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TOXICOLOGICAL EVALUATIONS

BG RCI

Kurfürsten-Anlage 62 · D-69115 Heidelberg, Germany
Telefon: +49 6221 5108-28451
E-Mail: toxikologischebewertungen@bgrci.de
Internet: www.bgrci.de/toxicologicalevaluations

TOXICOLOGICAL EVALUATION

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Di-2-ethyl-hexylamine

No. 166

CAS No. 106-20-7

BG Chemie
Berufsgenossenschaft der chemischen Industrie

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BG Chemie
P.O.B. 10 14 80, 69004 Heidelberg, Germany
Telephone: +49 (0) 6221 523 400
E-Mail: praevention@bgchemie.de
Internet: www.bgchemie.de

Di-2-ethylhexylamine

Di-2-ethylhexylamine belongs to the class of compounds of the amines and may therefore possibly react with the nitrite or nitrate present in the body to form nitrosamines. A number of different nitrosamines are known and confirmed carcinogens.

1 Summary and assessment

Di-2-ethylhexylamine is harmful on single oral administration in rats as well as on single dermal application in rabbits (LD_{50} rat oral approx. 1000 and 1640 mg/kg body weight, depending on the source of information; LD_{50} rabbit dermal 958 mg/kg body weight) and following a single inhalative exposure it is toxic in rats (LC_{50} rat, 4 hours 910 mg/m³, tested as an aerosol). In the inhalation hazard test all rats subjected to a single 8-hour exposure to di-2-ethylhexylamine survived. Following intraperitoneal administration in the mouse the LD_{50} is approx. 50 mg/kg body weight. Clinical symptoms observed following oral administration include dyspnoea, apathy and diarrhoea, whereas inhalation mainly leads to local irritation of the respiratory tract and the eyes, and intraperitoneal administration causes dyspnoea, reeling, tremor and convulsions. In the Alarie test in mice di-2-ethylhexylamine mainly causes pulmonary irritation. The RD_{50} (concentration at which the respiratory rate is reduced by 50%) drops steadily over the exposure period of 45 minutes, reaching a value of approx. 44 mg/m³ in the last third of the exposure period.

Di-2-ethylhexylamine has a severely irritating to corrosive effect on the skin of rabbits and it is a strong irritant to the rabbit eye.

In the Salmonella/microsome assay, di-2-ethylhexylamine is not mutagenic in *Salmonella typhimurium* strains TA 100, TA 1535, TA 97 and TA 98, with and without metabolic activation.

In the production and handling of di-2-ethylhexylamine no cases of skin sensitisation have been observed in humans.

2 Name of substance

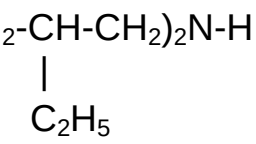
2.1	Usual name	Di-2-ethylhexylamine
2.2	IUPAC name	Di-(2-ethylhexyl)amine
2.3	CAS No.	106-20-7
2.4	EINECS No.	203-372-4

3 Synonyms, common and trade names

Bis-2-ethylhexylamin
Bis(2-ethylhexyl)-amin
2,2'-Diethyldihexylamin
2,2'-Diethyldihexylamine
Di-2-ethylhexylamin
Dihexylamine, 2,2'-diethyl- (6CI, 7CI, 8CI)
Diisooktylamin
2-Ethyl-N-(2-ethylhexyl)-1-hexanamin
2-Ethyl-N-(2-ethylhexyl)-1-hexanamine
1-Hexanamine, 2-ethyl-N-(2-ethylhexyl)-(9CI)

4 Structural and molecular formulae

4.1 Structural formula



4.2 Molecular formula $C_{16}H_{35}N$

5 Physical and chemical properties

5.1	Molecular mass, g/mol	241.46	
5.2	Melting point, °C	< –70	(BASF, 1995)
5.3	Boiling point, °C	157–159 (at 27 hPa)	(BASF, 1995)

5.4	Vapour pressure, hPa	0.01 (at 20 °C) 0.1 (at 55 °C)	(BASF, 1995) (BASF, 1991 a)
5.5	Density, g/cm³	0.806 (at 20 °C)	(BASF, 1995)
5.6	Solubility in water	4.5 g/l (at 20 °C)	(BASF, 1995)
5.7	Solubility in organic solvents	Miscible with nearly all usual solvents	(BASF, 1987)
5.8	Solubility in fat	Partition coefficient n-octanol/water log P_{ow}: 6.75	(BASF, 1995)
5.9	pH value	> 7	(BASF, 1995)
5.10	Conversion factor	1 ml/m³ (ppm) ≙ 9.86 mg/m³ 1 mg/m³ ≙ 0.10 ml/m³ (ppm) (at 1013 hPa and 25 °C)	

6 Uses

Used in the chemical industry as an intermediate in the manufacture of textile auxiliaries, dyestuffs, pesticides, polymers, polycondensation products, corrosion inhibitors and petroleum additives; stabiliser for organic halogen compounds (BASF, 1987).

7 Experimental results

7.1 Toxicokinetics and metabolism

No information available.

7.2 Acute and subacute toxicity

Acute toxicity

The acute oral toxicity of di-2-ethylhexylamine was studied in groups of 5 rats (sex not specified). The animals received the four dosages in a geometrical series with an incremental factor of 2 and were observed for 14

days. The LD_{50} was 1640 (1440 to 1870) mg/kg body weight (no further details); Smyth et al., 1949).

In another study investigating the acute oral toxicity of di-2-ethylhexylamine, male and female rats (number per group not specified) were given the substance by gavage as a 20-percent aqueous emulsion with tragacanth gum. The LD_{50} after a 7-day observation period was approx. 1000 mg/kg body weight. Signs of toxicity observed included dyspnoea, slight apathy and diarrhoea. The post-mortem revealed intestinal atony (BASF, 1967).

For the dermal LD_{50} in the rabbit a value of 1.19 ml/kg body weight was given, which corresponds to 958 mg/kg body weight, (no further details; UCC, 1968).

The acute inhalation toxicity of di-2-ethylhexylamine (purity: 99.6%) was tested in accordance with OECD guideline No. 403 in 5 male and 5 female Wistar rats (average initial weights 260 and 181 g, respectively) per concentration. The concentrations as determined by analysis were 280, 530, 840, 1280 and 2850 mg/m³ of air for the aerosols with median aerodynamic diameters of 1.4 to 1.8 µm and geometric standard deviations in the range from 3.3 to 3.8. The single exposure lasted 4 hours and the observation period was 14 days. The LC_{50} was determined as 910 mg/m³ for male and female rats. The clinical signs primarily observed were local irritation of the respiratory tract and the eyes. At post-mortem the lungs of the deceased rats showed focal hyperaemia and moderate emphysema. The post-mortem conducted at the end of the observation period did not reveal any pathological findings (BASF, 1991 b).

In an inhalation hazard test 6 male rats were subjected to a single 8-hour exposure to an atmosphere saturated with di-2-ethylhexylamine at room temperature. The post-exposure observation period was 14 days. All rats survived. No details of the clinical signs and the post-mortem findings were given (Smyth et al., 1949; UCC, 1968).

In a further inhalation hazard test at 20 °C di-2-ethylhexylamine was tolerated by 6 male and 6 female rats which were also subjected to a single 8-hour exposure followed by a 14-day observation period. The clinical symptoms observed included signs of mucous membrane irritation and at autopsy isolated cases of bronchial pneumonia were seen (BASF, 1967).

In order to determine the intraperitoneal LD_{50}, male and female mice (number per group not specified) were treated with di-2-ethylhexylamine as a 1-percent emulsion with tragacanth gum which was injected into the abdominal cavity. The observation period was 7 days. The LD_{50} was approx. 48 mg/kg body weight. The clinical signs observed included dyspnoea, reeling, tremor and convulsions. The post-mortem revealed intestinal atony as well as adhesions in the abdominal cavity (BASF, 1967).

An additional LD_{50} value has been reported as being 0.8 ml/kg body weight, which corresponds to 645 mg/kg body weight after intraperitoneal administration in the mouse (no further details; RTECS, 1996).

Sensory irritation

The sensory irritation potential of di-2-ethylhexylamine (purity: 99.7%) was tested in groups of 4 male Swiss mice (average initial weight ranging from 24.2 to 28.1 g) in the whole body plethysmograph. The animals were exposed to analytically determined concentrations of 0 (controls), 7.88, 32.6 and 48.6 mg/m³ for 45 minutes by means of a head-nose inhalation system. Exposure was followed by a recovery period of 15 minutes and an observation period of 7 days. The respiratory parameters were determined in each animal during the control period (minutes 6 to 15 prior to the beginning of exposure) and the exposure and recovery periods. The drop in respiratory rate observed during 3 10-minute intervals (early, middle, late) was calculated for each animal as a percentage of the respiratory rate seen during the control period. These percentages yielded RD_{50} (concentration which depresses the respiratory rate by 50%) values of 1411.7, 115.7 and 43.7 mg/m³ for the early phase, the middle and the late phase of exposure, respectively. The RD_{50} thus dropped steadily over the course of the experiment, reaching its lowest value in the last third of the exposure period. At all 3 concentrations investigated, the drop in respiratory rate seen in the recovery period was not reversible. No clinical signs of toxicity were observed during the study. Necropsy did not show any macroscopic findings. The lung weights of the exposed animals and those of the control animals were similar. These results thus demonstrate that di-2-ethylhexylamine mainly leads to pulmonary irritation (BASF, 1997).

7.3 Skin and mucous membrane effects

The skin irritancy of di-2-ethylhexylamine was tested in the abdominal skin of 5 rabbits. They were scored similarly to the Draize method. Following a 24-hour nonocclusive exposure to 10 µl of undiluted substance, di-2-ethylhexylamine produced grade 5 irritation, i. e. it led to strong erythema, oedema or slight necrosis (no further details; Smyth et al., 1949). The substance thus proved to be a strong irritant in this study.

In the standard test according to Draize, a 24-hour application of 2 mg di-2-ethylhexylamine to the rabbit skin led to signs of severe irritation (no further details; Marhold, 1986).

In a study with undiluted di-2-ethylhexylamine, exposure times of 1, 5 and 15 minutes caused reddening in the dorsal skin of rabbits (2 animals) and severe oedema extending beyond the area of exposure. One week later slight reddening, rhagades and slight necrosis (after the 1-minute and 5-minute exposures), severe necrosis (following the 15-minute exposure) and induration of the application site were observed. On application of undiluted di-2-ethylhexylamine to the dorsal skin of the rabbit, 20-hour exposure led to slight reddening, severe oedema and severe necrosis. After 8 days, severe necrosis and induration of the application site were observed (BASF, 1967). The substance thus proved to be corrosive to the skin in this study.

On application to the rabbit ear and 20-hour exposure, di-2-ethylhexylamine produced severe reddening and oedema. After 8 days severe necrosis and very severe oedema were observed (BASF, 1967). The substance thus also proved to be corrosive to the skin of the rabbit ear.

In an eye irritancy study in rabbits (2 animals), one hour and 24 hours upon instillation of 50 µl of the undiluted substance strong reddening, severe oedema and slight clouding of the cornea were seen, which was still present 8 days later (BASF, 1967). The substance thus proved to be severely corrosive.

In the standard test according to Draize the rabbit eye showed severe irritation upon instillation of 50 µg di-2-ethylhexylamine (no further details; Marhold, 1986).

In a further irritancy study of di-2-ethylhexylamine in the rabbit eye, the substance led to an ”injury grade” of 8 on a 10-point scale, i. e. 5 µl of a 15-

percent solution caused an irritation score of more than 5.0, and 5 µl of a 5-percent solution caused an irritation score of not more than 5.0 (no further details; Smyth et al., 1949; Carpenter and Smyth, 1946; UCC, 1968).

7.4 Sensitisation

No information available.

7.5 Subchronic and chronic toxicity

No information available.

7.6 Genotoxicity

7.6.1 In vitro

Di-2-ethylhexylamine (no indication of purity; solvent dimethyl sulfoxide) was tested in the Salmonella/microsome preincubation assay using the *Salmonella typhimurium* strains TA 100, TA 1535, TA 97 and TA 98 with and without metabolic activation (S-9 mix from Aroclor 1254-induced hamster and rat liver). The concentrations used were in the range from 3 to 6666 µg/plate. Starting at 166 µg/plate bacteriotoxicity was observed. Di-2-ethylhexylamine proved not to be mutagenic either with or without metabolic activation in these assays (Zeiger et al., 1988).

7.6.2 In vivo

No information available.

7.7 Carcinogenicity

No information available.

7.8 Reproductive toxicity

No information available.

7.9 Effects on the immune system

No information available.

7.10 Neurotoxicity

No information available.

7.11 Other effects

In rats, di-2-ethylhexylamine improved the in vivo penetration of the skin by pharmaceuticals dissolved in the amine. According to the authors, this effect was not due to increased capillary permeability or accelerated transport away from the skin, but solely to an increase in the permeability of the stratum corneum (Creasey et al., 1971).

8 Experience in humans

In the production and handling of di-2-ethylhexylamine in 4 plants no cases of skin sensitisation have been observed so far. As regards acute dermal effects, 4 cases of skin irritation were recorded from 1989 until June 1997 following acute local exposure during occupational handling of the substance (BASF, 1998).

9 Classifications and threshold limit values

No information available.

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