



Danish Ministry of the Environment
Environmental Protection Agency

**Evaluation of health hazards by exposure to
N,N-Dimethyl-1,3-propanediamine
and proposal of a health-based quality
criterion for ambient air.**

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Evaluation of health hazards by exposure to N,N-Dimethyl-1,3-propanediamine and proposal of a health-based quality criterion for ambient air

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Preface

The Danish Environmental Protection Agency has requested an evaluation of health hazards by exposure to N,N-Dimethyl-1,3-propanediamine and proposal of a health based quality criterion for ambient air. This resulted in 2006 in the present report, which was prepared by Elsa Nielsen and Ole Ladefoged, Department of Toxicology and Risk Assessment, Danish Institute for Food and Veterinary Research, i.e. the present Division of Toxicology and Risk Assessment, National Food Institute, Technical University of Denmark.

The report has been subjected to review and discussion and has been endorsed by a steering committee consisting of representatives from the following Danish authorities:

The Danish Working Environment Authority,
The Danish Ministry of Food, Agriculture and Fisheries (The Faculty of Agricultural Sciences),
The Danish Veterinary and Food Administration,
The National Board of Health, Denmark,
The Danish Environmental Protection Agency

The Danish Environmental Protection Agency
Copenhagen, September 2013.

1 General description

The toxicological properties for N,N-Dimethyl-1,3-propanediamine (DMAPA) are evaluated in this document with the purpose of setting a health based quality criterion in ambient air as DMAPA has been proposed as a substituent for the use of triethylamine in a foaming process.

1.1 Identity

Molecular formula:	$C_5H_{14}N_2$
Structural formula:	$NH_2-CH_2-CH_2-CH_2-N-(CH_3)_2$
Molecular weight:	102.18
CAS-no.:	109-55-7
Synonyms:	3-Aminopropyldimethylamine Dimethyl aminopropylamine 3-(Dimethylamino)propylamine DMAPA

1.2 Physical / chemical properties

Description:	DMAPA is a colourless liquid with a smell of ammonia.
Purity:	The technical product generally yielded with a purity of >98%.
Melting point:	< -60 °C
Boiling point:	135 °C
Density:	0.816-0.818 g/ml (at 20°C)
Vapour pressure:	6.0-7.5 mmHg (8-10 hPa) (at 20°C)
Concentration of saturated vapours:	33500-41900 mg/m ³ (at 20°C and 760 mmHg)
Vapour density:	(air = 1)
Conversion factor:	1 ppm = 4.25 mg/m ³ (at 20°C and 760 mmHg) 1 mg/m ³ = 0.235 ppm
Flash point:	32 °C (closed cup)
Flammable limits:	2.3-12.3 (v/v% in air)

Autoignition temp.:	215 °C, 305 °C
Solubility:	Water: miscible (at 20°C)
logP _{octanol/water} :	-0.352, -0.4
Henry's constant:	1.46 x 10 ⁻² ; 4.4 x 10 ⁻⁴ (Pa x m ³) / mol (at 20°C)
pK _a -value:	pK ₁ = 9.91; pK ₂ = 7.67
Stability:	-
Incompatibilities:	-
Other properties:	pH ca. 12.2-12.7 at 100 g/l water (at 20°C)
Odour threshold, air:	-
References:	BUA (1998), IUCLID (2000)

1.3 Production and use

DMAPA is produced from acrylonitrile and dimethyl amine in a 2-stage process. In the first stage, acrylonitrile and dimethyl amine react to form 3-dimethyl aminopropionitrile, which, in the second stage, is hydrogenated to DMAPA. (BUA 1998).

DMAPA is used as an intermediate in the production of binding agents, ion-exchange materials, flocculating agents (water treatment), cosmetic agents, washing and cleaning agents (betaines), additives for petrol and other fuels, polyurethane fibres and lubricants, dyes, agrochemicals, agents used in the photographic and textile industries, etc. DMAPA is also used directly as a hardener in epoxy resins (paints and varnish sector) in the plastics industry, as a cross-linking agent for cellulose fibres in the paper industry, and as an anti-shrinking agent for leather. (BUA 1998).

1.4 Environmental occurrence

No data regarding the occurrence of DMAPA in ambient air, water, soil, or foodstuffs have been found.

1.5 Environmental fate

1.5.1 Air

No data have been found.

For the reaction of DMAPA with OH radicals in the atmosphere, a half-life of 3.2 hours has been calculated (BUA 1998).

1.5.2 Water

In a closed bottle test, DMAPA was not readily biodegradable as the pass level of 60% degradation was reached only after 10 days incubation (BUA 1998).

According to the results of a test carried out with adapted activated sludge (OECD TG 302B), DMAPA is inherently biodegradable (BUA 1998).

The Henry's Law constant indicate a slow volatilisation of DMAPA from water into the atmosphere (BUA 1998).

1.5.3 Soil

The available data on biological degradation in aquatic systems indicate that biodegradation can also occur in the soil. Depending on soil moisture content, geoaccumulation in soil may occur. (BUA 1998).

1.5.4 Bioaccumulation

The n-octanol/water partition coefficient (ca. -0.4) indicates no potential for bioaccumulation.

1.6 Human exposure

The general population can be exposed to DMAPA in consumer products such as cosmetics, detergents, cleansing solutions, and disinfectants, containing betaines as e.g., cocamidopropyl betaine (CAPB). DMAPA may be present in these products as an impurity resulting from the manufacturing of the betaines.

Exposure of the general population due to emission from processing plants can also take place.

2 Toxicokinetics

2.1 Absorption, distribution, elimination

No data have been found.

2.2 Mode of action

No data have been found.

3 Human toxicity

3.1 Toxicity and irritation

A study (1974) has examined the respiratory effects in 25 mold room workers (7 assemblers, 8 pressmen, and 10 other) exposed to an epoxy resin system containing DMAPA in a ski factory in the USA and in 9 controls (Sargent et al. 1976). All subjects worked a 10-hour shift, Monday through Thursday. The examination included two parts, a standardised questionnaire and pulmonary function tests (forced vital capacity (FVC), one-second forced expiratory volume ($FEV_{1.0}$), and maximum expiratory flow at 25 and 50% of lung volume (MEF25% and MEF50%)) carried out at the beginning and at the end of the Monday and Thursday shifts. DMAPA was present in the mold room at concentrations ranging from 0.41 to 0.71 ppm (1.7 to 3.0 mg/m^3); however, the concentrations in the region of the assemblers tended to be the highest and personnel samplers worn by the assemblers showed concentrations of DMAPA ranging from 0.55 to 1.38 ppm (2.3 to 5.9 mg/m^3). Acute symptoms were only reported by mold room workers. A dry cough was the most common complaint of the pressmen while assemblers more often complained of wheezing or chest tightness; eye, nose, and throat irritation were also reported with the highest prevalence in assemblers. Also among the assemblers, a significant decrease in lung function was observed during Monday as well as during the course of the working week (significantly decreased FVC, $FEV_{1.0}$, MEF25% and MEF50% over Monday and over the week); the pressmen as well as the 'other mold room workers' showed no significant change in lung function.

A cross-sectional study (Brubaker et al. 1979) was conducted at the same factory with 34 workers (8 assemblers, 6 gluers, 8 pressmen, 6 with non-specified tasks, and 6 office workers). This study was one of a series of studies in order to determine the effectiveness of ventilation improvements in reducing the level of DMAPA and in eliminating the decrease in pulmonary function over the workshift. The examination included two parts, a standardised questionnaire and lung function tests (forced vital capacity (FVC), one-second forced expiratory volume ($FEV_{1.0}$), forced mid-expiratory flow ($FEF_{25-75\%}$), and forced end-expiratory flow ($FEF_{75-85\%}$)) carried out at the beginning and at the end of the Monday and Thursday shifts. An average DMAPA concentration of 0.13 ppm (0.55 mg/m^3) was measured in the respiratory zone of the assemblers; this was a reduction to nearly one-seventh of the average level of 0.9 ppm (3.8 mg/m^3) in 1974. Of the 28 persons exposed to DMAPA, 5 complained of irritation of the nasal mucosa and 2 of phlegm (increased mucous formation in the respiratory tract); the control persons (office workers) had no respiratory complaints. The lung function of assemblers and pressmen was not decreased significantly over the workshift (mid- and end-expiratory flows actually increased for assemblers). Among the 6 workers with non-specified tasks ('other mold room workers'), a significant reduction (3.9%) in vital capacity (FVC) was observed at the end of the first working day of the week compared with results obtained prior to starting work. Comparison of the data on pulmonary function in the five different subgroups showed no significant differences in any function between the groups.

3.2 Sensitisation

Some studies and case stories are available on the sensitising potential of DMAPA in shampoos, detergents, cleansing solutions, and disinfectants containing betaines. Furthermore, a few case stories are available regarding allergic contact dermatitis caused by DMAPA in chemical products.

Among 1200 eczematous patients tested with cocamidopropyl betaine (CAPB, 1% aqueous solution), 46 subjects (3.8%) showed contact allergy. Thirty of these patients were subsequently tested with the substances used in the synthesis of CAPB. In all 30 subjects, positive reactions were obtained to a 1% aqueous solution of DMAPA. (Angelini et al. 1995).

In a further study, 34 patients with contact allergy to DMAPA were patch tested with DMAPA at various concentrations in water. At 0.1%, 18 subjects showed a positive response while none showed a response to concentrations up to 0.01%. This study also showed that the sensitising chemical structures in DMAPA (and related molecules) are the primary amine and the tertiary (dimethyl-substituted) amine groups, when separated by either 2 or 3 carbon atoms. (Angelini et al. 1996).

When 285 patients with dermatitis were patch tested with a European standard series, supplemented with oleamidopropyl dimethylamine (use in moisturising creams and lotions, hair conditioners and shampoos, and other hair care products), CAPB and DMAPA (1% aqueous solution), 23 subjects (8%) had positive reactions to DMAPA (Foti et al. 1995).

A non-atopic woman with suspected shampoo dermatitis of the scalp and neck showed a positive response when patch tested with a 1% aqueous solution of DMAPA and an equivocal response when patch tested with a 1% DMAPA in petrolatum. However, hairdressers with hand dermatitis (79 persons) showed no response when patch tested with a 1% DMAPA in petrolatum (79 persons) or when patch tested with a 1% aqueous solution of DMAPA (35 persons) following use of products containing DMAPA for about 3 years. (Uter 1999).

Ten individuals with a clinical history of contact allergy to CAPB were tested in a repeated open application test, which used a CAPB-based shower gel at 25% with a DMAPA concentration below 1 ppm. None of the subjects showed positive allergic reactions. Later, all 10 subjects were patch tested to 3 different concentrations of DMAPA (0.1, 0.3 and 1%); one subject showed an allergic reaction to DMAPA at all 3 concentrations. (Fartasch et al. 1999).

Ten subjects, who previously have tested positive to CAPB on patch testing, used a hair shampoo, hand soap, and body wash containing CAPB for 1 to 6 weeks or until a reaction developed. Later, they were patch tested to various substances, including DMAPA. None reacted positively to DMAPA at 0.1% in petrolatum. (Fowler et al. 1997).

A non-atopic woman with a long standing history of hand dermatitis reacted positively only to DMAPA when she was patch tested with a modified European standard allergen series (omitting nickel sulphate), a series of antimicrobials, and series of cosmetics; the authors concluded that she was sensitised to DMAPA due to her occupational exposure to shampoos. (Kanerva et al. 1996).

A male spray painter developed hand dermatitis and periocular dermatitis after 6 years of occupational exposure to paints and solvents, including 2-component epoxy paints, which contained e.g., DMAPA (as a hardener). He was patch tested

with a series of epoxy resin compounds, including DMAPA; DMAPA did not give a positive reaction. (Kanerva et al. 1998).

A male production foreman in a chemical factory, who had little direct contact with amines including DMAPA, developed a red itchy face, which some times involved the neck, shoulders, arms and hands. Patch testing revealed positive findings for DMAPA. (Speight et al. 1993 – quoted from Toxline 2003).

A male process operator in a chemical factory, who had direct, job-related contact with DMAPA, developed a red, scaly face and right palm. Patch testing revealed a positive finding for DMAPA. (Speight et al. 1993 – quoted from Toxline 2003).

In a patch test carried out among 32 individuals sensitised to ethylene diamine, no positive reaction was recorded following application of 1% of DMAPA in petrolatum (Balato et al. 1986 – quoted from BUA 1998 and IUCLID 2000).

4 Animal toxicity

4.1 Single dose toxicity

4.1.1 Inhalation

In an acute inhalation study in rats, performed according to OECD TG 403, the LC₅₀-value (4 hours) was greater than 4310 mg/m³; DMAPA was stated to be irritating to eyes at aerosol-vapour exposures (BASF 1991 unpublished results – quoted from BUA 1998 and IUCLID 2000).

Following 30 minutes exposure to an atmosphere saturated with DMAPA (33500-41900 mg/m³ at 20°C), no rats died, while exposure periods of 2, 4, or 8 hours resulted in mortality of 1/6, 2/6, or 4/6, respectively (BASF 1958 unpublished results – quoted from BUA 1998 and IUCLID 2000).

In male mice (6 animals/group), 15 minutes inhalation exposure to DMAPA at concentrations of 344 to 1262 mg/m³ resulted in bradypnoea. A threshold concentration for the depression of respiratory frequency by 50% (RD₅₀) of 748 mg/m³ was determined (95% confidence interval: 642-837 mg/m³). (Gagnaire et al. 1989 - quoted from BUA 1998 and IUCLID 2000).

4.1.2 Oral intake

Oral LD₅₀-values ranging from 922 to 1640 mg/kg have been reported for rats (several studies cited in BUA 1998 and IUCLID 2000).

In mice, LD₅₀-values of 1500 and 1640 mg/kg have been reported for DMAPA, whereas an LD₅₀-value of 5730 mg/kg has been reported for neutralised DMAPA (studies cited in BUA 1998 and IUCLID 2000).

Oral administration of 1309 mg/kg of neutralised DMAPA resulted in the death of 1/3 rabbits within 30 minutes; doses of 2618 or 5235 mg/kg resulted in the death of 3/3 animals (BASF 1961 unpublished study – quoted from BUA 1998 and IUCLID 2000).

4.1.3 Dermal contact

No data have been found.

4.2 Irritation

4.2.1 Skin irritation

Necrosis was observed in rabbits following 24 hours exposure of shaven, intact, abdominal skin of undiluted DMAPA (0.01 ml, 8.2 mg/animal, uncovered); the skin reaction was evaluated as grade 6 (strongly irritating to corrosive) on a scale of 10 (Smyth et al. 1949 – quoted from BUA 1998 and IUCLID 2000).

Exposure for 24 hours of the inner surface of rabbit's ear to 0.5 ml DMAPA had a very strong irritating effect (Bayer 1979 unpublished study – quoted from BUA 1998 and IUCLID 2000).

In an occlusive patch test, a corrosive effect was observed following exposure to 0.5 ml DMAPA for one hour (Hoechst 1979 unpublished study – quoted from BUA 1998 and IUCLID 2000).

In rabbits, exposure for one minute to undiluted DMAPA resulted in mild erythema (assessed 24 hours after treatment), which was no longer apparent after 8 days. Exposure for 15 minutes resulted in inflammation (assessed 24 hours after treatment) and after 8 days, a scab had formed. (BASF 1958 unpublished study – quoted from BUA 1998).

4.2.2 Eye irritation

Instillation of 0.005 ml of undiluted DMAPA into the conjunctiva of rabbits' eyes for 18 to 24 hours resulted in necrosis, which affected 63-87% of the surface of the cornea. The reaction was evaluated as grade 9 (severe corrosion) on a scale of 10 (Carpenter & Smyth 1946 – quoted from BUA 1998 and IUCLID 2000).

Following instillation of about 0.1 ml of DMAPA into the conjunctiva of rabbits' eyes, moderate irritation to corrosion of the cornea was observed (Bayer 1979 unpublished study – quoted from BUA 1998).

4.3 Sensitisation

In a guinea pig maximisation test performed according to OECD TG 406, DMAPA showed a skin sensitising effect; 93% of the animals were stated to respond positively. No further details are available. (Allied Corporation 1985 unpublished study – quoted from BUA 1998 and IUCLID 2000).

A skin sensitising effect has also been found in a modified Buehler test with guinea pigs. For induction, DMAPA was applied once a week (6 hours) over 3 weeks as an aqueous solution (5% for the 1st and 2nd application; 2.5% for the 3rd application). Challenge was performed 2 weeks after the induction with a 2% aqueous solution of DMAPA (6 hours). Nine of 10 animals showed mild erythema after 2nd and 3rd application (induction phase) and 7/10 animals showed mild erythema following challenge treatment. DMAPA was considered to be a skin sensitiser in this study. (Dow Chemical Company 1988 unpublished study – quoted from BUA 1998).

No sensitising effect was observed in a skin painting test in guinea pigs following uncovered exposure to DMAPA (BASF 1962 unpublished study – quoted from BUA 1998). The high vapour pressure of DMAPA implicates that uncovered exposure cannot be considered as an adequate testing for skin sensitising properties in this study and therefore, the result of this study is not reliable.

No data have been found regarding respiratory sensitisation.

4.4 Repeated dose toxicity

4.4.1 Inhalation

No data have been found.

4.4.2 Oral intake

Wistar rats (5 animals/sex/group) were administered DMAPA by gavage at doses of 0, 10, 50, or 250 mg/kg b.w./day for 28 days (OECD TG 407). Due to a high rate of mortality (3/5) among high-dose females during the initial study, a second trial in 5 females receiving 250 mg/kg b.w./day was conducted with data combined for the 10 high-dose females. Four high-dose females died; gross findings included discoloured lungs with surface red spots and foamy content. Clinical signs observed intermittently in high-dose females between study days 11 and 24 and mainly among the intercurrent decedents included hypoactivity, stilted gait, swollen abdomen, and laboured breathing. One high-dose male showed impaired respiration. No other treatment-related findings were observed among high-dose animals and no treatment-related findings were observed in the lower dose groups. The NOAEL in this study is 50 mg/kg b.w./day. (Hoechst 1996 unpublished study – quoted from BUA 1998 and Toxline 2003).

When DMAPA (in the form of neutralised solution, pH 7) was administered by gavage to rabbits (the number of animals not stated) at a dose of 818 mg/kg b.w./day for 4, 5, or 10 days, all animals died or had to be killed in a moribund condition (10 doses). The main effect was irritation of the gastrointestinal mucosa. No damage to the parenchymatous organs was observed. No further details are available. (BASF 1961 unpublished study – quoted from BUA 1998 and IUCLID 2000).

Four cats received daily oral doses of 650 mg/kg b.w./day of DMAPA (neutralised solution, pH 7) for 2 to 4 days. One animal died following administration of the second dose, while the remaining 3 animals survived treatment. The main finding was irritation of the gastrointestinal mucosa. No further details are available. (BASF 1961 – quoted from BUA 1998 and IUCLID 2000).

4.4.3 Dermal contact

No data have been found.

4.5 Toxicity to reproduction

In the 28-day oral study in rats (OECD TG 407), gross and histopathological examination of testes, epididymis, ovaries and uterus showed no treatment-related effects (Hoechst 1996 unpublished study – quoted from BUA 1998).

No data on fertility or developmental toxicity have been found.

4.6 Mutagenic and genotoxic effects

4.6.1 *In vitro* studies

DMAPA showed negative results in the Ames test in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 when test in the presence and absence of metabolic activation (rat or hamster S9) at concentrations from 33 to 10000 µg/plate (Zeiger et al. 1987 – quoted from BUA 1998 and IUCLID 2000).

4.6.2 *In vivo* studies

No data have been found.

4.7 Carcinogenic effects

No data have been found.

5 Regulations

5.1 Ambient air

-

5.2 Drinking water

-

5.3 Soil

-

5.4 Occupational Exposure Limits

-

5.5 Classification

DMAPA is classified for flammability (R10 – inflammable), acute toxic effects (Xn;R22 – harmful if swallowed), corrosive effects (C;R34 – causes burns) and for sensitising effect (R43 – may cause sensitisation by skin contact) (MM 2002).

5.6 Cosmetics

DMAPA is not included in Annex 2 of the Statutory Order on cosmetic products (MM 2003). Annex 2 lists the chemical substances, which are not allowed intentionally as ingredients in cosmetic products.

5.7 IARC

-

5.8 US-EPA

-

6 Summary and evaluation

6.1 Description

DMAPA is a colourless liquid with a smell of ammonia. DMAPA is miscible with water and has a vapour pressure of about 6.0-7.5 mmHg.

6.2 Environment

No data regarding the occurrence of DMAPA in ambient air, water, soil, or foodstuffs have been found.

No data have been found regarding the fate of DMAPA in ambient air; however, a half-life of 3.2 hours has been calculated for the reaction of DMAPA with OH radicals in the atmosphere.

Biodegradation may occur in water and in soil; however, the few available data indicate that DMAPA is not readily biodegradable in water. Volatilisation of DMAPA from water into the atmosphere is expected to be slow. DMAPA may have a potential for geoaccumulation in soil may occur; a potential for bioaccumulation is not expected.

6.3 Human exposure

The general population can be exposed to DMAPA in consumer products containing betaines, in which DMAPA may be present as an impurity resulting from the manufacturing of betaines.

6.4 Toxicokinetics

No data have been found.

6.5 Human toxicity

Two studies have provided evidence of possible respiratory impairment in humans as a result of occupational inhalation exposure to DMAPA.

In the first study, acute symptoms (cough, wheezing, chest tightness, and eye, nose and throat irritation) were reported by workers exposed to concentrations ranging from 1.7 to 5.9 mg/m³ with the highest prevalence among workers exposed at the highest concentrations (2.3 to 5.9 mg/m³). Also among workers with the highest exposures, a significant decrease in lung function was observed during the first workday in the week as well as during the course of the working week.

In a follow-up study, a few workers complained of irritation of the nasal mucosa and of increased mucous formation in the respiratory tract. Among the 6 workers with non-specified tasks, a significant reduction (3.9%) in vital capacity was observed at the end of the first working day of the week compared with results obtained prior to starting work while impairment of respiration during the course of

the working day was not observed among other workers. Comparison of the data on pulmonary function in the different subgroups showed no significant differences between the groups. An average concentration of 0.55 mg/m³ was measured in the respiratory zone of the assemblers.

Some studies and case stories indicate that DMAPA is the actual sensitiser in shampoos, detergents, cleansing solutions, and disinfectants containing betaines. Furthermore, a few case stories are available indicating allergic contact dermatitis caused by DMAPA in chemical products. No data have been found regarding respiratory sensitisation.

No data have been found regarding toxicity to reproduction, mutagenic and genotoxic effects, and carcinogenic effects in humans following exposure to DMAPA.

6.6 Animal toxicity

6.6.1 Single dose toxicity

The LC₅₀-value (4 hours) was greater than 4310 mg/m³ in rats (OECD TG 403). No rats died following 30 minutes exposure to a saturated atmosphere saturated (33500-41900 mg/m³ at 20°C), while exposure periods of 2, 4, or 8 hours resulted in mortality of 1/6, 2/6, or 4/6, respectively. In male mice, an RD₅₀ of 748 mg/m³ has been determined; 15 minutes inhalation exposure to concentrations of 344 to 1262 mg/m³ resulted in bradypnoea.

Oral LD₅₀-values ranging from 922 to 1640 mg/kg have been reported for rats, and of 1500 and 1640 mg/kg in mice.

No data have been found regarding acute dermal toxicity.

6.6.2 Irritation

Direct contact with DMAPA has a strongly irritating to corrosive effect on the skin and eyes of rabbits.

6.6.3 Sensitisation

DMAPA has shown a strong skin sensitising potential in a guinea pig maximisation test; a skin sensitising effect has also been reported in a modified Buehler test with guinea pigs. No sensitising effect was observed in guinea pigs following uncovered dermal exposure to DMAPA; however, the high vapour pressure of DMAPA implicates that uncovered exposure cannot be considered as an adequate testing for skin sensitising properties in this study and therefore, the result of this study is not reliable.

No data have been found regarding respiratory sensitisation.

6.6.4 Repeated dose toxicity

In a 28-day study (OECD TG 407) in rats, no effects were observed at oral doses (gavage) up to 50 mg/kg b.w./day; at 250 mg/kg b.w./day, clinical symptoms were observed and 4/10 females died.

All rabbits died or had to be killed following daily doses of 818 mg/kg b.w./day (neutralised solution, pH 7) for 4, 5, or 10 days and 1/4 cats following 2 oral doses 650 mg/kg b.w./day (neutralised solution, pH 7); the main finding was a strong irritative effect on the mucosa of the gastrointestinal tract. No further details are available.

No data have been found regarding repeated dose toxicity of DMAPA following inhalation or dermal application.

6.6.5 Toxicity to reproduction

No treatment-related effects on testes, epididymis, ovaries and uterus were observed in the 28-day oral study in rats (OECD TG 407).

No data on fertility or developmental toxicity have been found.

6.6.6 Mutagenic and genotoxic effects

DMAPA was negative in the Ames test in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 with and without metabolic activation.

No other data have been found.

6.6.7 Carcinogenic effects

No data have been found.

6.7 Evaluation

DMAPA is a skin sensitiser. Several of the available human studies and case stories strongly indicate that DMAPA is the actual sensitiser in shampoos, detergents, cleansing solutions, and disinfectants containing betaines in which DMAPA may be present as an impurity resulting from the manufacturing of the betaines. Furthermore, a few case stories are available indicating allergic contact dermatitis caused by DMAPA in chemical products. The available data indicate that a threshold exists for elicitation. One study has shown that none of 34 patients with contact allergy to DMAPA showed a response at concentrations up to 0.01% in water while 18 subjects showed a positive response at 0.1% in water. DMAPA has also shown a skin sensitising potential in a guinea pig maximisation test and in a modified Buehler test with guinea pigs. DMAPA is classified for a skin sensitising properties according to the EU classification criteria. No data have been found regarding respiratory sensitisation.

DMAPA has a strong potential for exerting irritative effects following inhalation of vapours or by direct contact. Among workers exposed to concentrations ranging from 1.7 to 5.9 mg/m³ symptoms such as cough, wheezing, chest tightness, and

eye, nose and throat irritation were reported with the highest prevalence among the workers exposed at the highest concentrations (2.3 to 5.9 mg/m³). In a follow-up study three years later, a few workers still complained of irritation of the nasal mucosa although the exposure concentration (average) had been reduced to 0.55 mg/m³.

In conventional studies on skin and eye irritation in experimental animals, DMAPA has a strongly irritating to corrosive effect on the skin and eyes of rabbits. In male mice, an RD₅₀ of 748 mg/m³ has been determined. DMAPA is classified as a corrosive substance according to the EU classification criteria.

Among workers exposed to DMAPA by inhalation at concentrations from 2.3 to 5.9 mg/m³, a significant decrease in lung function was observed during the first workday in the week as well as during the course of the working week.

A low order of acute inhalational toxicity is indicated by an LC₅₀-value (4 hours) greater than 4310 mg/m³ in a well-performed study in rats (OECD TG 403).

In a 28-day study (OECD TG 407) in rats, no effects were observed at oral doses (gavage) up to 50 mg/kg b.w./day; at 250 mg/kg b.w./day, clinical symptoms were observed and 4/10 females died probably due to a strong irritative effect of DMAPA on the gastrointestinal mucosa. No repeated inhalation studies in experimental animals have been found

No data on toxicity to reproduction in humans or in experimental animals have been found. In the 28-day oral study in rats, no treatment-related effects on testes, epididymis, ovaries and uterus were observed. Toxic effects to reproduction are not expected to occur at concentrations in ambient air as DMAPA primarily will react with the first site of contact.

DMAPA has not shown a potential to induce mutations in the Ames test. No other data regarding mutagenic and genotoxic effects have been found.

No data regarding carcinogenic effects in humans or in experimental animals have been found. Carcinogenic effects are not expected to occur at concentrations in ambient air as DMAPA primarily will react with the first site of contact.

6.7.1 Critical effect and NOAEL

Based on the available data, the critical effect in humans following exposure to DMAPA is considered to be the sensitising effect observed in both humans and experimental animals following dermal contact with DMAPA. No data are available to elucidate whether DMAPA is a respiratory sensitiser.

Furthermore, DMAPA has a strong potential for exerting irritative effects following inhalation of vapours or by direct contact.

For the purpose of estimating a health based quality criterion for DMAPA in ambient air, 0.55 mg/m³ is considered as a LOAEC for irritative effects following inhalation of DMAPA based on the complaints of irritation of the nasal mucosa in workers reported in the study by Brubaker et al. (1979).

7 Quality criterion in air

The quality criterion in air QC_{air} is calculated based on a LOAEC of 0.55 mg/m^3 for irritative effects following inhalation of DMAPA in workers reported in the study by Brubaker et al. (1979).

$$\begin{aligned} QC_{\text{air}} &= \frac{\text{LOAEC}}{UF_{\text{I}} * UF_{\text{II}} * UF_{\text{III}}} = \frac{0.55 \text{ mg/m}^3}{1 * 10 * 50} \\ &= 0.0011 \text{ mg/m}^3 \end{aligned}$$

The uncertainty factor UF_{I} is set to 1 as human data are used. The UF_{II} accounting for intraspecies variability is set to 10 reflecting the range in biological sensitivity within the human population. The UF_{III} is set to 50 because a LOAEC is used instead of a NOAEC, because it cannot be excluded that DMAPA might be a respiratory sensitiser, and because no data are available regarding the potential of inducing effects following long term inhalation exposure.

A quality criterion of 0.0011 mg/m^3 has been calculated.

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Evaluation of health hazards by exposure to N,N-Dimethyl-1,3-propanediamine and proposal of a health-based quality criterion for ambient air

The Danish Environmental Protection Agency has requested an evaluation of health hazards by exposure to N,N-dimethyl-1,3-propanediamine. This resulted in 2006 in the present report which includes a health-based quality criterion for the substance in ambient air.



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