CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

International Chemical Identification:

di-*n*-butylamine

EC Number: **203-921-8**

CAS Number: **111-92-2**

Index Number: **612-049-00-0**

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on behalf of the Austrian Competent Authority (Austrian Federal Ministry for Sustainability and Tourism, Stubenring 1, 1010 Vienna, Austria)

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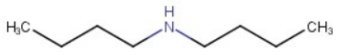
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	N-butylbutan-1-amine
Other names (usual name, trade name, abbreviation)	Dibutylamine Di-*n*-butylamine 1-Butanamine, N-butyl- N-Butyl-1-butanamine Dibutilamina N-butylbutan-1-amine N-Dibutylamine Di-(*n*-butyl)amine
ISO common name (if available and appropriate)	Not applicable
EC number (if available and appropriate)	203-921-8
EC name (if available and appropriate)	Di-*n*-butylamine
CAS number (if available)	111-92-2
Other identity code (if available)	RTECS Number: HR7780000 ICSC Number: 1337 UN Number: 2248 PubChem CID: 8148
Molecular formula	$C_8H_{19}N$
Structural formula	 **(source:** European Chemicals Agency, http://echa.europa.eu/**)**
SMILES notation (if available)	CCCCNCCCC
Molecular weight or molecular weight range	129.247 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	Not applicable
Description of the manufacturing process and identity of the source (for UVCB substances only)	Not applicable
Degree of purity (%) (if relevant for the entry in Annex VI)	≥ 80 wt %

1.2 Composition of the substance

Di-*n*-butylamine is a mono-constituent substance.

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)
di-*n*-butylamine (EC 203-921-8)	Not applicable	Flam. Liq. 3; H226 Acute Tox. 4*; H332 Acute Tox. 4*; H312 Acute Tox. 4*; H302	Flam. Liq. 3; H226 Acute Tox. 2; H330 Acute Tox. 3; H311 Acute Tox. 4; H302 Skin Corr. 1A; H314

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
Not relevant				

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
Not relevant					

Table 5: Test substances (non-confidential information)

Identification of test substance	Purity	Impurities and additives (identity, %, classification if available)	Other information	The study(ies) in which the test substance is used
The test substance is di-*n*-butylamine in all studies where the test substance was explicitly stated. The purity is given in the study records below if available.				

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 6: Classification and labelling of di-*n*-butylamine

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	612-049-00-0	di-*n*-butylamine	203-921-8	111-92-2	Flam. Liq. 3 Acute Tox. 4 * Acute Tox. 4 * Acute Tox. 4 *	H226 H332 H312 H302	GHS02 GHS07 Wng	H226 H332 H312 H302			
Dossier submitters proposal	612-049-00-0	di-*n*-butylamine	203-921-8	111-92-2	**Add** Skin Corr 1B Eye Dam 1 STOT SE 3 **Modify** Acute Tox. 2 Acute Tox. 3 Acute Tox. 3 **Retain** Flam. Liq. 3	**Add** H314 H318 H335 **Modify** H330 H311 H301 **Retain** H226	**Add** GHS05 **Modify** GHS06 Dgr **Retain** GHS02	**Add** H314 **Modify** H330 H311 H301 **Retain** H226		**Add** Oral: ATE = 220 mg/kg bw Dermal: ATE = 768 mg/kg bw Inhalation: ATE = 1.15 mg/L	
Resulting Annex VI entry if agreed by RAC and COM	612-049-00-0	di-*n*-butylamine	203-921-8	111-92-2	Flam. Liq. 3 Acute Tox. 2 Acute Tox. 3 Acute Tox. 3 Skin Corr 1B Eye Dam 1 STOT SE 3	H226 H330 H311 H301 H314 H318 H335	GHS02 GHS05 GHS06 Dgr	H226 H330 H311 H301 H314		Oral: ATE = 220 mg/kg bw Dermal: ATE = 768 mg/kg bw Inhalation: ATE = 1.15 mg/L	

Table 7: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	*hazard class not assessed in this dossier*	No
Flammable gases (including chemically unstable gases)	*hazard class not assessed in this dossier*	No
Oxidising gases	*hazard class not assessed in this dossier*	No
Gases under pressure	*hazard class not assessed in this dossier*	No
Flammable liquids	*hazard class not assessed in this dossier*	No
Flammable solids	*hazard class not assessed in this dossier*	No
Self-reactive substances	*hazard class not assessed in this dossier*	No
Pyrophoric liquids	*hazard class not assessed in this dossier*	No
Pyrophoric solids	*hazard class not assessed in this dossier*	No
Self-heating substances	*hazard class not assessed in this dossier*	No
Substances which in contact with water emit flammable gases	*hazard class not assessed in this dossier*	No
Oxidising liquids	*hazard class not assessed in this dossier*	No
Oxidising solids	*hazard class not assessed in this dossier*	No
Organic peroxides	*hazard class not assessed in this dossier*	No
Corrosive to metals	*hazard class not assessed in this dossier*	No
Acute toxicity via oral route	Acute Tox 3; H301	Yes
Acute toxicity via dermal route	Acute Tox 3; H311	Yes
Acute toxicity via inhalation route	Acute Tox 2; H330	Yes
Skin corrosion/irritation	Skin Corr 1B, H314	Yes
Serious eye damage/eye irritation	Eye Dam 1, H318	Yes
Respiratory sensitisation	*hazard class not assessed in this dossier*	No
Skin sensitisation	*hazard class not assessed in this dossier*	No
Germ cell mutagenicity	*hazard class not assessed in this dossier*	No
Carcinogenicity	*hazard class not assessed in this dossier*	No
Reproductive toxicity	*hazard class not assessed in this dossier*	No
Specific target organ toxicity-single exposure	STOT SE 3, H335	Yes
Specific target organ toxicity-repeated exposure	*hazard class not assessed in this dossier*	No
Aspiration hazard	*hazard class not assessed in this dossier*	No
Hazardous to the aquatic environment	*hazard class not assessed in this dossier*	No
Hazardous to the ozone layer	*hazard class not assessed in this dossier*	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

Di-*n*-butylamine had a harmonized classification under the Dangerous Substances Directive (67/548/EEC). This was translated to a harmonized CLP classification in Annex VI, Regulation (EC) No 1272/2008 (CLP Regulation) and a minimum classification (according Annex VII) was applied to acute toxicity for all routes (marked as Acute Tox. 4 * for all routes).

The current harmonized classification (CLP, Annex VI Table 3.1) for di-*n*-butylamine is:

Flam. Liq. 3; H226

Acute Tox. 4*; H332

Acute Tox. 4*; H312

Acute Tox. 4*; H302

Self-classification:

The frequency of hazard classifications among all C&L notifications (occurring in at least 10% of notifications) was retrieved from ECHA dissemination site [accessed 12/2020] and is given below. In total, 731 notifiers provided information on their hazard classifications (14 aggregated notifications):

Hazard code	Hazard statement	% of notifications
H226	Flammable liquid and vapour	100
H302	Harmful if swallowed	99.7
H312	Harmful in contact with skin	71.1
H311	Toxic in contact with skin	28.7
H332	Harmful if inhaled	71.3
H330	Fatal if inhaled	18.7
H314	Causes severe skin burns and eye damage	28.6
H318	Causes serious eye damage	13

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

[B.] Justification that action is needed at Community level is required.

Reason for a need for action at Community level:

- Change in existing entry due to changes in the criteria (translation from DSD to CLP)
- Disagreement by DS with current self-classification

Further detail on need of action at Community level

There is a harmonised classification entry in Annex VI to CLP containing a minimum classification (*) and it is concluded that a refinement of the classification based on available data is justified. Differences in self-classification between different notifiers in the C&L Inventory and registration dossier are discovered.

Di-*n*-butylamine is an important industrial chemical. A correct classification for acute toxicity and corrosion is essential to minimize uncertainties in classification along the supply chain and to ensure a high level of protection of workers by setting the right risk management measures.

5 IDENTIFIED USES

Di-*n*-butylamine is manufactured and/or imported in the European Economic Area in 1 000 - 10 000 tonnes per year. Identified uses are manufacture, formulation or re-packing, and use at industrial sites (see Table 8 for details) (ECHA dissemination site, July 2019).

Table 8: Registered uses of di-*n*-butylamine (according to ECHA dissemination site, July 2019)

Uses at industrial sites	Use as laboratory chemical
	Industrial use resulting in manufacture of another substance
	Use as processing aid (catalyst) in rubber production (vulcanisation)
Uses at formulation or re-packing	Use as processing aid (catalyst) in rubber production (vulcanisation)
	Formulation of preparations

6 DATA SOURCES

Systematic searches for publications and other relevant data were performed based on the following databases:

- U.S. National Library of Medicine, Pubmed.gov[1]
- TOXNET[2], ChemID*plus*[3], IPCS[4], eChemPortal[5], EPA Comptox Dashboard[6], EPA Chemview[7]

[1] https://www.ncbi.nlm.nih.gov/pubmed assessed at 7.2.2019
[2] https://toxnet.nlm.nih.gov/ assessed at 7.2.2019
[3] https://chem.nlm.nih.gov/chemidplus/ assessed at 7.2.2019
[4] http://www.inchem.org/ assessed at 7.2.2019
[5] http://www.echemportal.org/echemportal/page.action?pageID=9 assessed at 7.2.2019
[6] https://comptox.epa.gov/dashboard/
[7] https://chemview.epa.gov/chemview

- Chemical Abstracts, Medline, Biosis, Embase, SciSearch, PQScitech (at host STN International Europe[8])

in addition to unspecific databases (e.g., *google scholar*).

The REACH registration dossier for di-*n*-butylamine, available from ECHA's disseminated database (accessed 2019) has been analysed for study references, which then have been considered as data sources for this CLH report.

Relevant reviews and monographs with toxicological risk assessments on di-*n*-butylamine were analysed for study references. Used reviews are AGS (2006) and TCEQ (2016).

Whenever secondary sources were encountered, it was attempted to retrieve the respective primary sources.

[8] http://www.stn-international.de/index.php?id=123 assessed at 13.2.2019

7 PHYSICOCHEMICAL PROPERTIES

Table 9: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101.3 kPa	Liquid	ECHA Dissemination (2019)	Visual observation
Melting/freezing point	-57 – -59 °C	ECHA Dissemination (2019)	Measured, at 1013.25 hPa
Boiling point	160 °C	ECHA Dissemination (2019)	Measured, at 1013.25 hPa
Density	0.7577 g/cm³	ECHA Dissemination (2019)	Measured, at 22.9 °C
Vapour pressure	2.26 hPa	ECHA Dissemination (2019)	Measured, at 20.3 °C and up to 1013.25 hPa
Surface tension	50.6 mN/m	ECHA Dissemination (2019)	Measured, at 20 °C, concentration of 1.005 g/L
Water solubility	3.8 g/L	ECHA Dissemination (2019)	Measured, at 20 °C and approx. pH 12
Partition coefficient n-octanol/water	2.1	ECHA Dissemination (2019)	Measured, at 23 °C and pH 12
Flash point	40.5 °C	ECHA Dissemination (2019)	Measured, at 1013 hPa
Flammability	Flammable liquid	ECHA Dissemination (2019)	Measured
Explosive properties	Non explosive	ECHA Dissemination (2019)	Derived from chemical structure
Self-ignition temperature	255 °C	ECHA Dissemination (2019)	Measured, at 1013 hPa
Oxidising properties	No oxidising properties	ECHA Dissemination (2019)	Derived from chemical structure
Granulometry	Not applicable	-	-
Stability in organic solvents and identity of relevant degradation products	Not applicable	ECHA Dissemination (2019)	Justification given: expert judgement
Dissociation constant	11 (pKa)	ECHA Dissemination (2019)	Measured, at 20 °C
Viscosity	0.85 mPa*s	ECHA Dissemination (2019)	Measured, at 20 °C

8 EVALUATION OF PHYSICAL HAZARDS

Not performed for this substance.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Evaluation not performed for this substance.

10 EVALUATION OF HEALTH HAZARDS

Acute toxicity

10.1 Acute toxicity - oral route

Table 10: Summary table of animal studies on acute oral toxicity

Method, guideline, reliability	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
Acute oral toxicity Similar to OECD 401 GLP: no Reliability (REACH registration): 2, key study Reliability (this assessment): 3	Rat, Wistar 5 animals, sex not stated	Dibutylamine No information on source No information on purity	Dose levels not known. Single application via gavage Vehicle: 1% Tergitol	550 mg/kg bw (95% CI: 480 – 620 mg/kg bw)	Smyth et al. (1954) [key study, REACH registration]
Acute oral toxicity Similar to OECD 401 GLP: no Reliability (this assessment): 3	rat, strain not specified 10 male and 10 female per dose group	Dibutylamine Technical purity, no further information on purity Source: Former VEB Synthesewerk Schwarzheide (today BASF Schwarzheide GmbH)	Several dose levels tested (males: 5, females: 6). Doses not specified Single application via gavage Variable concentration in vehicle (peanut oil): constant volume 5 mL/kg	male: 310 mg/kg bw (95% CI: 251 - 382) female: 220 mg/kg bw (95% CI: 191 - 253)	Schmidt et al. (1974)
Acute oral toxicity Similarity to guideline unknown GLP: no Reliability (this assessment): 3	Rat, Wistar 3-5 male and 3-5 female per dose group	Dibutylamine No information on source No information on purity	No information on dose levels Application via gavage Vehicle: oil	male: 189 mg/kg bw female: 239 mg/kg bw	Ciugudeanu et al. (1985) No English translation obtainable
Acute oral toxicity	Mouse and guinea pig (unknown	Dibutylamine No information	No information given	290 mg/kg bw (mouse)	Secondary source:

Method, guideline, reliability	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
Similarity to guideline unknown GLP: no Reliability (this assessment): 4	strains) No information on group size and sex	on source No information on purity		230 mg/kg bw (guinea pig)	Sax and Lewis (1989) Primary source not obtainable (given as "Gigiena i Sanitariya-40(11),21,75")

10.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

No animal study is available that is sufficiently conform to a guideline and is conclusive on its own. Two old studies, similar to OECD Guideline 401, are available (Table 10). However, lacking information on purity of the test material is limiting their reliability. These studies determined LD_{50} values of 220 – 550 mg/kg bw in rats (Smyth, 1954 and Schmidt, 1974). Two additional references provide LD_{50} values of 230 mg/kg bw for guinea pigs and 290 mg/kg bw for mice, but the primary sources are not obtainable (Sax and Lewis, 1989) or could not be evaluated due to the lack of a translation (Ciugudeanu et al., 1985).

No human studies with relevance for comparison with the CLP criteria are available.

10.1.2 Comparison with the CLP criteria

According to Table 3.1.1 of Regulation (EC) No. 1272/2008 a substance shall be classified as

- Acute Tox 4 (oral) if the LD_{50}/ATE values are > 300 and ≤ 2000 mg/kg bw.
- Acute Tox 3 (oral) if the LD_{50}/ATE values are > 50 and ≤ 300 mg/kg bw.

All available studies are of limited reliability. In a WoE approach, the studies by Smyth (1954) and Schmidt (1974) are given more weight, as they provide clearly more information to judge the relevance of the determined LD_{50} values for comparison with the CLP criteria. The LD_{50} by the key study in the dossier (LD_{50} rat = 550 mg/kg bw) corresponds to a classification as acute oral toxicity category 4 (300 – 2000 mg/kg bw), while the Schmidt study (LD_{50} rat, female: 220 mg/kg bw, male: 310 mg/kg bw) indicates a classification as category 3 (50 – 300 mg/kg bw). There is no apparent reason to prefer one of these two studies over the other and the CLP regulation envisages the use of the lower ATE for comparison with the CLP criteria. In addition, the less reliable studies both determined values also leading to a classification in category 3. In conclusion, the weight of evidence leads to a classification for acute oral toxicity, category 3 for di-*n*-butylamine.

10.1.3 Conclusion on classification and labelling for acute dermal toxicity

Based on the CLP-Criteria di-*n*-butylamine has to be classified in category 3 for acute oral toxicity (Acute Tox 3, H301).

Based on the lowest LD_{50} used for classification an ATE value of 220 mg/kg bw is indicated.

10.2 Acute toxicity - dermal route

Table 11: Summary table of animal studies on acute dermal toxicity

Method, guideline, reliability	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Value LD_{50}	Reference
Acute dermal toxicity Similar to OECD 402 GLP: no Reliability (REACH registration): 2, key study Reliability (this assessment): 3	Rabbit, New Zealand White 4 males per dose group	Di-*n*-butylamine No information on source No information on purity	No information on dose levels Occlusive application 24 h exposure	768 mg/kg bw (95% CI: 620 – 1130 mg/kg bw) (reported as 1.01 mL/kg bw with a 95% CI: 0.68 – 1.49 mL/kg bw)	Primary source: (Smyth et al., 1954) [key study, REACH registration]

10.2.1 Short summary and overall relevance of the provided information on acute dermal toxicity

There is very limited data available on dermal toxicity. Only a single animal study with limited reliability (due to lacking information on purity) is available. An additional result which is found in secondary literature (Sax and Lewis, 1989) is actually a conversion mistake of the former study and is not reported in Table 11.

No human studies with relevance for comparison with the CLP criteria are available.

10.2.2 Comparison with the CLP criteria

According to Table 3.1.1 of Regulation (EC) No. 1272/2008 a substance shall be classified as

- Acute Tox 4 (dermal) if the LC_{50}/ATE values are > 1000 and ≤ 2000 mg/kg bw
- Acute Tox 3 (dermal) if the LC_{50}/ATE values are > 200 ≤ 1000 mg/kg bw

A classification is proposed based on the only available study, although the reliability is limited. A major concern is the lacking information on purity, however, using this study is expected to err on the conservative side. Therefore, use of this study is considered acceptable in a conservative approach. This study reports a LD_{50} of 768 mg/kg bw, which corresponds to category 3 of the CLP criteria for acute dermal toxicity (200 – 1000 mg/kg bw).

10.2.3 Conclusion on classification and labelling for acute dermal toxicity

According to the CLP-criteria di-*n*-butylamine has to be classified in category 3 for acute dermal toxicity (Acute Tox 3, H311).

Based on the available LD_{50} value an ATE = 768 mg/kg bw is indicated.

10.3 Acute toxicity - inhalation route

Table 12: Summary table of animal studies on acute inhalation toxicity

Method, guideline, reliability	Species, strain, sex, no/group	Test substance, form	Dose levels, duration of exposure	Value LC_{50}	Reference
Acute inhalation toxicity Equivalent to OECD 403 GLP: yes Reliability (REACH registration): 2, key study Reliability (this assessment): 1	Rat, Sprague-Dawley 5 males and 5 females per dose group	Dibutylamine, as vapour Purity > 99.5 % No information on source	0, 0.76, 1.08, 1.18, 1.39, 3.91 mg/L 4 h exposure 14 days post exposure observation	1.15 mg/L mortalities C: m 0/5, f 0/5 0.76 mg/L: m 2/5, f 0/5 1.08 mg/L: m 0/5, f 2/5 1.18 mg/L: m 3/5, f 1/5 1.39 mg/L: m 5/5, f 5/5 3.91 mg/L: m 5/5, f 5/5	Primary source: unnamed study report, 1987 [Study 001, REACH registration]
Acute inhalation toxicity Similarity to guideline unknown GLP: no Reliability (REACH registration): 2 Reliability (this assessment): 3	Rat, Wistar 6 male rats per dose	Dibutylamine, as vapour No information on source No information on purity	No information on concentrations 4 h whole body exposure 14 days post exposure observation	> 1.34 mg/L & < 2.68 mg/L Mortalities 1.34 mg/L: 0/6 2.68 mg/L: 6/6	Primary source: Smyth et al. (1954) [Study 002, REACH registration]
Acute inhalation toxicity Similarity to guideline unknown GLP: no Reliability (this assessment): 4	Rat, strain not specified No information on group size and sex	Dibutylamine No information on source No information on purity	No information on concentrations 4 h exposure No further information on exposure	2.68 mg/L	Secondary Source: (Greim et al., 1998) Primary source not sufficiently specified (data provided by industry)

10.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

A guideline- and GLP-conform study on rats is available (proprietary study, reported as key study in the registration dossier). This study is of high quality and is on its own conclusive for comparison with the CLP

criteria. After 4 h exposure, this study determined a LC50 of 1.15 mg/L. During exposure the rats showed signs of sensory irritation like partial closing of the eyes, reduced respiratory rate, abnormal respiratory movements and adoption of an anormal body posture. Less frequently gasping, exsessive salivation. Lacrimation and convulsion were observed. When removed from the test chamber previously exposed rats showed abnormal breathing, lethargy, ataxia, prone posture and intermittent convulsions. Abnormal breathing, rales and sneezing were evident till day 2 with normal appearance on day 3.

One additional study in rats of insufficient reliability (study 002 in ECHA Dissemination, 2019), as well as a LC_{50} value for rats reported in a secondary source, without sufficient documentation on the primary source (Greim et al., 1998), could be found. These studies provide a range of >1.34 mg/L to 2.68 mg/L as LC_{50} values.

No human studies with relevance for comparison with the CLP criteria are available.

10.3.2 Comparison with the CLP criteria

According to Table 3.1.1 of Regulation (EC) No. 1272/2008 a substance shall be classified as

- Acute Tox 4 (inhal) if the LC_{50} values are > 10.0 mg/L and ≤ 20.0 mg/L (4h exposure)
- Acute Tox 3 (inhal) if the LC_{50} values are > 2.0 mg/L and ≤ 10.0 mg/L (4h exposure)
- Acute Tox 2 (inhal) if the LC_{50} values are > 0.5 and ≤ 2 mg/L (4h exposure)

The key study results in a LC_{50} value (1.15 mg/L, 4 h exposure), which corresponds to a classification as category 2 (0.5 – 2 mg/L). The other available study results with insufficient reliability support this classification, yet the upper bound of the determined LC_{50} range by these studies slightly exceeds the boundaries of category 2. However, given the significantly higher relevance of the key study, this has no impact on the assessment.

10.3.3 Conclusion on classification and labelling for acute inhalation toxicity

Based on the CLP criteria di-*n*-butylamine has to be classified in category 2 for acute inhalation toxicity (Acute Tox 2, H 330).

The key study gives an LC_{50}/ATE value of 1.15 mg/L.

10.4 Skin corrosion/irritation

Table 13: Summary table of animal studies on skin corrosion/irritation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results -Observations and time point of onset -Mean scores/animal -Reversibility	Reference
OECD 404 Non GLP	Rabbit, Vienna White (1m, 1f)	Dibutylamine >99.5%	0.5ml Occlusive (2x2cm) 3min, 1h	Erythema score, 3min exposure Mean (24, 48, 72h) = 4 Max. score = 4	Anonymous (1978) [key study, REACH

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results -Observations and time point of onset -Mean scores/animal -Reversibility	Reference
Reliability (REACH registration): 2, key study			test substance removed after exposure time Observation 8d	Not reversible Erythema score, 1 h exposure Mean (24, 48, 72h) = 4 Max. score = 4 Not reversible Edema score, 3 min exposure Mean (24, 48, 72h) = 2 Max. Score = 2 Not reversible Edema score, 1 h exposure Mean (24, 48, 72h) = 2 Max. Score = 2 Not reversible Necrosis after 24h observed	registration]
Draize-method	Rabbits, New Zealand White N=6	Dibutylamine (100%)	0.5 ml 4h Clipped intact skin One-inch square Observations: 4, 24, 48h	Erythema score, 4h exposure Mean (24, 48h) = 4 Max. score = 4 Not reversible Edema score, 1 h exposure Mean (24, 48h) = 1.58 Max. Score = 3 Necrosis at all timepoints	Virginia chemicals, 1973 OTS0515256
Skin irritation test	Albino rabbits N=3	Dibutylamine	0.5 ml 24h Clipped, intact and abraded skin	15min: skin turned brown 24h: large necrotic lesions 48h: dry, hard lesions, cracking, raw rat tissue	Pennwalt Corp (1986) OTS0513616

10.4.1 Short summary and overall relevance of the provided information on skin corrosion/irritation

For the evaluation of skin irritation/corrosion one OECD 404 study is available. Two rabbits (one male, one female) were exposed (occlusive, 2x2 cm, clipped) to 0.5 ml of undiluted dibutylamin (>99.5%) for 3 min or 1 h. The test substance was removed at the end of exposure period with Lutrol and Lutrol/water (1:1). Animals were observed for 8 days. Untreated skin of the same animal served as control. The 3 min and 1 h

exposure caused severe erythema and slight to moderate edema (see Table 14). After 24 h necrosis was observed (no earlier observations documented). At the end of the observation period of 8 days leathery necrosis was observed; this was considered as a full thickness necrosis.

Table 14: Individual animal data and mean scores after an exposure duration of 3min or 1h (Anonymous, 1978).

Exposure time	animal #	Erythema score				Edema score			
		24h	48h	72h	Mean	24h	48h	72h	Mean
3 min	#1	4	4	4	4.0	2	2	2	2.0
	#2	4	4	4	4.0	2	2	2	2.0
1 h	#1	4	4	4	4.0	2	2	2	2.0
	#2	4	4	4	4.0	2	2	2	2.0

In a Draize test 6 rabbits (clipped, intact skin) were exposed to 0.5ml of undiluted dibutylamine for 4h (Virginia chemicals, 1973). Scores and necrosis were recorded after 4, 24 and 48h of exposure and are presented below.

Table 15: Individual erythema and edema scores scores after 4h of exposure (Virginia chemicals, 1973).

Animal No	Erythema score			Edema score			Necrosis		
	4h	24h	48h	4h	24h	48h	4h	24h	48h
1	4	4	4	3	3	1	yes	yes	yes
2	4	4	4	2	2	1	yes	yes	yes
3	4	4	4	2	2	1	yes	yes	yes
4	4	4	4	2	2	1	yes	yes	yes
5	4	4	4	2	2	1	yes	yes	yes
6	4	4	4	2	2	1	yes	yes	yes

In another test (Pennwalt Corp, 1986) 0.5 ml of dibutylamine was applied to three Albino rabbits for 24h. Each had one intact and one abraded skin site (clipped, occlusive). As a result is was recorded that the sample spread beyond the intended sites of contact and caused pain in every instance. The skin turned brown within 15 minutes. 24h after the first contact large necrotic lesions were described. These lesions became dry, hard and concave within 48h. In the following they cracked and peeled exposing raw tissue.

In a publication by Smyth (1952) corrosive effects to skin for the substance dibutylamine are reported without further details.

Registrants also mention another Draize study (Air products, 1975; Val. 2), where severe erythema, edema and necrosis persisting through 72 h were observed after 4h of exposure. Corrosive skin effects were also mentioned in another study (Elf Atochem 1976; Val. 3). However, no further details can be provided as original literature could not be located.

10.4.2 Comparison with the CLP criteria

A corrosive substance is a substance that produces destruction of skin tissue, namely, visible necrosis through the epidermis and into the dermis, in at least 1 tested animal after exposure up to a 4 hour duration. Classification is done as follows:

		Corrosive in >1 of 3 animals	
	Subcategories	Exposure	Observation
Category 1: Corrosive	1A	≤ 3 min	≤ 1h
	1B	> 3 min - ≤ 1h	≤ 14 d
	1C	> 1 h - ≤ 4 h	≤ 14 d

In the available guideline study necrosis was observed 24 h after start of exposure (3 min or 1h) in 2 of 2 animals tested. Mean erythema and edema scores were 4 and 2, respectively. At the end of the observation period (day 8) leathery necrosis was documented.

Necrosis as well as severe erythema and moderate edema were also observed in a Draize test after 4h exposure (Virginia Chemicals, 1973). Another skin irritation study with an exposure duration of 24h showed heavy necrosis after 24h (Pennwalt Corp, 1986).

10.4.3 Conclusion on classification and labelling for skin corrosion/irritation

Necrosis, severe erythema and edema were observed in animal studies. Exposure of rabbits to 0.5 ml of undiluted dibutylamine for 3 min resulted in necrosis 24h after start of exposure. Based on the CLP criteria a classification as Skin Corr. 1B is indicated.

10.5 Serious eye damage/eye irritation

Due to a classification of di-*n*-butylamine for Skin Corrosion Category 1 serious damage to eyes is implicit as reflected in the hazard statement for skin corrosion (H314: Causes severe skin burns and eye damage) (ECHA, 2017). However, a studies on eye irritation/corrosion are available and presented in the table below.

Table 16: Summary table of animal studies on eye corrosion/irritation

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance,**	**Dose levels duration of exposure**	**Results** **-Observations and time point of onset** **-Mean scores/animal** **-Reversibility**	**Reference**
OECD 405 Non GLP Reliability (REACH registration): 2, key study	Rabbit N=4	C-902 (dibutylamine)	0.1ml (not rinsed off) Observation 7 days	Conjunctivae score Mean 24h = 2.3 (max 3) Not fully reversible within 7 days Chemosis score Mean (24h) = 2.3 (max 3) Not fully reversible within 7 days	Anonymous, 1985 OTS 0515257

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results -Observations and time point of onset -Mean scores/animal -Reversibility	Reference
				Cornea opacity score Mean 24h = 4 (max 4) Not fully reversible within 7 days	
-	Albino rabbits	dibutylamine	0.1ml in both eyes One eye was washed after 15 sec with water, other remained unwashed		Pennwalt Corp (1986) OTS0513616

10.5.1 Short summary and overall relevance of the provided information on eye corrosion/irritation

In the available study (Anonymous, 1985) eyes of four rabbits were exposed to 0.1 ml of dibutylamine. The test substance produced severe ocular irritation in two of the four animals. After 24h severe conjunctival irritation (redness, chemosis, discharge, necrosis), iridial changes or iritis and corneal opacity, stippling and ulceration and corneal bulging (indicative of increased intraocular pressure) are described. No information on scoring at 48h and 72h is available. By day 7, two of the four animals still exhibited conjunctival irritation, iridial changes and corneal opacity, stippling and/or ulceration, corneal bulging and pannus (neovascilarization of the corneal surface). The other two animals exhibited only slight conjunctival irritation and/or iridial changes and stippling which were reversible after 7 d. Individual animal data are presented in the table below.

Table 17: eye irritation testing – individual scoring (Anonymous, 1985)

Effect		Animal #1, f		Animal #2, m		Animal #3, f		Animal #4, f	
		24h	Day 7	24h	Day 7	24h	Day 7	24h	Day 7
	Redness	3	1	2	1	2	1	2	1
Conjunctivae	Chemosis	3	2	2	1	2	1	2	1
	Discharge	3	1	3	0	3	0	3	0
	Necrosis	N	N	0	0	N	0	N	0
	Ulceration	0	0	0	0	0	0	0	0
	score	18	8	14	4	14	4	14	4
Iris	Iris	1	+	+	0	1	+	1	+

	score	5	0	0	0	5	0	5	0
Cornea	Opacity	3	1	1	0	2	1	2	0
	Area	4	3	2	0	4	4	4	0
	Stippling	2	2	2	0	2	1	2	1
	Ulceration	4	0	2	0	4	1	2	0
	Fluorescein	F	F	F	F	F	F	F	F
	Score	60	15	10	0	40	20	40	0
Totol score		83	23	24	4	59	24	59	4

Note: readability of the individual scoring in the available OTS documentation was limited

In the second study (Pennwalt Corp, 1986) 0.1ml of dibutylamine was placed in the conjunctival sac of both eyes of albino rabbits (n=3). After 15 seconds one eye of each animal was washed with water, the other eye remained unwashed. Scoring was done for a periode of 7 days. The reactions in the washed and unwashed eyes were identical. The mean scores are described in the table below. Signs of recovery were evident on day 6.

Table 18: Mean scores (washed and unwashed compiled) (Pennwalt Corp, 1986).

Time	Cornea	Iris	Conjunctivae redness	Conjunctivae chemosis
10min	0	<1	2	1
1h	0	<1	2	1
2h	0	<1	2	1
4h	0	<1	2	1
24h	0	<1	3	1
48h	0	<1	3	1
72h	0	<1	3	1
4d	0	<1	3	1
5d	0	<1	2	1
6d	0	0	1	0
7d	0	0	1	0

10.5.2 Comparison with the CLP criteria

Category 1	A substance that produces: (a) in at least one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or (b) in at least 2 of 3 tested animals, a positive response of: (i) corneal opacity ≥ 3 and/or (ii) iritis > 1,5 calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material.
Category 2	Substances that produce in at least in 2 of 3 tested animals, a positive response of: (a) corneal opacity ≥ 1 and/or (b) iritis ≥ 1, and/or (c) conjunctival redness ≥ 2 and/or (d) conjunctival oedema (chemosis) ≥ 2 calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and which fully reverses within an observation period of 21 days

For comparison with the given classification criteria only limited data is available. In the first study (Anonymous, 1985) scores at 24h were 4 for corneal opacity and about 1 for iritis in at least 2 of 4 animals (no scoring at 48/72h). Observations were only done till day 7, where no reversibility was reported for 2/4 animals. In a second study immediate conjunctivae redness, increasing till day 3 was observed.

10.5.3 Conclusion on classification and labelling for skin corrosion/irritation

Di-*n*-butylamine showed severe effects in the eyes of rabbits (conjunctivae chemosis and necrosis, cornea ulceration, cornea opacity). Due to limited reporting no final conclusion can be drawn based on the documented scoring in the study by Anomymous, 1985. In the second test a mean score (24-72h) for conjunctival redness of 3 is reported indicating classification as Category 2 irritant.

However the substance showed corrosive effects in skin irritation studies and is therefore proposed to be classified as Skin Corr. 1B. According to the CLP guidance (ECHA, 2017) serious damage to eyes is implicit indicated as Eye Dam 1, which is supported by the severe effects seen in the study by Anonymous (1985).

10.6 Respiratory sensitisation

Evaluation not performed for this substance.

10.7 Skin sensitisation

Evaluation not performed for this substance.

10.8 Germ cell mutagenicity

Evaluation not performed for this substance.

10.9 Carcinogenicity

Evaluation not performed for this substance.

10.10 Reproductive toxicity

Evaluation not performed for this substance.

10.11 Specific target organ toxicity-single exposure

For evaluation of STOT-SE acute toxicity studies are available. The studies are presented in Chapter 10.1, 10.2 and 10.3. For most of the studies only limited descriptions are available. No effects relevant for a classification as STOT SE 1 or 2 could be identified. However one acute inhalation toxicity study is available with relevant effects for respirator tract irritation. This study is described in detail below.

Table 19: Summary table of relevant animal studies on acute toxicity

Method, guideline, reliability	**Species, strain, sex, no/group**	**Test substance, form**	**Dose levels, duration of exposure**	**Value** **LC_{50}**	**Reference**
Acute inhalation toxicity Equivalent to OECD 403 GLP: yes Reliability (REACH registration): 2, key study Reliability (this assessment): 1	Rat, Sprague-Dawley 5 males and 5 females per dose group	Dibutylamine, as vapour Purity > 99.5 % No information on source	0, 0.76, 1.08, 1.18, 1.39, 3.91 mg/L 4 h exposure 14 days post exposure observation	1.15 mg/L mortalities C: m 0/5, f 0/5 0.76 mg/L: m 2/5, f 0/5 1.08 mg/L: m 0/5, f 2/5 1.18 mg/L: m 3/5, f 1/5 1.39 mg/L: m 5/5, f 5/5 3.91 mg/L: m 5/5, f 5/5 - partial closing of the eyes - reduced respiratory rate, - abnormal respiratory movements - adoption of an anormal body posture - gasping, exsessive salivation, lacrimation	Anonymous (1987) [Study 001, acute Tox, inhalation, REACH registration]

10.11.1 Short summary and overall relevance of the provided information on specific target organ toxicity – single exposure

In this guideline- and GLP-conform study rats were exposed to dibutylamine (vapour) in 5 different concentrations. After 4 h exposure, this study determined a LC50 of 1.15 mg/L. During exposure (concentration not indicated) the rats showed signs of sensory irritation like partial closing of the eyes, reduced respiratory rate, abnormal respiratory movements and adoption of an anormal body posture. Less frequently gasping, exsessive salivation, lacrimation and convulsion were observed. When removed from the test chamber previously exposed rats showed abnormal breathing, lethargy, ataxia, prone posture and intermittent convulsions. Abnormal breathing, rales and sneezing were evident till day 2 with normal appearance on day 3.

10.11.2 Comparison with the CLP criteria

Category 1	Substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following single exposure Substances are classified in Category 1 for specific target organ toxicity (single exposure) on the basis of: a) reliable and good quality evidence from human cases or epidemiological studies; or b) observations from appropriate studies in experimental animals in which significant and/or severe toxic effects of relevance to human health were produced at generally low exposure concentrations. Guidance dose/concentration values are provided below (see 3.8.2.1.9) to be used as part of weight-of-evidence evaluation.
Category 2	Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following single exposure Substances are classified in Category 2 for specific target organ toxicity (single exposure) on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose/concentration values are provided below (see 3.8.2.1.9) in order to help in classification. In exceptional cases, human evidence can also be used to place a substance in Category 2 (see 3.8.2.1.6).
Category 3	Transient target organ effects This category only includes narcotic effects and respiratory tract irritation. These are target organ effects for which a substance does not meet the criteria to be classified in Categories 1 or 2 indicated above. These are effects which adversely alter human function for a short duration after exposure and from which humans may recover in a reasonable period without leaving significant alteration of structure or function. Substances are classified specifically for these effects as laid down in 3.8.2.2

There are currently no validated animal tests that deal specifically with respiratory tract irritation, however, useful information may be obtained from the single and repeated inhalation toxicity tests. For example, animal studies may provide useful information in terms of clinical signs of toxicity (dyspnoea,

rhinitis etc) and histopathology (e.g. hyperemia, edema, minimal inflammation, thickened mucous layer) which are reversible and may be reflective of characteristic clinical symptoms. Such animal studies can be used as part of weight of evidence evaluation.

According to the CLP guidance (ECHA, 2017) it is a reasonable assumption that corrosive substances may also cause respiratory tract irritation when inhaled at exposure concentrations below those causing frank respiratory tract corrosion. If there is evidence from animal studies or from human experience to support this then Category 3 may be appropriate. In general, a classification for corrosivity is considered to implicitly cover the potential to cause RTI and so the additional Category 3 is considered to be superfluous, although it can be assigned at the discretion of the classifier. The Category 3 classification would occur only when more severe effects in the respiratory system are not observed.

For evaluation of transient target organ effects one acute toxicity study (inhalation) is available, showing effects like partial closing of the eyes, reduced respiratory rate, abnormal respiratory movements and adoption of an anormal body posture. Less frequently gasping, exsessive salivation, lacrimation and convulsion were observed. These effects were fully reversible. Tissue changes were not investigated.

10.12 Conclusion on classification and labelling for STOT SE

The available acute toxicity study shows sensory irritation (reduced respiratory rate, abnormal respiratory movements) after short term 4h exposure of rats to vapour of di-n-butylamine. As the substance shows corrosive properties in skin irritation studies these irritant effects may be expected, when tested as vapour. A classification for corrosivity is considered to implicitly cover the potential to cause respiratory tract irritation but STOT SE 3 can be assigned in addition. Therefore, a classification as STOT SE Category 3 for di-*n*-butylamine is proposed.

10.13 Specific target organ toxicity-repeated exposure

Evaluation not performed for this substance.

10.14 Aspiration hazard

Evaluation not performed for this substance.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Evaluation not performed for this substance.

12 EVALUATION OF ADDITIONAL HAZARDS

Evaluation not performed for this substance.

13 ADDITIONAL LABELLING

Not applicable for this substance.

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