Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

di-*n*-butylamine

EC Number: 203-921-8
CAS Number: 111-92-2

CLH-O-0000007007-79-01/F

Adopted

10 June 2021

10 June 2021

CLH-O-0000007007-79-01/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **di-*n*-butylamine**

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

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

The proposal was submitted by **Austria** and received by RAC on **19 December 2019.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Austria has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **3 February 2020**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **3 April 2020**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Ivan Dobrev**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **10 June 2021** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	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	
RAC opinion	612-049-00-0	di-*n*-butylamine	203-921-8	111-92-2	**Add** Skin Corr 1B Eye Dam 1 **Modify** Acute Tox. 2 Acute Tox. 3 Acute Tox. 3	**Add** H314 H318 **Modify** H330 H311 H301	**Add** GHS05 **Modify** GHS06 Dgr **Retain** GHS02	**Add** H314 **Modify** H330 H311 H301		**Add** Oral: ATE = 220 mg/kg bw Dermal: ATE = 300 mg/kg bw Inhalation: ATE = 1.2 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	H226 H330 H311 H301 H314 H318	GHS02 GHS05 GHS06 Dgr	H226 H330 H311 H301 H314	EUH071	Oral: ATE = 220 mg/kg bw Dermal: ATE = 300 mg/kg bw Inhalation: ATE = 1.2 mg/L (vapours)	

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Di-n-butylamine is an important industrial chemical registered (as dibutylamine) at 1000 to 10000 tonnes per annum. Identified uses are manufacture, formulation or re-packing, and use at industrial sites.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

Oral

Two older acute toxicity studies via the oral route in rats (similar to OECD TG 401) revealed LD_{50} values of 220 and 550 mg/kg bw (Smyth, 1954 and Schmidt, 1974). LD_{50} values of 230 mg/kg bw for guinea pigs and 290 mg/kg bw for mice were also reported (Sax and Lewis, 1989), however the primary sources were not available to the DS. In a weight of evidence assessment, the DS proposed classification for acute oral toxicity in category 3, H301 with an ATE of 220 mg/kg bw.

Species	**LD_{50} (95% CI) mg/kg bw**	**Reliability (DS)**	**Study**	**Remark**
Rat, Wistar (n=5)	550 (480–620)	3	Smyth *et al*., 1954	Similar to OECD TG 401, non-GLP
Rat, no strain 10/sex/group	male: 310 (251-382) female: 220 (191-253)	3	Schmidt *et al*., 1974	Similar to OECD TG 401, non-GLP
Rat, Wistar 3-5/sex/group	male: 189 female: 239	3	Ciugudeanu *et al*., 1985	No guideline, non-GLP
Mouse, guinea pig	mouse: 290 guinea pig: 230	4	Sax and Lewis, 1989	No guideline, unknown group size and strains

Dermal

Based on LD_{50} of 768 mg/kg bw from a single acute toxicity study with limited reliability, the DS proposed classification as Acute Tox 3, H311 for the dermal route of exposure.

Species	**LD50 (95% CI) mg/kg bw**	**Reliability (DS)**	**Study**	**Remarks**
Rabbit, NZ White 4 males/dose	768 (620–1130)	3	Smyth *et al*., 1954	Similar to OECD TG 402; occlusive application for 24h; LD50 reported as 1.01 mL/kg bw (95% CI: 0.68–1.49)

Inhalation

An acute inhalation toxicity study in rats performed according to GLP and OECD TG 403 revealed a LC_{50} of 1.15 mg/L (vapour) after 4 h exposure. Further data from secondary sources provide a range of LC_{50} values from >1.34 mg/L to <2.68 mg/L. Considering the outcome of the most reliable study, the DS proposed classification in category 2, H330, and ATE value of 1.15 mg/L.

Species	LC_{50} (mg/L)	Reliability (DS)	Study	Remarks
Sprague-Dawley rat, 5/sex/dose	1.15 (both sexes combined)	1	Anonymous, 1987	OECD TG 403, GLP; Dose levels: 0, 0.76, 1.08, 1.18, 1.39, 3.91 mg/L (vapour)
Wistar rat, 6 males/dose	>1.34 (0/6 dead) <2.68 (6/6 dead)	3	Smyth *et al*., 1954	No guideline specified, 4 h whole body exposure to vapour
Rat, strain, sex and group size not specified	2.68	4	Greim *et al*., 1998	4h exposure, no further details

Comments received during consultation

Two MSCA supported the proposed classifications on acute toxicity. Considering the (low) quality of the available studies, one MSCA proposed using the generic ATEs for classification of mixtures: 100 mg/kg bw for acute oral toxicity, and 300 mg/kg bw for acute dermal toxicity.

Assessment and comparison with the classification criteria

Oral

All available studies are lacking information on the specific study design and the purity of the test substance. Smyth (1954) established an LD_{50} of 550 mg/kg bw in rats, while the study by Schmidt (1974) reported an LD_{50} of 220 mg/kg bw in female and 310 mg/kg bw in male rats. An additional reference (Ciugudeanu *et al*., 1985) provided LD_{50} values of 189 mg/kg bw in male and 239 mg/kg bw in female rats, however direct access to the study is not available. A secondary source (Sax and Lewis, 1989) reported LD_{50} of 230 mg/kg bw for Guinea pigs and 290 mg/kg bw for mice.

In agreement with the DS evaluation, RAC considers the reliability of all studies as low. The studies by Smyth (1954) and Schmidt (1974) provide slightly more information on animal numbers and similarity to test guideline protocols thus allowing comparison with the CLP criteria. An LD_{50} of 550 mg/kg bw in rats indicates classification in category 4 (300–2000 mg/kg bw), while an LD_{50} of 220 mg/kg bw in female rats points to a classification in category 3 (50–300 mg/kg bw). According to DS, there were no apparent reasons to give stronger preference to one of these two studies, therefore category 3 was proposed based on the lower ATE value. Additional support is provided by the few less reliable studies with LD_{50} values within the range for category 3. RAC agrees with this weight of evidence assessment and supports the classification in category 3 for acute oral toxicity of di-n-butylamine with an ATE of 220 mg/kg bw.

During consultation, one MSCA proposed using the generic ATE of 100 mg/kg bw for classification of mixtures due to the overall low quality of the studies. RAC notes that the range of all LD_{50} values (220-550 mg/kg bw) is at least a factor of 2 to 5 above the generic ATE and supports using the lowest LD_{50} of 220 mg/kg bw established in female rats.

Dermal

The single acute dermal toxicity study in NZ White rabbits is reported as similar to OECD TG 402 (Smyth *et al*., 1954), however the lack of information on purity of the test substance and applied doses limit its reliability. The study reports an 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). RAC agrees with DS proposal for classification of di-n-butylamine as **Acute Tox 3, H311.**

During consultation, one MSCA expressed preference for using the generic ATE of 300 mg/kg bw instead of the experimentally determined LD_{50} of 768 mg/kg bw. Considering the limitations of the study and the lack of any additional supporting data, RAC agrees on using the generic ATE of 300 mg/kg bw as a more conservative choice reflecting the uncertain database.

Inhalation

One OECD TG 403 study on rats conforming to GLP and one additional study in rats of limited reliability were available to DS for this endpoint.

In the guideline study (Anonymous 1987), Sprague-Dawley rats (5/sex/dose) were exposed for 4 hours to vapour of di-n-butylamine at concentrations of up to 3.91 mg/L. Recorded mortalities in each dose group are summarized below.

Dose level (mg/L)	**0**	**0.76**	**1.08**	**1.18**	**1.39**	**3.91**
Mortality						
males	0/5	2/5	0/5	3/5	5/5	5/5
females	0/5	0/5	2/5	1/5	5/5	5/5

The study determined an LC_{50} of 1.15 mg/L. Signs of sensory irritation such as partial closing of the eyes, reduced respiratory rate, abnormal respiratory movements and abnormal body posture were reported during exposure. Frequently gasping, excessive salivation, lacrimation and convulsion were observed to a lesser degree. After exposure, rats showed abnormal breathing, lethargy, ataxia, prone posture and intermittent convulsions. Abnormal breathing, rales and sneezing were evident during the first two days post exposure with normal appearance on day 3.

One less reliable study and a secondary source provided a range of LC_{50} values for rats between >1.34 mg/L and <2.68 mg/L. No mortalities were reported after 3 days nose-only exposure of 10 Wistar rats (5M/5F, 6h/day) to 0.450 mg/L (vapour) di-n-butylamine (Buschman *et al*., 2003; details in STOT SE section).

Based on the outcome of the most reliable study, the DS proposed classification as **Acute Tox. 2, H330 with an ATE value of 1.15 mg/L**. RAC agrees to the proposal and concludes that a rounded ATE of 1.2 mg/L is warranted.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier Submitter's proposal

For the evaluation of skin irritation/corrosion endpoint one OECD TG 404 study in rabbits, one Draize test, and one further skin irritation test in rabbits are available.

Necrosis, as well as severe erythema and oedema were observed in all of these studies. In the guideline study (Anonymous, 1978), exposure of rabbits to 0.5 ml undiluted di-n-butylamine for 3 min resulted in necrosis 24h after treatment. Further, necrosis, severe erythema and moderate oedema were also observed in a Draize test (Virginia Chemicals, 1973), and in a skin irritation study with an exposure duration of 24h (Pennwalt Corp, 1986). Based on these findings, and in accordance with the CLP criteria the DS proposed classification as Skin Corr. 1B, H314.

Method	Species	Exposure/ Dose levels	Main Findings	Reference
OECD TG 404 Non GLP	Rabbit, Vienna White N=2	0.5 ml for 3 min or 1 h Occlusive application on 2x2cm	Erythema score 4 (mean 24, 48, 72h), not reversible after either 3 min or 1 h exposure Oedema score 2 (mean 24, 48, 72h), not reversible after either 3 min or 1 h exposure Necrosis after 24h	Anonymous (1978)
Draize-method	Rabbit, New Zealand White N=6	0.5 ml for 4 h Clipped intact skin of one-inch square	Erythema score 4 (mean 24, 48h), not reversible Oedema score 1.58 (mean 24, 48h), max. score 3 Necrosis at all time points	Virginia chemicals, 1973
Skin irritation test	Albino rabbit N=3	0.5 ml for 24 h Clipped, intact and abraded skin	15 min: skin turned brown 24 h: large necrotic lesions 48 h: dry, hard lesions, cracking, raw rat tissue	Pennwalt Corp (1986)

Comments received during consultation

One MSCA supported the proposed classifications.

Assessment and comparison with the classification criteria

In a skin irritation/corrosion study according to OECD TG 404, two Vienna White rabbits (one male, one female) were dermally exposed (occlusive, on 2x2 cm clipped skin) to 0.5 ml of undiluted di-n-butylamine (>99.5%) for 3 min or 1 h (Anonymous, 1978). The test substance was removed after the end of exposure, and the observation period was 8 days. Grading scores and necrosis were recorded after 24, 48, and 72h of exposure. Severe erythema (individual and mean scores of 4) and slight to moderate oedema (individual and mean scores of 2) were reported uniformly in all animals at all time points (Table 14 in CLH report). Necrosis was first reported 24h after exposure, and leathery necrosis was observed at the end of the observation period of 8 days.

In a Draize test (no specific guideline mentioned), 6 NZ White rabbits were exposed to 0.5 ml of undiluted di-n-butylamine on clipped, intact skin for 4h (Virginia chemicals, 1973). Individual erythema/oedema scores and necrosis were recorded after 4, 24 and 48h of exposure (Table below).

Animal No.	Erythema score			Oedema 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

Necrosis and severe erythema were reported in all animals at all observation time points, as well as moderate oedema (mean score of 1.58, with a maximum of 3).

Large necrotic skin lesions were described in three Albino rabbits after exposure to 0.5 ml di-n-butylamine on intact and abraded skin site (clipped, occlusive) for 24 hours (Pennwalt Corp, 1986). The test item application caused pain, and the skin turned brown within 15 minutes of application. These lesions became dry, hard and concave within 48h. Subsequently, they cracked and peeled exposing the raw tissue.

The DS mentioned several secondary sources reporting corrosive effects, severe erythema, oedema and necrosis persisting through 72 h after exposure, however there were no specific details available.

Comparison with the criteria

According to CLP Annex I: 3.2.2.1.1.1., a "*substance is corrosive to skin when it produces destruction of skin tissue, namely, visible necrosis through the epidermis and into the dermis in at least one tested animal after exposure for up to 4 hours"*.

In the guideline skin irritation/corrosion study, exposure of two rabbits to 0.5 ml undiluted di-n-butylamine for 3 minutes resulted in skin necrosis in both animals 24h after the start of exposure. Based on the CLP criteria for sub-category 1B "*Corrosive responses in at least one animal following exposure >3 min and ⩽1 h and observations ⩽ 14 days*", RAC supports the DS proposal for classification as **Skin Corr. 1B, H314**.

RAC evaluation of serious eye damage/eye irritation

Summary of the Dossier Submitter's proposal

Two rabbit studies were available to DS for evaluation of this endpoint. In the first study (Anonymous, 1985), severe effects on the eyes such as conjunctivae chemosis and necrosis, corneal ulceration, and corneal opacity were observed. Mean scores of 4 for corneal opacity and about 1 for iritis were reported in at least 2 out of 4 animals at 24h reading. No information on scoring at 48h and 72h was available. In the second study (Pennwalt Corp, 1986), a mean score of 3 for conjunctival redness was reported following exposure of both eyes of Albino rabbits to 0.1 ml of the test substance.

The DS noted that due to limited reporting of the study by Anonymous (1985), no conclusion could be drawn based on the single scoring at 24 h. In the second test, a mean score of 3 for conjunctival redness from the 24, 48 and 72h readings points to a classification as Category 2 eye irritant. However, in accordance with the CLP criteria, the substance is classified as Skin Corr. 1B, and therefore serious damage to the eyes is indicated and supports classification as Eye Dam 1, H318.

Method	Species	Exposure/ Dose levels	Main Findings	Reference
OECD TG 405 Non-GLP	Rabbits, N=4	0.1 ml (not rinsed off) Observation period of 7 days	Mean scores at 24h reading: • Conjunctivae: 2.3 (max. 3) • Chemosis: 2.3 (max 3) • Cornea opacity: 4 (max. 4) All effects were not fully reversible within 7 days	Anonymous, 1985
	Albino rabbits, N=3	0.1 ml in both eyes Only one eye washed after 15 sec	Mean score conjunctivae redness for 24, 48 and 72 h reading: 3 Scoring for 7 days, with signs of recovery on day 6.	Pennwalt Corp (1986)

Comments received during consultation

Two MSCA supported the proposed classification.

Assessment and comparison with the classification criteria

In a key study reported as similar to OECD TG 405 (Anonymous, 1985), severe ocular effects were observed in the eyes of two out of four rabbits exposed to 0.1 ml di-n-butylamine. Severe conjunctival irritation (redness, chemosis, discharge, and necrosis), iridial changes or iritis and corneal opacity, stippling and ulceration and corneal bulging (indicative of increased intraocular pressure) were described 24h after exposure. Conjunctival irritation, iridial changes and corneal opacity, stippling and/or ulceration, corneal bulging and pannus (neovascularization of the corneal surface) were still present in two of the four animals by the end of the observation period of day 7. Conjunctival irritation and/or iridial changes and stippling were reversible after 7 days in the remaining two animals.

RAC notes that the CLP criteria require assessment of the mean scores for corneal, iridial and conjunctival effects following grading at 24, 48 and 72 hours after installation of the test material, and an observation period of 21 days post exposure. In this study, observations were reported only until day 7, and no information on gradings at 48h and 72h is available. Therefore, a direct comparison with the classification criteria is not possible.

In a second study (Pennwalt Corp, 1986), 0.1 ml of di-n-butylamine was installed in the conjunctival sac of both eyes of albino rabbits (n=3). After 15 seconds, one eye of each animal was washed out with water, while the other eye remained unwashed. The gradings were performed for 7 days, and reactions in the washed and unwashed eyes were identical. A mean score of 3 from the readings at 24, 48, and 72h for conjunctival redness was reported. Signs of recovery were evident on day 6 (Table 18 in the CLH report).

Comparison with the criteria

According to Annex I: 3.3.1.1. "*Serious eye damage means the production of tissue damage in the eye, or serious physical decay of vision, following application of a test substance to the anterior surface of the eye, which is not fully reversible within 21 days of application"*.

Both available studies allow only limited possibility for comparison with the CLP classification criteria. In the key study, observation period was 7 days with gradings reported only at 24h and day 7 post-exposure. In the second study (Pennwalt Corp, 1986), the mean score of 3 for conjunctival redness indicates a classification as Category 2 eye irritant, however reversibility within 21 days cannot be assed due to the shorter observation period. Thus, no firm conclusion can be drawn based on the reported data. Nevertheless, the classification of di-n-butylamine as

Skin Corr. 1B implicitly entails a classification as Eye Dam 1 as stated in Regulation (EC) No 1272/2008. In line with the argumentation of DS, RAC agrees to classify di-n-butylamine as **Eye Dam. 1**. The corresponding hazard statement (H318: Causes serious eye damage) is not indicated on the label to avoid redundancy.

RAC evaluation of specific target organ toxicity-single exposure

Summary of the Dossier Submitter's proposal

For evaluation of STOT SE, several acute toxicity studies are available. Reporting of the most studies is only limited, and no effects relevant for a classification as STOT SE 1 or 2 were identified by DS. However, signs of sensory irritation (reduced respiratory rate, abnormal respiratory movements) were reported in rats after short-term exposure to vapour of di-n-butylamine (Anonymous 1987). Specific doses at which these effects occurred were not indicated.

Acknowledging that classification for skin/eye corrosivity implicitly covers the potential of a substance to cause respiratory tract irritation, the DS proposed an additional classification as STOT SE 3; H335 to address effects at exposure concentrations below those causing frank respiratory tract corrosion.

Species	Dose levels (mg/L)	Reliability (DS)	Study	Remarks
Sprague-Dawley rat, 5/sex/dose	0, 0.76, 1.08, 1.18, 1.39, 3.91 4-h exposure	1	Anonymous 1987 OECD TG 403, GLP	Reported effects: • partial closing of the eyes • reduced respiratory rate, • abnormal respiratory movements • abnormal body posture • gasping, excessive salivation, lacrimation

Comments received during consultation

One MSCA and one manufacturer provided comments on this endpoint. The commenting MSCA disagreed with the proposed classification as STOT SE 3; H335 pointing out that the data is not sufficient to conclude on respiratory tract irritation, and a classification for corrosivity would implicitly cover these effects. The manufacturer disagreed with a classification of the pure substance arguing that respiratory tract irritation is already covered by corrosivity but proposed to classify mixtures as STOT SE 3; H335 including specific concentration limits of 1% ≤ C ≤ 5% to indicate the hazard at concentrations that are not corrosive.

Assessment and comparison with the classification criteria

RAC notes that the acute studies in animals did not reveal evidence of toxicity to any specific target organ that are not explicitly addressed under other hazard classes, which is a requirement for classification in categories 1 and 2. As regards classification with STOT SE 3 (narcotic effects), no narcotic effects were reported in any of the toxicity studies.

Classification STOT SE 3; H335 for respiratory tract irritation is primarily based on information from human studies, however no such data was identified for di-n-butylamine. While there are currently no validated animal tests dealing specifically with this endpoint, animal studies can be used as a part of a weight of evidence evaluation.

Signs of sensory irritation such as partial closing of the eyes, reduced respiratory rate, abnormal respiratory movements and abnormal posture are reported in an acute inhalation study with di-n-butylamine performed according to OECD TG 403 (Anonymous 1987). Gasping, excessive salivation, lacrimation and convulsions were observed less frequently. When removed from the test chamber, rats showed abnormal breathing, lethargy, ataxia, prone posture and intermittent convulsions. Abnormal breathing, rales and sneezing were evident until day 2 with normal appearance on day 3. These effects are consistent with sensory irritation and were fully reversible after cessation of exposure in surviving animals. Taking into account the corrosive nature of the substance, the described effects on the respiratory system seem to be associated with its irritating properties. However, the available acute toxicity data is not sufficient to conclude on respiratory tract irritation.

According to the CLP guidance (ECHA, 2017), "*a classification for corrosivity is considered to implicitly cover the potential to cause respiratory tract irritation and so the additional Category 3 is considered to be superfluous"*. RAC concludes that the classifications for acute inhalation toxicity and corrosivity adequately cover the toxicological profile of the substance for this endpoint. Consequently, **no classification for STOT SE is warranted**.

Additional labelling

According to Annex I: 3.1.2.3.3. of the CLP regulation, "*In addition to the application of the classification for acute inhalation toxicity, the substance or mixture must also be labelled as EUH071 where data are available which indicate that the mode of toxic action was corrosivity (see Note 1 to Table 3.1.3)"*.

There is no specific data on the mode of action of di-n-butylamine provided in the CLH dossier, and the DS did not propose any additional labelling. The substance is strongly alkaline with a dissociation constant (pKa) of 11, and the reported effects on rabbit skin (necrosis after exposure for 3 minutes to undiluted substance) and eye (severe conjunctival reactions such as redness, chemosis, discharge and necrosis) are consistent with its corrosive properties. A common MoA for amines with a high pKa is the release of a hydroxide ion after protonation causing local necrosis upon contact with tissues at physiologic pH. Thus, for the category of aliphatic secondary amines, the corrosive properties are expected to be a general feature in relation to acute toxicity and respiratory tract effects (OECD 2013).

Based on the above, RAC considers that there is relevant evidence indicating that the mechanism of toxicity is corrosivity and therefore proposes **additional labelling with the EUH071: Corrosive to the respiratory tract**.

Additional references

Y. Alarie, Sensory irritation by airborne chemicals. CRC Crit. Rev. Toxicol. 2, 299-363 (1973).

Buschmann, J, C Dasenbrock, R Fuhst, G Pohlmann, W Bartsch, O Creutzenberg, H Ernst, M Ketkar, B Schneider, H Ott. 2003. Effects of di-n-butylamine on the respiratory system of Wistar (WU) rats after subchronic inhalation. Inhal Toxicol 15:701-13.

Gagnaire, F, S Azim, P Simon, B Cossec, P Bonnet, and J De Ceaurriz. 1993. Sensory and pulmonary irritation of aliphatic amines in mice: A structure-activity relationship study. J Applied Toxicology 13: 129-135

Nielsen, GD, and M Yamagiwa. 1989. Structure-activity relationships of airway irritating aliphatic amines. Receptor activation mechanisms and predicted industrial exposure limits. Chem.-Biol. Interactions 71: 223-244.

Organisation for Economic Co-operation and Development (OECD). 2013. CoCAM4, 16-18 April 2013. US/ICCA. SIDS Initial Assessment Profile, Aliphatic Secondary Amines

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).