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Nordic Expert Group for Criteria Documentation
of Health Risks from Chemicals

110. Diethylamine, Diethylenetriamine, Dimethyleamine and Ethylenediamine

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ARBETS MILJÖ INSTITUTET
NATIONAL INSTITUTE OF OCCUPATIONAL HEALTH

A Center for Research on Occupational Health

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Preface

The Nordic Council is an intergovernmental collaborative body for the five countries, Denmark, Finland, Iceland, Norway and Sweden. One of the committees, the Nordic Senior Executive Committee for Occupational Environmental Matters. initiated a project in order to produce criteria documents to be used by the regulatory authorities in the Nordic countries as a scientific basis for the setting of national occupational exposure limits.
The management of the project is given to an expert group. At present the Nordic Expert Group consists of the following member:

Helgi Gudbergsson	Municipal Institute of Public Health, Iceland
Petter Kristensen	National Institute of Occupational Health, Norway
Per Lundberg (chairman)	National Institute of Occupational Health, Sweden
Vesa Riihimäki	Institute of Occupational Health, Finland
Adolf Schaich Fries	National Institute of Occupational Health, Denmark

For each document an author is appointed by the Expert Group and the national member acts as a referent. The author searches for literature in different data bases such as Toxline, Medline, Cancerlit and Nioshtic. Information from other sources such as WHO, NIOSH and the Dutch Expert Committee is also used as are handbooks such as Patty's Industrial Hygiene and Toxicology. Evaluation is made of all relevant scientific original literature found. In exceptional cases information from documents difficult to access are used. The draft document is discussed within the Expert Group and is finally accepted as the Group's document.

An editorial work is performed by the Group's Scientific Secretary, Brita Beije, at the National Institute of Occupational Health in Sweden.

Only literature judged as reliable and relevant for the discussion is referred to in this document. Concentrations in air are given in mg/m^3 and in biological media in mol/l. In case they are otherwise given in the original papers they are if possible recalculated and the original values are given within brackets.

The documents aim at establishing a dose-response / dose-effect relationship and defining a critical effect based only on the scientific literature. The task is not to give a proposal for a numerical occupational exposure limit value.

The evaluation of the literature and the drafting of this document on Diethylamine, Diethylenetriamine, Dimethyleamine and Ethylenediamine was made by Dr Eva Andersson and Dr Bengt Järvholm, Department of Occupational Medicine, Sahlgrenska Hospital, St. Sigfridsgatan 85, S-412 66 Gothenburg, Sweden. The final version was accepted by the Nordic Expert Group February 24, 1994 as its document.

Brita Beije
Scientific Secretary

Per Lundberg
Chairman

Contents

Diethylamine

1. Physical-Chemical Data

Chemical name:	Diethylamine (DEA)
CAS-number:	109-89-7
Synonyms:	Ethanamine, diethamine
Formula:	$C_4H_{11}N$
Structural formula:	$H_3C - H_2C - NH - CH_2 - CH_3$
Molecular weight:	73.14
Boiling point:	55°C
Melting point:	-38.9°C
Vapour pressure (20°C):	25.9 kPa
Density (20°C):	0.7074
pH (1 molar)	12.5 (24)
Flash point:	-26°C (closed cup)
Odour threshold:	0.06 - 0.13 ppm (2, 19) (0.18 - 0. 39 mg/m^3)
Conversion factor for air concentrations at 20°C, 101.3 kPa:	1 ppm = 3.03 mg/m^3 1 mg/m^3 = 0.33 ppm

DEA is a colourless, alkaline, flammable liquid with a smell of ammonia. It is miscible with water, alcohol and most organic solvents. The explosive limits in air are between 1.8% and 10.1%. Contact with strong oxidizers can cause fire and explosions. Toxic gases and vapours may be released in a fire involving DEA (1, 20).

2. Use and Occurrence

2.1. Use

DEA is used in chemical and pharmaceutical industries (1, 26). It is used in colours and resins, as floatation agent and in the rubber industry as an accelerator. In polymerization reactions it can be used both as a catalyzer and inhibitor. It can also be used in photo development, plating and as a corrosion inhibitor and in pesticides. DEA may occur in some food as spinach, apples, beans, peas and in fish (16). It may occur in the surface water.

2.2. Air concentrations in work environment

No information.

2.3. Methods for analyses of air concentration

NIOSH reports absorption on silica gel and subsequent analysis on GC with a flame ionization detector, alternatively, nitrogen-specific detector (15). Derivatisation at sampling with 1-naphtylisothiocyanate and analysis with an HPLC and UV detector is also reported. The reagent can either be used for pump sampling or for diffusive sampling (12). Derivatisation from a solid phase on-line in connection with HPLC analysis has also been described (9).

3. Kinetics

3.1. Absorption

Beard and Noe (3) report that aliphatic and cyclic amines can easily be absorbed from airways, gastrointestinal tract and the skin but they mention no empiric evidence for their conclusions. LD_{50} at percutaneous application is of the same order as for oral ingestion (23).

3.2. Distribution

No information.

3.3. Biotransformation

The enzymes monoamine oxidase and diamine oxidase are widespread in tissues, occurring particularly in the liver, kidneys and intestinal mucosa (27). Primary and secondary amines are mainly metabolized to the corresponding carboxylic acid and urea. After oral intake of diethylaminehydrochloride (5 g in a single dose) 86% was excreted unchanged in urine in man (18), indicating a low grade of biotransformation.

3.4. Excretion

In a human experiment (one person) 86% of perorally ingested DEA-HCl (5 g in a single dose) was excreted in the urine within one day (18).

3.5. Biological monitoring

No information.

4. General Toxicology

4.1. Mechanism, in vitro-studies

DEA is a strong alkaline substance with corrosive and irritant properties.

4.2. Factors influencing toxicity

Concentrated DEA is a strong alkali and its irritant effects will probably decrease at neutralisation.

4.3. General findings

LC_{50} in rats was 4 000 ppm (12 139 mg/m^3) by inhalation for 4 hours (23). After oral administration, LD_{50} was 450 mg/kg for rats (23) and 500 mg/kg for mice (17). After dermal application to rabbits LD_{50} was 820 ml/kg (23). Inhalation of saturated vapour (26 000 ppm, calculated value, not reported by author) killed all rats within 5 minutes (23). Inhalation of 250 ppm (759 mg/m^3) DEA 6.5 hours/day, 5 days a week for 24 weeks caused decreased weight gain in rats (14).

5. Organ Effects

5.1. Effects on skin and mucous membranes

Upper airways and eyes are irritated by DEA. Smyth et al (22, 23) found the skin irritating effect of DEA to be (only) grade 4, i.e. slight erythema, on a ten-grade scale where ten is most irritating. In the test concentrated DEA was applied on the skin of an albino rabbit and the animal was observed after 24 hours (21).

A 1% solution caused necrosis and opacity of the cornea in rabbits (5, 23). Rabbits exposed to 50 ppm (152 mg/m^3) DEA 7 hours/day, 5 days a week for 6 weeks had multiple erosions on the cornea (4).

5.2. Effects on the respiratory system

Seven healthy persons, one female and six men inhaled DEA to study the effect in the nose (13). Four persons stayed in a climate chamber with 25 ppm (76 mg/m^3) DEA for 15 minutes. There were no changes in nasal volume or nasal resistance as measured by

acoustic rhinometry or rhinomanometry. There is no information about symptoms in these persons. Five persons were exposed to increasing concentrations of DEA up to 12 ppm (36 mg/m^3) during an hour (time weighted average 10 ppm - 30 mg/m^3) and reported irritation in the eyes and the nose. A moderately strong olfactory response was observed and there was a correlation between nasal irritation and olfactory response.

To study the irritant effects of amines in the upper airways the respiratory frequency was measured in mice exposed to DEA during 15 minutes in concentrations between 60 and 600 ppm (182 - 1821 mg/m^3). At 200 ppm (607 mg/m^3) the respiratory frequency decreased to 50%, RD_{50} (8). Damgård-Nielsen et al (6) reported RD_{50} to 184 ppm (558 mg/m^3) in mice. The threshold value for decrease of the respiratory frequency at inhalation through the nose was 32 ppm (97 mg/m^3).

Inhalation of 250 ppm (759 mg/m^3) DEA 6.5 hours/day, 5 days a week for 24 weeks caused damages in the nasal mucous membranes in rats (14). The respiratory epithelium showed squamous metaplasia and there were suppurative rhinitis and lymphoid hyperplasia. Sneezing, tearing and reddened noses were also reported.

Rabbits exposed to 50 or 100 ppm (152 or 303 mg/m^3) DEA 7 hours/day, 5 days a week for 6 weeks had inflammatory changes in the airways (4). There was moderate peribronchitis, occasional focal collection of lymphocytic cells and slight thickening of vascular walls. The rabbits exposed to the highest concentration also showed cell infiltration and bronchopneumonia. Thickening of interalveolar septa and accumulations of acid mucopolysaccharides in the interstitial substance of the alveolar connective tissue of rats exposed to 4.19 mg/m^3 (1.4 ppm) DEA for 3 months have been reported (25 cited in 14).

5.3. Effects on the liver

Rabbits exposed to 100 ppm (303 mg/m^3) DEA for 30 days had "marked parenchymatous degeneration with recent cell regeneration" of the liver while rabbits exposed to 50 ppm (152 mg/m^3) had "occasional foci of moderate parenchymatous degeneration" (4). Rats and rabbits receiving oral doses of DEA (6 mg/kg up to 7 months) had normal liver function tests (11 cited in 14).

Male rats received DEA intraperitoneally and the histological liver changes and different serum enzymes (ornithine carbamyl transferase, sorbitol dehydrogenase, aspartate aminotransferase, isocitric dehydrogenase, alanine aminotransferase) were measured (7). DEA was neutralized to pH 7.4 with hydrochloric acid and given in single doses of 250, 500 and 1 000 mg DEA per kg respectively. The concentration of enzymes and histology was studied after 0, 2, 6, 12, 24 and 48 hours and the changes were graded from 0 - 4. At 250 mg/kg there were slight changes after 2 hours, grade 1, with dilated sinusoides. Changes of grade 2 were noted after 6 hours. At 500 mg/kg there were changes of grade 2 after 2 hours and of grade 4 after 6 hours, i.e., a marked degeneration with periportal necrosis and hydropic degeneration. After 12 hours there were changes of grade 1 and after that no changes. At 1 000 mg/kg there were changes of grade 4 after 2 hours, grade 2 after 6 hours and grade 1 after 12 and 24 hours. After 48 hours there were no changes in the liver. The serum enzyme that best correlated to the histological changes was ornithine carbamyl transferase.

5.4. Effects on the kidneys

Rabbits exposed to 100 ppm (303 mg/m^3) DEA for 30 days had a slight nephritis and slight tubular changes while no certain kidney changes could be observed after exposure to 50 ppm (152 mg/m^3) for 30 days (4). Exposure to 250 ppm (759 mg/m^3) DEA for 120 days caused increased levels of blood urea nitrogen (BUN) in rats but there were no histological signs on kidney damage (14).

5.5. Effects on the gastro-intestinal tract

No information.

5.6. Effects on the cardiovascular system

Rabbits exposed to 50 ppm (152 mg/m^3) DEA, 7 hours/day, 5 days a week, for 30 days had very slight cardiac muscular degeneration while no changes were reported in rabbits exposed under similar circumstances to 100 ppm (303 mg/m^3) (4). There was no sign of cardiotoxicity (ECG or histology) in rats exposed to 0, 25 or 250 ppm (0, 76 or 759 mg/m^3) DEA 6.5 hours/day, 5 days a week for 24 weeks (14).

5.7. Effects on blood and bloodforming organs

Exposure to 250 ppm (759 mg/m^3) for 6.5 hours/day, 5 days a week for 24 weeks in rats caused no changes of hemoglobin, hematocrit or differential blood counts (14).

5.8. Effects on the central nervous system

It is reported that aliphatic amines may cause headache, nausea, faintness and anxiety in man but the sources are not reported (3). Intraperitoneal administration of 32 mg/kg DEA caused somnolence in mice (17).

5.9. Effects on the peripheral nervous system

No information.

6. Immunotoxicity and Allergy

No information.

7. Mutagenicity and Genotoxicity

There was no mutagenic activity of DEA in the Salmonella strains TA 100, TA 1535, TA 1537 or TA 98 with or without metabolic activation (10, 28).

8. Carcinogenicity

8.1. Human studies

No information.

8.2. Animal studies

There is no study of carcinogenicity available. Rats, exposed to 250 ppm (759 mg/m^3) DEA 6.5 hours/day, 5 days a week for 24 weeks and sacrified at the end of exposure, had squamous metaplasia of the respiratory epithelium in the nasal mucosa (14). No such changes were registered in rats exposed to 0 or 25 ppm in a similar way.

9. Reproduction Toxicology

There were signs of decreased production of sperms in rats exposed to 250 ppm (759 mg/m^3) DEA for 24 weeks. However, as the changes were mostly observed in only one of the testis they were not interpreted as an effect of DEA (14).

10. Relation between Exposure, Effect and Response

10.1. Effects of short-term exposure

In an experiment, five persons exposed to DEA in increasing concentration during 1 hour (time-weighted average 10 ppm = 30 mg/m^3, maximum concentration 12 ppm = 36 mg/m^3) reported irritation in the eyes and the airways (13), table 1.

Single exposures of 250, 500 and 1 000 mg/kg neutralized DEA intraperitoneally caused transient liver changes in rats (7). A single exposure to 1% DEA in the eyes of rabbit caused severe damages on the cornea (23).

Table 1. Effects of short-term exposure to DEA.

Concentrations/time	Species	Effects
30 mg/m^3 (TWA)/1 hour	Humans	Irritation in eyes and airways

10.2. Effects of long-term exposure

There are no human studies on effects of long-term exposure.
All rabbits exposed to 50 or 100 ppm (152 or 303 mg/m^3) DEA, 7 hours/day, 5 days a week for 6 weeks, survived (4). At 50 ppm there were multiple erosions and oedema in the eyes and there were inflammatory changes in the airways and a moderate parenchymal degeneration in the liver. At 100 ppm the changes in the airways and the liver were more marked and there were a slight nephritis and slight tubular changes in the kidneys, table 2.

Lynch (14) exposed rats to 0, 25 or 250 ppm (0, 76 and 759 mg/m^3 respectively) DEA 6.5 hours/day, 5 days a week for 24 weeks. At 25 ppm there were no changes in the organs. However, no histological examination of the nasal mucosa was done. The rats exposed to 250 ppm had a slower weight gain and showed irritation in the upper airways with tearing, sneezing and squinting. In the nasal mucosa there were histological changes as squamous cell metaplasia and lymphoid hyperplasia. There were no effects on organ weights, histology, hematology or clinical chemistry apart from an increased BUN.

Table 2. Effects of long-term exposure to DEA.

Concentrations/time	Species	Effects	Ref.
152 mg/m^3/6 wk 7 h/d; 5 d/wk	Rabbits	Erosions and oedema in the eyes, inflammatory changes in the airways	4
303 mg/m^3/6 wk 7 h/d; 5 d/wk	Rabbits	Cell infiltration and bronchopneumonia in lungs, marked parenchymatous liver degeneration, nephritis	4
759 mg/m^3/24 wk 7 h/d; 5 d/wk	Rats	Tearing, sneezing, squinting and squamous cell metaplasia of nasal mucosa, slower weight gain	14

11. Research Needs

There are no epidemiological studies. No experimental study has evaluated the effects of exposure during more than half a year.

12. Discussion and Evaluation

The critical effect is irritation in the eyes and the airways. One hour's exposure to 10 ppm (30 mg/m^3) caused irritation in the upper airways and eyes in healthy humans (13). Animal experiments have shown liver changes at exposure to 50 ppm (152 mg/m^3) for 6 weeks (4) and at single doses of 250 ml/kg (neutralized, intraperitoneal) (7). Mutagenicity tests indicate that DEA is non-mutagenic. There are no studies of possible carcinogenic effect. Splashes of DEA in the eyes can cause severe damages to the cornea.

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Diethylenetriamine

1. Physical-Chemical Data

Chemical name:	Diethylenetriamine (DETA)
CAS-number:	111-40-0
Synonyms:	Aminoethylethandiamine, 3-Azapentan-1,5-diamine, N-(-2-Aminoethyl)ethylendiamine, Bis (2-aminoethyl) amine, 2,2-Diaminodiethylamine, 2,2 Iminobisethylamine, Bis(Beta-Aminoethyl)amine
Formula:	$C_4H_{13}N_3$
Structural formula:	$NH_2 - CH_2 - CH_2 - NH - CH_2 - CH_2 - NH_2$
Molecular weight:	103.17
Boiling point:	206.7°C
Melting point:	-39°C
Vapour pressure (20°C):	0.03 kPa
Density (20°C):	0.9586
pH (1 molar):	12.0 (29)
Flash point:	102°C (open cup)
Odour threshold:	No information
Conversion factor for air concentration at 20°C, 101.3 kPa:	1 ppm = 4.28 mg/m^3 1 mg/m^3 = 0.23 ppm

DETA is a somewhat viscous, yellow, alkaline and hygroscopic liquid with a smell of ammonia. It is miscible with water and ethanol and soluble in some organic solvents. DETA is corrosive on copper and it's alloys (1, 23). A high purity sample of DETA contained 1.8% N-(2-aminoethyl)piperazine, 0.7% diethanolamine, 0.5% ethylenediamine and 0.3% triethanolamine (6). A commercial grade sample contained 8.9% N-(2-aminoethyl)piperazine and 0.3% ethylenediamine.

2. Use and Occurrence

2.1. Use

DETA is used in chemical and pharmaceutical industry (1, 27). It can be used as a solvent for colours, resins, acid gases and sulphur and as a hardener in epoxy resins. It is also used in wetstrengthening resins in the paper industry, in cleaning agents and in corrosion inhibitors and as a fuel component.

2.2. Air concentration in work environment

DETA in the breathing zone of workers using asphalth with amidoamines and free polyamines was 1.3 mg/m^3, while the concentration was below detection limit (level not reported) in three work places using DETA in coolants and lubricants, and as a hardener in epoxy resins (Riihimäki, personal communication).

2.3. Methods for analyses of air concentration

NIOSH reports sampling on Amberlite XAD-2, impregnated with 1-naphthylisothiocyanate and subsequent HPCL-analysis with UV-detection as a standard method for DETA (18). A glass fiber filter can also serve as carrier for the derivatisation reagent (17). Sampling on a Tenax-absorbent coated with 1-naphthyl acetic acid anhydride followed by HPLC-analysis with flouroscens detection has been reported (33). Another method is sampling on silica gel and derivatisation with m-toluoyl chloride during desorption and analysis with HPLC and UV-detection (24).

3. Kinetics

3.1. Absorption

DETA can at room temperature be inhaled as a gas. Beard and Noe (2) reported that aliphatic and cyclic amines easily are absorbed from the airways and the gastrointestinal tract but they reported no empirical data for their conclusions. DETA can also be absorbed through the skin and LD_{50} at oral ingestion is of the same order as with topical application on the skin (11, 26).

3.2. Distribution

No information.

3.3. Biotransformation

No information.

3.4. Excretion

No information.

3.5. Biological monitoring

No information.

4. General Toxicology

4.1. Mechanism, in vitro-studies

DETA is a strong alkaline substance with corrosive and irritating properties.

4.2. Factors influencing toxicity

DETA is a strong alkaline substance and its irritant effects will probably decrease at neutralization.

4.3. General findings

LD_{50} was 71 mg/kg for mice and 74 mg/kg for rats at intraperitoneal administration. The rat oral LD_{50} was 1 080 mg/kg (11). At topical application on the skin LD_{50} was 1 090 ml/kg for rabbit and 170 ml/kg for guinea pig (26). Rats survived exposure to 300 ppm (1284 mg/m^3) DETA (22). ACGIH (1) reported that the exposure occurred during 8 hours but this information is not in the primary report by Savitt (22). Smyth (26) reported that all rats survived 8 hours exposure to air saturated with DETA but details about the experiment were not published. Weight gain, general appearence and behaviour were normal in eight rabbits ingesting 1 mg DETA per kg body weight and day in drinking water for 6 months (31, cited in 3). Growth was unaffected in six guinea-pigs given 0.6 mg DETA per kg body-weight and day in drinking water for 6 months (31, cited in 3).

5. Organ Effects

5.1. Effects on skin and mucous membranes

DETA may cause skin and eye irritation as well as skin sensitization.

A 0.05% solution of DETA in water was tested in a closed patch test on 20 volunteers for 24 hours (15). The test was evaluated after 24, 48, 72 hours and 2 weeks. There was no report on irritation. Petrolatum with 0.5 - 1.0% DETA or 0.1 - 1.0% DETA in water are used for 24/48 hours patch tests and can therefore be regarded as non irritant concentration for most persons (3).

Undiluted DETA caused necrosis and severe skin irritation in rabbits (11, 26). A drop of 0.02 ml undiluted DETA caused severe damage of the cornea in rabbit (4). Solutions of between 15 - 100% DETA in water caused permanent cornea damages while a solution of 5% DETA in water caused a slight damage in rabbits (22).

Mice developed open wounds after application of 25 µl 10% DETA in water solution on the skin, daily for two weeks (6). Of 50 mice receiving 25 µl 5% DETA on the skin, three times per week during their lifetime, four had necrosis, three dermatitis and two hyperkeratosis.

Ingberman and Walton (13) reported that 10% DETA in ethanol sensitized all tested guinea pigs and that DETA sensitized about 75% of regularly exposed persons. Details of these studies have, however, not been published. Dernehl (7) found that 50% of volunteers were sensitized by DETA in an experiment, while a substituted DETA-compound (bishydroxyethyl-DETA) did not cause sensitization.

In the guinea pig maximization test 0.5% solution of DETA sensitized 93% of 15 tested animals (30). Of the animals sensitized to DETA 20% also had a positive reaction to triethylenetetramine (TETA). A positive reaction to DETA was observed in 67% of the animals sensitized to TETA. Of the animals sensitized to tetraethylenepentamine 40% had a positive test to DETA. However, cross-sensitization could not be established since the substances were not absolutely pure in this experiment.

Rudzki and Krajewska (20) studied the cross-reaction between DETA and TETA in 137 patients with occupational exposure to epoxy resins. None was occupationally exposed to DETA. Of those with positive reaction to TETA 80% also had a positive reaction to DETA. Cross-reactivity was also reported in offshore workers exposed to polyamines in the lubricants used during drilling and in persons sensitized to ethylenediamine through skin creams (19).

Kanerva (14) described a case where a paper worker got a hand eczema caused by DETA during production of carbonless copy paper.

5.2. Effects on the respiratory system

DETA is reported to cause airway irritation and sensitization with asthma (1). There is one case of asthma reported in a non-smoking, 53-years old carpenter who got respiratory problems two months after having started working with a resin containing 14% DETA and 86% coal tar (21). A provocation during two minutes to DETA caused a late asthmatic reaction starting after two hours. Provocation with coal tar or epoxy resin caused no reactions. There were no IgE-antibodies against DETA.

The lung histopathology was normal in four rats exposed to 130 ppm (556 mg/m^3) DETA 6 hours/day for 15 days (8).

5.3. Effects on the liver

Rats fed with a diet containing 0.75 or 1.5 per cent DETA (375 and 750 mg/kg bw/day respectively, assuming a body weight of 200 g and a food consumption of 10 g/day) for 90 days had dose-dependent pathological effects in the liver. However, 0.1% caused no liver damages (32, cited in 16). Administration of 10 mg/kg body-weight and day of DETA in the drinking-water for 6 months caused "changes in certain liver enzymes" in rabbits but so did not 1 mg/kg (31, cited in 3). Six guinea pigs were given 0.6 mg/kg body-weight and day of DETA in the drinking-water for 6 months and that did not influence liver enzymes or levels of liver vitamin C (31, cited in 3). However, the details of these studies, e g controls and testing procedures, were not reported. Rats exposed to 130 ppm (556 mg/m^3) DETA, 6 hours/day for 15 days showed no microscopic changes in the liver (8).

5.4. Effects on the kidneys

A diet containing 0.75 or 1.5 percent DETA for 90 days caused dose-dependent pathological changes in kidneys in rats while 0.1 percent DETA in diet did not cause any kidney damages (32, cited in 16). DETA-hydrochloride given as single doses of 3.0 mmol/kg (310 mg/kg) intraperitoneally to mice did not cause proteinuria (28). Rats exposed to 130 ppm (556 mg/m^3) DETA 6 hours/day for 15 days had no histological changes in the kidneys (8).

5.5. Effects on the gastrointestinal tract

No information.

5.6. Effects on the cardiovascular system

No information.

5.7. Effects on blood and blood forming organs

The coagulation of the blood was affected in eight rabbits given 10 mg DETA/kg body-weight and day in drinking-water for 6 months while 1 mg/kg had no such effect (31, cited in 3).

5.8. Effects on the central nervous system

It is reported that aliphatic amines may cause headache, nausea, faintness and anxiety in man but the sources are not reported (2).

5.9 .Effects on the peripheral nervous system

No information.

6. Immunotoxicity and Allergy

DETA is a well-known cause of allergic eczema (5, 30). For further details se 5.1. One case of asthma to DETA has been reported but no IgE-antibodies were found against DETA (21).

7. Mutagenicity and Genotoxicity

DETA did not cause a significant increase in the frequency of micronucleated bone marrow polychromatic erythrocytes in CD-1 mice given 85, 283 or 850 mg/kg body-weight in a single dose by oral gavage (9). Treatment of Chinese hamster ovary cells with DETA in the presence or absence of metabolic activation did not increase the frequency of chromosomal aberration (9). In another experiment 2 out of 3 brands of DETA with different purity caused an increase in sister chromatid exchanges in hamster cells (25, cited in 3). It is not reported if the effect was caused by DETA or the impurities. DETA

induced unscheduled DNA-synthesis in rat hepatocytes (25, cited in 3). DETA was nonmutagenic in a sex-linked recessive lethal assay on Drosophila melanogaster (9).

A mutagenic effect of DETA was found in S.typhimurium (TA1535 and TA100) with and without metabolic activation (10). The authors indicated that the mutagenic activity may depend on alkylating impurities in DETA as DETA per se is not alkylating and the tested brand of DETA gave positive response in a reaction with 4-(p-nitrobenzyl)pyridine. DETA caused a slight mutagenic activity in S. typhimurium TA 100 (12). In one study, DETA (97% purity) caused no mutagenic activity in four strains of S. typhimurium (TA 100, TA 1535, TA 1537, TA 98) with or without metabolic activation (34).

8. Carcinogenicity

8.1. Human studies

No information.

8.2. Animal studies

The occurrence of skin tumours of DETA (two brands; high purity and commercial quality) was studied on male mice (6). Fifty mice were treated 3 times a week during their entire life span with 25 µl 5% DETA by dermal application (approximately 50 mg/kg body-weight, assuming a body weight of 25 g). Ten of the mice were sacrificed after 18 months and the rest were examined at death. There were no treatment-related skin tumours or any increased incidence of other tumours.

9. Reproduction Toxicology

No information.

10. Relation between Exposure, Effect and Response

10.1. Effects of short-term exposure

Concentrated DETA is a strong skin and eye irritant (4, 26). Closed patch tests with 0.05% DETA did not cause skin irritation (15). Exposure during 2 minutes to an unknown concentration caused a late asthma attack in a person previously exposed to DETA (21).

10.2. Effects of long-term exposure

Two male and two female rats exposed to 130 ppm (556 mg/m^3) DETA 6 hours/day for 15 days had no toxic signs, the organs were normal at section and there were no changes in blood or urine (8).

Rats given 0.75 or 1.5 percent DETA in the diet for 90 days showed dose-related changes in the liver and kidneys while 0.1 percent caused no changes (32, cited in 16). Weight gain, behaviour, liver enzymes and coagulation of blood were normal in eight rabbits, given 1 mg DETA/kg body-weight per day in drinking-water for half a year, while 10 mg/kg body-weight given in a similar way caused reduced clotting ability of the blood and changes in the activity of some liver enzymes (31, cited in 3). Weight gain, liver enzyme activities, the level of liver vitamin C and blood methemoglobin were unchanged in 6 guinea pigs receiving 0.6 mg/kg body-weight DETA per day in drinking-water for 6 months (31, cited in 3).

A water solution with 10% DETA applied to the skin for two weeks caused open wounds in mice while treatment with 25 µl 5% DETA 3 days/week for about 1.5 years caused two cases of hyperkeratosis, three cases of dermatitis and four cases of necrosis in 50 male mice but no skin tumours or changes in internal organs (6).

11. Research Needs

There are no human studies on effects at long and short term inhalation of DETA and there are no epidemiological studies. The risk of asthma should be further evaluated.

12. Discussion and Evaluation

The critical effect of DETA is the risk of skin sensitization and irritant effects on mucous membranes and airways. It is probable that DETA may cause asthma (21). There are no data available for the evaluation of the concentration causing irritant effects.

Most genotoxicity tests indicate that DETA is nongenotoxic. However, some mutagenicity tests have indicated that DETA, or commercial brands of DETA, have mutagenic activity. A limited animal skin experiment did not support the hypothesis that DETA is a carcinogenic substance.

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Dimethylamine

1. Physical-Chemical Data

Chemical name:	Dimethylamine (DMA)
CAS-number:	124-40-3
Synonyms:	N-methylmetanamine
Formula:	C_2H_7N
Structural formula:	CH_3 - NH - CH_3
Molecular weight:	45.08
Boiling point:	7.4°C
Melting point:	-96°C
Vapour pressure (20°C):	170 kPa
Density (4°C):	0.68
pH (1 molar):	12.5 (40)
Flash point:	-6.7°C (closed cup)
Odour threshold:	0.047 - 0.34 ppm (1, 2) (0.09 - 0.64 mg/m^3)
Conversion factor for air concentrations at 20°C, 101.3 kPa:	1 ppm = 1.87 mg/m^3 1 mg/m^3 = 0.53 ppm

DMA is a flammable gas at room temperature, but may also occur as a 25 - 60% alkaline water solution. DMA is soluble in water, alcohol and ether. It has a strong smell of ammonia. The explosive limits in air are 2.8 - 14%. DMA and nitrite may form dimethylnitrosoamine which is a potent carcinogen and also hepatotoxic. (1, 35, 41)

2. Use and Occurrence

2.1. Use and occurrence

DMA is used in chemical and pharmaceutical industries, when producing dimethylacetamide and dimethylformamide, in accelerators in the rubber industry, in cleaning agents and in the manufacturing of soaps, in pesticides, as a dehairing agent in tanning, as a gasoline stabilizer and as a floatation agent (1, 38, 42).

DMA occurs in some food, such as vegetables (cabbage and celery), corn, fish, coffee as well as in surface water (32). DMA is also formed in the body from methylamine and from lecithin, choline or trimethylamineoxide through trimethylamine, probably in the guts by bacteria (3). DMA may also be synthesized in the kidneys (39).

Zhang (47) states that trimethylamine-N-oxide in the diet is the main source of DMA in urine. The daily excretion of DMA is about 15 - 25 mg in man but may increase considerably after eating fish. DMA can also be found in saliva, gastric juice and blood (46). Experiments have shown that an increased intake of trimethylamine-N-oxide will cause a higher proportion of biotransformation to DMA (47).

2.2. Air concentrations in work environment

The concentration of DMA varied between 1.2 - 33.8 mg/m^3 in a German factory where DMA and other aliphatic amines were produced (5).

2.3. Methods for analyses of air concentration

NIOSH reports absorption on a silica gel with subsequent analysis on a GC with a flame ionization detector or a nitrogen specific detector as a standard method (33). A diffusive sampling method based on derivatization with 1-naphthylisothiocyanate is also reported (26).

3. Kinetics

DMA is absorbed through the airways, skin and gastrointestinal tract and is excreted unchanged in the urine.

3.1. Absorption

Persons occupationally exposed to DMA, and other monoamines, had an increased excretion of DMA in the urine (17 cited in 9).

Rats inhaling radioactively labeled DMA had the highest concentration of DMA in mucous membranes of the nose (28).

Beard and Noe (4) states that DMA can be absorbed through the skin but they reported no empiric data. No other study on skin absorption has been found.

DMA is easily absorbed from the intestines while the resorption from the stomach is low (22). Persons eating fish with a known concentration of DMA, monomethylamine and trimethylamine, had an increased excretion of DMA in urine (44), indicating absorption through the gastrointestinal tract.

Antibiotic therapy to sterilize the gut in three uremic patients decreased mean DMA serum concentrations from 633 to 108 µg/100 ml (37).

Guinea pigs receiving DMA (456 µg) injected into their ligated stomachs did not absorb any DMA during 20 minutes, while the same amount injected into the ligated intestines was rapidly absorbed ($t_{1/2}$ 11.8 minutes) (21 cited in 9).

The half time of DMA (250 µg) injected into ligated sections of the stomach, upper and lower intestines, appendix and colon were 198, 8.3, 11.6, 31.5 and 11.0 minutes respectively (22, 23).

3.2. Distribution

In rats the highest concentration of ^{14}C-labeled DMA inhaled in concentrations of 10 and 175 ppm (19 and 327 mg/m^3) respectively was found in the nasal mucosa immediately after inhalation (28). In the nose the concentration was more than a hundred times higher than in other organs at 10 ppm. The kidneys had three times higher level than the liver, lungs, brain and testis. The highest concentration of DMA five hours after an intravenous injection of 10 mg/kg to guinea pigs was found in kidney and spleen (7). In the kidneys and the spleen the concentrations were about twice as high as in the blood.

Dogs and ferrets received 50 mg/kg DMA intravenously in a single dose and the concentrations in blood and gastric juice were followed (45). Between 1 and 5 hours after the administration the concentration of DMA in gastric fluid was more than twice as high as in blood.

3.3. Biotransformation

The excretion data below (3.4) indicate that a small part of absorbed DMA is biotransformed in humans and rats. In vitro-tests with microsomes from the liver as well as the respiratory and olfactory mucosa of rats biotransformed DMA to formaldehyde and dimethylhydroxylamine (29).

3.4. Excretion

Absorbed DMA is mainly excreted in the urine but a small amount is excreted in feces. DMA excreted in the gastrointestinal tract may be resorbed.

In a man 91.5% of a single dose of 8 g DMA-hydrochloride given orally was excreted in the urine (34). Rats exposed to 10 and 175 ppm (19 and 327 mg/m^3) ^{14}C-labeled DMA, respectively, excreted 78% and 87%, respectively, in urine after 72 hours, 12.5 and 5% respectively in the feces and 1.5% as CO_2 in exhaled air (28). After 72 hours 8% and 7% of the radioactivity, respectively, remained still in the tissues. After intravenous injection of ^{14}C-labeled DMA more than 98% were found in the urine (28).

Elimination of DMA from the blood of rats could be described by a monoexponential function with a half-time of about 12 minutes after an intravenous injection (22, 23). Some DMA was excreted in the gastrointestinal tract and partly resorbed, the half-time in plasma being 15 minutes. The elimination from serum of ^{14}C-labeled DMA inhaled at the concentration of 175 ppm (327 mg/m^3) for six hours in rats was described by a two-compartment model with a half-time of 45 and 64 hours for the slow phase in two animals (28).

3.5. Biological monitoring

The concentration of DMA in serum and urine can be measured but it is not possible to distinguish between exogenous and endogenous sources of DMA.

4. General Toxicology

4.1. Mechanisms, in vitro-studies

DMA-hydroperchloride inhibited selectively the syntheses of rRNA in Xenopus embryonic neurula cells but the importance of this is unknown (36).

4.2. Factors influencing toxicity

DMA is a strong alkaline substance and neutralization will probably decrease the irritant effects.

4.3. General findings

LD_{50} was 316 mg/kg for mice, 698 mg/kg for rats and 240 mg/kg for guinea pigs and rabbits when DMA in water was given orally (10). If DMA was neutralized to pH 8 with hydrochloric acid LD_{50} was 8 100 mg/kg for albino rats, 1 070 mg/kg for guinea pigs and 1 600 mg/kg for rabbits. LC_{50} was 4 540 ppm (8 492 mg/m^3) in rabbits exposed to DMA for six hours, the follow-up time being 48 hours (38). Male rats and female mice exposed to 175 ppm (327 mg/m^3) DMA 6 hours a day for 5 days a week during 12 months had a decreased weight gain (6).

5. Organ Effects

5.1. Effects on skin and mucous membranes

Liquid DMA may cause necrosis on the skin and cause severe damage on the cornea with persistent opacity.

Persons occupationally exposed to a mixture of ammonia, dimethylformamide, monomethylamine, DMA and trimethylamine in a total concentration of about 20 mg/m^3 (reported as NH_3) had no changes due to exposure on cornea, conjunctiva or functions of the eye when examined with visus, corneal reflex, ophthalmoscopy and perimetri (31). However, only 75 out of 120 exposed persons were examined.

The guinea pig closed epicutaneous test showed that DMA caused skin sensitization (24). A 6% solution of DMA on the skin of rabbits caused reddening, thickening and ulceration after a single application (25 cited in 1). A 3% solution caused similar effects after five treatments.

A single drop of concentrated DMA in the eye of an anesthetized rabbit caused a white-blue colour on the cornea in a few seconds, which after a minute became white and sclerotic (30).

Rats exposed to 1 000 ppm (1 871 mg/m^3) DMA for 6 hours had corneal oedema (38). At 4 000 ppm (7 482 mg/m^3), and above, several had necrosis of cornea, iris and severe degeneration of the lens resembling acute cataract. Guinea pigs and rabbits but not rats and mice had cornea damages at 97 and 185 ppm (181 and 346 mg/m^3) DMA, 7 hours/day, 5 days a week for 18 - 20 weeks (18 cited in 38).

5.2. Effects on the respiratory system

Exposure to 10 ppm (19 mg/m^3) DMA 6 hours/day, 5 days a week for 12 months caused an increased incidence of chronic inflammation in vestibulum and of the respiratory epithelium in rats (6). Some animals had focal degeneration of the olfactory epithelium. After similar exposure to 50 ppm (94 mg/m^3) there were focal squamous metaplasia of the respiratory epithelium after 6 months and after 12 months a mild inflammation and epithelial hypertrophy and hyperplasia as well as damages on the olfactory epithelium. At 175 ppm (327 mg/m^3) there were similar but more severe changes and destruction of naso- and maxilloturbinates and fenestration of the nasal septum. There were similar findings when mice were exposed to these DMA concentrations.

Rats were exposed to 175 ppm (327 mg/m^3) DMA 6 hours/day for 1, 2, 4 or 9 days or two years (15). After only one day of exposure there were altered mucus flow patterns and small erosions on the respiratory epithelium, vacuolation of the olfactory and the respiratory epithelium. After 4 - 9 days of exposure there were losses of olfactory cells and erosions and ulcerations became more severe and extensive. When the inhalation continued for 2 years there were focal squamous metaplasia of the respiratory epithelium and destruction of the turbinates and the septum.

Rats exposed to 600 - 6 000 ppm (1 122 - 11 223 mg/m^3) DMA for 6 hours had severe congestion, ulcerative rhinitis and necrosis of the nasal turbinates (38).

The respiratory frequency was decreased to 50% (RD_{50}) at exposure to 573 ppm (1 072 mg/m^3) in rats and 511 ppm (956 mg/m^3) in mice (38). In another experiment RD_{50} was 70 ppm (131 mg/m^3) in mice (12).

Rats, rabbits, guinea pigs, monkeys and dogs exposed to 9 mg/m^3 (4.8 ppm) DMA continuously for 90 days showed interstitial inflammatory changes in the lungs of all species but no "specific chemically induced histopathological changes" (8). Rabbits and two of three examined monkeys showed "dilatation of the bronchi". The author describes these changes as a sign of mild inflammation. There is no information about findings in control animals and there was no histopathological examination of the upper airways.

Rats exposed to 600 - 6 000 ppm (1 122 - 11 223 mg/m^3) DMA for 6 hours had a mild tracheitis and epithelial hyperplasia at 600 ppm (38). At 1 000 ppm (1 871 mg/m^3) there was also suppurative tracheitis and at 2 500 ppm (4 676 mg/m^3) and above there was ulcerating tracheitis. At 600 ppm there was mild emphysema and at 1 000 ppm emphysema, bronchial hyperplasia and pneumonitis. At concentrations above 2 500 ppm there was peripheral emphysema and bronchopneumonia.

5.3. Effects on the liver

Exposure to 97 ppm (181 mg/m^3) DMA 7 hours/day, 5 days a week for 10 - 20 weeks caused a central lobular fatty degeneration and necrosis of the liver in rats, mice, guinea pigs and rabbits (18 cited in 38).

Exposure to DMA in concentrations of 1 000 ppm (1 871 mg/m^3) or lower for 6 hours caused no liver damages in rats (38). At 2 500 and 4 000 ppm (4 676 and 7 482 mg/m^3) there were a mild fatty degeneration and focal necrosis and at 6 000 ppm (11 223 mg/m^3) one animal had centrolobular necrosis.

Neutralized DMA in water at 1/10 of LD_{50} for 6 weeks, i.e., 107 mg/kg to guinea pigs or 160 mg/kg to rabbits caused an increase of the proportional weight of the liver (10).

A daily, peroral, dose of 10 or 20 mg DMA-HCl for 30 days to male rats did not cause any histopathological changes in the liver, no changes in the relation between liver-weight and body-weight and no pathological levels of liver enzymes (13). However, the quality of that study is questionable.

Guinea pigs receiving 3.5 mg/kg DMA (neutralized with hydrochloric acid in a water solution) for 8 months had an increased liver-weight compared to body-weight. Such changes were not reported in animals receiving 0.035 or 0.35 mg/kg(10).

No liver changes were reported in rats, guinea pigs, rabbits, monkeys or dogs exposed to 9 mg/m^3 (4.8 ppm) DMA continuously for 90 days (8).

5.4. Effects on the kidneys

Guinea pigs receiving 3.5 mg/kg DMA in water for 8 months had an increased concentration of urea in blood and an increased excretion of coproporphyrin in urine (10). DMA at 0.35 mg/kg caused an increase in urea during the 3rd and the 4th month, after which the urea was normalized.

Ten or twenty mg DMA-HCl given daily by gastric catheter, to groups of 8 male rats for 30 days did not cause any histopathological changes in the kidneys (13). However, the quality of that study is questionable.

No changes in kidneys were reported in rats, guinea pigs, rabbits, monkeys or dogs exposed to 9 mg/m^3 (4.8 ppm) DMA continuously for 90 days (8).

5.5. Effects on the gastrointestinal tract

Exposure to lethal doses of DMA caused extensive bleedings in the gastrointestinal tract in mice, rats, guinea pigs and rabbits (10).

5.6. Effects on the cardiovascular system

No changes were reported in rats, guinea pigs, rabbits, monkeys or dogs exposed to 9 mg/m^3 (4.8 ppm) DMA continuously for 90 days (8).

5.7. Effects on blood and bloodforming organs

Rats given 0.35 mg/kg DMA in water for 8 months caused a decrease in the phagocytic activity of leukocytes (10). Neutralized DMA in water given to guinea pigs (107 mg/kg) and rabbits (160 mg/kg) for 6 weeks caused an increase in hemoglobin and cholinesterase in blood (10).

Male rats exposed to 175 ppm (327 mg/m^3) DMA 6 hours/day, 5 days a week for 12 months had decreased platelet counts and female rats had increased counts of atypical lymphocytes (6). Female mice exposed in the same way had decreased mean red blood cell volume. The biological significance of these changes was questionable, according to the authors.

Exposure to 9 mg/m^3 (4.8 ppm) DMA continuously for 90 days did not cause any pathological changes in rats, guinea pigs, rabbits, monkeys or beagle dogs (number of leucocytes, hemoglobine or hematocrit) (8).

Steinhagen (38) cites two Russian ninety-days studies from the beginning of the 1970s. One study reported a decrease of serumprotein SH-content, whole blood cholinesterase, antibody-formation and vitamin C-levels in rats exposed to 0.02 or 0.5 ppm (0.04 or 0.9 mg/m^3) DMA. In another study there were increased numbers of aneuploid bone marrow cells in rats exposed to 0.27 or 0.54 ppm (0.5 or 1.0 mg/m^3) DMA continuously for 90 days (20).

5.8. Effects on the central nervous system

Rats given 0.35 or 0.035 mg/kg DMA in water for 8 months affected the conditioned reflexes (10). At 0.007 mg/kg no such effects were reported.

5.9. Effects on the peripheral nervous system

No information.

6. Immunotoxicity and Allergy

Guinea pig closed epicutaneous test showed that DMA caused skin sensitization (24).

7. Mutagenicity and Genotoxicity

DMA was nonmutagenic in the Salmonella strains TA 1531, TA 1532, TA 1964, TA 100, TA 1535, TA 1537 and TA 98 (with or without metabolic activation) and there was a weak mutagenic effect after metabolic activation for TA 1530 (14, 43). A negative result was observed in a host-mediated assay with TA 1951, TA 1952, TA 1534 and TA 1950 (14). DMA was negative in the unscheduled DNA synthesis on rat hepatocytes (27). DMA was negative or showed a marginal effect on the induction of sister chromatid exchanges, chromosome aberrations and gene mutations in Chinese hamster ovary cells (19). DMA induced mitotic gene conversion and point reverse mutation in the D7-strain of Saccharomyces cerevisiae (11).

Inhalation of 0.27 or 0.54 ppm (0.5 or 1.0 mg/m^3) DMA continuously for 90 days caused an increased number of aneuploid bone marrow erythrocytes in rats (20).

8. Carcinogenicity

8.1. Human studies

No information.

8.2. Animal studies

Exposure to 50 ppm (94 mg/m^3) 6 hours/day, 5 days a week for 6 months caused focal squamous metaplasia of the respiratory epithelium on the free margins of the turbinates in male and female mice (9 - 10 animals per sex) (6). Focal to diffuse squamous metaplasia of the respiratory epithelium was caused at 175 ppm (327 mg/m^3; 6 hours/day, 5 days a week) in male and female rats and mice (9 - 10 animals per sex and species) exposed in a similar way for one year.

Male rats (six animals) exposed to 175 ppm (327 mg/m^3) DMA 6 hours per day for two years had focal squamous metaplasia of the respiratory epithelium in the anterior region of the nose but they had no increased occurrence of tumours in the upper airways (15). The author did not report any observation from other organs.

In an industrial report (1990) cited in ACGIH (1) 95 mice and 95 rats were exposed to DMA in concentrations of 10, 50 or 175 ppm (19, 94 or 327 mg/m^3) 6 hours/day, 5 days a week for two years. There was no indication of an increased incidence of tumours.

9. Reproduction Toxicology

DMA-hydrochloride was injected intraperitoneally in doses of 0.25, 1, 2.5 and 5 mmol/kg (11, 45, 113 and 226 mg/kg) each day during day 1 - 17 in pregnant mice (16). All mice and embryos were studied on day 18 but there was no effect of DMA. An in vitro study of embryos cultivated from the 8th day of gestation exposed to DMA-hydrochlorid showed a concentration dependent decrease of the diameter of the yellow sac, crown-rump lengths, head lengths and embryo survival.

10. Relation between Exposure, Effect and Response

10.1. Effects of short-term exposure

The effects of short-term exposure are shown in Table 1. The earliest effects are irritation from the upper airways.

DMA in eyes or on the skin cause severe irritation (1, 30).

10.2. Effects of long-term exposure

The effects of long-term exposure to DMA are described in Table 2. The earliest effects are damages in the respiratory organs. The findings of Coon (8) is of uncertain relevance as there was no information about results in control animals. The findings may be due to infectious diseases in the animals. These authors did not evaluate the upper airways.

Apart from the data reported in Table 2 there is a Russian experiment on rat where there was an increase of aneuplodi in bone marrow cells at exposure to 0.27 or 0.54 ppm (0.5 or 1.0 mg/m^3) DMA continuously for ninety days (20). This is a finding of uncertain clinical relevance.

Table 1. Effects on animals after short-term exposure to DMA

Dose	Species	Effect	Reference
70 ppm, 15 minutes, (131 mg/m^3)	mouse	Severe influence on respiratory frequency	12
100 ppm, 10 minutes, (187 mg/m^3)	rat	Slight influence on respiratory frequency	38
175 ppm, 6 hours, (327 mg/m^3)	rat	Damages on nasal mucosa	15
600 - 2 500 ppm, 6 hours, (1 122 - 4 676 mg/m^3)	rat	Eye irritation, bloody secretion from the upper airways	38
3 983 ppm, 6 hours, (7 450 mg/m^3)	rat	Increased mortality	38

Table 2. Effects on animals of long-term exposure to DMA

Dose	Species	Effect	Reference
5 ppm (9.4 mg/m^3) continuously for 90 days	rat, guinea pig, rabbit, monkey, dog	Slight interstitial inflammatory changes in the lungs of uncertain relevance, see text	8
10 ppm (19 mg/m^3) 6 hours/day, 5 days a week, 12 months,	mouse rat	Slight changes in the nasal epithelium and olfactory cells	6
50 ppm (94 mg/m^3) 6 hours/day, 5 days a week, 12 months,	mouse, rat	Moderate changes in nasal epithelium and olfactory cells	6
97 - 185 ppm (181-346 mg/m^3) 7 hours/day, 5 days a week, 8 - 20 weeks,	mouse, rat, guinea pig, rabbit	Damages on cornea and liver changes	18 cited in 38
175 ppm (327 mg/m^3) 6 hours/day, 1 or 2 years,	rat	Marked changes in upper airway mucosa (squamous cell metaplasia, chronic inflammation) and destruction of turbinates, decrease in weight gain	6, 15

11. Research Needs

There is no study on short- or long-term exposure effects in humans. Possible sensitization potency on skin could be further evaluated by animal experiments as could the risk of skin absorption.

12. Discussion and Evaluation

DMA is a strong irritant, which is easily absorbed through the airways. It is highly water soluble and is deposited mainly in the upper airways (28). The critical effect is damages on mucosa in the upper airways, and on olfactory cells. Minor such effects were found in animals exposed to 19 mg/m^3 during 6 or 12 months (6). There is an animal study indicating slight inflammatory effects in the lungs after 90 days continuous exposure to 5 ppm (9.4 mg/m^3) (8). However, the study is of limited quality. An animal experiment indicate that DMA may cause skin sensitization (24). A water solution of DMA is a strong irritant to the skin and eyes.

DMA together with nitrite can form dimethylnitrosoamine, which is carcinogenic and hepatotoxic. DMA was nonmutagenic in most tests but positive in a test on yeast cells. An animal experiment did not support a carcinogenic effect.

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Ethylenediamine

1. Physical-Chemical Data

Chemical name:	Ethylenediamine (EDA)
CAS-number:	107-15-3
Synonyms:	1,2-ethandiamine, 1,2-diaminoethane, dimethylenediamine
Formula:	$C_2H_8N_2$
Structural formula:	$H_2N - CH_2 - CH_2 - NH_2$
Molecular weight:	60.10
Boiling point:	116.1°C
Melting point:	8.5°C
Vapour pressure (20°C):	1.4 kPa
Density (20°C):	0.898
pH (1 molar):	12.0 (39)
Flash point:	43.3°C (closed cup) 33.9°C (open cup)
Odour threshold:	1 - 11 ppm (30) (2.5 - 28 mg/m^3)
Conversion factor for air concentrations at 20°C, 101.3 kPa:	1 ppm = 2.49 mg/m^3 1 mg/m^3 = 0.40 ppm

EDA is a thick, colourless, alkaline and hygroscopic liquid with a smell of ammonia, insoluble in benzene, slightly soluble in ether and freely soluble in water. EDA is flammable (1, 32, 40).

2. Use and Occurrence

2.1. Use

EDA is used in the chemical and pharmaceutical industry (1, 36). It is an intermediate in the manufacturing of fungicide, chelating agents, synthetic waxes, polyamide resins, cleaning agents and rubber chemicals. EDA is used as a fuel additive and as a hardener in epoxy resins. It occurs as a free base or as a hydrochloride. As a hydrochloride it is a constituent of some drugs as teophyllamine and have been used in some skin creams. In the veterinary medicine it is used as a urine acidifier (44).

2.2. Air concentrations in work environment

Between 1975 and 1981 air concentrations of EDA was measured in a factory where EDA and a 50-50 mixture of EDA with n-butyl amine was used (3). A total of 1 053 measurements were done. In the years 1975 and 1980 the concentration exceeded 1 ppm (2.5 mg/m^3) in 25% and 19%, respectively, of the measurements and about 5% of the measurements these years showed concentrations above 10 ppm (25 mg/m^3). During 1976 - 1979 and 1981 the concentrations were more than 1 ppm in about 2% of the measurements and no measurement showed concentrations above 10 ppm. It is reported that the process was closed and equipped with good ventilation.

2.3. Methods for analyses of air concentration

NIOSH reports sampling on Amberlite XAD-2, impregnated with 1-naphthylisothiocyanate followed by a HPLC-analysis with UV-detection as a standard method (4, 23). Sampling on Tenax-absorbent covered with 1-naphthyl acetic acid anhydride with a HPLC-analysis with fluorescence detection has also been described (42) and a method with sampling on silica gel where the amine is derivated with m-toluoyl chloride during desorption and analyzed by HPLC and UV-detection (33). EDA has also been sampled in impingner and analyzed with isotachophoresis with a conductive UV-detector (13).

3. Kinetics

EDA can be absorbed through the lungs, gastrointestinal tract and the skin. It is partly biotransformed and excreted in urine and to some part in the feces.

3.1. Absorption

Rats receiving radioactively labeled EDA -dihydrochloride in single doses of 5, 50 and 500 mg/kg orally through intubation or endotracheally had a close to total absorption through the gastrointestinal tract or the lungs (43). Rats receiving 10, 25 or 50% radioactively labeled EDA-dihydrochloride in water with occlusion on the skin for 24 hours absorbed more than 12, 55 and 61% respectively of the dose (48). A large proportion of the doses (32, 12 and 11% respectively) was left on the dosing area of the skin.

3.2. Distribution

Rats receiving radioactively labeled EDA-dihydrochloride in single doses of 5, 50 or 500 mg/kg orally, endotracheally or intravenously showed radioactivity all over the bodies (43). Proportionally higher concentrations occurred in the thyroid, liver, kidneys and bone marrow while the concentration in the brain was low. Distribution between different tissues was similar at the different doses.

3.3. Biotransformation

Biotransformation was studied in Wistar rats receiving radioactively labeled EDA-dihydrochloride in single doses of 5, 50 or 500 mg/kg orally, endotracheally or intravenously (43). The major metabolite in urine was N-acetylethylenediamine (38 - 65% of excreted radioactivity in urine). Unchanged EDA also occurred in the urine (2 - 11% of radioactivity in urine at the dose 5 mg/kg and 44 - 49% at the dose 500 mg/kg) but the other metabolites in the urine could not be identified. 6 - 9% of the radioactivity was exhaled as CO_2 within 48 hours. In another experiment where rats received radioactively labeled EDA-dihydrochloride, 50 mg/kg per os, 10 - 22% was excreted as CO_2 (47).

The average half-time of elimination in plasma in rats receiving 25 or 50% EDA-dihydrochloride on the skin in a single dose was about five hours (48). Rats receiving a 10% solution in a similar way on the skin had an average half-time of nine hours but due to analytical difficulties the uncertainty of the half-time is large.

3.4. Excretion

Single doses of 5, 50 or 500 mg/kg ^{14}C labeled EDA-dihydrochloride were given to Wistar male rats orally, endotracheally or intravenously and the rats were studied for 48 hours (48). The major part was excreted during the first day but at the highest dose the excretion was proportionally higher during the second day compared to the lower doses. Of the radioactivity, 42 - 65% was excreted in the urine, 5 - 32% in the feces and 6 - 9% in exhaled air as $^{14}CO_2$.

Application of 408, 1 020 or 2 040 µg ^{14}C labeled EDA-dihydrochloride/cm^2 on about 10% of the skin of male rats showed that about 35% of the radioactivity was excreted in the urine at the two highest doses and 7% of the lowest dose (47). In the feces, 0.4 - 2 % was found.

3.5. Biological monitoring

No information.

4. General Toxicology

4.1. Mechanism, in vitro-studies

EDA is a GABA-A receptor agonist and the activity seems to depend on carbamate adducts that can be formed after reaction with bicarbonate (37). The clinical relevance of this after occupational exposure to EDA is unknown.

EDA may probably act as a hapten that together with a macromolecule, e.g., albumin, causes a specific immune response (2).

4.2. Factors influencing toxicity

The alkalinity influences the toxicity. Neutralized EDA (EDA-dihydrochloride) causes less irritant effects on skin and in eyes (44).

4.3. General findings

The LD_{50} for rats orally given one dose of EDA and followed for two weeks was 1 160 mg/kg (980 - 1 370) (35). LD_{50} after topical application on the skin and with two weeks follow up was 0.73 ml/kg (0.64 - 0.82). Exposure to 2 000 ppm (4 988 mg/m^3) EDA for eight hours caused no deaths in rats followed for two weeks while all rats exposed to 4 000 ppm (9 975 mg/m^3) died.

Rats given EDA in diet and followed for two years had a slower weight gain and an increased mortality at a dose of 350 mg/kg and day (45).

5. Organ Effects

5.1. Effects on skin and mucous membranes

EDA is irritating and may cause sensitization and allergic eczema.

Allergic eczema due to EDA is not uncommon and the prevalence in tested persons is reported to be between 0 and 18.8% with an average of about 2% in different populations (27). A Canadian examination of 542 patients with a suspected allergic eczema showed that EDA was the most common allergen for men (12.3%) and the third most common allergen for women (6.4%) (17).

Two cases of exfoliative erythroderma caused by EDA have been reported. One case was sensitized by a cream and was later treated for dyspnea with aminophylline (a mixture of 80% teophyllamine and 15% EDA-dihydrochloride) (26). The treatment was given in suppositories and continued for ten days before the association was revealed. Patch test showed a strong reaction to EDA-dihydrochloride but no reaction to other constituents of the cream. The second case showed a generalized exfoliative erythroderma after a few days treatment with aminophylline tablets due to asthma (5). After a few months the patient took another tablet of aminophylline and the erythema returned. Patch test with EDA-hydrochloride was positive while teophylline was negative. The patient had an occupational exposure to synthetic waxes containing EDA.

EDA was strongly irritant to the skin and the eyes in tests on rabbits while neutralized EDA (EDA-dihydrochloride) had a low irritant potency in the eyes or on the skin (44).

Solutions between 15 and 100% EDA caused persistent cornea damages while a 5% solution caused slight damage to the eyes of rabbits (31). Smyth (35) reported that EDA caused cornea damage of grade eight on a ten-grade scale. EDA may cause a delayed oedema of the cornea causing the individual to see coloured haloes about lights (11). This phenomenon is reported to occur at a concentration that cause no inconvenience when the exposure lasts for several hours.

5.2. Effects on respiratory system

Four persons were exposed to 100, 200 or 400 ppm (249, 499 or 998 mg/m^3) EDA for 5 - 10 seconds (28). One hundred ppm was reported to cause no inconvenience, 200 ppm caused slight irritation of the nasal mucosa and slight tingling sensations in the face. Four hundred ppm caused heavy irritation of the nasal mucosa.

Groups of 15 male and 15 female rats were exposed to 59, 132, 255 or 484 ppm (147, 329, 636 or 1 207 mg/m^3) EDA for 30 days, exposure time per day not reported (28). All rats exposed to the highest concentration died within 20 days and in 17 out of 28 examined rats the lungs were congested. Congestion also occurred in 1/3 of the rats exposed to 255 ppm EDA but about the same frequency of the controls had congested lungs. Rats exposed to 59 or 132 ppm had no lung changes.

In rats receiving 50, 250 or 1 000 mg/kg EDA-dihydrochloride a day in the diet for three months, an increased prevalence of tracheitis was reported in male rats receiving 1 000 mg/kg EDA-dihydrochloride per day (44).

EDA may cause asthma, both early, dual and late asthma is reported. IgE-antibodies against EDA have been found in persons with asthma (3, 10, 12, 19, 21, 22).

Gelfand (10) reported of twenty cases of asthma after exposure to EDA where all were positive at intradermal tests. The cases worked with rubber, cosmetics or shellac. Provocation with inhalation of EDA caused cough and asthmatic breathing immediately after exposure in the cases with asthma but not in the controls. All cases had atopy or allergic eczema. There is no information about exposure levels.

Lam (19) reported a case with reproducible late asthma after occupational exposure to EDA in photo chemicals. There is no information about exposure level. The case had no atopy and had negative intradermal skin test against EDA and there were no precipitating antibodies to EDA.

The incidence of occupational asthma was studied in a chemical factory where amines were used (12). EDA had been used in part of the production until 1978. The examination was done 1979 when about 130 persons were employed in the production but another 400 persons were also examined who had been employed between 1965 and 1979. Twenty-nine persons were considered to have asthma caused by piperazin and three by EDA. Two of the latter three cases had a dual reaction and one had only a late asthmatic reaction. One of the persons with EDA-asthma had an increased concentration of IgE in serum.

The frequency of EDA-related airway symptoms between 1974 and 1981 was studied in a factory producing EDA and a 50-50 mixture of EDA and n-butyl amine (3). In total 369 persons had been employed and acceptable answers on a questionnaire were received from 337. Of these, 38 persons were considered as "EDA sensitized". The diagnoses were based on information in medical records telling if the person had got rhinitis, cough and wheeze in the breast at exhalation when being in an environment with EDA and that the symptoms disappeared when they left that environment. The production where EDA occurs was separated and organic vapour respirators and full body protecting clothing were worn by all persons who entered the machine room or the chemical mix rooms. The concentration of EDA had been measured at 1 053 occasions in the room where the production occurred. Of the measurements 1975 and 1980, 19 and 25% respectively, exceeded 1 ppm while the other years only 2% of the samples showed concentrations of more than 1 ppm (2.5 mg/m^3). In 1975 and 1980 about 5% of the measurements showed values above 10 ppm (25 mg/m^3). The sensitized persons were similar to other workers with respect to gender, present and previous smoking habits, history of asthma and

history of allergy. Two of those with EDA-related airway symptoms had been sensitized to EDA before they got their airway symptoms. The average time between employment and occurrence of EDA-related airway symptoms was 15 months. Twenty-six percent of the machine operators had EDA-related airway symptoms. Corresponding frequencies for laboratory technicians, engineers and maintenance workers were 12, 11 and 5% respectively. The authors considered that the study indicates that there is a risk of sensitization of EDA if the concentrations exceed 1 ppm.

Two cases of EDA-induced late asthmatic reaction have been described from a chemical factory (21). After 4 and 7 months respectively, from onset of exposure to EDA their symptoms began. Provocation with inhalation of EDA was positive as was intradermal tests. After being moved to another work environment their symptoms disappeared. There is no information about exposure levels.

One person got asthmatic symptoms after three months work in a chemical factory where EDA occurred (22). Provocation test with 30 ppm (75 mg/m^3) EDA for 15 minutes was positive but the person also reacted on isopropyl alcohol (50 ppm for 15 minutes). Histamine test was positive and skin prick testing showed positive reactions to mite, house dust, dog fur, pollen and grass.

5.3. Effects on the liver

Rats exposed to 225 or 484 ppm (561 or 1 207 mg/m^3) EDA for 30 days (exposure time per day not reported) showed diffuse swelling of the liver and increased weight of the liver while these changes were not reported in rats exposed in a similar way to 59 or 132 ppm (147 or 329 mg/m^3) (28). Male or female rats (Fischer 344) that daily received 1 000 mg/kg EDA-dihydrochloride in diet for three months had a hepatocellular pleomorphism and patchy degeneration of hepatocytes and increased transaminases and ALP in serum (44). These rats also had decreased weight gain. These changes did not occur in rats receiving 50 or 250 mg/kg a day in the diet. Rats (Fischer 344) given 350 mg EDA-dihydrochloride per kg body-weight in diet for two years had hepatocellular pleomorphism after one year but not after six months (45). Rats receiving 20 or 100 mg/kg in a similar way had no liver changes.

5.4. Effects on the kidneys

Hemolysis, anuria and hypercalcemia were noted within four hours in a man splashed with EDA and inhaling the vapours for some minutes (24). The man died 55 hours after the accident.

Rats exposed to 225 or 484 ppm (561 or 1 207 mg/m^3) EDA for 30 days (exposure time per day not reported) had swelling of the kidneys and degeneration of tubuli (28). There were no such changes in rats receiving 59 or 132 ppm (147 or 329 mg/m^3) EDA. EDA-hydrochloride in a single dose of 5.0 mmol/kg intraperitoneally to a mouse caused moderate proteinuria (38).

5.5. Effects on the gastrointestinal tract

No change in the gastrointestinal tract is reported in rats receiving EDA-dihydrochloride in the diet (50, 250 or 1 000 mg/kg bodyweight per day for three months or 20, 100 or 350 mg/kg bodyweight per day for two years) (44, 45).

5.6. Effects on the cardiovascular system

Rats of both sexes (Fischer 344) receiving 1 000 mg EDA-dihydrochloride per kg body-weight in the diet for three months had a decreased cardiac weight but the general weight gain was also decreased and no abnormal pathological findings were reported (44). No cardiovascular changes were reported in rats receiving 20, 100 or 350 mg per kg bodyweight a day EDA-dihydrochloride in diet for two years (45).

5.7. Effects on blood and bloodforming organs

Rats receiving 1 000 mg EDA per kg bodyweight and day for three months in the diet had a decreased number of erythrocytes and decreased MCV (44). Female rats receiving 250 mg per kg bodyweight and day in a similar way had a decreased MCV. Male rats receiving 250 mg per kg bodyweight and day or female and male rats receiving 50 mg/kg and day had no such changes. Male rats receiving 350 mg EDA-dihydrochloride per kg bodyweight and day in the diet for two years had slight changes in blood, such as decreased numbers of erythrocytes, decreased Hb and decreased hematocrit (45).

5.8. Effects on the central nervous system

No information.

5.9. Effects on the peripheral nervous system

No information.

5.10. Other organ effects

Rats exposed to 132 ppm (329 mg/m^3) EDA for 30 days (exposure time per day not reported) had a slight depilatory effect (28). There was no depilatory effect at exposure to 59 ppm (147 mg/m^3).

ACGIH (1) cites an industrial report showing eye damages (cataract, conjunctivitis, cloudy cornea, retinal atrophy) in rats receiving 100 mg/kg EDA-hydrochloride (reported as free alkali) per day by gavage for three monthsbut no other organ damages. It is cited that the no-effect level for mice in the study was 100 mg/kg and day.

6. Immunotoxicity and Allergy

IgE-mediated allergy has been shown in two studies where persons with asthma had showed positive skin prick test to EDA (10, 21). There has also been a positive Prausnitz-Küstner reaction in some of these cases. No IgG-antibodies to EDA could be shown.

The guinea pig maximization test showed that a 0.5% solution of EDA sensitized 60% of the animals (41). Henck (16) patch tested albino guinea pig to EDA and Na_3EDTA. All guinea pigs were sensitized to EDA but none to Na_3EDTA.

Cross-reactivity occurs between EDA, DETA and triethylenetetramine (TETA). Rudzki and Krajewska (29) reported patch testing on 137 patients occupationally exposed to epoxy resins. Of these, 23 patients were sensitized to EDA and all of them were also positive to TETA. Another 48 patients were positive to TETA but negative to EDA.

Exposure to EDA in patients primarily sensitized to TETA could not be excluded but cross-reactivity was suspected. Ormerod (25) found cross-reactivity to polyamines in five patients sensitized to EDA and DETA and/or TETA after handling drilling mud containing DETA and TETA. None had previously been exposed to EDA. Of nine persons sensitized to EDA through skin creams, six were also sensitized to DETA and three to both DETA and TETA.

Routine patch testing of 542 patients with suspected allergic eczema showed that EDA caused a positive reaction to 8.7%, i.e., it was the second most common allergen in the total group of men and women (17). It was suspected that the high frequency partly was caused by prescription of skin creams containing EDA as a stabilizer.

7. Mutagenicity and Genotoxicity

EDA showed mutagenic activity to Salmonella strains TA 1535 and TA 100 with and without metabolic activation (15). The author discussed the possibility that there was an impurity causing the mutagenic activity. Another experiment with TA 100 showed a weak mutagenic activity of EDA (18).

EDA showed no positive mutagenic effect in Chinese hamster ovary gene mutation assay, the sister chromatid exchange test with CHO cells, or unscheduled DNA synthesis assays with primary rat hepatocytes or in a dominant lethal study with Fischer 344 rats (34).

8. Carcinogenicity

8.1. Human studies

No information.

8.2. Animal studies

No increased incidence of tumours was reported in Fischer 344 rats receiving 20, 100 or 350 mg EDA-dihydrochloride per kg bodyweight and day in the diet for two years (45).

The occurrence of skin tumours was studied in 50 C3H male mice, which were applicated three times a week with 25 µl (total dose not reported, calculated value = 66 mg/mouse = 2.7 mg/kg bodyweight) 1% EDA water solution during the lifetime of the animals, 1.5 - 2 years (8). EDA from two suppliers were used and none of the mice got skin tumours.

9. Reproduction Toxicology

EDA-dihydrochloride was fed to pregnant rats on gestation day 6 - 15 at doses of 50, 250 or 1 000 mg/kg a day (7, 9). The weight gain and food intake was decreased in females at the two highest doses. At the highest doses the weight and length of the fetus were decreased, the number of litters with resorptions increased and there were more skeletal variances and the frequency of missing or shortened innominate arteries was increased.

In a two-generation reproduction study of Fischer 344 rats the first generation of 25 male and 26 female rats received a diet containing 50, 150 or 500 mg/kg a day EDA-dihydrochloride and twice as many received a control diet (46). In the next generation 15 male and 26 female rats received the same diet while 30 male and 52 female rats received control diet. The mortality, weight gain, intake of food, organ weight and histological changes were studied. The reproduction was evaluated by fertility index, gestation length, gestation index, gestation survival index, 0 - 4 days survival and 4 - 14 and 4 - 21 day survival, number of pups born alive and number of pups veined per litter, weight of the pups at day 4, 14 and 21. The only negative effects were a reduction of body weight gain and changes in the liver and kidney weights in the adult rats at the high dosage level.

CD1 mice were fed with 400 mg/kg a day EDA orally during gestation days 6 - 13 (14). The maternal response variables were mortality, weight change and number of viable litters. One of the 50 mice died and the other variables of maternal mice were not significantly different from controls. The neonatal response variables were number of live born per litter, survival, birth weight and weight gain. The survival and number of live-born per litter were not significantly different from controls. There was a slight but significant decrease in birth weight and a slower weight gain in the pups.

10. Relation between Exposure, Effect and Response

Table 1. Effects of short-term exposure to EDA.

Concentration/time	Species	Effects	Reference
100 ppm/5-10 sec	Humans	"Not inconvenient"	28
200 ppm/5-10 sec	Humans	Irritation in the nose, tingling feeling in the face	28
400 ppm/5-10sec	Humans	Intolerable due to irritation in the nose	28
4 000 ppm/8 hours	Rats	All rats died	35

10.1. Effects of short-term exposure

Four persons exposed to 100, 200 or 400 ppm (249, 499 or 988 mg/m^3) EDA for 5 - 10 seconds did not find 100 ppm inconvenient, 200 ppm caused irritation of nasal muscosa and a tingling feeling in the face (28). Four hundred ppm was reported as intolerable due to irritation of the nasal mucosa.

A 36-years old worker died 55 hours after getting splashed with EDA on the skin (24). For a few minutes he inhaled the vapour before his clothing was removed and he was rinsed. Four hours later there were a generalized erythema and anuria.

Inhalation of 2 000 ppm (4 988 mg/m^3) EDA for eight hours caused no deaths in rats while 4 000 ppm (9 975 mg/m^3) killed all exposed rats (35).

EDA may cause an oedema in the cornea but the dose-response relation is not known (Grant 1974). Splash of concentrated EDA on the skin or in the eyes is strongly irritant and can cause necrosis or persistent cornea damage (35).

Table 2. Effects of long-term exposure to EDA.

Concentration/time	Species	Effect	References
Mostly below 1 ppm sometimes peaks to more than 10 ppm/variable time	Humans	26 % of exposed persons have airway symptoms indicating sensitization	3
59 ppm/30 d	Rats	No abnormal findings reported	28
132 ppm/30 d	Rats	A slight depilatory effect	28
225 ppm/30 d	Rats	Increased mortality	28
484 ppm/30 d	Rats	All rats died within 20 days	28

10.2. Effects of long-term exposure

One hundred and ninety-seven persons working with EDA for more than one month between 1947 and 1983 were evaluated through medical records (20). Three and a half percent were regarded as having certain sensitivity in the airways and 11.5% skin sensitization but these judgements were rarely based on patch test, skin prick test or similar testing but on a clinical judgement. Sensitization in skin and airways occurred independently of each other. Six of the seven persons that were regarded to have a sensitization in the airways to EDA occurred within a year after the employment. There is no information about concentration of EDA in the work environment. In a follow-up of the mortality there was no increased mortality. The total mortality was very low (SMR = 38) so there might be a selection bias in the material.

Pozzani (28) exposed 15 male and 15 female rats to 59, 132, 225 or 484 ppm (147, 329, 561 or 1 207 mg/m^3) EDA for 30 days. At 484 ppm all animals died within 20 days. There was swelling of the liver and kidneys and degeneration of tubuli in the kidney. At 225 ppm four rats survived 30 days and their liver and kidney weighted significantly more than controls, while the bodyweight was decreased. At 132 ppm no rats died due to EDA. The only finding was a slight depilatory effect. At 59 ppm there were no abnormal findings reported.

Ten Fischer 344 rats received 50, 250 or 1 000 ml EDA-dihydrochloride per kg body-weight and day in diet for three months (44). Rats receiving 1 000 ml/kg body-weight and day had a slower weight gain, a decreased number of erythrocytes and MCV and increased liver transaminases and ALP in blood. In the liver there were hepatocellular pleomorphism and patchy degeneration of hepatocytes and there was an increased prevalence of tracheitis in male rats. Female rats receiving 250 mg/kg bodyweight and day had a decreased MCV while male rats receiving a similar dose had no abnormalities. Fischer 344 rats received EDA-dihydrochloride (20, 100, 350 mg/kg bodyweight and day) for

two years. Rats at the dosage 350 mg/kg bodyweight and day had an increased mortality and an increased prevalence of hepatocellular pleomorphism, rhinitis and tracheitis (45).

11. Research Needs

Knowledge about the dose-response relationship for the occurrence of asthma is missing. Several amines may cause corneal oedema but there are no such studies of EDA.

12. Discussion and Evaluation

The critical effect for EDA is sensitization in airways, asthma and/or rhinitis and skin sensitization (6, 10). Data is missing for an accurate risk estimation for asthma at different exposure levels. An American study found that 26% of workers showed airway symptoms indicating sensitization in a work environment where most measurements showed level belows 1 ppm (2.5 mg/m^3) (3). During five of the seven years measurements were done, more than 97% of the measurements were below 1 ppm and during the other two years 75 and 81%, respectively, of the measurements were below 1 ppm. In two calender years about 5% of the measurements were above 10 ppm (25 mg/m^3). No value above 10 ppm was registered during the other five years. These results indicate that environments where the air concentration usually is below 1 ppm but with some peaks with higher levels, may cause airway symptoms and EDA sensitization in a considerable proportion of exposed persons.

Skin sensitization to EDA is common (17, 27).

EDA is strongly irritant on skin and in the eyes while neutralized EDA only is a weak irritant.

Mutagenic tests have shown contradictory results and it has been discussed if the positive findings were caused by impurities in EDA. Two animal studies, one with EDA in the food and one with EDA applicated to the skin showed no cancerogenic effect. Epidemiological studies of relevance to estimate the risk for cancer in humans are missing.

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Summary

Andersson E, Järvholm B. 110. Diethylamine, Diethylenetriamine, Dimethylamine, Ethylenediamine. Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. *Arbete och Hälsa* 1994;23:1-45.

This review evaluates the health effects of DEA, DETA, DMA and EDA.
The critical effect of DEA is irritation in the eyes and the airways.
DETA is a strong skin sensitizer with irritant effects on mucous membranes and airways. A case of asthma caused by DETA is reported.
The critical effect of DMA is damages on mucous membranes in the respiratory organs and on the olfactory cells.
The critical effect of EDA is the risk of sensitization in airways and skin. Epidemiological data suggest that airway symptoms, indicating EDA sensitization, can be a considerable risk at levels around 1 ppm.

Key words: Occupation, diethylamine, dimethylamine, ethylenediamine, diethylenetriamine, threshold limit values, toxicology, review.

Sammanfattning

Andersson E, Järvholm B. 110. Dietylamin, Dietylentriamin, Dimetylamin, Etylendiamin. Nordiska expertgruppen för kriteriedokumentation av kemiska hälsorisker. *Arbete och Hälsa* 1994;23:1-45.

Denna översiktsartikel utvärderar hälsoeffekterna av DEA, DETA, DMA och EDA.
Den kritiska effekten för DEA är irritation i ögon och luftvägar.
DETA är en stark hudsensibiliserare med irritationseffekter på slemhinnor och luftvägar. Ett astmafall orsakat av DETA har rapporterats.
Den kritiska effekten för DMA är skador på slemhinnorna i andningsorganen och på luktceller.
Den kritiska effekten för EDA är risken för sensibilisering i luftvägar och hud. Epidemiologiska data antyder att luftvägssymptom, troligen pga EDA sensibilisering, kan vara en avsevärd risk vid koncentrationer runt 1 ppm.

Nyckelord: Dietylamin, dietylentriamin, dimetylamin, etylendiamin, gränsvärde, toxikologi, yrkesmässig exponering, översiktsartikel.

This review is based on a literature research done in Riskline, NIOSHTIC, CISILO, Arbline, Toxline, RTEC, Current contents and Life Sciences.

Appendix

Permitted or recommended maximum levels of diethylamine in air

Country	ppm	mg/m^3	Comments	Year	Ref.
Denmark	10	30		1988	1
Finland	10	30	S, 15 min	1993	2
Iceland	10	30	S	1989	3
	15	45	15 min		
Netherlands	10	30		1989	4
Norway	10	30		1989	5
Sweden	10	30	S	1993	6
	15	45	15 min		
USA (ACGIH)	10	30		1991-92	7
	25	75	STEL		
(NIOSH)	10	30	TWA	1990-91	8
	25	75	STEL		

S: penetration through skin

Permitted or recommended maximum levels of diethylenetriamine in air

Country	ppm	mg/m^3	Comments	Year	Ref.
Denmark	1	4		1988	1
Finland	1	4	S	1993	2
	3	12	STEL		
Iceland	1	4.5	A, S	1989	3
	2	10	STEL		
Netherlands	1	4	S	1989	4
Norway	1	4	A, S	1989	5
Sweden	1	4.5	A, S	1993	6
	2	10	STEL		
USA (ACGIH)	1	4.2	S	1991-92	7
(NIOSH)	1	4		1990-91	8

A: allergenic, sensitizing
S: penetration through skin

Permitted or recommended maximum levels of dimethylamine in air

Country	ppm	mg/m^3	Comments	Year	Ref.
Denmark	10	18		1988	1
Finland	10	18	15 min	1993	2
Iceland	-	-		1989	3
Netherlands	1	1.8		1989	4
Norway	10	18		1989	5
Sweden	2	6		1993	6
	5	15	STEL		
USA (ACGIH)	10	18		1991-92	7
(NIOSH)	10	18		1990-91	8

S: penetration through skin

Permitted or recommended maximum levels of ethylenediamine in air

Country	ppm	mg/m^3	Comments	Year	Ref.
Denmark	10	25		1988	1
Finland	10	25		1993	2
	20	50	S, STEL		
Iceland	10	25	S	1989	3
	15	35			
Netherlands	10	25		1989	4
Norway	10	25	A	1989	5
Sweden	10	25	S	1993	6
	15	35	STEL		
USA (ACGIH)	10	25		1991-92	7
(NIOSH)	10	25		1990-91	8

A: allergenic, sensitizing
S: penetration through skin

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CRITERIA DOCUMENTS FROM THE NORDIC EXPERT GROUP

The Criteria Documents are in a Scandinavian language, with summary in English. Those marked with * are in English. Those marked with D are published in collaboration with the Dutch Expert Committee for Occupational Standards (DECOS). Those marked with N are published in collaboration with NIOSH, USA.

Acetaldehyde	Arbete och Hälsa 1986:25
Acetone	Arbete och Hälsa 1986:39
Acetonitrile	Arbete och Hälsa 1989:22, 1989:37*
Acrolein	Arbete och Hälsa 1991:45
Acrylates	Arbete och Hälsa 1983:21
Acrylonitrile	Arbete och Hälsa 1985:4
Allyl alcohol	Arbete och Hälsa 1986:8
Aluminium	Arbete och Hälsa 1992:45, 1993:1*
Ammonia	Arbete och Hälsa 1986:31
Arsenic, inorganic	Arbete och Hälsa 1981:22, 1991:9, 1991:50*
Arsine	Arbete och Hälsa 1986:41
Asbestos	Arbete och Hälsa 1982:29
Benomyl	Arbete och Hälsa 1984:28
Benzene	Arbete och Hälsa 1981:11
Boric acid, Borax	Arbete och Hälsa 1980:13
1-Butanol	Arbete och Hälsa 1980:20
Cadmium	Arbete och Hälsa 1981:29, 1992:26, 1993:1*
7/8 Carbon chain aliphatic monoketones	Arbete och Hälsa 1990:2*D
Carbon monoxide	Arbete och Hälsa 1980:8
Chlorine, Chlorine dioxide	Arbete och Hälsa 1980:6
Chloromequat chloride	Arbete och Hälsa 1984:36
4-Chloro-2-methylphenoxy acetic acid	Arbete och Hälsa 1981:14
Chlorophenols	Arbete och Hälsa 1984:46
Chromium	Arbete och Hälsa 1979:33
Cobalt	Arbete och Hälsa 1982:16
Copper	Arbete och Hälsa 1980:21
Creosote	Arbete och Hälsa 1988:13, 1988:33*
Cyclohexanone, Cyclopentanone	Arbete och Hälsa 1985:42
n-Decane	Arbete och Hälsa 1987:25, 1987:40*
Deodorized kerosene	Arbete och Hälsa 1985:24
Diacetone alcohol	Arbete och Hälsa 1989:4, 1989:37*
Diesel exhaust	Arbete och Hälsa 1993:34, 1993:35*
Diisocyanates	Arbete och Hälsa 1979:34, 1985:19
Dimethyldithiocarbamates	Arbete och Hälsa 1990:26, 1991:2*
Dimethylethylamine	Arbete och Hälsa 1991:26, 1991:50*
Dimethylformamide	Arbete och Hälsa 1982:28
Dimethylsulfoxide	Arbete och Hälsa 1991:37, 1991:50*
Dioxane	Arbete och Hälsa 1982:6
Epichlorohydrin	Arbete och Hälsa 1981:10
Ethyl acetate	Arbete och Hälsa 1990:35*D
Ethylbenzene	Arbete och Hälsa 1986:19
Ethylene bisdithiocarbamates	Arbete och Hälsa 1993:24, 1993:35*
Ethylene glycol	Arbete och Hälsa 1980:14
Ethylene glycol monoalkyl ethers	Arbete och Hälsa 1985:34
Ethylene oxide	Arbete och Hälsa 1982:7
Ethylene thiourea	Arbete och Hälsa 1993:24, 1993:35*
Formaldehyde	Arbete och Hälsa 1978:21, 1982:27
Furfuryl alcohol	Arbete och Hälsa 1984:24
Gasoline	Arbete och Hälsa 1984:7
Halothane	Arbete och Hälsa 1984:17
n-Hexane	Arbete och Hälsa 1980:19, 1986:20
Hydrazine, Hydrazine salts	Arbete och Hälsa 1985:6
Hydrogen fluoride	Arbete och Hälsa 1983:7
Hydrogen sulfide	Arbete och Hälsa 1982:31
Hydroquinone	Arbete och Hälsa 1989:15, 1989:37*
Inorganic acid aerosols	Arbete och Hälsa 1992:33
Isophorone	Arbete och Hälsa 1991:14, 1991:50*
Isopropanol	Arbete och Hälsa 1980:18
Lead, inorganic	Arbete och Hälsa 1979:24, 1992:43, 1993:1*
Limonene	Arbete och Hälsa 1993:2, 1993:35*
Manganese	Arbete och Hälsa 1982:10
Mercury, inorganic	Arbete och Hälsa 1985:20
Methacrylates	Arbete och Hälsa 1983:21
Methanol	Arbete och Hälsa 1984:41
Methyl bromide	Arbete och Hälsa 1987:18, 1987:40*
Methyl chloroform	Arbete och Hälsa 1981:12
Methylcyclopentadienyl manganese tricarbonyl	Arbete och Hälsa 1982:10
Methylene chloride	Arbete och Hälsa 1979:15, 1987:29, 1987:40*
Methyl ethyl ketone	Arbete och Hälsa 1983:25
Methyl formate	Arbete och Hälsa 1989:29, 1989:37*
Methyl isobutyl ketone	Arbete och Hälsa 1988:20, 1988:33*
Microorganisms	Arbete och Hälsa 1991:44, 1991:50*
Mineral fibers	Arbete och Hälsa 1981:26
Nickel	Arbete och Hälsa 1981:28
Nitrilotriacetic acid	Arbete och Hälsa 1989:16, 1989:37*
Nitroalkanes	Arbete och Hälsa 1988:29, 1988:33*
Nitrogen oxides	Arbete och Hälsa 1983:28
N-Nitroso compounds	Arbete och Hälsa 1990:33, 1991:2*
Nitrous oxide	Arbete och Hälsa 1982:20
Oil mist	Arbete och Hälsa 1985:13
Organic acid anhydrides	Arbete och Hälsa 1990:48, 1991:2*
Ozone	Arbete och Hälsa 1986:28
Paper dust	Arbete och Hälsa 1989:30, 1989:37*
Permethrin	Arbete och Hälsa 1982:22
Petrol	Arbete och Hälsa 1984:7
Phenol	Arbete och Hälsa 1984:33
Phthalate esters	Arbete och Hälsa 1982:12
Propylene glycol	Arbete och Hälsa 1983:27
Propylene glycol ethers and their acetates	Arbete och Hälsa 1990:32*N
Propylene oxide	Arbete och Hälsa 1985:23
Refined petroleum solvents	Arbete och Hälsa 1982:21
Selen	Arbete och Hälsa 1992:35, 1993:1*
Silica, crystalline	Arbete och Hälsa 1993:2, 1993:35*
Styrene	Arbete och Hälsa 1979:14, 1990:49, 1991:2*
Sulfur dioxide	Arbete och Hälsa 1984:18
Synthetic pyretroids	Arbete och Hälsa 1982:22
Tetrachloroethylene	Arbete och Hälsa 1979:25
Thiurams	Arbete och Hälsa 1990:26, 1991:2*
Toluene	Arbete och Hälsa 1979:5, 1989:3, 1989:37*
1,1,1-Trichlorethane	Arbete och Hälsa 1981:12
Trichloroethylene	Arbete och Hälsa 1979:13, 1991:43, 1991:50*
n-Undecane	Arbete och Hälsa 1987:25, 1987:40*
Vanadium	Arbete och Hälsa 1982:18
Vinyl acetate	Arbete och Hälsa 1988:26, 1988:33*
Vinyl chloride	Arbete och Hälsa 1986:17
Welding fumes	Arbete och Hälsa 1990:28, 1991:2*
White spirit	Arbete och Hälsa 1986:1
Wood dust	Arbete och Hälsa 1987:36
Xylene	Arbete och Hälsa 1979:35
Zinc	Arbete och Hälsa 1981:13