Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the 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

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Substance name: di-*n*-butylamine
EC number: 203-921-8
CAS number: 111-92-2
Dossier submitter: Austria

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
02.04.2020	Germany		MemberState	1
Comment received				
In Table 6 the column „Specific Conc. Limits, M-factors and ATE" the ATE for inhalation should be amended to read: "Inhalation: ATE = 1.15 mg/L (vapours)" in the subsequent RAC Oppinion, if agreed upon.				
Dossier Submitter's Response				
Thank your for this comment. "(vapours)" has to be assigned to specify the form of inhaled di-n-butylamine.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
23.03.2020	France		MemberState	2
Comment received				
Acute toxicity: For the acute toxicity by oral, dermal, and inhalation routes, FR agrees with the classification proposal of the DS. However, for the oral and dermal routes, considering the quality of the studies available, FR would be of the opinion to use the generic ATE for the classification of mixture, that is to say : - Acute oral toxicity : 100 mg/kg - Acute dermal toxicity : 300 mg/kg				

Dossier Submitter's Response
Thank you for your support. Concerning the ATE values the use of converted ATE values based on CLP regulation (Table 3.1.2) can be discussed in the light of the reliability of the studies. - Acute oral toxicity : The available studies for oral toxicity are of low reliability especially due to missing information on purity and they resulted in LD_{50} values for rats ranging from 220 to 550 mg/kg bw. Two additional references provide LD_{50} values of 230 mg/kg bw for guinea pigs and 290 mg/kg bw for mice supporting the range of toxicity and the proposed ATE value of 220 mg/kg bw. The converted ATE (100 mg/kg bw) value is about a factor of 2 lower. - Acute dermal toxicity : The available study is scored with a reliability of 2 by the reigstrants, however, as information on puritiy is missing it was scored with a lower reliability in this evaluation. However, the publication series on "range-finding toxicity data" from Smyth (1954) is used in many registrations as main reference for the evaluation of acute toxicity. The ATE value based on experimental data (768 mg/kg bw) is a factor of 2.5 higher than the converted ATE of 300 mg/kg. Based on the limited available data the converted ATE can be supported.
RAC's response
RAC agrees with the argumentation of the DS and supports an ATE of 220 mg/kg bw for acute oral toxicity. In line with MSCA proposal, a converted ATE of 300 mg/kg bw is preffered for the dermal route of exposure due to the very limited database.

Date	Country	Organisation	Type of Organisation	Comment number
02.04.2020	Germany		MemberState	3
Comment received				
The Austrian CA proposes to change the current Annex VI entry from Acute Tox. 4 (H302, 312, 332) to Acute Tox. 3 (H301, H311) and Acute Tox. 2 (H330). The proposal for Acute Tox. oral classification (Cat. 3, H301) is based on a WoE approach. Based on the lowest LD50 (Schmidt et al.1974) used for classification an ATE value of 220 mg/kg bw is indicated. We agree with Acute Tox. 3 (H301) classification as well as an oral ATE of 220 mg/kg bw. The proposal for Acute Tox. dermal classification (Cat.3, H311) is based on one available study similar to OECD TG 402. LD50 of 768 mg/kg bw is reported. We agree with Acute Tox. 3 (H311) classification as well as a dermal ATE of 768 mg/kg bw. The proposal for Acute Tox. inhalative classification (Cat.2, H330) is based on a guideline- and GLP-conform study, which results in a LC50 of 1.15 mg/L (4 h exposure). The German CA agrees with Acute Tox. 2 (H330) classification as well as an inhalative ATE of 1.15 mg/L.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted. Please refer to comment number 2 for setting the ATE via dermal application.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
23.03.2020	France		MemberState	4
Comment received				
FR agrees with the proposal of the DS for these endpoints.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
02.04.2020	Germany		MemberState	5
Comment received				
The Austrian CA proposes to add classification as Skin Corr. 1B (H314) to Annex VI. The proposal for Skin Corr. classification (Cat 1B, H314) is based on one study similar to OECD TG 404, which reports necrosis 24 h after start of exposure (3 min or 1h) in 2 of 2 animals tested. Furthermore, necrosis as well as severe erythema and moderate edema were observed in a Draize test after 4h exposure. Another skin irritation study with an exposure duration of 24h showed heavy necrosis after 24h. The German CA agrees with Skin Corr. 1B (H314) classification.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
23.03.2020	France		MemberState	6
Comment received				
FR agrees with the proposal of the DS for these endpoints.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
02.04.2020	Germany		MemberState	7
Comment received				

The Austrian CA proposes to add classification as Eye Dam. 1 (H318) to Annex VI. Two studies are available for the evaluation of Eye Dam. classification, whereby one study is similar to OECD TG 405. Severe effects in the eyes of rabbits such as conjunctivae chemosis and necrosis, cornea ulceration, cornea opacity were observed. However, due to limited reporting, no final conclusion can be drawn based on the documented scoring. The proposed classification of Di-n-butylamine as Skin Corr. 1B implicitly entails a classification as Eye Dam. according to Regulation (EC) No 1272/2008 "Skin corrosive substances shall be considered as leading to serious eye damage (Category 1)". In conclusion, the German CA agrees with Eye Dam. 1 (H318) classification.
Dossier Submitter's Response
Thank you for your support.
RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
02.04.2020	Germany		MemberState	8
Comment received				
The Austrian CA proposes to add classification as STOT SE 3 (H335) to Annex VI. The proposal for STOT SE 3 is based on one study in rats equivalent to OECD TG 403. This study determined a LC50 of 1.15 mg/L (4 h exposure) and observed transient effects (reduced respiratory rate, abnormal respiratory movement, gasping). During the observation period, previously exposed rats showed abnormal breathing, lethargy, ataxia, prone posture and intermittent convulsions till day 2 with normal appearance on day 3. Tissue changes were not investigated. No further animal tests are available to be used as part of weight of evidence evaluation and no human data is reported to apply the Criteria for respiratory tract irritation (3.8.2.2.1. of Regulation (EC) No 1272/2008,). On the basis of limited data available and taking into account the substance properties as Skin Corr. 1B and Acute Tox. inhalative Cat. 2, the described effects on the respiratory system seem to be associated with the aforementioned irritating properties. However, the available acute toxicity data is not sufficient to conclude on respiratory tract irritation. In addition, "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" according to the CLP guidance (ECHA, 2017). The proposed "classification as acutely toxic and corrosive is considered to cover and communicate the specific toxicological effect(s) adequately" (CLP Guidance, ECHA, 2017). In conclusion, the German CA does not agree with STOT SE 3 (H335) classification.				
Dossier Submitter's Response				
See response to comment number 9.				
RAC's response				
RAC notes that the acute toxicity data provided in the dossier is not sufficient to conclude on respiratory tract irritation. The trancient effects on the respiratory tract reported in the				

acute studies are already covered by the classification of the substance as corrosive. Clear signs of respiratory tract irritation were only seen after repeated exposure at doses close to those causing mortality. These effects are covered by the classification as acutely toxic via inhalation. Therefore, no additional classification for STOT SE 3 is needed.

Date	Country	Organisation	Type of Organisation	Comment number
03.04.2020	Germany	BASF SE	Company-Manufacturer	9
Comment received				
Please see the attached document ECHA note – An attachment was submitted with the comment above. Refer to public attachment 202003_Comments on CLH report_111-92-2.docx				
Dossier Submitter's Response				
Di-n-butylamine shows severe corrosive effects after short exposure time. The acute inhalation toxicity study reports mortality with an LC_{50} of 1.15 mg/L (maybe as a consequence of corrosivity) as well as reversible effects at lower concentrations. Letal effects are covered by the classification for acute inhalation toxicity and other effects are covered by classification for corrosivity. This classification can be considered adequate to cover the toxicological effects of the substance. The argument to understate the true hazard for this route of exposure by the assignment of STOT SE 3 can be followed. The proposal to include specific concentration limits for STOT SE 3 in addition to the generic concentration limits for classification of mixtures with corrosive ingredients can be supported based on the available data. STOT SE 3, H335: 1% ≤ C ≤ 5%				
RAC's response				
RAC agreed that the effects on the respiratory tract observed in the acute studies are already covered by the classification of the substance as corrosive and acutely toxic via inhalation. Clear signs of respiratory tract irritation were only seen after repeated exposure at doses close to those causing mortality. Therefore, no additional classification for STOT SE 3 is needed. There are no specific data provided in the dossier supporting a SCL of 1% ≤ C ≤ 5%. Thus, SCL was not proposed.				

Date	Country	Organisation	Type of Organisation	Comment number
23.03.2020	France		MemberState	10
Comment received				
FR agrees with the proposal of the DS for these endpoints.				
Dossier Submitter's Response				
Thank you for your support but also see response to comment No 9.				
RAC's response				
Noted.				

PUBLIC ATTACHMENTS
1. 202003_Comments on CLH report_111-92-2.docx [Please refer to comment No. 9]