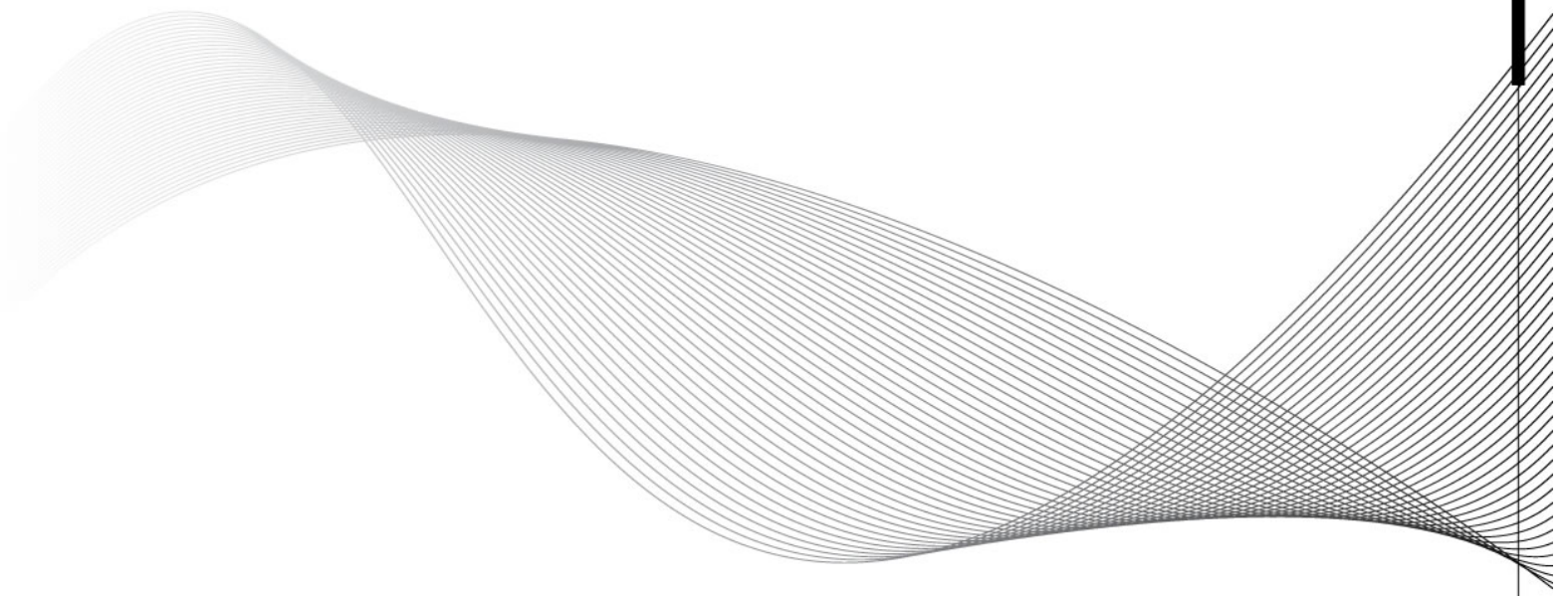
Social Europe



# Recommendation from the Scientific Committee on Occupational Exposure Limits for diethylamine

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European Commission

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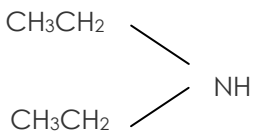
|---|---|---|
| 8 hour TWA | : | 15 mg/m³(5 ppm) |
| STEL (15 min.) | : | 30 mg/m³ (10 ppm) |
| Additional classification | : | none |

Substance

Diethylamine




Synonyms: DEA, Diethamine, N-Ethylethanamine, N,N-Diethylamine, Ethanamine, Amin, diethyl-
EINECS N° : 612-003-00-X
EEC N° : 203-716-3
CAS N°: 109-89-7

MWt : 73.14

Conversion factor : 1 ppm = 3.04 mg/m³ ; 1mg/m³ = 0.334 ppm

# 1. Occurrence/use

Diethylamine (DEA) is an alkaline, colourless, volatile liquid with a strong ammoniacal odour. The human olfactory threshold for diethylamine is 0.14 ppm (0.42 mg/m³), it is miscible in water and many organic solvents. The boiling point is 56.3 °C, the vapour pressure is 0.261 hPa at 20°C. Diethylamine reacts strongly alkaline, and is incompatible with strong oxidisers and flammable.

Diethylamine forms nitrosamines (N-Nitrosodiethylamine) easily by nitrosating substances (e.g. $NO_2$ in air).

Diethylamine is used in the production of the corrosion inhibitor N, N-diethylethanolamine (DEAE), and in the production of some pesticides and insect repellents, pharmaceuticals (e.g. the alcohol antagonist disulfiram ANTABUS®, flurazepam, lidocaine) and rubber processing chemicals. Diethylamine is also used in the paint, lacquer, and varnish industries. Workers who handle triethylamine, a volatile amine used as a catalyst, are indirectly exposed to diethylamine, since it has been shown that triethylamine is metabolised to form diethylamine in humans (Akesson et al., 1989).

# 2. Health significance

Little toxicokinetic information is available. After oral intake diethylamine (DEA) is excreted nearly totally unmetabolised in humans. (Rechenberger, 1940).

After single oral exposure the $LD_{50}$ was 540 mg/kg body weight in rat (Smyth et al. 1951) and 500-650 mg/kg bw in mouse (Kagan 1965, Patel et al. 1985). The lowest concentration reported to cause death in mice following a 2-hr inhalation exposure period was 3000 mg/m³ (Anon, 1995). After dermal exposure (24-hr covered contact) the $LD_{50}$ was 820 mg/kg bw in rabbits (Smyth et al. 1951).

In relation to irritancy, in rabbits corneal erosion occurred after 2 weeks of exposure to 150 mg/m³ (50 ppm) DEA; the rabbits also exhibited conjunctival and pulmonary irritation (Grant, 1974). High vapour concentration of DEA can cause severe irritation and burning of the skin. In tests to investigate contact dermatitis in patients, covered 24/48-hr patch tests were conducted with 1, 2 and 5% DEA in petrolatum. These concentrations would therefore be expected not to cause overt irritation in most healthy individuals (Kaniwa et al., 1994). Considerable vision defects were still present after 1 month after eye contact with neat liquid DEA (Peyersblanques, 1963).

In a study on perceived acute sensory effects four subjects were exposed for 15 min to DEA at 75 mg/m³ (25 ppm) and five subjects for 60 min to DEA concentrations gradually increasing from 0 to 36 mg/m³ (12 ppm) (Lundqvist et al. 1992). Nasal airway volume (NAV) and nasal airway resistance (NAR) were measured before, during (NAV only) and after exposure to 75 mg/m³ (25 ppm) for 15 minutes; no difference was seen in these parameters. In the study where the DEA concentration was gradually increased from 0 to 36 mg/m³ (12 ppm) over 60 minutes, as the concentration rose significant correlations were found between increasing self-reported nose/eye irritation and increasing odour perception. Over the 60 minutes the time-weighted exposure level was 30 mg/m³ (10 ppm) DEA. Although, as the authors pointed out, the study has some limitations, such as the lack of a blind experimental design and the small number of subjects, it suggests that some symptoms of eye and nose irritation might start to occur with DEA exposures of about 30 mg/m³ (10 ppm).

In a repeated exposure study by Lynch et al. (1986) male and female Fischer 344 (F-344) rats were exposed at 0, 75 mg/m³ (25 ppm) or 750 mg/m³ (250 ppm) DEA vapour, 6.5 hr per day, 5 days per week, for 24 weeks in order to assess cardiac and other organ system toxicity. Scheduled sacrifices were performed following 30, 60, and 120 days of exposure. During the first 2 weeks of exposure, the rats exposed at 750 mg/m³ DEA did not gain weight. After 2 weeks, however, the rate of weight gain of these rats was greater than that of controls. Nevertheless, mean body weights for both sexes of rats exposed at 750 mg/m³ DEA remained depressed compared to controls throughout the study. Sneezing, tearing, and reddened noses were seen in rats exposed at 750 mg/m³ DEA. Histopathologic examinations revealed lesions of the nasal mucosa of rats exposed at 750 mg/m³ DEA (rats exposed at 75 mg/m³ were not evaluated for nasal effects). These lesions of the nasal respiratory epithelium consisted of squamous metaplasia, suppurative rhinitis, and lymphoid hyperplasia. There were no pronounced treatment-related effects on organ weights, hematology, or clinical chemistry indices except for blood urea nitrogen which was evaluated in rats of both sexes exposed at 750 mg/m³ DEA for 24 weeks. In contrast to the high-dose animals, no treatment-related effects were observed in rats intermittently exposed at 75 mg/m³ DEA for up to 24 weeks. No evidence of cardiotoxicity was seen in rats exposed to either DEA concentration for up to 24 weeks. The results of shorter exposure (30 and 60 days either 75 and 750 mg/m³ DEA,10 animals of both sexes; 120 days 75 mg/m³ DEA, 50 animals of both sexes) and the pathological findings of this study were summarised in a report by NIOSH (1983). Marked signs of toxicity were not seen in rats exposed to 75 mg/m³ and 750 mg/m³ DEA after 30 and 60 days. After 120 days of exposure to 75 mg/m³ DEA the incidence of slight bronchial lymphoid hyperplasia was twice as high in the exposed group than in the control group. The authors of the original study considered that this was not a reflection of DEA toxicity, as the lesion was also seen in control animals and there was no clear dose-response relationship across the three groups. However, SCOEL felt that there was some doubt about this point, and concluded that 75 mg/m³ represented a LOAEL.

A Soviet study reports lung changes in rats exposed (continuously) to 4.19 mg/m³ DEA for 3 months, with mild effects on the central nervous system and altered blood chemistry at a concentration of 0.37 mg/m³, no adverse effects occurred with the exposure to 0.05 mg/m³ in the same study. Number, sex of animals or purity of DEA were not provided. (Tkachev, 1971).

In rabbits exposed to 150 and 300 mg/m³ to DEA by inhalation for 7 hr/day, 5 days/wk for 6 weeks, dose-related changes in heart, liver and lungs occurred (Brieger & Hodes, 1951). At 150 mg/m³ moderate peribronchitis and occasional focal collection of lymphocytic cells and slight thickening of vascular cells were found in lung tissue. In rabbits exposed to 300 mg/m³ DEA there was cell infiltration and bronchopneumonia. At 150 mg/m³ occasional foci of moderate parenchymatous degeneration in the liver and questionable very slight muscular degeneration in the heart were reported; such effects were more evident at the higher dose. Changes of the kidney were not definitive at the concentration of 150 mg/m³ diethylamine, but at 300 mg/m³ nephritis with slight tubular changes was described. The authors also found multiple punctate erosions and oedema of the cornea in rabbits exposed to 150 mg/m³ diethylamine after 6 weeks..

In the standard Ames test, diethylamine gave no evidence of mutagenicity either in the presence or absence of a mammalian liver metabolic activation system (Hedenstedt, 1978; Zeiger et al. 1987). In the only *in vivo* study identified, there was no increase in unscheduled DNA synthesis in the kidney cells of two male rats given a single oral dose of 500 mg diethylamine/kg bw (Loury et al. 1987).

There are no standard carcinogenicity studies on DEA itself. A number of studies have examined the combined effects of DEA and nitrite, the concern being the potential for the formation of diethylnitrosamine, a potent animal carcinogen, which causes almost 100% tumour incidences in rodents treated orally with 1-15 mg/kg bw/day for life (IARC 1972, Sen et al. 1975). However, a low yield of diethylnitrosamine has been reported in experiments with cats and rabbits given this combined exposure, as well as *in vitro* tests with gastric juices from humans and various laboratory animals, the yield being greatest under acidic conditions (Sen 1969). Little, if any, diethylnitrosamine is formed in an alkaline environment (Sander, 1968, Sen et al. 1969).

With this hypothesis in mind, an increased incidence of tumours in the liver (the only organ examined microscopically), when compared with untreated controls, was seen in mice given single doses of diethylamine hydrochloride and sodium nitrite, each at a dose level of 50 mg/kg bw. No convincing increase was seen in 15 mice given 50 mg/kg bw of diethylamine hydrochloride alone or in eleven mice given 50 mg/kg bw of sodium nitrite alone (Rijhsinghani et al. 1982). No tumours were induced in the lung, liver or kidney of 65-wk-old mice whose mothers had received 100 mg diethylamine hydrochloride/kg bw/day or 50 mg sodium nitrite/kg bw/day by stomach tube from day 12 of pregnancy to delivery. However, simultaneous administration of diethylamine hydrochloride and sodium nitrite (at 100 and 50 mg/kg bw/day respectively) resulted in a slight increase in liver tumour incidence (Vesselinovictch, 1975). None of these studies is considered to be informative about the carcinogenic potential of DEA itself.

In the only study available focussing on potential reproductive effects, no overt effects on reproduction were apparently seen in a two-generation study in which 67 rats were simultaneously administered 500 mg diethylamine hydrochloride/kg bw/day in the diet and 100 mg sodium nitrite/kg bw/day in the drinking water for their entire life span (Druckrey et al., 1963).

## Recommendations

In relation to the establishment of an 8h TWA limit value the key study was taken to be that of Lynch et al (1986). Using the summary report by NIOSH (1983) of the pathology seen in this study, 75 mg/m³ was a LOAEL. The older study of Brieger and Hodes (1951) indicated toxicity towards several organs with exposures of 150 and 300 mg/m$^3$. The inhalation study of Tkachev (1971) is not to be taken into consideration for the lack of data provided on study design. Based on the LOAEL of 75 mg/m$^3$, an 8h TWA value of 15 mg/m$^3$ (5 ppm) is recommended.

Lundqvist et al. (1992) found an increase of nose and eye irritation, and odour perception, with gradually increasing DEA concentrations of 0 – 36 mg/m$^3$ (12 ppm) over 60 minutes [time-weighted average concentration of 30 mg/m$^3$]. In order to minimise such irritation symptoms, a 15-minute STEL of 30 mg/m$^3$ (10 ppm) is recommended.

There are no reports of corneal oedema with exposure to relatively low levels of DEA, in contrast to certain other amines such as triethylamine.

The potential for DEA to be absorbed across the skin is unclear, but the primary effects of concern are local, site-of-contact irritation/inflammation and skin irritation should limit the extent of skin contact. Hence a "Sk" notation is not proposed.

At the recommended TWA of DEA difficulties of air measurement are not to be expected.

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