyes. In the 2-year study no NOAEC for atrophy of the olfactory mucosa was obtained. A Benchmark concentration of 4 ml/m³ (BMDL05) as a substitute for a NOAEC is calculated from the data of the mouse, the most sensitive species. Therefore, the MAK value for diethylamine is lowered to 2 ml/m³. The chronic NOAEC for systemic toxicity is judged to be 16 ml/m³. As local effects are critical, the assignment to Peak Limitation Category I is confirmed. The excursion factor of 2 is set with a read-across to cyclohexylamine. The momentary value is lowered to 5 ml/m³. Because there are no studies on developmental toxicity, the assignment to Pregnancy Risk Group D is confirmed as well. Diethylamine is not genotoxic and not carcinogenic. Skin contact may contribute significantly to systemic toxicity and diethylamine is designated with an "H" notation. Sensitization is not expected from the limited data.

Keywords

diethylamine; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; irritation; allergenic effects; genotoxicity; carcinogenicity; peak limitation; prenatal toxicity; germ cell mutagenicity; absorption through the skin; sensitization; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

Author Information

[1] Chair of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Department of Food Chemistry and Toxicology, Institute for Applied Biosciences, Karlsruhe Institute of Technology (KIT), Adenauerring 20a, Geb. 50.41, 76131 Karlsruhe, Germany

[2] Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Kennedyallee 40, 53175 Bonn, Germany

[*] Email: A. Hartwig (andrea.hartwig@kit.edu), MAK Commission (arbeitsstoffkommission@dfg.de)

Diethylamine

[109-89-7]

Supplement 2016

MAK value (2015)	**2 ml/m³ ≙ 6.1 mg/m³**
Peak limitation (2015)	**Category I, excursion factor 2 momentary value 5 ml/m³**
Absorption through the skin (2015)	**H**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (1994)	**Pregnancy Risk Group D**
Germ cell mutagenicity	**–**
BAT value	**–**
Vapour pressure at 20 °C	253 hPa (ECHA 2013)
log K_{OW}[1]	0.58 (ECHA 2013)
Solubility	miscible with water (ECHA 2013)
pKa value	11.09 (ECHA 2013)
1 ml/m³ ≙ 3.03 mg/m³	**1 mg/m³ ≙ 0.33 ml/m³**

Documentation for diethylamine was published in 1984 (documentation "Diethylamin" 1984, available in German only), followed by supplements in 1996 (supplement "Diethylamin" 1996, available in German only) and 2002 (supplement "Diethylamin" 2002, available in German only).

A 2-year study has since become available (NTP 2011) that has made a re-evaluation of the MAK value necessary.

In 2014, the Commission started using a physiologically and empirically-based method for deriving MAK values for substances that have an effect on the upper respiratory tract and eyes; it also describes criteria for classification as a sensory irritant (Brüning et al. 2014). The MAK value is reviewed on the basis of this approach.

1 octanol/water partition coefficient

Toxicokinetics and Metabolism

There are no studies available.

Undiluted diethylamine is corrosive to the skin. Therefore, studies with undiluted diethylamine cannot be used to evaluate absorption through the skin. The concentration that no longer causes irritation of the skin has yet to be determined (ECHA 2013). The corrosive structural analogue triethylamine is classified as irritating to the skin at concentrations of 1% and above (ECHA 2014). Fluxes of 64, 8.3 and 15.7 μg/cm^2 and hour, respectively, are calculated using the models of Fiserova-Bergerova et al. (1990), Guy and Potts (1993) and Wilschut et al. (1995) for a 0.5% aqueous solution of diethylamine that presumably no longer causes irritation. Assuming the exposure of a 2000 cm^2 surface area of skin for 1 hour, this would correspond to absorbed amounts of 128, 17 and 31 mg, respectively.

The mathematical models were applied also to the base 2-aminoethanol; they agreed well with the in vitro data for skin penetration in humans.

Effects in Humans

According to a study that is of only limited usefulness, the exposure of volunteers to an average concentration of 10 ml/m^3 for 60 minutes induced subjective irritation of the eyes and nose (Lundqvist et al. 1992; see also supplement "Diethylamin" 1996, available in German only).

One patient with sensitization to rubber glove components was found to react to 1% diethylamine in petrolatum in the patch test. The authors also reported that one other patient had a questionable reaction to 2% and another to 5% diethylamine, whereas another patient did not react to 1% diethylamine. Control persons were apparently not tested with the formulations (Kaniwa et al. 1994; supplement "Diethylamin" 1996, available in German only).

Animal Experiments and in vitro Studies

Acute toxicity

Inhalation

The RD_{50} was 200 ml/m^3 in Swiss OF-1 mice (Gagnaire et al. 1993).

Subacute, subchronic and chronic toxicity

Inhalation

Groups of 5 male and 5 female B6C3F1 mice and F344 rats were exposed to diethylamine concentrations of 31, 62.5, 125, 250 or 500 ml/m^3 for 6 hours a day, on 5 days a week, for **2 weeks**. Necrosis was observed in the nasal turbinates of the mice at 31 ml/m^3 and above. Therefore, a NOAEC (no observed adverse effect concentra-

tion) was not obtained in this study. Rats were less sensitive because 31 ml/m³ was the NOAEC and respiratory metaplasia and inflammation were observed only at 62.5 ml/m³ and above (NTP 2011).

Groups of 10 male and 10 female B6C3F1 mice and F344 rats were exposed to diethylamine concentrations of 8, 16, 32, 62 or 125 ml/m³ for 6 hours a day, on 5 days a week, for **2 weeks**. In rats, a statistically significant increase in the incidence of atrophy of the olfactory epithelium and hyperplasia of the respiratory epithelium was found at 62 ml/m³ and above. The statistical NOAEC was thus 32 ml/m³. However, hyperplasia of the respiratory epithelium was still observed in 3 of 10 male rats at 16 ml/m³. In addition, sperm motility was significantly reduced at 32 ml/m³ and above. The systemic NOAEC for rats was thus 16 ml/m³. The local NOAEC for mice was 16 ml/m³; atrophy of the olfactory epithelium was observed at 32 ml/m³ and above; systemic effects were not found (NTP 2011).

Groups of 50 male and 50 female B6C3F1 mice and F344 rats were exposed to diethylamine concentrations of 31, 62.5 or 125 ml/m³ (rats) and 16, 31 or 62.5 ml/m³ (mice) for 6 hours a day, on 5 days a week, for **2 years**. In rats, the incidence of atrophy of the olfactory epithelium was almost 100% even at the low concentration of 31 ml/m³. Therefore, it was not possible to calculate a BMDL. Furthermore, the accumulation of hyaline droplets in various areas of the nose and hyperplasia of the respiratory epithelium was observed at this concentration. In addition, inflammation of the pleura and alveolar histiocytic cellular infiltration were found in the females, but the concentration–effect relationship was less steep than that for nasal effects. Systemic effects did not occur. In mice, hyperostosis of the turbinates was detected in all concentration groups (23/50 at 16 ml/m³). In rats, this finding was observed far less frequently even at a concentration that was 8 times higher (3/50 and 2/50 at 125 ml/m³). As the anatomy of the upper respiratory tract of mice is much more like that of rats than that of humans, the incidence of this effect in rats would be expected to be similar to that in mice. Therefore, mice seem to be particularly sensitive and the relevance of this finding for humans is questionable. Like in rats, atrophy of the olfactory epithelium was observed in male and female mice at the lowest concentration of 16 ml/m³ and above and respiratory metaplasia of the olfactory epithelium occurred in female mice. In mice, the accumulation of hyaline droplets in the nasal epithelium was additionally observed. The incidences of most findings increased with the increase in the concentration. There was no evidence of concentration-related or substance-induced systemic effects in mice (NTP 2011).

In this study, hyaline droplets in the nasal epithelium were found also in control rats with incidences of 10% to 20% and in control mice with incidences of 10% to 30%. Therefore, the question remains whether the increased incidence in exposed animals is adverse or merely an adaptive effect. This effect was regarded as adaptive also in the case of dimethylamine (Monticello et al. 1990).

The NOAECs of the individual studies are summarized in Table 1 and the incidences of the most important end points in the 2-year study are given in Table 2.

Table 1 NOAECs (ml/m³) (no statistically significant increase in incidences compared with in the control animals) for diverse end points in the studies with diethylamine in rats and mice; incidences given in brackets (NTP 2011)

End points	Rat ♂			Rat ♀			Mouse ♂			Mouse ♀		
	2 weeks	3 months	2 years	2 weeks	3 months	2 years	2 weeks	3 months	2 years	2 weeks	3 months	2 years
nose: suppurative inflammation	31 (0)	62 (2/10)	62 (10/50)	62 (2/5)	62 (3/10)	31 (4/49)	125 (3/5)	62 (0)	31 (6/50)	62 (0)	62 (3/10)	31 (3/50)
respiratory epithelium: squamous metaplasia	31 (0)	62 (1/10)	31 (2/50)	62 (2/5)	62 (0)	62 (5/50)	62 (0)	62 (1/10)	16 (7/50)	62 (0)	62 (1/10)	16 (0)
respiratory epithelium: hyperplasia	–	32 (3/10 also at 16 ml/m³!)	< 31 (34/50; controls: 5/49)	–	32 (0)	< 31 (31/49; controls: 7/50)	–	–	–	–	–	–
respiratory epithelium: hyaline droplets	–	–	< 31 (29/50; controls: 0/49)	–	–	< 31 (48/49; controls: 4/50)	–	–	31 (19/50)	–	–	? not related to concentration
glands, respiratory epithelium: hyaline droplets	–	–	< 31 (45/50; controls: 60/49)	–	–	< 31 (46/49; controls: 9/50)	–	–	16 (5/50)	–	–	< 16 (28/49; controls: 16/50)
olfactory epithelium: atrophy	125 (0)	32 (0)	< 31 (49/50; controls: 2/49)	125 (0)	32 (2/10)	< 31 (47/49; controls: 1/50)	62 (0)	16 (0)	< 16 (19/50; controls: 9/50)	62 (1/5)	16 (0)	< 16 (29/49; controls: 8/50)

Table 1 (continued)

End points	Rat ♂			Rat ♀			Mouse ♂			Mouse ♀		
	2 weeks	3 months	2 years	2 weeks	3 months	2 years	2 weeks	3 months	2 years	2 weeks	3 months	2 years
olfactory epithelium: respiratory metaplasia	–	–	–	–	–	–	–	–	16 (15/50)	–	–	< 16 (15/49; controls: 4/50)
olfactory epithelium: hyaline droplets	–	–	< 31 (49/50; controls: 8/49)	–	–	< 31 (49/49; controls: 11/50)	–	–	–	–	–	–
turbinates: necrosis	62 (0)	125 (1/10)	62 (1/50)	62 (0)	125 (1/10)	62 (0)	< 31 (5/5)	62 (0)	62 (3/50)	< 31 (4/5)	62 (0)	62 (1/50)
turbinates: hyperostosis	–	–	125 (3/50)	–	–	125 (2/50)	–	–	< 16 (23/50; controls: 5/50)	–	–	< 16 (23/49; controls: 4/50)
alveoli: inflammation	–	–	–	–	–	< 31 (24/50; controls: 13/50)	–	–	–	–	–	–

<: A NOAEC was not obtained at the lowest concentration tested. Nevertheless, the incidence was high for some end points at the statistical NOAEC, for example "suppurative inflammation, male rats, 2 years": 10/50
–: This end point was not observed in the study.

Table 2 The most important end points in the 2-year study with diethylamine in rats and mice (NTP 2011)

Rat		Concentration (ml/m³)			
		Controls	31	62.5	125
glands, respiratory epithelium: hyaline droplets	♂	6/49	45/50**	42/50**	45/50**
	♀	9/50	46/49**	45/50**	44/50**
olfactory epithelium: hyaline droplets	♂	8/49	49/50**	49/50**	42/50**
	♀	11/50	49/49**	50/50**	48/50**
olfactory epithelium: atrophy	♂	2/49	**49/50****	50/50**	50/50**
	♀	1/50	**47/49****	48/50**	50/50**
respiratory epithelium: hyaline droplets	♂	0/49	29/50**	42/50**	11/50**
	♀	4/50	48/49**	46/50**	39/50**
respiratory epithelium: hyperplasia	♂	5/49	34/50**	35/50**	47/50**
	♀	7/50	31/49**	41/50**	50/50**
turbinates: hyperostosis	♂	0/49	0	0	3/50
	♀	0/50	0	0	2/50
alveoli: histiocytic infiltration	♀	13/50	24/49**	27/50**	35/50**
pleura: chronic inflammation	♀	6/50	14/49*	12/50	21/50**
Mouse		Concentration (ml/m³)			
		Controls	16	31	62.5
glands, respiratory epithelium: hyaline droplets	♂	5/50	5/50	16/50**	33/50**
	♀	16/50	28/49**	45/50**	42/50**
olfactory epithelium: atrophy	♂	9/50	**19/50***	50/50**	50/50**
	♀	8/50	**29/49****	49/50**	50/50**
olfactory epithelium: respiratory metaplasia	♂	14/50	15/50	44/50**	50/50**
	♀	4/50	15/49**	48/50**	50/50**
turbinates: hyperostosis	♂	5/50	23/50**	50/50**	50/50**
	♀	4/50	23/49**	49/50**	50/50**

*$p \leq 0.05$; **$p \leq 0.01$; bold type: most sensitive end point relevant to humans

If hyperostosis is regarded as a particularly sensitive end point in mice that cannot be applied directly to humans and if the adversity of hyaline droplets is unclear, then the end point relevant for deriving a limit value is atrophy of the olfactory epithelium. In rats, a NOAEC cannot be established for this end point, nor can a benchmark concentration be calculated. The concentration–effect relationship is sublinear for male mice and linear for female mice (Figure 1). However, a sublinear course might have been obtained also for female mice at concentrations below 16 ml/m³.

In mice, the end point of respiratory metaplasia in the olfactory epithelium has a less steep concentration–effect relationship than atrophy of the olfactory epitheli-

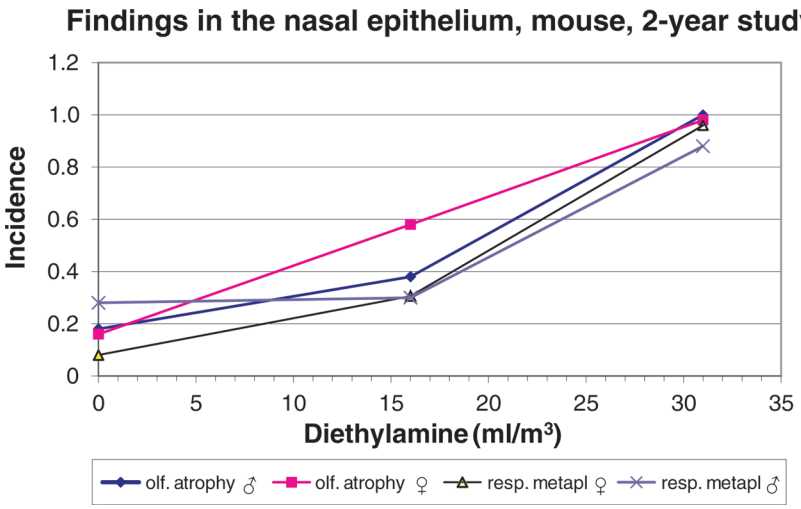

Figure 1 Concentration–effect relationships (without the high concentration because an incidence of almost 100% was recorded at the middle concentration) for atrophy and respiratory metaplasia in the olfactory epithelium in mice after exposure to diethylamine for 2 years (NTP 2011)

um. Male mice are less sensitive. Thus, the most sensitive end point in female mice is atrophy of the olfactory epithelium.

The benchmark dose software (BMDS 1.4.1) of the US EPA was used to calculate a benchmark dose (BMD_{05}) and its lower 95% confidence limit ($BMDL_{05}$) based on the data of the 2-year study in mice for a 5% increase in the incidence of atrophy of the olfactory epithelium over the incidence in control animals (Table 3).

The models that yield the lowest AIC (Akaike Information Criterion) are used to calculate the BMDL. The $BMDL_{05}$ is 1.4 ml/m³ for females and 11.5 ml/m³ for males. Females are thus clearly more sensitive than males, although there is no obvious reason for this large sex-based difference. The concentration–effect relationship in females appears to be linear; this is not very plausible because the courses of the concentration–effect relationships were sublinear after 3 months (Figure 2). However, the 2-year study did not include a lower concentration that might have substantiated a sublinear course. Therefore, calculating the BMD from the linear course of the concentration–effect relationship for female mice in the 2-year study is to be regarded as a conservative approach. Female mice continued to be more sensitive than males even after 3 months (Figure 2). This sex difference applies also to rats (Figure 3), but a comparison of the incidences at 31 ml/m³ after 3 months shows that rats are generally less sensitive than mice: female rats: 20%; male rats: 0%; female mice: 90%; male mice: 40%.

Table 3 Benchmark dose calculations for atrophy of the olfactory epithelium of male and female mice in the 2-year study of the NTP (2011)

Model	AIC	P	BMD_{05} (ml/m³)	$BMDL_{05}$ (ml/m³)
♀				
gamma restr/not restr	126.037	0.99	7.8	4.0
log-logistic	126.077	0.88	9.3	6.2
multistage 2-degree polynomial restr	**124.877**	**0.6798**	**4**	**1.4**
multistage 3-degree polynomial restr	126.037	1	2.8	1.0
log-probit restr/not restr	126.039	0.97	9.0	5.9
probit	125.5	0.50	1.9	1.5
Weibull restr/not restr	126.037	0.999	5.5	2.7
♂				
gamma restr/not restr	118.377	0.79	12.2	10.3
logistic	134.66	0.0001	2.9	2.1
log-logistic restr/not restr	**117.547**	**0.999**	**14.5**	**11.5**
multistage 2-degree polynomial restr	131.8	0.005	4.5	3
multistage 3-degree polynomial restr	122.294	0.18	7.6	4.3
log-probit restr/not restr	119.546	0.99	14.5	11.5
probit	133.969	0.0013	2.4	1.9
quantal	152.094	0	0.9	0.7
Weibull not restr	119.546	0.9981	12.1	8.5
Weibull restr	119.546	0.9975	12.1	8.5

restr/not restr = with/without parameter restriction

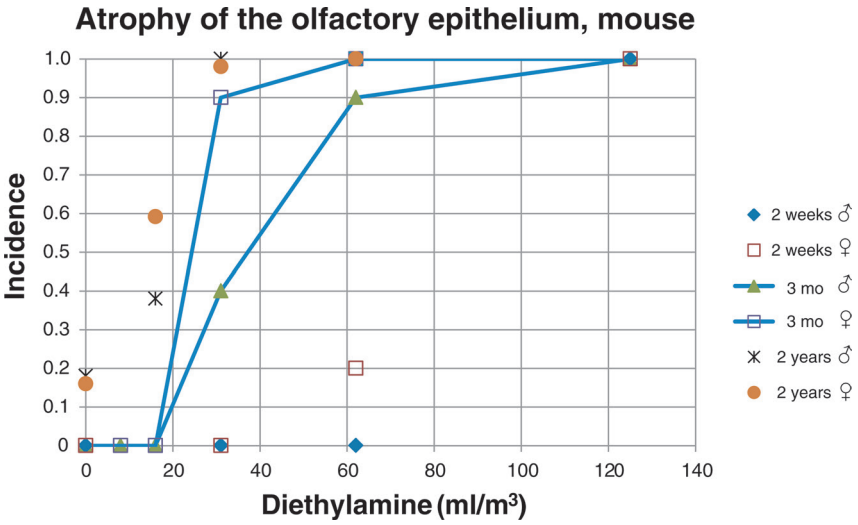

Figure 2 Incidences of atrophy of the olfactory epithelium after exposure to diethylamine in mice (NTP 2011)

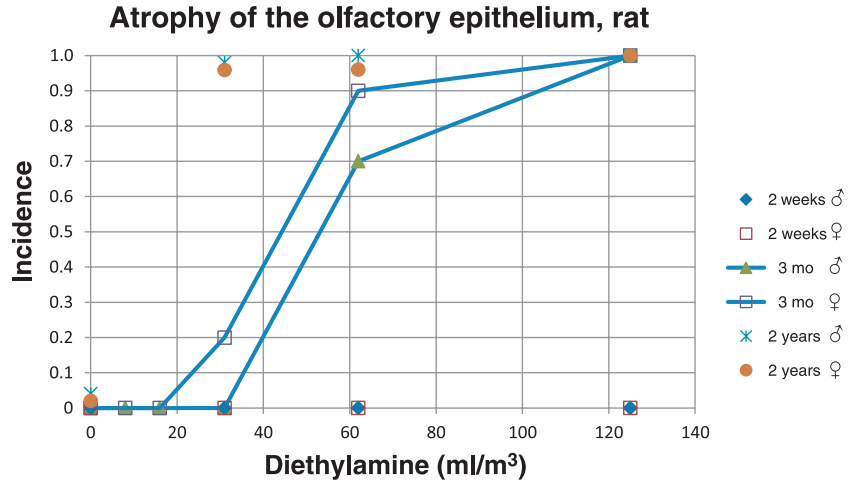

Figure 3 Incidences of atrophy of the olfactory epithelium after exposure to diethylamine in rats (NTP 2011)

Conclusion:
A linear concentration–effect course in female mice after 2 years is not plausible because a sublinear concentration–effect relationship is more common for local irritation and was observed also after 3 months. This would be expected also after 2 years, but cannot be substantiated because a lower concentration was not tested. Therefore, the derivation of the BMDL from the data for female mice is to be regarded as conservative. A $BMDL_{05}$ of 4 ml/m³ would be consistent also with the gamma, log-logistic and log probit benchmark models (much better fit (high p value) than the multistage degree-2 model) while still reflecting the higher sensitivity of the females. The multistage model leads to a relatively linear extrapolation of the further course of the concentration–effect curve and is not really suitable for sublinear courses, which becomes evident when the data for females from the 3-month study are considered. The multistage degree-2 model calculated a BMDL of 4 ml/m³ based on these data, even though an unequivocal NOAEC of 16 ml/m³ had been obtained. Therefore, an overall NAEC (no adverse effect concentration) of 4 ml/m³ can be derived from the 2-year study. A N(O)AEC cannot be derived from the data for rats. However, as the incidences after 3 months show that mice have a greater sensitivity, this can be assumed to be the case also after 2 years.

Local effects on skin and mucous membranes

Diethylamine has corrosive effects on the skin and eyes (supplement "Diethylamin" 1996, available in German only).

Allergenic effects

In a modified maximization test, groups of 5 Crl:(HA)BR guinea pigs were treated with various concentrations of test formulations for induction. Formulations of 0.01% to 0.3% in corn oil were used for intradermal induction and formulations of 0.3% to 10% in corn oil were used for topical induction. After 48 hours, only 1 of 5 animals induced with 0.3%/10% (A) and 0.1%/3% (B) reacted to challenge treatment with 3% and 10% diethylamine in corn oil, respectively. Likewise, 1 of 5 animals reacted in the groups induced with 0.03%/1% (C) and 0.01%/0.3% (D), respectively, but only after 24 hours. In groups A and B, 3 of 5 animals in each group reacted to challenge treatment with 30% diethylamine after 48 hours. In groups C and D, no animal and 1 animal, respectively, reacted after 48 hours and 2 and 4 of 5 animals reacted after 24 hours. No reactions were observed in the control animals (van Och et al. 2001).

The local lymph node assay (LLNA) in male and female BALB/c mice yielded a value of about 40% for the diethylamine concentration in acetone/olive oil (4:1) that leads to a tripling of lymphocyte proliferation (EC3 value) (van Och et al. 2000, 2001).

Likewise, the LLNA results after the addition of sodium dodecyl sulfate were more indicative of irritation caused by the combination of substances (De Jong et al. 2002): A 1% and 10% formulation of sodium dodecyl sulfate led to a stimulation index of 1.1 and 17.1, respectively, and a 20% diethylamine formulation resulted in

a stimulation index of 0.9. Stimulation indices of 3.7 and 20.1 were obtained for the combination of 1% sodium dodecyl sulfate and 20% diethylamine and for the combination of 10% sodium dodecyl sulfate and 20% diethylamine, respectively. The second, but not the first combination led to more pronounced stimulation of IL-4 and IFN-γ secretion compared with that caused by the 10% formulation of sodium dodecyl sulfate (De Jong et al. 2002).

Diethylamine was found to have only very slight effects in vitro in an assay with murine HEL-30 cells and in a test with a cell line derived from human keratinocytes (HaCaT). Diethylamine concentrations of about 10×10^6 µM (HEL-30) or about 2×10^4 µM (HaCaT) were necessary to triple IL-1α stimulation (for comparison, 2,4-dinitrochlorobenzene (DNCB): about 2×10^{-2} µM and 5×10^{-2} µM). Concentrations of about 640 µM (HEL-30) or about 11×10^3 µM (HaCaT) were necessary to triple IL-18 stimulation (for comparison DNCB: about 3×10^{-5} and 5×10^{-3} µM) (van Och et al. 2005).

Genotoxicity

Diethylamine was not mutagenic in a Salmonella mutagenicity test with pre-incubation using the strains TA98, TA100, TA1535 or TA1537 at concentrations of 33 to 3333 µg/plate with and without the addition of metabolic activation (supplement "Diethylamin" 1996, available in German only); likewise, it was not mutagenic in other mutagenicity tests (documentation "Diethylamin" 1984, available in German only).

The ECHA registration database includes further tests with negative results: another bacterial mutagenicity test in Salmonella typhimurium TA98, TA100 and E. coli WP2 uvrApKM 101, an HPRT (hypoxanthine guanine phosphoribosyl transferase) test with mouse lymphoma cells and a micronucleus test in mice (ECHA 2013).

Carcinogenicity

The 2-year NTP study, in which groups of 50 male and 50 female B6C3F1 mice and F344 rats were exposed to 0, 31, 62.5 or 125 ml/m³ (rats) and 0, 16, 31 or 62.5 ml/m³ (mice) for 6 hours a day, on 5 days a week, for 2 years, did not reveal increased incidences of tumours in rats or mice (Section "Subacute, subchronic and chronic toxicity"; NTP 2011).

Manifesto (MAK value/classification)

Irritation of the olfactory epithelium of rats and mice is the critical effect.

MAK value. The findings of the volunteer study (Lundqvist et al. 1992) are not suitable for deriving a NOAEC or a MAK value because an increasing concentration was used. The most sensitive relevant end point is the atrophy of the olfactory epithelium observed in rats and mice even at the lowest concentrations tested (NTP 2011). It was

not possible to calculate a BMDL for rats from the 2-year study because of the high concentrations used. The $BMDL_{05}$ (NAEC) for mice is 4 ml/m³. The results of the 3-month study for this end point showed that rats are far less sensitive than mice at the same concentration. A MAK value of 2 ml/m³ was obtained from the long-term $BMDL_{05}$ of 4 ml/m³ for atrophy of the olfactory epithelium after extrapolating the effects on the olfactory epithelium from animal studies to humans (1:2) according to the method described by Brüning et al. (2014).

A MAK value can be derived also from the 3-month study:

By extrapolating the effects on the olfactory epithelium from animal studies to humans (1:2) and taking into consideration that the effects increased in intensity after long-term exposure (1:2) according to the method described by Brüning et al. (2014), it is possible to derive a concentration of 4 ml/m³ for rats and mice from the NOAEC of 16 ml/m³ for atrophy of the olfactory epithelium after medium-term exposure. Using the preferred value approach, this likewise leads to a MAK value of 2 ml/m³.

The MAK value for diethylamine has therefore been lowered to 2 ml/m³.

As regards systemic effects, the NOAEC for spermatotoxicity in rats was 16 ml/m³ after 3-month exposure. The concentration of 16 ml/m³ is assumed also to be the NAEC after long-term exposure because it is based on data from a complete spermatogenesis cycle. The MAK value of 2 ml/m³ thus provides protection also against this effect.

Peak limitation. Because local effects are primary, classification in Peak Limitation Category I has been retained. A LOAEC (lowest observed adverse effect concentration) of 10 ml/m³ was obtained from the volunteer study (Lundqvist et al. 1992; see also supplement "Diethylamin" 1996, available in German only). An excursion factor of 2 has therefore been established. This excursion factor is supported by a volunteer study with cyclohexylamine (Juran et al. 2012), which showed that an average concentration of 2 ml/m³ with peaks of 4 ml/m³ is the NOAEC for subjective and objective symptoms. As the RD_{50} of diethylamine is 4 times higher than that of cyclohexylamine, cyclohexylamine causes severer irritation than diethylamine and the comparison is a worst-case assumption. The momentary value of diethylamine has been lowered to 5 ml/m³ because marked irritation was reported for a cyclohexylamine concentration of 10 ml/m³ and the diethylamine concentration of 10 ml/m³ was established to be the LOAEC for local effects also in the study of Lundqvist et al. (1992).

Prenatal toxicity. There are no studies available for the developmental toxicity of the substance. Therefore, diethylamine remains in Pregnancy Risk Group D.

Carcinogenicity. There was no increased incidence of tumours in rats or mice in the 2-year study. Diethylamine is therefore not classified in any of the categories for carcinogens.

Germ cell mutagenicity. The studies available for genotoxicity in vitro and in vivo yielded negative results. Diethylamine is therefore not classified in any of the categories for germ cell mutagens.

Absorption through the skin. An absorbed amount of up to 128 mg is estimated for humans using a model calculation based on the exposure of a 2000 cm^2 surface area of skin for 1 hour and a 0.5% solution, which is presumed to be not irritating. As the NAEC for systemic toxicity (spermatotoxicity) is 16 ml/m^3 (48 mg/m^3) after long-term inhalation exposure in rats, a systemically tolerable amount of 120 mg is calculated when this value is extrapolated to humans (48 $mg/m^3 \times 10\ m^3$ / 2 (animal study–humans) / 2 (respiratory volume at the workplace)). The amount absorbed through the skin is thus more than 25% of the systemically tolerable amount, and the substance is designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. The few human data available for this corrosive substance and the experimental findings from animal studies cannot be evaluated with certainty because of the irritation caused by the substance. However, the findings are generally classified as non-specific or irritative. There are no data available for sensitizing effects on the respiratory tract. Diethylamine is therefore not designated with "Sh" or "Sa" (for substances which cause sensitization of the skin or airways).

References

Brüning T, Bartsch R, Bolt HM, Desel H, Drexler H, Gundert-Remy U, Hartwig A, Jäckh R, Leibold E, Pallapies D, Rettenmeier AW, Schlüter G, Stropp G, Sucker K, Triebig G, Westphal G, van Thriel C (2014) Sensory irritation as a basis for setting occupational exposure limits. Arch Toxicol 88: 1855–1879

De Jong WH, Tentij M, Spiekstra SW, Vandebriel RJ, Van Loveren H (2002) Determination of the sensitising activity of the rubber contact sensitisers TMTD, ZDMC, MBT and DEA in a modified local lymph node assay and the effect of sodium dodecyl sulfate pretreatment on local lymph node responses. Toxicology 176: 123–134

ECHA (European Chemicals Agency) (2013) Information on registered substances. Dataset on diethylamine (CAS Number 109-89-7), joint submission, first publication 03.03.2011, last modification 16.12.2013, http://echa.europa.eu/web/guest/information-on-chemicals

ECHA (2014) Information on registered substances. Dataset on triethylamine (CAS Number 121-44-8), joint submission, first publication 03.03.2011, last modification 26.05.2014

Fiserova-Bergerova V, Pierce JT, Droz PO (1990) Dermal absorption potential of industrial chemicals: criteria for skin notation. Am J Ind Med 17: 617–635

Gagnaire F, Azim S, Simon P, Cossec B, Bonnet P, De Ceaurriz J (1993) Sensory and pulmonary irritation of aliphatic amines in mice: a structure-activity relationship study. J Appl Toxicol 13: 129–135

Guy RH, Potts RO (1993) Penetration of industrial chemicals across the skin: a predictive model. Am J Ind Med 23: 711–719

Juran SA, van Thriel C, Kleinbeck S, Schäper M, Falkenstein M, Iregren A, Johanson Gl (2012) Neurobehavioral performance in human volunteers during inhalation exposure to the unpleasant local irritant cyclohexylamine. Neurotoxicology 33: 1180–1187

Kaniwa M, Isama K, Nakamura A, Kantoh H, Hosono K, Itoh M, Shibata K, Usuda T, Asahi K, Osada T, Matsunaga K, Ueda H (1994) Identification of causative chemicals of allergic con-

tact dermatitis using a combination of patch testing in patients and chemical analysis: application to cases from rubber gloves. Contact Dermatitis 31: 65–71

Lundqvist GR, Yamagiwa M, Pedersen OF, Nielsen GD (1992) Inhalation of diethylamine – acute nasal effects and subjective response. Am Ind Hyg Assoc J 53: 181–185

Monticello TM, Morgan KT, Uraih L (1990) Nonneoplastic lesions in rats and mice. Environ Health Perspect 85: 249–274

NTP (National Toxicology Program) (2011) Toxicology and carcinogenesis studies of diethylamine (CAS No. 109-89-7) in F344/N rats and B6C3F1 mice (inhalation studies). Technical Report 566,
http://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr566.pdf

van Och FM, Slob W, de Jong WH, Vandebriel RJ, van Loveren H (2000) A quantitative method for assessing the sensitizing potency of low molecular weight chemicals using a local lymph node assay: employment of a regression method that includes determination of the uncertainty margins. Toxicology 146: 49–59

van Och FM, Vandebriel RJ, Prinsen MK, De Jong WH, Slob W, van Loveren H (2001) Comparison of dose-responses of contact allergens using the guinea pig maximization test and the local lymph node assay. Toxicology 167: 207–215

van Och FM, Van Loveren H, Van Wolfswinkel JC, Machielsen AJ, Vandebriel RJ (2005) Assessment of potency of allergenic activity of low molecular weight compounds based on IL-1alpha and IL-18 production by a murine and human keratinocyte cell line. Toxicology 210: 95–109

Wilschut A, ten Berge WF, Robinson PJ, McKone TE (1995) Estimating skin permeation. The validation of five mathematical skin permeation models. Chemosphere 30: 1275–1296

completed 25.02.2015