n-Butylamine

(CAS No: 109-73-9)

Health-based Reassessment of Administrative Occupational Exposure Limits

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

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1 Introduction

The present document contains the assessment of the health hazard of *n*-butylamine 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 of the Academic Medical Centre, Amsterdam, the Netherlands).

The evaluation of the toxicity of *n*-butylamine has been based on the review by the American Conference of Governmental Industrial Hygienists (ACG96). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, literature was retrieved from the databases Medline, Toxline, Chemical Abstracts, and Embase, (starting from 1966, 1967, 1970, and 1988, respectively), and HSEline, Cisdoc, Mhidas, and NIOSHTIC (from 1997 backwards), and using the following key words: n-butylamine and 109-73-9. The final literature search was carried out in October 1997.

In March 2000, the President of the Health Council released a draft of the document for public review. Comments were received by the following individuals and organisations: P Wardenbach, Ph.D. (Bundesanstalt für Arbeitsschutz und Arbeitsmedizin, Dortmund, Germany). These comments were taken into account in deciding on the final version of the document.

An additional literature search in May 2002 did not result in information changing the committee's conclusions.

2 Identity

name	:	*n*-butylamine
synonyms	:	1-butanamine; 1-aminobutane; mono-*n*-butylamine; monobutylamine; butylamine
molecular formula	:	$C_4H_{11}N$
molecular structure	:	CH_3-CH_2-CH_2-CH_2-NH_2
CAS number	:	109-73-9

3 Physical and chemical properties

molecular weight	:	73.14
boiling point	:	77.8°C
melting point	:	-50°C
flash point	:	-12°C (closed cup); -1°C (open cup)
vapour pressure	:	at 20°C: 10.9 kPa
solubility in water	:	miscible
log $P_{octanol/water}$	:	0.97 (experimental); 0.83 (estimated)
conversion factors	:	1 mg/m^3 = 0.33 ppm
(20°C, 101.3 kPa)		1 ppm = 3.0 mg/m^3

Data from ACG96, NLM02, http://esc.syrres.com.

n-Butylamine is a clear colourless liquid with a pungent fish- or ammoniac-like odour. Air odour thresholds were reported to be between 0.24 and 2 mg/m^3 (0.08 and 1.8 ppm) (Amo83, Rut86). Referring to unpublished industrial information, it was stated that the odour was moderately strong at levels of 6-15 mg/m^3 (2-5 ppm), strong at 15-30 mg/m^3 (5-10 ppm), and strong and irritating at higher levels (Bea81, Ben94).

4 Uses

n-Butylamine is used as an intermediate for the production of pharmaceuticals, dyestuffs, emulsifying agents, insecticides, synthetic tanning agents, and rubber chemicals (ACG96).

5 Biotransformation and kinetics

The committee did not find quantitative data on the (toxico)kinetics of *n*-butylamine. However, based on its structure (a short-chain, non-substituted, primary amine), it will be metabolised readily by monoamine oxidase to its corresponding aldehyde, which would be oxidised further to the corresponding carboxylic acid, and ammonia, which would be eliminated as urea (Ben94).

In vitro, in guinea pig liver slices, one of the metabolites found was acetoacetic acid (Ben94).

6 Effects and mechanism of action

Human data

Referring to unpublished industrial information, it was stated that direct skin contact with liquid *n*-butyl amine caused severe primary irritation and deep second-degree burns (blistering) in humans. Nose, throat, and eye irritation and headaches were said to have been experienced by workers with daily exposures to 15-30 mg/m^3 (5-10 ppm). Higher levels (30-75 mg/m^3 or 10-25 ppm) were unpleasant to intolerable for more than a few minutes. No complaints or symptoms were said to occur at levels below 15 mg/m^3 (5 ppm) (mostly between 3 and 6 mg/m^3 (1 and 2 ppm)) (Bea81, Ben94).

Animal data

Direct contact of a solution of *n*-butylamine may induce extensive irritation to the eyes. Guthrie and Seitz determined that the weakest solution causing microscopic epithelial damage would be a 0.5% (v/v) *n*-butylamine solution (Gut75). When instilled into the eyes of rabbits, *n*-butylamine scored an injury grade of 8 on a scale from 1 to 10, which was defined as producing a certain injury score, representative of ‘severe injury’, 18 to 24 hours after application of

an ‘excess’ of a 5% solution (Smy44; see also Car46). *n*-Butylamine was stated to be irritating to the eyes of rabbits in an unpublished study (no details) (EC00)*.

Following uncovered application of 0.01 mL of undiluted material to the clipped skin (abdomen) of albino rabbits (n=5), *n*-butylamine scored an injury grade of 6 on a scale from 1 to 10, which was defined as giving rise to ‘necrosis from undiluted material’ (Smy44; see also Smy51 and Smy62). *n*-Butylamine was stated to be corrosive to the skin of rabbits in an unpublished study (no details) (EC00).

In an unpublished guinea pig maximisation test conducted according to OECD Guide-line 406, *n*-butylamine was stated to be not sensitising (no details available) (EC00).

Nielsen and Vinggaard studied the sensory irritation of *n*-butylamine in CF-1 male mice by determining the decrease in respiratory rate during a 30-minute oronasal exposure to increasing concentrations of the test compound. The concentration resulting in a 50% decrease in the respiratory rate (RD_{50}) was estimated to be 362 mg/m^3 (121 ppm; range: 302-431 mg/m^3). The pulmonary irritation was determined from the decrease in respiratory rate in tracheally cannulated mice ($RD_{50}TC$). The plateau-level was reached slowly. The $RD_{50}TC$ for *n*-butylamine was found to be 900 mg/m^3 (300 ppm) (Nie88). In male NMRI mice and using the same methods, Vinggaard *et al*. (Vin89) found RD_{50} and $RD_{50}TC$ values of 738 and 1086 mg/m^3 (246 and 362 ppm), respectively (Vin89). In another study using male OF_1 mice, an RD_{50} value of 336 mg/m^3 (112 ppm) was determined (exposure time: 15 minutes) (Gag89).

Rats could tolerate exposure to a concentrated, probably saturated level** of *n*-butylamine without mortality occurring for a maximum of 2 minutes (Smy44). When exposed for 4 hours, rats survived exposure to 6000 mg/m^3 (2000 ppm) (Smy56), while exposure to 12,000 mg/m^3 (4000 ppm) caused mortality in 2-4/6 rats (observation time: 14 days) (Car49). In an unpublished study, a 4-hour LC_{50} of 4200 mg/m^3 (1386 ppm) was found in rats (EC00). In mice, a 2-hour LC_{50} of 800 mg/m^3 (264 ppm) has been reported (Izm82).

Following dermal application, an LD_{50} of 0.5 mL/kg bw (370 mg/kg bw) has been found in guinea pigs (Smy44). In a separate study, LD_{50} values for guinea pigs were 0.58 mL/kg bw (425 mg/kg bw) when applied to intact abdomen and

* See remark in ‘References’.

** Theoretically, the concentration in saturated vapour can amount to 327,000 mg/m^3 (109,000 ppm; calculated from: (vapour pressure in Pa/10^5 Pa) x 10^6 ppm).

>1.5 mL/kg bw (>1110 mg/kg bw) when applied to abraded back. This was thought to be due to the fact that extensive and severe necrosis of the skin of the abdomen was more likely to lead to complications and death than necrosis over a larger area involving primarily the back (Rou65). For rabbits, dermal LD_{50} values of 0.85 mL/kg bw (630 mg/kg bw) (NIO02) and >1.5 mL/kg bw (>1110 mg/kg bw) (abraded back skin) (Rou65) were listed.

Oral LD_{50} values were 366 and 382 mg/kg bw in male and female Sprague-Dawley CD rats, respectively (Che82), 500 mg/kg bw in male Wistar rats (Smy44), and 720 mg/kg bw in not further specified rats (EC00). Further, LD_{50} values of 430-450 mg/kg bw were listed for rats, mice, and guinea pigs (no details) (Izm82). In their oral rat studies administering doses of 100, 200, 300, 400, 500, and 600 mg/kg bw, Cheever *et al*. observed signs of toxicity such as sedation, ataxia, nasal discharge, gasping, salivation, and, at higher doses, convulsions and death, which generally occurred within 1 to 3 hours after administration. Gross post-mortem examination of animals that died following treatment showed pulmonary oedema while animals surviving the 14-day observation period appeared normal. The authors did not present data on dose-effect/response relationships (Che82).

Widy-Tyszkiewicz and Czlonkowski studied the effect of single intraperitoneally injected doses of aliphatic monoamines on motor activity of male Swiss mice, using electronic activity cages. No effects were found after a dose of 3 mg/kg bw butylamine. A dose of 100 mg/kg bw caused a transient inhibition of the locomotor activity, and did not produce autonomic symptoms (e.g., tremor, salivation, piloerection, urination, exophthalmus, and Straub tail). More severe effects were seen when the animals were given pentylamine or hexylamine at the same doses (Wid63).

In an *in vitro* experiment using cultured mouse peritoneal macrophages, Riches and Stanworth demonstrated that *n*-butylamine at millimolar concentrations released substantial amounts of lysosomal ß-glucuronidase and ß-galactosidase activities. It has been known that these cells perpetuate inflammatory lesions by secreting a wide repertoire of biologically active materials in response to appropriate stimuli (Ric80). In another *in vitro* experiment using rabbit reticulocytes to study the influence of *n*-butylamine on iron uptake, Glass and Nunez reported that the compound (1) retards the internalisation of transferrin bound to transferrin receptors on the plasma membrane of reticulocytes, (2) retards the externalisation of internalised transferrin, and (3) blocks transport of iron released from transferrin into the cytosol (Gla86).

The committee did not find data from repeated-dose toxicity studies, including carcinogenicity and reproduction toxicity.

n-Butylamine was negative when tested both with and without adding a metabolic activating system from induced rat and hamster livers in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 at concentrations of 3.3-3333 µg/plate (Zei87).

In vivo, in an unpublished micronucleus assay conducted according to OECD Guideline 474, *n*-butylamine (hydrochloride) was stated to be negative following intraperitoneal injections of doses of 200, 400, and 800 mg/kg bw into NMRI mice (no details available) (EC00).

7 Existing guidelines

The current administrative occupational exposure limit (MAC) of *n*-butylamine in the Netherlands is 15 mg/m^3 (5 ppm), as a ceiling limit.

Existing occupational exposure limits for *n*-butylamine in some European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

Unpublished human data suggest that *n*-butylamine is an eye and skin irritating compound and that daily exposure to concentrations of 15-30 mg/m^3 (5-10 ppm) and higher can cause irritation of eyes, nose, and throat and headaches with severity increasing with concentration. Exposure to levels below 15 mg/m^3 (5 ppm) (mostly between 3 and 6 mg/m^3 (1 and 2 ppm)) were said to induce no complaints or symptoms.

In experimental animal studies, *n*-butyl amine was found to be a severely eye- and skin-irritating compound. Rats survived a 4-hour exposure to 6000 mg/m^3 (2000 ppm), while exposure to 12,000 mg/m^3 (4000 ppm) caused mortality in 2-4/6 rats. The dermal (in guinea pigs) and oral (in rats) LD_{50} values were 3700 and ca. 375-500 mg/kg bw, respectively.

The committee did not find data on repeated-dose toxicity, including carcinogenicity and reproduction toxicity. *n*-Butylamine was negative in an *in vitro* mutation assay in bacteria and an *in vivo* micronucleus test in mice.

The committee considers the toxicological database on *n*-butylamine too poor to justify recommendation of a health-based occupational exposure limit.

The committee concludes that there is insufficient information to comment on the level of the present MAC-value.

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NLM02 US National Library of Medicine (NLM), ed. n-Butylamine. In: Hazardous Substances Data Bank (HSDB) (last revision date *n*-butylamine file: 31 January 1999); http://toxnet.nlm.nih.gov.

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* This dossier is a compilation based on data reported by the European Chemicals Industry following 'Council Regulation (EEC) No 793/93 on the Evaluation and Control of the Risks of Existing Substances' to allow a risk assessment by member states of the EC. However, the data in this dossier have not undergone any evaluation by any EC member state yet.

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Annex

Occupational exposure limits for *n*-butylamine 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	15	ceiling	administrative	S	SZW02
Germany						
-AGS	5	15	8 h		S	TRG00
	20	60	15 min			
-DFG MAK-Kommission	5	15	8 h		S,[d]	DFG02
	10	30	15 min, momentary value[c]			
Great-Britain						
-HSE	5	15	15 min	OES	S	HSE02
Sweden	5	15	ceiling		S	Swe00
Denmark	5	15	ceiling		S,[e]	Arb02
USA						
-ACGIH	5	-	ceiling	TLV	S	ACG02b
-OSHA	5	15	ceiling	PEL	S	ACG02a
-NIOSH	5	15	ceiling	REL	S	ACG02a
European Union						
-SCOEL	-	-				EC02

[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] I.e., a concentration that should not be exceeded at any time; maximim number per shift: 4, with a minimum interval between peaks of 1 hour.

[d] Listed among compounds for which no information regarding possible damage to the embryo or fetus was found for pregnancy risk group classification.

[e] Holds for all isomers of butyl amine.