Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

Dibutyltin maleate

EC Number: 201-077-5
CAS Number: 78-04-6

CLH-O-0000007032-86-01/F

Adopted

16 September 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: Dibutyltin maleate
EC number: 201-077-5
CAS number: 78-04-6
Dossier submitter: Austria

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
27.01.2021	Sweden	ChemSec	International NGO	1
Comment received				
We strongly support the proposed classification which should be implemented without delay. However in our opinion one major part is missing in this suggested classification. The inclusion of environmental relevant parts, including aquatic toxicity, persistence, bio-accumulation and endocrine disrupting properties. Such properties should not be set aside but complement this CLH proposal. Further we support the group approach to handle DBT-compounds. As mentioned in the report they all have the same toxic properties for both HH and ENV.				
Dossier Submitter's Response				
Thank you for your support. We agree that aquatic toxicity and other hazard properties should also be evaluated for this group of compounds. We adressed as a first step the human health hazards, since a substance fullfilling Repr. 1B criteria shall be subject to harmonised classification and labelling (Article 36, CLP Reg). Work on ENV hazards will be decided in a second step taking into account developments for similar substances.				
RAC's response				
Thank you for your support.				

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2021	France		MemberState	2
Comment received				
We agree with the proposed category approach. DBTM belongs to the dibutyltin compounds. As shown by Umweltbundesamt, 2019, under acid pH, the distannoxane ClBu2SnOSnBu2Cl is formed as observed with the other proposed compounds of the category (DBTC, DBTL, DBTO, DBTA). As DBTL and DBTO, there are information that the substance DBTM can be converted to DBTC.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your support.				

Date	Country	Organisation	Type of Organisation	Comment number
29.01.2021	Sweden		MemberState	3
Comment received				
We support the use of the category for read-across purposes and prediction of similar toxicological properties based on the common hydrolytic behavior of its members and the hypothesis that a common intermediate, a dibutyltin compound, is formed after hydrolysis at neutral or low pH and is responsible for the toxic effects observed after oral exposure. Moreover, a category approach including DBTO, DBTC, DBTM, DBTA, DBTP and DBTL has previously been accepted by RAC in the CLH proposal for DBTP, as well as DBTA.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your support.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2021	France		MemberState	4
Comment received				
We agree with the DS's proposal to classify DBTM as Muta. 2, H341 based on read-across approach.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your support.				

Date	Country	Organisation	Type of Organisation	Comment number
21.01.2021	Germany		MemberState	5
Comment received				
The proposed classification for mutagenicity is supported by taking into account the read-across data for the category.				

Dossier Submitter's Response
Thank you for your support.
RAC's response
Thank you for your support.

Date	Country	Organisation	Type of Organisation	Comment number
29.01.2021	Sweden		MemberState	6
Comment received				
The SE CA supports the proposed harmonised classification of DBTM as Muta. 2, H341 based on a category approach.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your support.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2021	France		MemberState	7
Comment received				
We agree with the DS's proposal to classify DBTM as Repr. 1B, H360FD based on read-across approach				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your support.				

Date	Country	Organisation	Type of Organisation	Comment number
21.01.2021	Germany		MemberState	8
Comment received				
The proposed classification for reproductive toxicity is supported by taking into account the read-across data for the category.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your support.				

Date	Country	Organisation	Type of Organisation	Comment number
29.01.2021	Sweden		MemberState	9
Comment received				
The SE CA supports the proposed harmonised classification of DBTM as Repr. 1B, H360FD based on a category approach.				
Dossier Submitter's Response				
Thank you for your support.				

RAC's response
Thank you for your support.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2021	France		MemberState	10

Comment received
* Acute oral toxicity (page 21) Based on the most reliable study in rat, we agree that a classification as Acute Tox. 4 H302 is warranted for DBTM. With regards to ATE, as females were less sensitive than males in the study Anonymous, 1982a, an ATE of 422 mg/kg may be more appropriate than the combined LD50 of 510 mg/kg. * Acute toxicity, inhalation route (page 23) Based on the results of the acute toxicity study in rats (Anonymous, 1982b), we agree that DBTM warrants to be classified as Acute Tox. 2 with the proposed ATE. * Acute toxicity, dermal (page 22) In the rat study conducted according to OECD TG 402, the acute dermal LD50 values were > 2000 mg/kg bw in both males and females. No classification is warranted for acute toxicity via the dermal route in rats. Nevertheless, in rabbits, although few details were available in the study, the higher sensitivity of rabbits compared to rats is of concern and may need to be considered for classification. Editorial: the references for the rabbit study differs in the table 13 and in the text in 10.2.1, could you please clarify?
Dossier Submitter's Response
Thank you for your support. The ATE value of 510 mg/kg bw for oral toxicity was chosen considering the wide range of confidence intervals and resulting limited evidence on different sensitivity of females and males. Due to the limited reporting of the acute dermal toxicity study in rabbits (no information on test material, no information on strain and age of animals) only limited reliability was assigned and the study was not used for classification purpose. Thank you for the editorial remark. The correct reference for the rabbit study is Anonymous, 1950.
RAC's response
Thank you for your support.

Date	Country	Organisation	Type of Organisation	Comment number
21.01.2021	Germany		MemberState	11
Comment received				
Acute Toxicity – inhalation To add the harmonised classification as Acute Tox. 2, H330 is supported. Acute Toxicity – dermal The proposed non-classification for Acute Tox., dermal is supported. Acute Toxicity – oral To add the harmonised classification as Acute Tox. 4, H302 is supported.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your support.				

Date	Country	Organisation	Type of Organisation	Comment number
29.01.2021	Sweden		MemberState	12
Comment received				
The SE CA supports the proposed harmonised classification of DBTM as Acute Tox. 4, H302, based on the most sensitive LD50 (510 mg/kg bw (m/f), 422 mg/kg bw (m) and 647 mg/kg bw (f) from an OECD TG 401 oral acute toxicity study, and Acute Tox. 2, H330 based on the LC50 (317 mg/m3 (m/f), 313 mg/m3 (m) and 319 mg/m3 (f)) from a non-guideline inhalation acute toxicity study. We note that the ATE values were based on mean male/female LD50/LC50 values and set at 510 mg/kg bw for Acute Tox. 4 and 0.317 mg/L for Acute Tox. 2. We consider that this could be appropriate considering that there seems to be no apparent difference in sensitivity between males and females for either oral acute toxicity or inhalation acute toxicity and the rather large ranges of confidence intervals for the LD50/LC50 values.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your support.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
21.01.2021	Germany		MemberState	13
Comment received				
To add the harmonised classification as Skin Corr. 1, H314 is supported.				
Dossier Submitter's Response				
Thank you for your support.				

RAC's response
Thank you for your support.

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2021	France		MemberState	14
Comment received				
Based on the irreversible effects seen in rats and rabbits, a classification of DBTM as Skin Corr. 1 is warranted as proposed. As the effects occurred following 4h exposure, sub-category 1C could be considered.				
Dossier Submitter's Response				
Thank you for your support. Subcategory 1C based on irreversibility documented in the dermal irritation study in rabbits after 4h of exposure (Anonymous, 1988b) can be followed.				
RAC's response				
Thank you for your support. As no time points shorter than 4 h were included in the studies, it cannot be excluded that shorter exposure might also induce skin corrosion. For this reason, RAC prefers to not assign a subcategory.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
21.01.2021	Germany		MemberState	15
Comment received				
To add the harmonised classification as Eye Dam. 1, H318 is supported.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your support.				

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2021	France		MemberState	16
Comment received				
Based on the rabbit study, we agree that a classification as Eye. Dam. 1 is warranted for DBTM.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your support.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
21.01.2021	Germany		MemberState	17

Comment received

Specific target organ toxicity – single exposure
Although the presented data from two mechanistic animal studies are not well documented, they give a hint on at least significant toxicological effects on the thymus after a single exposure to DBTC. According to the category approach, the data can be used for a read across approach concerning systemic effects, including Specific Target Organ Toxicity (SE and RE). The reported effective dose range after single exposure is similar to the toxicological effective ranges of toxicological effects on the thymus in repeated dose studies. Although the effects were shown to be reversible in the study performed by Snoeij et al., 1989, reversibility of effects is not a criterion for not assigning hazard categories according to the CLP Guidance. In this assessment, DBMT is proposed with the classification STOT RE1 H372 (causes damage to the immune system). The argumentation that a classification according to STOT SE is not necessary, with reference to the classification STOT RE 1, is not valid.

Therefore, classification as STOT SE 1, H370 is proposed.

Dossier Submitter's Response

The study, that would justify a STOT SE 1 classification (Snoeij et al., 1989) has some drawbacks: (1) only 3 animals were included per group, (2) only one dose of 15 mg/kg bw/day was applied (single application via gastric intubation).

After single application body weight, thymus weight and number of cells isolated from the thymus as well as incorporation of DNA, RNA and protein precursors into isolated thymocytes, were measured 1, 2, 3, 4, 7 and 9 day(s) after dosing. The authors report that absolute and relative thymus weight is reduced from the second day of dosing, however no numeric results are provided for thymus and body weight reduction. It is reported, that thymus weight reduction was maximal at day 4 and reverted to normal values at day 9. With regard to cell counts of the thymus, numerical details are provided in the publication. Total cell count and the percentage of small (volume < 130 μm^3), intermediate (volume between 130 and 225 μm^3) and large cells (volume > 225 μm^3) were determined. The cell numbers isolated from this gland diminished significantly at day 3, 4 and 7 after administration of 15 mg/kg bw/day exposure. Total cell count was most markedly reduced at day 4 (by -70%), while at day 9 values were at control level again. The large cells were significantly decreased at day 1 and 2, which is associated by a decrease on incorporation of DNA, RNA and protein precursors. The authors conclude based on these findings, that DBTC induced thymus atrophy is initiated by a reduction of rapidly proliferating thymic lymphoblasts.

The second listed study for this endpoint is a mechanistic study with mice (n=36) engrafted with human foetal thymus and liver tissue fragments, which is an unusual procedure for regulatory studies (de Heer, 1995). Mice were exposed to single doses of 0, 0.03 and 1 mg DBTC /kg bw via the intraperitoneal route and sacrificed five days later. The human thymus transplants were removed and assessed morphometrically and histopathologically. Treatment resulted in reduced cortical size of the human thymus graft and reduction in the relative size of the thymus cortex.

The studies of Snoeij et al. (1989) and de Heer et al. (1995) have been also considered in previous harmonised classification discussions (e.g. of Dibutylbis(pentane-2,4-dionato-O,O')tin, CAS: 22673-19-4), which do not have resulted in STOT SE classification, but have been considered for mechanistic considerations. We are of the opinion that the thymus toxicity in repeated dose toxicity is investigated more comprehensive. In the study of Snoeij (1989) only one and rather high concentration was applied via gastric intubation. The applied dose (15 mg/kg bw) is much higher compared to LOAEL (0.8-1.25 mg/kg bw- extrapolated to 90 day exposure, see CLH report Table 62) in repeated dose studies. The design of the studies has limitations to determine the hazard to human health after single exposure. Thus, we consider STOT RE 1 as the appropriate hazard class for the observed thymus toxicity effects.
RAC's response
RAC agrees with the dossier submitter that the strength of evidence from these two studies is insufficient for classification as STOT SE 1. In addition, the mouse study was performed by intraperitoneal injection, which is generally considered to be of limited relevance.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2021	France		MemberState	18
Comment received				
We agree with the DS's proposal to classify DBTM as STOT RE 1 (immune system) based on read-across approach.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your support.				

Date	Country	Organisation	Type of Organisation	Comment number
21.01.2021	Germany		MemberState	19
Comment received				
To add the harmonised classification as STOT RE 1, H372: causes damage to the immune system is supported.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your support.				

Date	Country	Organisation	Type of Organisation	Comment number
29.01.2021	Sweden		MemberState	20
Comment received				
The SE CA supports the proposed harmonised classification of DBTM as STOT RE 1, H372 (immune system) based on a category approach.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your support.				