NEG and NIOSH Basis for an Occupational Health Standard

2-diethylaminoethanol

Kjell Torén
A memorandum has been signed between the Centers for Disease Control, National Institute for Occupational Safety and Health (NIOSH), USA, and the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG). The purpose of the memorandum is to exchange information and expertise in the area of occupational safety and health. One product of this agreement is the development of documents to provide scientific basis for establishing recommended occupational exposure limits. The exposure limits will be developed separately by each country according to the different national policies.

This document on the health effects of occupational exposure to 2-dimethylaminopropanol is a product of that agreement. The document was written by Kjell Torén, MD (Department of Occupational Medicine, Sahlgrenska Hospital, St. Sigfridsgatan 85, S-412 66 Gothenburg, Sweden), and was reviewed by NEG and the Division of Standards Development and Technology Transfer (DSDTT), NIOSH.

Richard W. Niemeier
Director/DSDTT
National Institute for Occupational Safety and Health
USA

Per Lundberg
Chairman/NEG
National Institute of Occupational Health
Sweden
Contents

1. Physical and Chemical Properties

2. Occurrence and Use
   2.1. Occurrence
   2.2. Air concentrations in the environment,
   2.3. Methods for analysis of air concentrations

3. Kinetics
   3.1. Absorption
   3.2. Distribution
   3.3. Elimination
   3.4. Metabolism
   3.5. Biological indicators of exposure

4. General Toxicology
   4.1. Non-inhalation toxicology
   4.2. Inhalation toxicology

5. ORGAN EFFECTS
   5.1. Systemic symptoms
   5.2. Upper airways and skin
   5.3. Effects on the lower airways
   5.4. Effects on the liver
   5.5. Renal effects
   5.6. Gastrointestinal effects.
   5.7. Effects on the cardiovascular system
   5.8. Effects on blood and blood-forming organs
   5.9. Effects on the central nervous system
   5.10. Effects on peripheral nerves
   5.11. Other effects.

6. Immunotoxicity

7. Mutagenicity and Genotoxicity

8. Carcinogenicity

9. Effects on the Reproduction

10. Case Reports

11. Exposure Effect Relations

12. Research Needs

13. Discussion and Conclusions

14. Summary

15. Summary in Swedish

16. References
1. Physical and Chemical Properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical name:</td>
<td>2-Diethylaminoethanol</td>
</tr>
<tr>
<td>CAS number:</td>
<td>100-37-8</td>
</tr>
<tr>
<td>Synonyms:</td>
<td>N,N-Diethylethanolamine; DEAE, DEEA,</td>
</tr>
<tr>
<td></td>
<td>2-Diethylaminooctyl alcohol, Diethyl-(2-Hydroxyethyl)amino</td>
</tr>
<tr>
<td>Summary formula:</td>
<td>C₈H₁₅NO</td>
</tr>
<tr>
<td>Structure formula:</td>
<td>CH₃-CH₂-N-CH₂-CH₂-OH</td>
</tr>
<tr>
<td></td>
<td>CH₂</td>
</tr>
<tr>
<td></td>
<td>CH₃</td>
</tr>
<tr>
<td>Molecular weight:</td>
<td>117.2</td>
</tr>
<tr>
<td>Boiling point (101kPa):</td>
<td>163°C</td>
</tr>
<tr>
<td>Melting point:</td>
<td>-70°C</td>
</tr>
<tr>
<td>Density (25°C):</td>
<td>0.88</td>
</tr>
<tr>
<td>Vapour pressure (20°C):</td>
<td>0.19 kPa</td>
</tr>
<tr>
<td>Flash point (closed cup):</td>
<td>52.2°C</td>
</tr>
<tr>
<td>Autoignition temperature:</td>
<td>250°C</td>
</tr>
<tr>
<td>Conversion factors:</td>
<td>1 ppm = 4.8 mg/m³</td>
</tr>
<tr>
<td></td>
<td>1 mg/m³ = 0.21 ppm</td>
</tr>
</tbody>
</table>

The alkanolamine 2-diethylaminoethanol (DEAE) is a colourless hygroscopic liquid base with a nauseating odour. Its explosive limit in air is between 1.9% and 28%. DEAE is soluble in water, alcohol, benzene and ether. Its water solubility has been stated as unlimited (2). The odour threshold is reported to be 0.05 mg/m³ (0.011 ppm) (2).

2. Occurrence and Use

2.1. Occurrence

The alkanolamines have been widely used in industry, especially in the chemical and pharmaceutical industries (3). The tertiary amine DEAE is mainly used as an anti-corrosive agent in humidifiers and in water-based steam heating systems. Owing to its alkalinity, it reacts with gases such as carbon dioxide to neutralize the acidity and thus prevent the corrosion of different metals such as iron. DEAE has also been used as a reagent in different chemical analyses. In anion exchange chromatography, DEAE is coupled to cellulose as the anion exchanger (22). It has also been used as a reagent in a colorimetric method for the determination of trinitrotoluene in air (14).
2.2. Air concentrations in the environment.

A laboratory worker removing animals from an exposure chamber was described as having been exposed to an estimated concentration of 480 mg/m³ (100 ppm) or less (8).

The concentrations of DEAE in steam condensate were analyzed by Malaiyandi et al. (23). In the first hospital 225 g of DEAE was added daily to the boiler. The levels in the steam were highest in samples taken 30 minutes after the addition of DEAE, 2050 mg/l, and decreased during the following 24 h to about 15 mg/l. In the second hospital a mixture of DEAE and octadecylamine (ODA) were continuously metered into the boiler feed water, 2400 g each 24 hour period. The levels of DEAE and ODA were fairly constant over time, 3.6 - 5.2 mg/l for DEAE and 0.11 - 0.14 mg/l for ODA.

In a museum, air concentrations of 0.05 mg/m³ and 0.04 mg/m³ were found in two out of 14 samples. The DEAE had been added to the humidification system (10).

In a laboratory investigation, release of steam from a boiler system resulted in air concentrations between 0.04 mg/m³ (8.6 ppb) and 0.14 mg/m³ (29.8 ppb) (20, cited from ref. 17).

The air concentrations of DEAE were assessed in a combined office and electrical laboratory in the basement of a building that was steam heated and steam humidified (9). A mixture of DEAE and cyclohexylamine was added to the water. The humidity in the investigated room varied between 42% and 61%. Cyclohexylamine and DEAE were collected in four-five minute sample periods, hourly, for a total of 30 hours.

When the humidity was 42%, the mean concentration was 0.00029 mg/m³ (0.6 ppb) and when the humidity was increased to 61% the mean concentration of DEAE was 0.012 mg/m³ (2.4 ppb). At the end of the study the humidifier was cut out, after which the concentration of DEAE increased to 0.039 mg/m³ (8.2 ppb).

In the above cited situations, the concentrations of cyclohexylamine were 0.7 ppb, 0.8 ppb and 3.8 ppb respectively.

2.3. Methods for analysis of air concentrations

The general procedure of analyzing DEAE is to sample it on silica gel and then desorb with methanol. The solution is alkalinized and then analyzed by gas chromatography (30).

Earlier DEAE aerosols in air were absorbed in distilled water and then extracted with purified ethylene chloride (26). Methyl orange is then added, and the complex of methyl orange and DEAE was determined colorimetrically.

3. Kinetics

3.1. Absorption

DEAE is absorbed in the airways, in the gastrointestinal tract and through the skin. The dermal penetration rate for 132 substances, including DEAE, have been calculated based on their physical properties (11). DEAE was found to have a high dermal penetration rate, meaning that dermal absorption of DEAE will raise the biological levels 30% above those occurring during inhalation of concentrations equal to TLV. Other substances with comparable properties were ethanolamine and diphenylamine. Besides this study no quantitative estimations of the absorption of DEAE have been found in the literature.

3.2. Distribution

A dog was given 11 g DEAE intravenously, and three hours later the distribution in various tissues was examined (33). The highest concentration, 1227 mg/kg was found in the spleen. The concentrations in the liver, in the lungs, in the brain and in the heart were 955 mg/kg, 447 mg/kg, 223 mg/kg and 134 mg/kg, respectively. The concentration in the plasma was 70 mg/kg.

After oral administration of 5.6 g DEAE to two humans, the peak plasma levels were reached after three hours (33).

H¹³-labelled DEAE was administered intravenously to rats. High concentrations of DEAE were found in the lungs, in the hypophysis and in the adrenals (25).

3.3. Elimination

Two subjects received 5.6 g of DEAE intravenously, and they excreted in the urine 20% and 21% as unchanged DEAE (33). The same subjects also obtained 5.6 g DEAE orally and then excreted 27% and 23% as unchanged DEAE. The time period for the excretion is not mentioned in the paper.

In rats given radioactively labelled DEAE intravenously, 20% was excreted in the urine during the first 24 h and 46% after 48 h (25). In fases, 9% was excreted after 24 h and 30% was excreted after 48 h. No radioactivity was found in the expired air from rats. The biliary excretion was monitored through a canula in the common bile duct, and after 6 h 9% of the DEAE was excreted in the bile.

3.4. Metabolism

In rats, about 70% of DEAE is excreted unmetabolised in fases or in urine (25). DEAE was administered to five rats by orogastric intubation (37). After 24 h small amounts of triethylamine oxide, diethylamine and monomethylamine were found in the urine. Unmetabolized DEAE and choline were found in the liver of
rats fed DEAE (4). The authors claimed that they also found diethylmethyl-ethanolamine in the liver (4).

Procaine, a local anaesthetic drug, is rapidly metabolized in serum to DEAE and paraaminobenzoic acid (PABA) (5). This hydrolysis is catalyzed by plasma cholinesterase, also known as procaine esterase (19).

3.5. Biological indicators of exposure

No systematic studies of such indicators have been found in the literature. However, DEAE is excreted in the urine (23) and this may be used as a method of assessing exposure.

4. General Toxicology

4.1. Non-inhalation toxicity

LD₅₀ (rat orally)
- Neutralized DEAE 5.6 g/kg (8)
- Nonneutralized DEAE 1.3 g/kg (35)
- Given as water solution (10%) 2.5 g/kg (1)
LD₅₀ (guinea pig, dermal, undiluted) 1.0 ml/kg (35)
LD₅₀ (rabbit, dermal, undiluted) 1.3 ml/kg (1)
LD₅₀ (rat, intraperitoneal) 1.2 g/kg (34)
LD₅₀ (mouse, intraperitoneal) 0.3 g/kg (34)
LD₅₀ (mouse, Intramuscular) 0.4 g/kg (34)
LD₅₀ (mouse, Intravenous) 0.2 g/kg (34)
LD₅₀ (mouse, subcutaneous) 1.6 g/kg (34)

4.2. Inhalation toxicity

There are only two published papers in which the inhalation toxicity of DEAE in animals has been evaluated (8, 17). In this chapter the design of the studies and their observations regarding the general toxicity are presented. The organ specific observations are presented separately for each organ system.

Twenty rats were exposed to DEAE, 2400 mg/m³ (500 ppm) for six hours daily over five days. All animals lost 20-40% of their weight, and four rats died (8). In the second part of the study, 16 rats were exposed to 960 mg/m³ (200 ppm) DEAE for six hours daily over five days. In this group the animals gained about 10% in weight, and no animals died. It is not stated clearly in the paper whether or not there were controls in this part of the study. In the third part of the study, 50 rats were exposed to 960 mg/m³ (200 ppm) for six hours daily, five days a week up to six months. As controls, 32 rats were exposed to air. The rats were periodically sacrificed and examined. During the first month, seven of the exposed rats showed progressive weight loss and died. The remaining animals also showed depression of growth during the first month as compared with the controls. However, at the end of the observation period the exposed and unexposed animals were comparable with respect to body and organ weights.

Sixty rats, twenty for each exposure group, ten for each gender, were exposed to DEAE for five plus four days, with two intermediate exposure-free days, to 48 mg/m³ (10 ppm), 270 mg/m³ (56 ppm) or 1440 mg/m³ (301 ppm) (17). There were also 19 unexposed rats. In the 1440 mg/m³ (301 ppm) group 50% of the male rats and half of the female rats died. In the other exposure groups no rats died during the exposure.

The study also included long-term exposure, 40 rats being exposed six hours a day, five days a week for fourteen weeks. The exposure levels were 53 mg/m³ (11 ppm), 120 mg/m³ (25 ppm), and 365 mg/m³ (76 ppm). Twenty rats served as unexposed controls. Rats exposed to 365 mg/m³ (76 ppm) exhibited a slower growth rate during the first two weeks, and this initial decrement was never recovered. There was no increased mortality in the long-term study.

5. Organ Effects

5.1. Systemic symptoms

Fourteen patients with ventricular premature arrhythmias were given 0.5 g - 5 g DEAE intravenously as an 11.2% water solution (33). Shortly after the injection most subjects felt sensations of warmth, dizziness and a fluttering in front of their eyes. Fifteen percent experienced nausea and vomiting. These symptoms disappeared after 15 minutes.

A laboratory worker who was removing animals from an exposure chamber was exposed during 30 s to 480 mg/m³ (100 ppm) or less of DEAE. Within five minutes he became nauseated and vomited (8).

In 1981, employees in the office area of a production building complained of headaches. DEAE had been added to the air-handling system (24, cited from ref. 28).

In 1988, most of the workers in an assembly industry developed nausea, vomiting and dizziness (16, 28). Cyclohexylamine and DEAE had been added to the humidification system, but sampling four days after the incident failed to identify any remaining DEAE.

The case reports (10, 16, 24) are described in greater detail in chapter 10.

5.2. Upper airways and skin

Twenty rats were exposed to DEAE, 2400 mg/m³ (500 ppm) for six hours daily for five days. On the first exposure day the animals showed signs of marked eye and nasal irritation, which continued throughout the whole exposure period.
Among the rats corneal opacities were observed. Sixteen rats exposed in a similar way to 960 mg/m³ (200 ppm) DEAE showed mild eye irritation on the first day, and slight nasal irritation in the third day. However, in a subsequent six-month inhalation study of 50 rats exposed to 960 mg/m³ (200 ppm), there were no signs of nasal and eye irritation as compared with 32 air-exposed control rats. In this study it is not stated whether or not histopathological examinations of the upper airways were performed (8). Rats exposed to 1440 mg/m³ (301 ppm) of DEAE for two weeks showed marked signs of nasal distress, ocular discharges and opacities (17). This was not noted among the control rats, or in rats exposed to 48 mg/m³ (10 ppm) or 270 mg/m³ (56 ppm). However, ten of 20 rats exposed to 270 mg/m³ (56 ppm) showed mononuclear inflammatory cell infiltrations in the mucosa of the nasal turbinate. This was found in one out of 19 rats in the 48 mg/m³ (10 ppm) group, and also in one rat in the control group.

In the same study, 20 rats were exposed for 14 weeks to 53 mg/m³ (11 ppm), 120 mg/m³ (25 ppm) or 365 mg/m³ (76 ppm) of DEAE (17). There were also 20 unexposed control rats. The main findings in this long-term study were histopathological changes in the upper respiratory tract, as infiltration of inflammatory cells, hypertrophy of the goblet cells and hyperplasias, indicating an inflammatory reaction in the upper airways (Table 1).

There was also a high incidence of corneal opacities among the rats (17). This was first noticed in the high exposure group, but by the end of the study it was observed in all animals, including unexposed controls.

Table 1. Prevalence of histopathological changes* in the nasal mucosa after 14 weeks exposure to DEAE. Data from ref. 17.

<table>
<thead>
<tr>
<th>Concentration (mg/m³)</th>
<th>Immediate post-exposure, week 14</th>
<th>One month post-exposure, week 15</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percent</td>
<td>Fraction</td>
</tr>
<tr>
<td>365/76 (76 ppm)</td>
<td>95</td>
<td>19/20</td>
</tr>
<tr>
<td>120 (25 ppm)</td>
<td>55</td>
<td>9/20</td>
</tr>
<tr>
<td>53 (11 ppm)</td>
<td>25</td>
<td>5/19</td>
</tr>
<tr>
<td>Unexposed</td>
<td>15</td>
<td>3/20</td>
</tr>
</tbody>
</table>

* defined as infiltration of inflammatory cells, hypertrophy or hyperplasia of the goblet cells.

ACGIH cited unpublished information which stated that 0.005 ml undiluted DEAE or a 15% solution of DEAE in glycol (unspecified) instilled in the eyes of a rabbit caused severe eye injury. However, if a 5% solution of DEAE in glycol is instilled, the eye injury will not be classified as severe (1).

In 1981, 24 employees in an office developed skin rashes. Many of them also complained of dry throats. DEAE had been added to the air-handling system of the office. The investigators from NIOSH concluded that the skin rashes resulted from exposure to a condensation or reaction product of DEAE (24, cited from ref. 28).

In a museum, 1982 workers complained of eye irritation (10). DEAE had been added to the humidification system and DEAE concentrations of 0.05 and 0.06 mg/m³ were found in the air in two out of 14 samples.

In 1985, 70 out of 84 workers in an assembly industry complained of irritation from the nose, eye and throat together with nausea (16). It was found that DEAE and cyclhexylamine had been added to the humidification system, but measurements four days after the accident did not reveal any remaining DEAE.

5.3. Effects on the lower airways

Sixteen of twenty rats were autopsied after five days exposure to 2400 mg/m³ (500 ppm) DEAE (8). Four of the rats died during the exposure. All of them showed acute purulent bronchiolitis with infiltration of inflammatory cells in the walls of the bronchioles. Rats exposed to 960 mg/m³ (200 ppm) for five days showed no histopathological changes in the lower airways. Seven of the 50 rats exposed to 960 mg/m³ (200 ppm) DEAE during six months (and one of 32 unexposed controls) died during the first two months. The probable cause of death for all of them was bronchopneumonia. Histopathological examinations of the surviving animals, after ceased exposure showed no increased prevalence of abnormalities in the airways.

Rats exposed to 1440 mg/m³ (301 ppm) DEAE for nine days showed overt signs of respiratory distress such as rales, laboured breathing and gasping (17). Such effects were not observed in groups exposed to 48 mg/m³ (10 ppm) or 270 mg/m³ (56 ppm).

In a study over 14 weeks the rats were either exposed to 48 mg/m³ (10 ppm), 120 mg/m³ (25 ppm) or 365 mg/m³ (76 ppm) DEAE, or they were unexposed. In the 365 mg/m³ (76 ppm) group, rales and other respiratory noises were observed in the second week. Among the less exposed animals the same observations were made in subsequent weeks. Every day, the respiratory noises disappeared within one hour after exposure, except in the 365 mg/m³ (76 ppm) group where some rats continued to exhibit these signs overnight. In the necropsied animals no exposure-related findings were present in the lower respiratory tract.

5.4. Effects on the liver

Fifteen rats, given 50 mg or 100 mg DEAE daily in their drinking water for six months, showed no exposure-related changes in function or histopathology of the liver (8). Neither were such signs observed among rats exposed to 2400 mg/m³ (500 ppm) for five days or 960 mg/m³ (200 ppm) for six months (8).

No effects on the liver were reported in rats exposed to 48 mg/m³ (10 ppm), 270 mg/m³ (56 ppm) or 1440 mg/m³ (301 ppm) of DEAE for two weeks, or in rats exposed to 53 mg/m³ (11 ppm) or 120 mg/m³ (25 ppm) for 14 weeks (17).
However, rats exposed to 365 mg/m³ (76 ppm) of DEAE for 14 weeks showed slightly but significantly increased liver weight (17).

5.5. Renal effects

Among rats fed 50 mg or 100 mg DEAE daily for six months, increased weight of the kidneys were observed but no microscopic abnormalities were found (8).

Among rats exposed to 48 mg/m³ (10 ppm), 270 mg/m³ (56 ppm) or 1440 mg/m³ (301 ppm) of DEAE for two weeks no macroscopic or functional abnormalities of the kidneys were reported (17). Rats exposed to 53 mg/m³ (11 ppm) or 120 mg/m³ (25 ppm) of DEAE for 14 weeks showed no exposure-related abnormalities with regard to kidney or kidney function. Among the rats exposed to 365 mg/m³ (76 ppm) DEAE for 14 weeks, increased weight of the kidneys were observed.

5.6. Gastrointestinal effects.

Rats exposed to 2400 mg/m³ (500 ppm) or 960 mg/m³ (200 ppm) DEAE for five days and rats exposed to 960 mg/m³ (200 ppm) DEAE for six months, had no exposure-related abnormalities in the gastrointestinal tract (8).

At necropsy rats exposed to 1440 mg/m³ (301 ppm) DEAE for two weeks showed pathological amounts of intestinal gas. No exposure-related abnormalities in the gastrointestinal tract occurred among animals exposed to 48 mg/m³ (10 ppm) or 270 mg/m³ (56 ppm) of DEAE (17).

5.7. Effects on the cardiovascular system

Four grams of DEAE administered intravenously to man resulted in a prompt rise in the skin temperature which was maintained for a "considerable period of time" (32). In dogs DEAE was somewhat more effective than procaine in reversing cardiac arrhythmias to sinus rhythm. In a middle-aged hypertensive woman, cardiac arrhythmia was rapidly suppressed by 0.5 g DEAE administered intravenously (32).

Dogs given intravenous injections of DEAE up to 0.4 g per kg had no side effects (33). Fourteen patients with ventricular premature beats were given 0.5 g - 5 g DEAE intravenously. In ten of the patients a transient therapeutic effect was observed. In three cases the premature beats had not reappeared in a week. Patients with ventricular tachycardia, auricular fibrillation and supraventricular tachycardia have also been treated with DEAE intravenously with no effect on the arrhythmias (33).

In a review paper DEAE is mentioned, without further comments, as exhibiting a hypotensive effect of short duration (31).

5.8. Effects on blood and bloodforming organs

Rats fed 50 mg or 100 mg DEAE daily during six months showed no alterations of the haemoglobin concentrations in the blood or in the histopathology of the spleen (8). This was also the case when rats were exposed to 2400 mg/m³ (500 ppm) or 960 mg/m³ (200 ppm) or DEAE for five days or 960 mg/m³ (200 ppm) of DEAE for six months.

Rats exposed to 1440 mg/m³ (301 ppm) of DEAE for nine days showed reduced weight of the spleen at necropsy. Haematological parameters (counts of erythrocytes, leucocytes, reticulocytes, platelets and haemoglobin concentration) were not available for the 1440 mg/m³ (301 ppm) group, but they were normal among the rats exposed to 48 mg/m³ (10 ppm) or 270 mg/m³ (56 ppm) DEAE for nine days. The haematological parameters and the spleen were not affected among rats exposed to 53 mg/m³ (11 ppm), 120 mg/m³ (25 ppm) or 365 mg/m³ (76 ppm) DEAE for 14 weeks (17).

5.9. Effects on the central nervous system

In 1940s, DEAE has been used with good effect for post-operative analgesia (32). Certain amines have been shown to cause a "walking syndrome", i.e. hyperactivity and impaired co-ordination in rats. In a study where several amines were screened with regard to this, DEAE was not found to produce the "walking syndrome" (13).

Rats were decapitated and their brains were removed and placed in artifical cerebrospinal fluid (7). DEAE was added to the fluid in different concentrations. DEAE increased the firing threshold in certain brain cells. At higher concentrations, DEAE also decreased the action potential spike amplitude.

5.10. Effects on peripheral nerves

DEAE has, as a main metabolite of procaine, a local anesthetic effect (32). It has been shown that DEAE inhibits action potentials (15), especially when the DEAE-solution is alkaline (6).

5.11. Other effects.

Rats exposed to 1440 mg/m³ (301 ppm) DEAE for nine days showed increased weight for the adrenals at necropsy (17). This was not observed neither in rats exposed to 48 mg/m³ (10 ppm) or 270 mg/m³ (56 ppm) for nine days, nor in rats exposed to 53 mg/m³ (11 ppm), 120 mg/m³ (25 ppm) or 365 mg/m³ (76 ppm) for 14 weeks.
6. Immunotoxicity

Rats exposed to 1440 mg/m³ (301 ppm) of DEAE for nine days showed decreased weight of the thymus (17). This was not observed at lower exposure levels.

7. Mutagenicity and Genotoxicity

DEAE was not mutagenic in Salmonella strains TA98, TA100, TA1535 and TA1537, with or without metabolic activation (36).

8. Carcinogenicity

Squamous metaplasia was found in the nose of one rat exposed to 270 mg/m³ (56 ppm) for two weeks (17). When exposed for 14 weeks, immediately post-exposure squamous metaplasias were found in the noses of five rats exposed to 120 mg/m³ (25 ppm) and in nine rats exposed to 365 mg/m³ (76 ppm). One month post-exposure, squamous metaplasias were found in three rats exposed to 120 mg/m³ (25 ppm) and in six rats exposed to 365 mg/m³ (76 ppm) (17).

Procaine, which is rapidly metabolised to DEAE and PABA is not regarded as a carcinogen (24).

The nitrosation potential of DEAE has been earlier discussed (29). Nitrosation is normally slower for tertiary amines (such as DEAE) than for secondary amines (27). However, the nitrosation potential is hard to predict, as it is affected by many factors, such as alkalinity, substrate concentration and presence of microorganisms (18). On the basis of its chemical structure, DEAE has the potential to be nitrosated to N-nitrosodiethylamine (NDEA) and N-nitrosocetyl-
ethanolamine. Both these compounds are regarded as potent carcinogens in animals (18). However, no data on such reactions in the work environment have been found.

When considering the nitrosation potential of DEAE, one should be aware that the commercial product may be contaminated with different secondary amines, such as diethylamine, ethylacetoacetamide and diethylamine (29), which could be nitrosated to N-nitrosodiethylamine (NDEA), NDEA and ethylhydroxy-
ethylnitrousin.

9. Effects on the Reproduction

Rats exposed to 1440 mg/m³ (301 ppm) DEAE for nine days showed decreased gonad weight at necropsy (17). This was not observed either in rats exposed to 48 mg/m³ (10 ppm) or 270 mg/m³ (56 ppm) for nine days, or in rats exposed to 53 mg/m³ (11 ppm), 120 mg/m³ (25 ppm) and 365 mg/m³ (76 ppm) for 14 weeks.

Any differences between the sexes were not highlighted in the report. However, which is rapidly metabolized to DEAE and PABA have not been associated with an increased risk of congenital malformations (12).

10. Case Reports

There are three reports of clusters of cases that have been associated with exposure to DEAE.

In 1981, 24 employees in the office of a factory developed skin rashes. Many of them also complained of dry throat, headache and chest tightness (24). DEAE had been added to the air-handling system, and the investigators from the US NIOSH concluded without further specification that the dermatitis resulted from exposure to a condensation or reaction product of DEAE.

In 1982, employees in a museum where DEAE had been added to the humidification system reported eye irritation and dermatitis (10). DEAE had been added to the water in 1977 in a concentration of approximately 15 ppm of water. Ten air samples obtained with a low sampling rate showed no DEAE, the detection limit was 0.4 mg/m³. In two out of four air samples obtained with a high flow rate, concentrations of 0.05 mg/m³ and 0.04 mg/m³ were found. With high flow rates the detection limit was 0.04 mg/m³. The employees had also noticed an oily film on the surfaces of the display cases. The film contained 30 mg DEAE/m² of exposed area. Sixteen out of 35 employees reported eye irritation, and 13 reported some sort of skin irritation since beginning work at the museum. The investigators concluded that sporadic contact with surfaces containing DEAE may have been associated with some of the reported irritative effects.

In 1988, 70 out of 84 assemblers in an electrical manufacturing firm developed nausea, vomiting, dizziness, and eye, nose and throat irritation (16, 28). The symptoms occurred shortly after the employees detected an ammonia or radiator-like smell. The odour coincided with the introduction of steam, derived from the plant boiler, into the building for humidification. The steam was turned off, but when it was reintroduced three days later, the same odour appeared. Investigators from NIOSH discovered that DEAE and cyclohexylamine had been added to the boiler at four times the normal strength. Four days later the steam was once again reintroduced for collecting samples from air and boiler water. However, no remaining DEAE or cyclohexylamine was detected. The investigators thought this might be caused by dilution in the system over the preceding four days.
11. Exposure Effect Relations

The effects of DEAE on humans and experimental animals are summarized in tables 2 - 4.

Table 2. Effects of DEAE on man

<table>
<thead>
<tr>
<th>Dose</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 g - 5 g Oral</td>
<td>Feeling of warmth, dizziness and flushing in front of the eyes</td>
<td>33</td>
</tr>
<tr>
<td>4 g Intravenous</td>
<td>Increased skin temperature</td>
<td>32</td>
</tr>
<tr>
<td>0.5 g</td>
<td>Transient effect on premature ventricular beats</td>
<td>33</td>
</tr>
<tr>
<td>480 mg/m³ Inhalation</td>
<td>Nausea and vomiting</td>
<td>8</td>
</tr>
</tbody>
</table>

Table 3. Effects of DEAE on experimental animals after non-inhalation exposure routes

<table>
<thead>
<tr>
<th>Route (mg/kg b.w.)</th>
<th>Dose (mg/kg)</th>
<th>Animal</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>5600 mg/kg</td>
<td>Rat</td>
<td>LD₅₀ neutralized</td>
<td>8</td>
</tr>
<tr>
<td>Oral</td>
<td>2500 mg/kg</td>
<td>Rat</td>
<td>LD₅₀, water solution</td>
<td>1</td>
</tr>
<tr>
<td>Subcut.</td>
<td>1000 mg/kg</td>
<td>Mouse</td>
<td>LD₅₀</td>
<td>34</td>
</tr>
<tr>
<td>Oral</td>
<td>1300 mg/kg</td>
<td>Rat</td>
<td>LD₅₀, alkaline</td>
<td>35</td>
</tr>
<tr>
<td>I. p.</td>
<td>1200 mg/kg</td>
<td>Guinea Pig</td>
<td>LD₅₀</td>
<td>34</td>
</tr>
<tr>
<td>Oral</td>
<td>500 mg/kg daily</td>
<td>Rat</td>
<td>Slightly decreased growth, increased kidney weights</td>
<td>8</td>
</tr>
<tr>
<td>I. m.</td>
<td>400 mg/kg</td>
<td>Mouse</td>
<td>LD₅₀</td>
<td>34</td>
</tr>
<tr>
<td>I. p.</td>
<td>300 mg/kg</td>
<td>Mouse</td>
<td>LD₅₀</td>
<td>34</td>
</tr>
<tr>
<td>Oral</td>
<td>250 mg/kg daily</td>
<td>Rat</td>
<td>Increased kidney weights</td>
<td>8</td>
</tr>
<tr>
<td>I. v.</td>
<td>200 mg/kg</td>
<td>Mouse</td>
<td>LD₅₀</td>
<td>34</td>
</tr>
</tbody>
</table>

Only a few studies permit the assessment of dose-dependent effects. In man, exposure of up to 400 - 500 mg/m³ for 30 s has produced nausea and vomiting within five minutes.

In rats, exposure to levels exceeding 1400 mg/m³ for a few days seems to produce a wide range of toxicological effects. The most pronounced effects seem to be severe irritation of both the upper and lower airways. Mortality is also high. Exposure to 100 - 1400 mg/m³ results in less severe irritation in both the upper and lower airways. The lowest level at which increased mortality was observed was 960 mg/m³. The rats died of bronchopneumonia. The lowest concentration at which valid histopathological signs of inflammation in the upper airways could be found was exposure to 120 mg/m³ for 14 weeks.

However, rats exposed to 53 mg/m³ developed rales after some weeks of exposure. No histopathological changes were found in the lower airways of those rats. Exposure to concentrations less than 53 mg/m³ for 14 weeks seems not to cause any morphological changes in the upper airways, and no sign of irritation has been reported.

Table 4. Effects of DEAE in rats in inhalation studies

<table>
<thead>
<tr>
<th>Concentration mg/m³</th>
<th>Period</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2400</td>
<td>6 h/day</td>
<td>Decreased weight, increased respiratory irritation</td>
<td>8</td>
</tr>
<tr>
<td>1440</td>
<td>6 h/day</td>
<td>14/50 rats died</td>
<td>17</td>
</tr>
<tr>
<td>960</td>
<td>6 h/day</td>
<td>14/50 rats died</td>
<td>17</td>
</tr>
<tr>
<td>960</td>
<td>6 h/day</td>
<td>14/50 rats died</td>
<td>17</td>
</tr>
<tr>
<td>365</td>
<td>6 h/day</td>
<td>Decreased growth</td>
<td>17</td>
</tr>
<tr>
<td>270</td>
<td>6 h/day</td>
<td>Nasal irritation</td>
<td>17</td>
</tr>
<tr>
<td>120</td>
<td>6 h/day</td>
<td>Nasal irritation</td>
<td>17</td>
</tr>
<tr>
<td>53</td>
<td>6 h/day</td>
<td>No signs of nasal irritation</td>
<td>17</td>
</tr>
<tr>
<td>48</td>
<td>6 h/day</td>
<td>No signs of irritation in upper respiratory tract</td>
<td>17</td>
</tr>
</tbody>
</table>
12. Research Needs

DEAE has probably many uses, in different industrial processes and as a corrosion inhibitor in water-based systems. There is a remarkable lack of exposure data. Hence, studies investigating exposure in different occupational groups should be performed. There is also a need for exposure assessments regarding nitrosamines.

DEAE is excreted in urine, and studies should be performed to investigate if this could be used for biomonitoring.

Based on theoretical calculations DEAE seems to have properties to be absorbed through the skin. This should be evaluated in experimental studies.

There is a great need of basic toxicological tests regarding sensitization, reproductive and developmental effects. There is also a need for tests with regard to mutagenicity and genotoxicity. There are no cancer studies, and such studies should be performed.

There is also a great need of inhalation studies in the lower dose interval (<100 mg/m³), both on man and animals. These studies should be directed towards investigation of inflammatory changes in the upper and lower airways.

13. Discussion and Conclusions

In animals, the critical effect of DEAE seems to be the irritative effect on the mucous membranes in both lower and upper airways. In humans, due to very limited information, the critical effect seems to be irritation of the mucous membranes and skin. DEAE also has effects on the nervous system and the heart, but this is not of importance in occupational settings.

Like other alkylamines DEAE is a potent irritant of the mucous membranes in the airways. This is probably owing to its alkalinity. In rats there is some support for a dose-response relation regarding irritation in the upper airways. In rats, effects on the upper airways seem to develop at exposure levels of 120 mg/m³.

The exposure time is of importance. Rats exposed to 48 mg/m³ for nine days showed no sign of respiratory impairment. Rats exposed to 53 mg/m³ developed severe symptoms after two weeks of exposure. These exposure levels, 53 mg/m³ and 48 mg/m³ are the lowest concentrations to which animals have been exposed. Hence, it is not possible on the basis of the literature, to determine a no-effect concentration for DEAE.

14. Summary


The literature on 2-diethylaminoethanol has been reviewed and health effects of DEAE have been evaluated. There is very limited information on health effects in humans. Based on these limited data, the critical effect seems to be irritation of the mucous membranes and skin. In animals, the critical effect seems to be irritation of the mucous membranes of both lower and upper airways.

Key words: 2-diethylaminoethanol, occupational exposure, occupational exposure limits

15. Summary in Swedish


Genomgång av litteraturen om 2-diethylaminoethanol samt utvärdering av hälsoeffekter. Informationen om hälsoeffekter hos människor är mycket begränsad. På grundval av dessa data tycks den kritiska effekten vara irritation av slemhinnor och hud. Hos djur tycks den kritiska effekten vara irritation av slemhinnor i övre och nedre luftvägar.

Nyckelord: 2-diethylaminoethanol, hygieniskt gränsvärde, yrkesmässig exponering
16. References

1. ACGIH, Documentation of the threshold limit values and biological exposure indices, 5th ed. Cincinnati, Ohio: American Conference of Governmental Industrial Hygienists Inc. 1986.


Submitted for publication September 1994.
Appendix 1.

Permitted or recommended maximum levels of 2-diethylaminoethanol in air

<table>
<thead>
<tr>
<th>country</th>
<th>ppm</th>
<th>mg/m³</th>
<th>comments</th>
<th>year</th>
<th>ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark</td>
<td>10</td>
<td>50</td>
<td>H</td>
<td>1988</td>
<td>1</td>
</tr>
<tr>
<td>Finland</td>
<td>10</td>
<td>15</td>
<td>15 min, H</td>
<td>1993</td>
<td>2</td>
</tr>
<tr>
<td>Iceland</td>
<td>-</td>
<td>-</td>
<td></td>
<td>1989</td>
<td>3</td>
</tr>
<tr>
<td>Netherlands</td>
<td>10</td>
<td>50</td>
<td>H</td>
<td>1994</td>
<td>4</td>
</tr>
<tr>
<td>Norway</td>
<td>10</td>
<td>50</td>
<td>H</td>
<td>1989</td>
<td>5</td>
</tr>
<tr>
<td>Sweden</td>
<td>-</td>
<td>-</td>
<td></td>
<td>1993</td>
<td>6</td>
</tr>
<tr>
<td>USA (ACGIH)</td>
<td>10</td>
<td>48</td>
<td>Skin</td>
<td>1991</td>
<td>7</td>
</tr>
<tr>
<td>(NIOSH)</td>
<td>10</td>
<td>50</td>
<td>Skin</td>
<td>1950</td>
<td>8</td>
</tr>
</tbody>
</table>

H = dermal absorption
Skin = the cutaneous route, including mucous membranes and eyes (vapour or contact) contributes significantly to the overall exposure.

References

Instruktion för författare

Innehåll
I Arbete och Hälso publiceras i första hand vetenskapliga originalarbete, men även litteraturöversikter. Specielt är normalt att författarna skriver dock vanligtvis på engelska.

Manuskript
Manuskriptet lämnas i sex exemplar. Detai-
gerade manuskriptsökare lämnas av institutets informationsenhet. Manuskriptet återges i samma form som det skrivits ur. Manuskriptet ingår med ett ställeblad, meddelande (medversa-
er) i mitten och därunder författarnamnet och övriga vänster hörnet skrivs Arbete och Hälso, följd av året och författarens namn (t.ex. 1990/22). Avsnittet utsätts efter en nyblivande och eventuellt av Eva Nilsson på informationsenheten, tel 08- 730 94 88.

På sid 6 skrivs eventuellt ett kort förord som rekommenderas för varför och hur arbetet utfördes. I förordet bör även omnämna personer som deltagit i arbetet utan att stå som medförfat-
tare. Förordestranguleringasprojekteraderna
eller erfarenchef. På sid 4 bör innehållsförteckningen skrivas om inte manuskriptet är mycket kort.

Sammanfattning
Sammanfattningar på svenska och engelska (Summary) skriver efter texten före referenslistan. Den ska vara skriftligt 150 ord. Sam-
manfattningen ska innehålla med fullständiga referensuppsatser (format see nedan). Efter texten skiljs högst 10 nyckelord på svenska resp. engelska.

Referenser
Referenser skrivs efter sammanfattningen och uppställs alfabetiskt och numrerat. I tex-
ten anges referens med referensnumret inom parentes,扑克biser datatidstagit upp
i referenslistan utan endast i texten. ExPet-
terse (spätt. 1975). När får författarnamnet anges i texten och anstalt
forfattare är mer än två ska endast förste
författarnamn anges: Peterson et al. I referenslistan anges samtliga forfattare. I övriga avseenden skall referenser skiljas i runduppsatser i enlighet med VOCUPYSYSTEMET.

Tidskriftsverktyg ingår anges som I Index
Medlem, inom parantes, i typsnitt. For
artiklar som ej är skrivna på nordiska
språk, franska, tyska eller engelska, ingår
an hopeless engelska 0015 med pluss
med originalspråket.

Exempel:
a. Tidskriftsreferat
1. Akademi NO, Sundell L. Mining, lung car-