Diisopropylamine

(CAS No: 108-18-9)

Health-based Reassessment of Administrative Occupational Exposure Limits

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

No. 2000/15OSH/080, The Hague, 22 October 2003

Preferred citation:
Health Council of the Netherlands: Committee on Updating of Occupational Exposure Limits. Diisopropylamine; Health-based Reassessment of Administrative Occupational Exposure Limits. The Hague: Health Council of the Netherlands, 2003; 2000/15OSH/080.

1 Introduction

The present document contains the assessment of the health hazard of diisopropylamine 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 diisopropylamine has been based on the reviews by the American Conference of Governmental Industrial Hygienists (ACGIH) (ACG99), the Swedish Criteria Group (Lun91), and the US Cosmetic Ingredient Review Panel (Pan95). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in November 1997, literature was searched in the databases Medline, Embase, and Chemical Abstracts, starting from 1966, 1988, and 1970, respectively, and using the following key words: diisopropylamine and 108-18-9. NIOSHTIC and HSELINE (from 1997 backwards) and Poltox (Toxline, Cambridge Sc Abstr, FSTA), databases available from CD-ROM, were consulted as well. The final literature search was carried out in Toxline and Medline in January 2003.

In April 2003, the President of the Health Council released a draft of the document for public review. The committee received no comments.

2 Identity

name	:	diisopropylamine
synonyms	:	*N*-(1-methylethyl)-2-propanamine
molecular formula	:	$C_6H_{15}N$
structural formula	:	$(CH_3)_2$-CH-NH-CH-$(CH_3)_2$
CAS number	:	108-18-9

3 Physical and chemical properties

molecular weight	:	101.2
boiling point	:	84°C
melting point	:	-61°C; -96°C
flash point	:	-6.7°C (closed cup); 1.7°C (open cup)
vapour pressure	:	at 20°C: 8.0 kPa
solubility in water	:	soluble (at 25°C: 11 g/100mL)
Log $P_{octanol/water}$	:	1.4 (experimental); 1.64 (estimated)
conversion factors	:	at 20°C, 101.3 kPa: 1 mg/m^3 = 0.24 ppm 1 ppm = 4.22 mg/m^3

Data from ACG99, NLM01, http://esc.syrres.com.

Diisopropylamine is a colourless, flammable, volatile liquid with a characteristic amine odour. It is strongly alkaline (ACG99).

Odour thresholds of 0.5 to 7.6 mg/m^3 (0.1-1.8 ppm) have been reported (ACG99, Lun91).

4 Uses

Diisopropylamine is used as a reagent and catalyst in the production of paint pigments, pharmaceuticals, and pesticides (ACG99, Lun91, NLM01). It has also been used for adjusting pH in cosmetic formulations, in colognes, and toilet waters (Pan95).

5 Biotransformation and kinetics

The committee did not find data on the (toxico)kinetics of diisopropylamine.

6 Effects and mechanism of action

Human data

Transient dimness of vision and, in a few instances, nausea and headaches were reported among men engaged in the distillation of diisopropylamine in a pilot-plant operation. The visual distress occurred within 2 to 3 hours after exposure to

unusually high concentrations of the vapour and persisted for one to 2 hours after the men went out into fresh air. The mean concentration of diisopropylamine in the pilot plant were said to be of the order of 100 to 200 mg/m^3 (ca. 25-50 ppm), with 5-10-minute peaks of about 740 mg/m^3 (ca. 180 ppm), occurring 2 or 3 times daily, near a drum into which diisopropylamine was being drained (Tre49).

In clinical pharmacology, diisopropylamine is known as an antihypertensive agent when given intravenously to hypertensive patients (Lie72, Ret80, Sch74, Tei72). It exerts its action - described as lowering of arterial blood pressure, reduction of stroke volume and cardiac output, and total peripheral resistance rises - immediately after the injection. The doses used were from 25 to 200 mg as diisopropylamine hydrochloride (Sch74).

Animal data

Irritation

When instilled into the eyes of rabbits, Smyth et al. reported for diisopropylamine an injury grade of 8 on a scale from 1 to 10. This grade indicated irritation with scores up to 5 points (maximum possible points:10) from an excess of 5% diisopropylamine or severe irritation with scores higher than 5 points from a 15% solution (Smy54). Instillation of 0.1 mL of undiluted diisopropylamine was reported to be corrosive to the eyes of rabbits. No details were given about the testing methods, number of animals used, irritation scores, observation times, etc. (Lon85a).

When 0.01 mL of undiluted diisopropylamine was applied to the clipped skin of 5 albino rabbits for 24 hours, Smyth et al. reported an injury grade of 1 (i.e., giving rise to 'the least visible capillary injection') on a scale from 1 to10 (Smy54). Application of 0.5 mL of undiluted diisopropylamine applied for 4 or 24 hours was reported to be corrosive to the skin of rabbits. No details were given about the testing methods, number of animals used, irritation scores, observation times, etc. (Lon85a).

In an unpublished, range-finding dermal toxicity study, moderate to severe irritation was seen in rats (Charles River CD(SD)BR; n=3/sex/group) dermally treated with 450 to 2000 mg/kg bw/day, for 5 consecutive days, while no irritation was seen at doses of 150 mg/kg bw or lower (Hey87).

In a dermal sensitisation test, 0.3 mL of 10% diisopropylamine was applied under occlusive patches to the shaved backs of 5 male and 5 female Hartley guinea pigs, 6 hours/day, 3 days/week, for 3 weeks (induction phase). After a 2-week non-treatment period, the animals were challenged with 0.3 mL

diisopropylamine at a previously untreated site. At this time, an additional group (n=3/sex) was also treated with diisopropylamine to be used as an irritation control group. Since severe irritation was observed in the induction phase after the first and second application of the 10% solution, the concentration was reduced to 5%, but irritation persisted throughout the induction period. However, since none of the animals responded to the challenge patch, the authors concluded that diisopropylamine has the potential to cause moderate to severe irritation after repeated dermal exposure, but that it is not a sensitiser (Lon85b).

Gagnaire et al. evaluated the sensory irritation of the upper respiratory tract in mice (male Swiss OF_1; n=10/group) during a 15-minute oronasal exposure to increasing concentrations of diisopropylamine ranging from 370-1478 mg/m^3 (88-351 ppm). The airborne concentration resulting in a 50% decrease in the respiratory rate (RD_{50}) was 678 mg/m^3 (161 ppm). The substance was also tested for pulmonary toxicity in mice and for the effects of a 120-minute exposure on the respiratory rates of non-anaesthetised, tracheally cannulated mice ($RD_{50}TC$). The $RD_{50}TC$ value for diisopropylamine was found to be 429 mg/m^3 (102 ppm). From these results (i.e., the ratio $RD_{50}TC/RD_{50}$), it was concluded that diisopropylamine is essentially a lower respiratory tract-irritating compound (Gag89). In another study in male Swiss OF_1 mice, Zissu found an RD_{50} of 733 mg/m^3 (174 ppm) (Zis95).

Irritation of eyes, nose, and respiratory tract following exposure to diisopropylamine vapours was observed in several animal species (see below), e.g., in rats and guinea pigs exposed to ca. 4000 mg/m^3, for 30 minutes (Pan95), or in rats exposed to 5000 mg/m^3, for 4 hours (Lon87).

Acute toxicity

Two-hour LC_{50} values of 4800 and 4210 mg/m^3 (1140 and 1000 ppm) have been reported in rats and mice, respectively (Izm82). Following exposure of rats to 4210 mg/m^3 (1000 ppm) diisopropylamine, for 4 hours, 2 out of 6 animals died (observation time: 14 days). When exposed to saturated vapour*, all 6 rats exposed died within 5 minutes (Smy54). When rats (Sprague-Dawley; n=5/sex/group) were exposed to mean analytical concentrations of 5000 and 5300 mg/m^3 (1200, 1272 ppm), for 4 hours, one male animal exposed to 5300 mg/m^3 died during the study (observation time: 14 days). Clinical signs observed

* The (theoretic) concentration in saturated air can be calculated using the formula: (vapour pressure in Pa x 10^6 ppm)/10^5 Pa. Using a vapour pressure of 8000 Pa, the committee estimates that these animals could have been exposed to 80,000 ppm or (roughly) 340,000 mg/m^3.

were laboured breathing, high-pitched respiratory sounds, partially or completely closed eyelids, nasal and ocular discharges and encrustation, ocular opacity, pitted/raised corneal surface, and tremors. At necropsy, only corneal opacity was seen (Lon87). Rats and guinea pigs (n=5/sex/species/concentration) were exposed to 4046, 7410, and 21,555 mg/m^3 (961, 1760, 5120 ppm), for 30 minutes. All animals survived exposure to 4046 mg/m^3, while mortality was reported in 1/10 rats and 2/10 guinea pigs exposed to 7410 mg/m^3 and in 10/10 rats exposed to 21,555 mg/m^3 (no data on guinea pigs presented). Exposure to the lowest concentration induced irritation of eyes and nose, dyspnoea, generalised depressed activity, reduced body weight gain (female rats), and increased lung weight; there were no histological lesions. In the animals of the mid-concentration group, irritation, dyspnoea, depressed activity, as well as decreased body weights (in rats and female guinea pigs), lung weights (female guinea pigs), and heart weights (male rats) were observed. In only one of the guinea pigs that died, treatment-related effects including congestion and corneal erosion and oedema were seen, while in the rat that died, there were pulmonary congestion, inflammation, haemorrhage, and oedema. For the high-concentration animals, only respiratory distress and renal proximal tubular and bronchial epithelial degeneration in rats and hepatocelluar vacuolar degeneration in guinea pigs were reported (Pan95). When rats, rabbits, guinea pigs, and cats (n=2/species/concentration) were exposed to 8950 mg/m^3 (2207 ppm), all animals died within 3 hours while all animals but one rabbit survived a 7-hour exposure to 3150 mg/m^3 (777 ppm). Effects observed included sneezing, coughing, retraction of the head, rubbing of the nose, nasal discharge, lachrymation, salivation, respiratory distress, tremors, and prostration, time of onset and severity depending on concentration and species. In rabbits, cats, and guinea pigs, cloudy corneas were reported (Tre49).

A dermal LD_{50} of 2900 mg/kg bw has been reported for albino rabbits (Lon85a).

Oral LD_{50} values found in rats were 420 and 770 mg/kg bw (Lon85a, Smy54).

Repeated-dose toxicity

When male Swiss OF_1 mice (n=10/group) were exposed to 261, 733, and 1836 mg/m^3 (63, 176, 441 ppm; i.e., 0.3xRD_{50}, RD_{50}, 3xRD_{50}, respectively; see above), 6 hours/day, 5 days/week, for 4, 9, or 14 days, two principal sites were affected: the anterior respiratory epithelium adjacent to the vestibule, and the olfactory epithelium (slight loss of isolated sensory epithelium). The lesions reached

maximum severity following 4-day exposure. Histological examinations of the trachea and lungs from all exposed animals showed no differences when compared to the control group. A NOAEL could not be established since the lesions mentioned were still seen at 261 mg/m^3 (63 ppm), the lowest level tested (Zis95).

When male and female Sprague-Dawley rats (n=15/sex/group) were exposed to diisopropylamine vapour concentrations of 0, 100, 600, and 2000 mg/m^3 (0, 24, 144 and 480 ppm), 6 hours/day, 5 days/week, for 1 month, one male and 2 female animals of the high-concentration group died during the study. Signs of toxicity in the rats of this group included respiratory difficulties, mucous membrane irritation, and non-responsiveness. The body weights of animals in the mid- and high-concentration groups were lower than those of the control group throughout the study (as much as 10 and 41%, respectively). Corneal lesions were observed in 13, 75, and 100% of the animals of the low-, mid-, and high-concentration group, respectively. Erythrocyte count, haemoglobin, and haematocrit values were increased (5-11%) in the male and female rats of the high-concentration group and in the females of the mid-concentration group. All treated male rats had reduced leukocyte counts (by 28-33%) due to reductions in lymphocytes. There were also changes in the values measured for albumin, total protein, alkaline phosphatase, and/or serum glutamic pyruvic transaminase, and cholesterol, but the changes were not considered to be treatment related. At necropsy, changes in organ weights found in the animals exposed to 2000 mg/m^3 included, amongst others, increased relative adrenal gland, heart, and kidney weights and decreased relative spleen weights in males and females, and increased relative liver weights in females. All rats exposed to 600 or 1000 mg/m^3 and most of the rats exposed to 100 mg/m^3 had hyperplasia and metaplasia of the nasal turbinates. Inflammation, mucosal erosion/ulceration, and necrosis/dissolution of turbinate septal cartilage or bone were also observed in all animals exposed to 1000 mg/m^3 and in most of the animals exposed to 600 mg/m^3. Almost all rats exposed to 2000 mg/m^3 had also lesions in the trachea (mucosal epithelial hyperplasia/metaplasia; inflammation) and in the lungs (bronchiolar epithelial hyperplasia/metaplasia) (Rol87). The committee could not set a NOAEL since exposure to 100 mg/m^3 (24 ppm) (6 hours/day, 5 days/week, for 1 month), the lowest level tested, induced reduced leukocyte and lymphocyte counts and corneal and nasal lesions.

In a range-finding dermal toxicity study, groups of male and female Charles River CD(SD)BR rats (n=3/sex/group) were dermally exposed to 0, 50, 150, 450, 1350, and 2000 mg/kg bw/day of undiluted diisopropylamine, for 5 consecutive days. Dose-dependent, moderate to severe dermal irritation was observed at

doses of 450 mg/kg bw and higher, which led to sacrificing all animals treated with 2000 mg/kg bw after 3 days. Other effects reported were limited to slight body weight decreases (6-9%) in male animals treated with doses of 150 mg/kg bw and greater and in female animals treated with 1350 mg/kg bw. In the definitive study, doses of 0, 15, 50, and 150 mg/kg bw/day were applied to the skin of 10 animals/sex/group, 5 times/week, for 1 month. The results showed that the body weight gain and feed consumption in the test groups did not differ from those of the control group. Mild skin dryness was observed at the sites of application, but because of a lack of dose-response relationship, this was considered to be the consequence of repeated applications and evaporation rather than a compound-related effect. Treatment did not cause changes in the haematology and clinical chemistry parameters. Decreases were found in the absolute (19%) and relative (12%) heart weights of the male rats from the high-dose group, and increases in the absolute (4-5%) and relative (10-14%) testes weights of the males from the mid- and high-dose groups. However, no microscopic changes were found in these organs. Incidences of mild splenic congestion amounted to 2/10, 1/10, and 2/10 males and 4/10, 1/10, and 6/10 females of the low-, mid-, and high-dose groups, respectively, while this was not seen in the control groups. However, since there was no dose-response relationship and no concomitant changes in splenic weights and haematology parameters, the authors considered the splenic congestion not treatment related. Overall, it was concluded that there was no evidence of dermal toxicity in rats exposed to doses up to 150 mg/kg bw/day, for 1 month (Hey87).

The committee did not find data on the potential carcinogenicity or reproduction toxicity of diisopropylamine.

Mutagenicity and genotoxicity

Diisopropylamine (purity: 99%) was negative when adequately tested with and without metabolic activation systems from induced rat or hamster livers in a pre-incubation assay using *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 (dose range: 33-10,000 µg/plate) (Mor86). In a separate study, negative results were reported when testing *S. typhimurium* strains TA1535 and TA1537 both with and without metabolic activation with induced rat liver S9 mix as well as strain TA1538 with metabolic activation. Unequivocal dose-response relationships were observed with strains TA98 and TA100 with and without metabolic activation and in strain TA1538 with metabolic activation. The

concentrations used in these experiments ranged from 0.1-10.0 µg/plate while toxicity was reported at levels of 10-50 µg/plate (Gel82).

Diisopropylamine was negative when tested in the DNA repair assay in cultured rat hepatocytes at concentrations of 0.1-5000 µg/mL (preliminary assay) and 10-2500 µg/mL (replicate assay). The compound was cytotoxic at a concentration of 5000 µg/mL. At concentrations of 500 µg/mL and above, pH changes of the test media occurred which was not adjusted for (Lon86).

The committee did not find other data on *in vitro* and *in vivo* mutagenicity/ genotoxicity tests.

The committee did not find data on the toxicity of diisopropylamine following subchronic or chronic exposure (including carcinogenicity) or on reproduction toxicity.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for diisopropylamine in the Netherlands is 20 mg/m^3 (5 ppm), 8-hour TWA, with a skin notation.

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

8 Assessment of health hazard

Limited human data has shown that exposure to about 100 mg/m^3 (50 ppm), with peaks of 740 mg/m^3 (ca. 180 ppm), induced complaints of visual disturbances, nausea, and headache.

In experimental animals, diisopropylamine was found not irritating to the skin in one study, but moderately to severely irritating or corrosive in other (unpublished) studies. The compound was severely irritating or corrosive to the eyes. There was no indication for a skin sensitising potential.

Acute inhalation studies showed 2-hour LC_{50} values of 4800 and 4210 mg/m^3 (1140 and 1000 ppm) in rats and mice, respectively. Dermal and oral LD_{50} values were 2900 (rabbits) and 420-770 (rats) mg/kg bw, respectively.

Acute and short-term inhalation experiments showed irritation of the eyes and the upper respiratory tract to be the critical effect, probably caused by the strong alkalinity of the compound. In a 1-month inhalation study in rats, corneal lesions, reduced leukocyte and lymphocyte counts, hyperplasia and metaplasia of nasal turbinates, and inflammation and necrosis of the turbinate septal cartilages

or bones were found at 100 mg/m^3 (24 ppm), the lowest level tested. In a dermal toxicity study, no systemic effects were found when doses up to 150 mg/kg bw were applied 5 times/week, for 1 month.

Diisopropylamine produced conflicting results *in vitro* in *S. typhimurium* (mutations) and was negative in rat hepatocytes (DNA repair). The committee did not find other data on *in vitro* and *in vivo* mutagenicity/genotoxicity tests.

The committee did not find data on the toxicity of diisopropylamine following subchronic or chronic exposure (including carcinogenicity) or on reproduction toxicity.

The committee takes the LOAEL of 100 mg/m^3 found in the 1-month inhalation study in rats (Rol87) as a starting point in deriving a health-based recommended occupational exposure limit (HBROEL). For the extrapolation to a HBROEL, an overall assessment factor of 27 is established. This factor covers the following aspects: the absence of a NOAEL and intra- and interspecies variation. Thus, applying this factor and the preferred value approach, a health-based occupational exposure limit of 5 mg/m^3 (1.2 ppm) is recommended for diisopropylamine.

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

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Annex

Occupational exposure limits for diisopropylamine 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	5	20	8 h	administrative	S	SZW03
Germany						
- AGS	-	20			c	
- DFG MAK-Kommission	-	-				TRG00 DFG02
Great-Britain						
- HSE	5	21	8 h	OES		HSE02
Sweden	5	20	8 h		S	Swe00
	10	40	15 min			
Denmark	5	20	8 h		S	Arb02
USA						
- ACGIH	5	21	8 h	TLV	S	
- OSHA	5	20	8 h	PEL	S	ACG03b
- NIOSH	5	20	8 h	REL	S	ACG03a ACG03a
European Union						
- SCOEL	-	-				EC03

[a] S = skin notation, which mean that skin absorption may contribute considerably to body burden;
[b] sens = substance can cause sensitisation.
[c] Reference to the most recent official publication of occupational exposure limits.
[d] It is noted that reaction with nitrosating agents may result in the formation of related, carcinogenic *N*-nitrosamine(s).