2,2'-Iminodi(ethylamine)

(CAS No: 111-40-0)

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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1 Introduction

The present document contains the assessment of the health hazard of 2,2'-iminodi(ethylamine), in this document referred to as DETA (diethylenetriamine), by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by AAE Wibowo, Ph.D. (Coronel Institute, Academic Medical Centre, Amsterdam, the Netherlands).

The evaluation of the toxicity of DETA has been based on the reviews by the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (And94), the Swedish Criteria Group (Lun95), and the American Conference of Governmental Occupational Hygienists (ACGIH) (ACG96). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in December 1997, literature was searched in the databases Medline, Chemical Abstracts, Embase (starting from 1966, 1970, and 1988, respectively), and HSELINE, NIOSHTIC, CISDOC, and MHIDAS (backwards from 1997) and Poltox (Toxline, Cambr Sc Abstr, FSTA) (backwards from 1994), using the following key words: diethylenetriamine, aminoethylethanediamine, diaminodiethylamine, iminobisethylamine, and 111-40-0.

In July 2000, the President of the Health Council released a draft of the document for public review. Comments were received from the following individuals and organisations: A Aalto (Ministry of Social Affairs and Health, Tampere, Finland). These comments were taken into account in deciding on the final version of the document.

An additional literature search in February 2005 did not result in information changing the committee's conclusions.

2 Identity

name	:	2,2'-iminodi(ethylamine)
synonyms	:	diethylenetriamine; di(2-aminoethyl)amine; bis(2-aminoethyl)-amine; 2,2-diaminodiethylamine; aminoethylethanediamine; *N*-(2-aminoethyl)-1,2-ethanediamine; 3-azapentane-1,5-diamine
molecular formula	:	$C_4H_{13}N_3$
structural formula	:	NH_2–CH_2-CH_2-NH-CH_2-CH_2-NH_2
CAS number	:	111-40-0

3 Physical and chemical properties

molecular weight	:	103.2
boiling point	:	207°C
melting point	:	-39°C
flash point	:	102°C (open cup); 97-98°C (closed cup)
vapour pressure	:	at 20°C: 49 Pa
solubility in water	:	soluble
log $P_{octanol/water}$	:	-2.13 (estimated)
conversion factors	:	at 20°C, 101.3 kPa: 1 ppm = 4.28 mg/m^3 1 mg/m^3 = 0.23 ppm

Data from ACG96, EC00, http://www.syrres.com/esc/est_kowdemo.htm.

DETA is a somewhat viscous, yellow, alkaline, and hygroscopic liquid with a smell of ammonia (ACG96). A 1 molar solution has a pH of 12.0 (And94). An odour threshold of 43 mg/m^3 (10 ppm) has been reported (NLM04).

4 Uses

DETA is used in chemical and pharmaceutical industry. 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 wet strengthening resins in the paper industry, in cleaning agents, in corrosion inhibitors, and as a fuel component (And94).

5 Biotransformation and kinetics

The substance is absorbed after inhalation of its vapour, through the skin, and by ingestion (And94, Lun95).

Leung and Tyler studied the metabolism and disposition of DETA by oral and endotracheal administration of single doses of [1,2-^{14}C]-DETA.3HCl of ca. 50 and 500 mg/kg bw and intravenous dosing of ca. 50 mg/kg bw to male rats (Fischer 344; n=4-5/group) and following the fate of radiolabelled material for 48 hours. DETA was readily absorbed from the gastrointestinal and respiratory tracts. The time course of radioactivity concentrations in the plasma, determined from intravenous dosing, was best described by a tri-exponential equation. Peak plasma concentrations occurred within one hour following oral and endotracheal administration and the bioavailability was 95 and 90%, respectively. Radioactivity was cleared from the plasma with terminal half-lives of ca. 9, 10, and 16 hours following endotracheal, intravenous, and oral administration,

respectively. The apparent volume of distribution (V_d), determined from plasma concentrations following intravenous dosing, indicated distribution in the total body water (V_d: 0.48 L/kg vs. total body water volume of 0.58 L/kg). Radioactivity was distributed throughout the body with generally similar distribution patterns. The kidney and the liver contained the highest concentrations, about 2.5-5 and 3 times that of blood, respectively. A less than proportional increase in tissue concentrations (7.5-fold) between the 2 doses (10-fold) was observed. Faeces and urine accounted for about 72-77 and 87% of the total low and high dose excreted, respectively, with slightly higher amounts in the faeces, while only little radioactivity was exhaled as CO_2 (ca. 1.1-1.3 and 0.5-0.6% of the total low and high dose excreted, respectively). About 2-3% was recovered from the carcass. Cation-exchange chromatography of the urine resulted in 4 radiolabel-containing fractions. The major fraction, accounting for ca. 45 and 70% of the total urinary radioactivity at the low and high dose, respectively, consisted of parent compound indicating only a limited extent of metabolism. The other fractions contained about 17-20, 15-18, and 2% of the radioactivity at the low dose and about 14, 5, and 1% at the high dose. These fractions were not analysed but they did consist of ethylenediamine or acid conjugates. The increase in the proportion of unchanged compound in the urine and the less than proportional increase in tissue concentrations from a dose of 50 to a dose of 500 mg/kg bw indicated saturation of the metabolism of DETA at the dose of 500 mg/kg bw. The study did not reveal significant differences with respect to the route of administration (oral vs. endotracheal) (Leu97c).

6 Effects and mechanism of action

Human data

Following testing in volunteers, Dernehl stated that DETA caused sensitisation in 50% of the subjects (no details presented) (Der63). Patch testing of a soluble cutting-oil antibacterial additive, containing sodium *o*-phenylphenate and thimerosal as antibacterial agents and DETA as a coupling agent, produced a positive response in 2/200 healthy adult white male volunteers. One of these subjects showed a positive response to DETA (Boo62). No reactions were observed when a 0.05% solution of DETA in water was tested in a closed patch test in 20 volunteers for 24 hours (readings after 24, 48, and 72 hours and 2 weeks) (Key61). In a maximisation test in which volunteers were induced and challenged with 1 mL of 10% DETA (vehicle probably petrolatum), applied

under occlusion for five 48-hour periods with one-day intervals, positive reactions were observed in 21/25 healthy adult subjects (Kli66).

Data on allergic skin effects due to occupational exposure to DETA are presented in Table 1.

Table 1 Summary of positive patch test results with DETA (adapted from Gre01).

number of persons tested	concentration (vehicle)	results	remarks	reference
22 patient sensitised to ethylenediamine	1% (petrolatum)	4/22 positive (no other details)	EDA-containing topical products; no reaction to TETA (0.1% in petrolatum)[a]	Bal84
32 patients sensitised to ethylenediamine	1% (petrolatum)	17/32 positive (no other details)	12/32 positive to TETA (% in petrolatum); 2/32 positive to piperazine	Bal86
1 shipwright sensitised to isophorondiamine	0.5% (petrolatum)	(1+; read after 48 and 96 h)	worked with epoxy resins; positive (1+) to phenylenediamine, diaminodiphenylmethane, TETA (0.5% in petrolatum)	Cam89
1 plumber with hand and finger dermatitis	1% (petrolatum)	(2+; read after 48 and 96 h)	worked with epoxy resin-containing 2-component bonding adhesives; positive (3+) to epoxy resin (0.5% in petrolatum)	Con93
1 nurse	0.5% (petrolatum)	positive after 48 hours (2+ after 72 h)	sensitised to EDA present in a drug (aminophylline)	Cor94
4897 patients	0.5% (petrolatum)	12 positive (9 x 1+, 2 x 2+, 1 x 3+; read after 72 h)	test period: 1992-1998; further 26 questionably erythematous or irritative responses	Gre01
4 aircraft workers	1% (petrolatum)	positive (no details)	worked with resin-containing composite materials (pre-pegs) or sealants; out of a group of 44 workers diagnosed with work-related allergic contact dermatitis (511 workers with dermatitis examined in period1993-1997 for relationship between dermatitis and work-related materials)	Hac99
124 patients exposed to epoxy resin	1% (petrolatum)	3/124 positive (no details)	2 out of these 3 positive responses were deemed relevant and work-related allergic contact dermatitis	Hol93
253 patients	1% (petrolatum)	4/253 positive (no details)	only patients with exposure to epoxy resins tested between 1984-1988	Jol90[b]
1 machinist with hand dermatitis[b]	1% (petrolatum)	(3+)	worked with DETA-containing microcapsule-coated carbonless copy paper; positive to 0.03% DETA (2+) and 0.5% TETA (in water; 2+)	Kan90, Kan93
1 spray painter with hand dermatitis[b]	1% (petrolatum)	(3+)	worked with 3.8% DETA-containing epoxy spray paints; negative to standard epoxy resin and other individual polyamines (e.g., EDA, TETA)	Kan90, Kan91

1 tiler with eczema of forearms and conjunctivitis and swelling of lids	1% (petrolatum)	(2+)	worked with 2-component mortar adhesive with a 98.5% DETA-containing hardener; negative to standard epoxy resin and EDA and TETA	Kan91
356 patients	1% (petrolatum	1/356 positive (no details)	patients with exposure to epoxy curing agents tested between 1991-1996; irritative response in 2/356	Kan99
2 employees of a goldsmith workshop	1% (petrolatum)	2/2 positive (2 x 3+; read after 72 h)	mixture of DETA and fatty acids used as a detergent in an ultrasonic cleaning bath	Med82
10 patients with dermatitis due to occupational exposure to oil-based drilling mud	0.5% (petrolatum)	5/10 positive (4 x 2+, 1 x 3+; read after 48 and 96 h)	polyamine-containing oil-drilling lubricants; 5/5 patients positive to EDA (0.5% in petrolatum), 4/5 positive to TETA (0.5% in petrolatum)	Orm89
3 water-pipe renovators	1% (petrolatum)	3/3 positive (1 x 1+, 1 x 2+, 1 x 3+)	worked with epoxy resins containing amongst others DETA	Ree99
65 patients occupationally exposed to epoxy resins	1% (water)	50/65 (no other details)	52/65 patients, among who all 40 patients positive to DETA positive to TETA (1% in water)	Rud76
1 condenser manufacturer with dermatitis (hand, face, forearms, neck)	no data	positive (no details)	positive to epoxy resin, EDA, and TETA	Tos88

[a] EDA: ethylenediamine; TETA: triethylenetetramine.
[b] This case may have been included in a summary report by this group listed in this table (Jol90).

Ryan et al. reported of asthma in a 53-year-old carpenter who experienced symptoms of cough, chest tightness, wheezing, and dyspnoea, two months after he had started working with an epoxy resin and hardener containing 86% coal tar and 14% DETA. The chest symptoms began 6-8 hours after each exposure and required treatment with oral theophylline for 4-5 days. The presence of asthma was confirmed by variable airflow obstruction. A provocation in the laboratory for 2 minutes to the hardener induced a late asthmatic response, starting after 2 hours, caused a reduction in FEV_1 (=forced expiratory volume in 1 second) of 57% at 5 hours, and required treatment with bronchodilators and corticosteroids. Histamine responsiveness 6 days later was similar to baseline. Conjugation of DETA to labelled human serum albumin did not reveal presence of IgE antibodies (Rya80).

Animal data

Irritation and sensitisation

Instillation of undiluted DETA and a 15% solution in water into the eyes of rabbits resulted in severe corneal injury; a 5% solution caused only minor injury (Sav55). DETA scored an injury grade of 5 (i.e., 0.005 ml of undiluted material gives an injury of up to 5.0 points - out of a maximum of 20 -; 0.02 mL over 5.0 points) on a scale of 1 to 10, 18 to 24 hours after instillation of undiluted test substance into the eyes of rabbits (Car46)*. In a later paper by the same authors, an injury grade of 8 (i.e., excess of 5% solution gives injury of up to 5.0 points of undiluted test substance; 15% over 5.0 points) was listed (Smy49; see also Car46). In a number of other unpublished studies, DETA was reported to be highly corrosive to the eyes of rabbits (EC00).

Following application to the uncovered clipped belly of 5 albino rabbits, DETA scored an injury grade of 6 (i.e., a 10% solution gives no reaction more severe than oedema; or necrosis by undiluted material) on a scale from 1 to 10 (Smy49; see also Smy54). Application of DETA to the patch-covered, clipped, intact or scarified skin of rabbits for 24 hours caused a Draize score of 8 (maximum score possible: 8). Similar scores were obtained when DETA was applied for 1 hour at 2 consecutive days (Hin58). In several unpublished studies, DETA was reported to be highly corrosive, causing severe burns, to the skin of rabbits (EC00).

Thorgeirsson studied the sensitisation capacity of various epoxy resin hardeners, including DETA, using the guinea-pig maximisation test. Fifteen animals were initially treated twice with intradermal injections and topical application of 0.5% aqueous DETA solutions, followed 2 weeks later by a 24-hour occluded patch test performed to the unshaved flank with a 2% solution. Control animals were initially treated with solvent only and then challenged with DETA. The challenge site was evaluated 24 hours after removal of the patch. Of the DETA-treated group, 93% of the animals reacted positively in the patch test showing redness and swelling. Of the animals sensitised to DETA, 20% reacted positively to triethylenetetramine while 67 and 40% of the animals sensitised to triethylenetetramine or tetraethylenepentamine, respectively, had a positive reaction to DETA. However, cross sensitisation could not be definitely established because the polyamines used were commercial products, possibly contaminated with traces of another (Tho78).

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* Grade 5 was also characterised as a ‘severe burn from 0.005 mL’(Smy54).

In a Magnusson-Kligman guinea-pig maximisation test, male and female Dunkin Hartley guinea pigs (n=10/sex) received, in the induction phase, intradermal injections of 0.1 mL of 5% solutions of DETA ('high purity'; not further specified) in water followed, 7 days later, by a 48-hour occluded topical application of a 50% aqueous solution. Twenty-one days thereafter, animals were challenged by a 24-hour occluded topical application of a 25% solution to the previously untreated site. Irritation control animals (n=5/sex), not induced, but only challenged, were included. Evaluation 24-48 hours after removal of the occluded patches showed positive skin sensitising responses in 16/20 animals. When DETA-induced animals were challenged with other alkyleneamines, positive reactions varying from 5/20 (for 5% ethylenediamine) to 18/20 animals (for 50% triethylenetetramine) were observed (Leu97a). In a similar, unpublished study conducted by the same laboratory, in which a commercial DETA (not further specified) was tested, 11/20 guinea pigs reacted positively. Of the animals induced with this commercial product, 11/20, 2/20, and 11/20 showed positive responses following challenge with high-purity DETA, 5% ethylenediamine, and 50% triethylenetetramine, respectively (Gre01).

Referring to a limitedly reported unpublished study, Greim cited positive reactions in 8/8 surviving animals out of 10 that received inducing, occlusive topical applications of 50% solutions of DETA in dimethylphthalate, once a week, for 3 weeks (Gre01).

In another unpublished study, amounts of ca. 0.1 mL of 10% solutions of DETA in acetone or water were applied to the shaved flank of 3 groups of 8-10 guinea pigs for 10 days, until clear irritation (crust formation, flaking) was observed in all animals. Twenty-four hours after the irritation had disappeared (10-12 days), animals were challenged with 1 and 3% solutions of DETA in acetone and water, respectively, on the other, previously untreated, shaved flank. No evidence of skin sensitisation was seen at evaluations after 8, 12, and 24 hours (BCG94).

In the local lymph node assay, using female CBA/Ca mice, positive results were reported for DETA tested at concentrations of 5 and 10% in acetone-olive oil (4:1) solutions (Bas94).

Rudzki and Krajewska studied the cross-reactions between DETA, triethylenetetramine, and ethylenediamine in guinea pigs. Out of 8 guinea pigs sensitive to triethylenetetramine, one reacted positive to DETA and another to DETA and ethylenediamine (Rud76).

In rats exposed to a DETA concentration of 1284 mg/m^3 (300 ppm), no irritation was reported (exposure duration not indicated) (Sav55).

Acute toxicity

All 6 rats survived an 8-hour exposure to a saturated vapour* of DETA (Smy49). Citing unpublished studies, it was stated that a 7-hour exposure to DETA vaporised at room temperature did not induce signs of toxicity in rats, while vapours generated at 100°C had caused slight eye irritation after 15 minutes and clear irritation of conjunctivae and nasal mucosal membranes and salivation at the end of the study. In another unpublished study, all rats, rabbits, guinea pigs, and cats (n=4/species) survived single 6- (rats) or 8-hour (rabbits, guinea pigs, cats) exposures to atmospheres saturated at 25°C without showing signs of toxicity (BCG94).

Following dermal application, LD_{50} values of 1045 and 163 mg/kg bw (1.09 and 0.17 mL/kg bw) were estimated in rabbits and guinea pigs, respectively (Smy44, Smy49). In unpublished studies using rabbits, LD_{50} values of ca. 670 and 4000 mg/kg bw were found for neat substance and a 10% solution, respectively (BCG94, EC00).

Following oral administration, LD_{50} values in rats ranged from 1080 to 2330 mg/kg bw (BCG94, EC00, Hin58, Smy44, Smy49) while values of 1440 and 600 mg/kg bw were reported for mice and guinea pigs, respectively (BCG94, EC00).

Regarding other routes, the intraperitoneal LD_{50} was 74 mg/kg bw in rats (Hin58) and 71 and 505 mg/kg bw in mice (Hin58, Sri88) and the subcutaneous LD_{50} 855 mg/kg bw in rats** and ca. 1690-2850 mg/kg bw in mice (EC00). A single intravenous injection of ca. 475 mg/kg bw was lethal to all rabbits (n=2) while no mortality was observed at an injection of 95 mg/kg bw (BCG94, EC00).

At oral or intraperitoneal administration, animals showed central nervous system effects consisting of an initial few minute-lasting excitement followed by convulsive seizures and, thereafter, depression. Gross and microscopic examination did not indicate any significant lesions other than those associated with irritation, or any evidence of degenerative changes in any of the organs examined (not further specified) (Hin58).

Repeated-dose toxicity

Apart from coarsened hair, no toxic signs were seen in Alderley Park specific-pathogen-free rats (n=2/sex) exposed to concentrations of DETA of 550 mg/m^3

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* Theoretically, the concentration in saturated vapour at 20°C can amount to 490 ppm (calculated from: (vapour pressure in Pa/10^5 Pa) x 10^6 ppm).

** In BCG94 listed for mice.

(130 ppm), 6 hours/day, 5 days/week, for 3 weeks. At gross and microscopic post-mortem examination, the organs (lungs, liver, kidney, spleen, adrenals, heart, jejunum, ileum, and thymus) were 'normal' (no more details presented) (Gag70). The committee considers this experiment not suitable for risk assessment because of the small number of animals exposed and the use of one concentration only.

In an unpublished 4-week dermal toxicity study, amounts equivalent to 38 and 780 mg/kg bw were applied daily (7 days/week) to the shaved dorsal skin of rabbits (New Zealand white; n=10/sex/group) while a control group (n=10/sex) was treated with vehicle (of unknown chemical identity) only. In each dose group, one male and one female animal were killed moribund. During the study, body weights of low-dose animals were 9-15% lower than those of controls; the body weighs of high-dose animals were about 25% lower at the end of week 1. In low-dose animals, local effects were observed such as erythema, oedema, flaking, peeling, and scab formation, for which severity increased from slight to very pronounced with duration. In the high-dose group, the local effects were such severe that treatment was stopped after 8 days. At the end of treatment of the low-dose animals, there were increases in alanine (ALAT) and aspartate aminotransferase (ASAT) and lactic dehydrogenase (LDH) activities, at evaluation of haematology and clinical chemistry parameters, and decreases in absolute testes and epididymides weights. At macroscopic and microscopic examination, only skin lesions were observed (hyperplasia, increased collagen content, polygranulomatous inflammation). In the high-dose group evaluated after 8 treatment days, only decreases in haemoglobin, haematocrit, and erythrocyte and increases in cholesterol and bilirubin values and decreases in absolute testes, epididymides, and brain weights were reported (BCG94).

In an unpublished 7-day study, in which male and female rats (Harlan-Wistar; n=5/sex/group) were given oral (diet) doses DETA of 240, 600, or 1350 and 240, 620, and 1580 mg/kg bw, respectively, no mortality occurred and body weights of mid- and high-dose animals as well as liver weights of high-dose males were reduced. No treatment-related lesions were seen at histological examinations (BCG94).

F344 rats (n=10/sex/group) were fed a diet containing the dihydrochloride salt of DETA at concentrations of 0, 1000, 7500, and 15,000 ppm (calculated corresponding doses: 0, 70, 530, and 1060 mg/kg bw/day for males and 0, 80, 620, and 1210 mg/kg bw/day for females) for 90 consecutive days. The high-dose and control groups contained an additional 10 animals/sex that were designated for 4-week exposure-free recovery period. There were no treatment-related clinical signs or mortality in either sex at any dose level. At the mid- and

high-dose levels, there were changes in haematology and clinical chemistry, including increases in mean corpuscular volume and mean corpuscular haemoglobin in males and increases in mean corpuscular volume, total leucocytes, and urinary pH and a decrease in serum glucose concentration in females. At these dose levels, dose-related decreases in body weight or body weight gain were observed in both sexes. The relative kidney, brain, and testes weights were increased in the high-dose males. In females, increases in the relative kidney, brain, and liver weights were found at 7500 and 15,000 ppm and in the relative heart and adrenal weights at 15,000 ppm. The animals from the recovery group showed only slightly improvement from the effects of the treatment. No macroscopic or microscopic lesions were observed at autopsy at week 13 and 17 (Leu97b). From this study, the committee concludes that the NOAEL for subchronic dietary exposure to the DETA dihydrochloride salt is 1000 ppm (or 70 mg/kg bw/day for males and 80 mg/kg bw/day for females).

Fujino treated groups of rats until death: one group daily with subcutaneous injections of 10 mg/kg bw, the second group every other day with subcutaneous injections of 50 mg/kg bw, and the third group every other day by skin application on the back of 0.4 mL of a diluted solution (1:10) of DETA. The fourth group was a control group. The average survival days were 335, 275, and 407 days in the 3 exposed groups, respectively, vs. 581 days in the control group. There were no notable pathological findings in the exposed groups. The numbers of erythrocytes and leucocytes and body weight changes were not different among the groups. Histological changes were observed mainly in the kidney and liver. The lesions were very marked in rats given 50 mg/kg bw subcutaneously, followed by the group given 10 mg/kg bw subcutaneously and the group treated by skin application. Renal tubular damage was characteristically demonstrated in rats given 10 mg/kg bw subcutaneously. Finally, pneumonia and some slight histological spleen and adrenal lesions were seen (Fuj70).

DePass et al. studied the dermal oncogenicity of various high purity or commercial grade polyamines, including DETA, in male C3H/HeJ mice (n=50/group). Twenty-five μL aliquots of 5% solutions of DETA, resulting in a dose of ca.1.25 mg per mouse per application, were applied thrice weekly until the death of the animals. The mean survival time of mice given high purity DETA was 587 days, without malignancy. Three animals had dermatitis, 2 hyperkeratosis, and 4 necrosis. The mean survival time of mice given commercial grade DETA was 662 days, with one malignancy (haemangioma) and one animal with epidermitis (DeP87). The committee concluded that DETA has no carcinogenic property under conditions of the study.

Mutagenicity and genotoxicity

In an abstract, Hulla et al. reported only slight activity when DETA was tested in a mutation assay using *S. typhimurium* strain TA100. Data on concentrations and the use of metabolic activation were not presented (Hul81). Hedenstedt found DETA positive in *S. typhimurium* strains TA1535 and TA100, but further examination showed that the positive response might be attributed to an alkylating impurity in the material tested (Hed78). On the other hand, DETA was negative in various published and unpublished studies in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 (BCG94, EC00, Leu94, Tak93, Zei87). In an unpublished study, DETA did not induce mutations in the yeast *S. cerevisiae* strain D4 (BCG94, EC00). DETA (purity: 98.9-100%) was negative when tested with and without metabolic activation in a CHO (HGPRT) gene mutation assay at concentrations of 0.125-4 µL/mL (Leu94). DETA did not significantly increase the frequency of mutations in sex-linked recessive lethal assay using male germ cells of *D. melanogaster* at the single concentration tested of 60 mM (Gol89).

DETA (purity: 98.9-100%) was negative in a SCE test in CHO cells, tested with and without metabolic activation at concentrations of 0.125-2 µL/mL (Leu94). No significant increases in the chromosomal aberration frequency were found when Chinese hamster ovary cells were treated with 250, 833, and 2500 µg/mL DETA in the presence and absence of metabolic activation system (Gol89).

Also, a negative result was obtained for DETA (purity: 98.9-100%) in a UDS test in rat hepatocytes (concentration range: 0.001-1 µL/mL) (Leu94).

In vivo, DETA did not induce a statistically significant increase in the frequency of micronucleated bone marrow polychromatic erythrocytes after single oral (gavage) administration to CD-1 mice at doses of 85, 283, and 850 mg/kg bw (Gol89).

Reproduction toxicity

The committee did not find data from reproduction toxicity studies on DETA.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for DETA in the Netherlands is 4 mg/m^3 (1 ppm), 8-hour TWA.

Existing occupational exposure limits for DETA in some European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

Following endotracheal and oral administration of radiolabelled DETA.3HCl to rats, radioactivity was rapidly and almost completely (90-95%) absorbed. The radioactivity was similarly distributed following endotracheal, intravenous, and oral administration with highest levels found in the liver and the kidneys (ca. 2.5-5 and 3 times that of blood, respectively). The radioactivity disappeared from the plasma with terminal half-lives of 9, 10, and 16 hours, respectively. The majority of the radiolabel was excreted in the faeces and the urine (ca. 70-80%), with slightly higher levels in the faeces, while only minor amounts (ca. 0.5-1%) were exhaled as CO_2. DETA was only limitedly metabolised. At doses of 50 and 500 mg/kg bw, parent compound accounted for 45 and 70% of the total urinary radioactivity, the remaining consisting of diethylenediamine and acid conjugates. At doses of 500 mg/kg bw, saturation of metabolism occurred.

Results from volunteer studies and case reports describing occupation-related allergic skin effects indicated that DETA is a skin-sensitising compound. Cross-reaction with other polyamines has also been reported.

Studies in experimental animals showed that DETA is corrosive to the eyes and skin of rabbits and sensitising to skin of guinea pigs. No irritation was observed in rats exposed to DETA concentrations of 1284 mg/m^3 (300 ppm).

Oral LD_{50} values of 1080-2330 mg/kg bw in rats and dermal LD_{50} values of 670 and 1080 mg/kg bw in rabbits indicate that DETA is harmful if swallowed or in contact with skin.

No signs of toxicity were observed in rats (n=2/sex) exposed to 550 mg/m^3 (130 ppm), for 4 weeks. Dermal application of doses of 780 mg/kg bw, 7 days/week, caused severe skin lesions which forced to cease treatment after 8 days; post-mortem examinations showed changes in haematological values and decreased absolute testes and epididymides weights, not accompanied by histological lesions. Application of doses of 38 mg/kg bw for 4 weeks, induced, apart from macroscopic and microscopic skin lesions, increases in ALAT, ASAT, and LDH activities and decreases in absolute testes and epididymides weights (no microscopic lesions). In an oral toxicity study, administration of doses of DETA.2HCl of 575 and 1135 mg/kg bw/day for 90 consecutive days caused changes in a number of haematological and clinical chemistry values, decreases in body weights and body weight gains and increases in relative kidney and liver weights, without macroscopic or microscopic lesions. No effects were seen at 70

or 80 mg/kg bw in males and females (i.e., 41-47 mg DETA/kg bw/day). Apart from a negative dermal carcinogenicity study in mice, the committee did not find data from long-term toxicity studies on DETA.

In *in vitro* studies, DETA did not induce mutations in bacteria, yeast, Chinese hamster ovary cells, and *D. melanogaster,* SCEs or chromosome aberrations in Chinese hamster ovary cells, or DNA damage (UDS) in rat hepatocytes. *In vivo*, it did not produce increases in the frequency of micronuclei in bone marrow obtained from mice given single oral doses of 85-850 mg/kg bw.

The committee did not find data from reproduction toxicity studies on DETA.

The committee takes the NOAEL of 47 mg/kg bw from the 90-day oral rat study (Leu90, Leu97b) as a starting point for deriving a health-based occupational exposure limit (HBROEL). Since workers are exposed for 5 days a week, this NOAEL from a continuous study (i.e., 7 days/week) is adjusted by multiplying it with a factor of 7/5 resulting in a no-adverse effect level (NAEL) of 66 mg/kg bw. For the extrapolation to a HBROEL, a factor of 4 for allometric scaling from rats to humans, based on caloric demand, and an overall factor of 27, covering inter- and intraspecies variation and the differences between experimental conditions and the exposure pattern of the worker, are applied, resulting in a NAEL for humans of 0.61 mg/kg bw. Assuming a 70-kg worker inhales 10 m^3 during an 8-hour working day and a retention of 100%, and applying the preferred-value approach, a health based occupational exposure limit of 5 mg/m^3 (1.2 ppm) is recommended for DETA.

The committee recommends a health-based occupational exposure limit for 2,2'-iminodi(ethylamine) of 5 mg/m^3 (1.2 ppm), as an 8-hour time-weighted average concentration.

Based on the acute dermal toxicity data (LD_{50} rabbit: 1045 mg/kg bw; guinea pig: 163 mg/kg bw) (see also ECE98), the committee recommends a skin notation.

The committee notes that 2,2'-iminodi(ethylamine) has skin sensitising properties.

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153-19 2,2’-Iminodi(ethylamine)

Annex

Occupational exposure limits for 2,2'-iminodi(ethylamine) in various countries

country - organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	reference[b]
	ppm	mg/m^3				
the Netherlands						
- Ministry of Social Affairs and Employment	1	4	8 h	administrative	S	SZW05
Germany						
- AGS	-	-				TRG04
- DFG MAK-Kommission	-	-[c]			sens	DFG05
Great-Britain						
- HSE	1	4.3	8 h	OES	S	HSE02
Sweden	1	4.5	8 h		S, sens	Swe00
	2	10	15 min			
Denmark	1	4	8 h		S	Arb02
USA						
- ACGIH	1	-	8 h	TLV	S	ACG05
- OSHA	-	-	-			ACG04
- NIOSH	1	4	10 h	REL	S	ACG04
European Union						
- SCOEL	-	-				EC05

[a] S = skin notation; which mean that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

[b] Reference to the most recent official publication of occupational exposure limits.

[c] Included in list of allergens.