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 bis(2-ethylhexanoate)

EC Number: 220-481-2
CAS Number: 2781-10-4

CLH-O-0000006845-64-01/F

Adopted

17 September 2020

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON DIBUTYLTIN BIS(2-ETHYLHEXANOATE)

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.

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Substance name: dibutyltin bis(2-ethylhexanoate)
EC number: 220-481-2
CAS number: 2781-10-4
Dossier submitter: Norway

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Germany	<confidential>	Company-Manufacturer	1
Comment received				
The Norwegian Competent Authority drafted a Proposal for Harmonized Classification and Labelling for Dibutyltin bis(2ethylhexanoate) (DBTE). The dossier is very well structured and the display of key information in form of tables supports a transparent scientific discussion. The proposal is to harmonize the Dossier submitters self proposal of a classification as: Muta 2 Repr 1B STOT RE 1 For it's proposal Noway prepared a category aproach Members of the category are: Dibutyltin bis(2-ethylhexanoate) (DBTE) Dibutyltin diacetate (DBTAc) Dibutyltin dichloride (DBTC) Dibutyltinoxide (DBTO) Dibutyltin Dilaurate (DBTL) Dibutyltin-bis(pentane 2,4-dionato-O,O')tin, Dibutyltin acetylacetonate, (DBTP) Dibutyltin maleinate (DBTM) We strongly disagree that the category as it is currently defined allows the hazard assessment of DBTE Dibutyltin dichloride should not be a member in this category and not be used as a source for reading across to the toxicological endpoints on concern.				

Chemistry / In-vitro metabolism
In a recent in-vitro metabolism study it was shown that DBTE exposed to an excess of HCl at pH 1.2 /37 °C/ 4 h did not form any DBTC. It formed a complex reaction mixture which consists of high molecular tin-carboxylate clusters. This low pH in vito metabolism is comparable to results found with Dioctyl bis(2ethylhexanoate), Dibutytin laurate and Dioctyltin Laurate. The tin carbonyl clusters are characterized by broad signal in the 119Sn-spectra.
This tin clusters are based on the structures of dimeric distannoxanes, which include additional tin-cabonyl moieties

Category approach
The dossier submitter believes that a category approach and reading across of certain dibutlytin compounds is possible and meaningful.
The category should be more substantiated by studies on the individual substances. The studies intended to simulate the gastric metabolism used in parts assumptions and analytical methods which did not allow the identification of the structure of the metabolites.
The more recent in-vitro metabolism studies done on different organotin compounds showed that the hydrolytical behavior at low pH may differ significantly which results in a variations of toxicokinects and toxicodynamics.
During the so called COLLA (Collaborative approach) project there have been constructive discussions between Industry, Member States CA and ECHA about formation of groups of substances and categories.
The dossier submitter would like to propose a similar approach for defining categories of substances based on scientific facts shared between Industry and other stakeholders.

Summary
Based on the results of a recent in-vitro metabolism study on DBTE the formation of DBTC under simulated mammalian gastric conditions can be excluded.
The main products of the gastric hydrolysis are complex tin-carboxylate clusters with a molecular weight > 1100 Da. They cannot pass the gastric mucosa and thus will not be bioavailable.
Reading across from DBTC to DBTE is not appropriate.
Also a category with DBTAc should not be formed based on low pH hydrolysis.
The hydrolytical behavior is comparable to that of DBTL. So a category with DBTL might be meaningful.
Meaningful only for toxicological data gained on the substance itself, not by reading across from DBTC.
The dossier submitter will address this fact in a dossier update removing all inappropriate read across data.

Dossier Submitter's Response

Thank you for your comments.

We are not aware of any in vitro studies on the metabolisme of DBTE, recent or otherwise. It would be useful to have a reference for this study. We cannot see that this study has been included in your registration either.

However, we are aware of two new studies on DBTA and DBTM (Hansen, 2019[1]; Ghobrial et al, 2019[2]). Both of these studies shed new light on how these substances behave in low pH. We do not agree however that the studies are a hinder for our category approach or for our classification proposal.

The fact that DBTC cannot be detected in the hydrolysis study (Hansen 2019) does not mean that the DBTC studies are irrelevant to our proposal.

The studies seem to show that a dimeric structure of distannoxanes is produced, and this seems to be the case for other category members as well. This means that although DBTC may not be the common metabolite as previously thought, there are other commen metabolites that are created, and that seem to have the same toxic properties.

We note that you write in your comments that DBTE has similar hydrolytical behaviour as DBTL. In that case the read-across is still valid since DBTL has a harmonised classification which is the same as we are proposing for DBTE. In addition you write in your registration (Echa dissemination site, summary and conclusion under basic toxicokinetics, key study 001) that "DBTL was hydrolysed to DBTC by 87.8% after 2 hours. The half-life was <0.5 hours." In other words, if you propose that DBTE has the same hydrolytic behaviour as DBTL, and you also have written in your registration that DBTL hydrolyses to DBTC, then the read-across to DBTC is valid.

Our assessment is that DBTE has the same hydrolytical behaviour as DBTL and DBTC, in other words that the same type of metabolites are formed in low pH and that these metabolites have the same toxicological properties.

We agree that "the category should be more substantiated by studies on the individual substances", but since there is not one single study performed with DBTE neither in your registration nor found elsewhere we have to use read-across. In this case, we find read-across to be meaningful and correct based on common hydrolytical behaviour.

We note that contrary to the information given in your comments above you use read-across to DBTC and other organotin-compounds extensively in your registration including proposing classification for reproductive toxicity, repeat dose toxicity and mutagenicity in the endpoint summaries on Echas dissemination site:
- "Based on animal data according to Directive 67/548/EEC the substance is assigned to Reproductive category 2 and is labelled with R60 – may impair fertility and R61 – may cause harm to the unborn child. Under GHS the substance is assigned to category 1B (Signal word: Danger; Hazard statement: H360 May damage fertility or the unborn child (Characteristic syndrome of oropharyngeal malformations)."
- "The substance is classified with R48/R25 according to Directive 67/548/EEC. According to Regulation (EC) no 1272/2008 the test substance would be classified as a STOT Rep. Exp. 1 with Hazard statement: H372: Causes damage to thymus through prolonged or repeated exposure and should be accompanied with the signal word 'Danger'."
- "According to directive 67/548/EEC the substance is assigned the classification Mutagenicity category 3 and labelled with R68 – possible risk of irreversible effects. According to Regulation (EC) no 1272/2008 the test substance would be classified as

[1] Hansen S (2019). Di-n-butyltin diacetate (DBTAc). Cas number: 1067-33-0. In-vitro metabolism study. TIB Chemicals AG, Mannheim Germany.
[2] Ghobrial M, Stocker E, Hölzl C, Mihovilovic M, Stanetty C (2019). Conversion of organotin compounds in the gastric environment. NMR based investigation of the hydrolysis of DOTE and DBTM. Report-0709. Umweltbundesamt, Vienna, Austria.

Muta. 2 with the Hazard statement: H341: Suspected of causing genetic defects and should be accompanied with the signal word 'Warning'."
RAC's response
Thank you for your comment. RAC agrees with the explanation provided by the dossier submitter and considers the proposed read-across approach valid.

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Germany		MemberState	2
Comment received				
- In section 1.1. the IUPAC name is stated as "Dibutylstannanebis(ylium) bis(2-ethylhexanoate)". We question if this is the correct IUPAC name. The suffix "ylium" usually is used in complex nomenclature for cations produced by formal loss of a hydride ion from a parent hydride. - The present CLH proposal for dibutyltin bis(2-ethylhexanoate) (DBTE) is based on a category approach assuming common hydrolylitc behaviour (generation of dibutyltin dichloride or derivatives thereof) and comparable toxicity of the category members. The fact that the other hydrolysis product of DBTE, 2-ethylhexanoic acid, is classified as Repr. 2 only, is not relevant in this context. The category approach is plausible and has been accepted by RAC for classification of several dibutyltin compounds. Therefore, the proposed classification of DBTE as Muta 2 (H341), Repr.1B (H360FD), and STOT RE1 (immune system) is supported.				
Dossier Submitter's Response				
Thank you for your support. We see that the registrants' proposal for IUPAC name Dibutylstannanebis(ylium) bis(2-ethylhexanoate) is not correct. We propose to change it to bis(2-ethylhexanoate)dibutyltin.				
RAC's response				
Thank you, RAC agrees with the DS's response.				

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	France		MemberState	3
Comment received				
The database of butyltin compounds have been evaluated at several occasions by RAC (DBTC, DBTL, DBTP) and the resulting classifications Muta 2, Repr 1B (FD) and STOT RE 1 are supported. The present dossier describes in details why the category approach on dibutyltin compounds with labile ligands is justified. There is no toxicokinetic data on DBTE. However, the structure fits very well within the category. The ligands of DBTE are similar in nature (saturated hydrocarbon structure) and intermediate in chain length between DBTA and DBTL. Both DBTA and DBTL have been shown to hydrolyse in dibutyltin moieties and the read-across for the category as a whole is considered fully applicable to DBTE. For STOT RE 1, the LOAEL based on thymus effects is low for DBTC and it remains clearly below guidance values for classification in category 1 after adjustment for the molecular weight of DBTE compared to DBTC.				

The proposed classifications for mutagenicity, reproductive toxicity (fertility and development) and repeated toxicity on the immune system are therefore supported.
Dossier Submitter's Response
Thank you for your support.
RAC's response
Thank you, RAC agrees with the DS's response.

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Sweden		MemberState	4
Comment received				
Comments on the category approach: In general we support this category for read-across purposes 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 DBTDL has previously been accepted by RAC in the CLH proposal for DBTP. Although we find the reasoning logical to include DBTE based on the common functional dibutyltin (Bu2Sn) group and presumed common hydrolytical behavior we note that DBTE does not have any substance specific data available (no hydrolysis data, no toxicological data) to support the inclusion in the category and prediction of similar toxicological properties. In addition, we think that a more thorough discussion on the additional hydrolysis product (besides DBTC or derivatives thereof) 2-EHA and its contribution to the toxicological profile of DBTE is warranted since currently it is not possible to fully predict the properties in question for DBTE by the available data of the dibutyltin category members. We have one minor general comment for clarity: It is unclear to us why dibutylti bis(EHMA) (CAS nr 10584-98-2) is included in table 5. Similarly, we wonder why dibutyltinbis(EHMA) is included in table 9. Dibutyltinbis(EHMA) does not fit within the applicability domain of the read-across hypothesis and further there is no toxicity data of dibutyltinbis(EHMA) being used to support classification of DBTE in this report.				
Dossier Submitter's Response				
Thank you for your comments. Yes there is very little data on DBTE, however based on common structure and chemistry it is likely that the substance will behave in the same way as the other category members, hydrolysing in low pH and create common metabolites with the toxic properties seen in the other category members. The additional hydrolysis product, 2-EHA, which DBTE does not have in common with the other category members, is not elaborately described in our dossier, apart from the reproductive toxicity. We see that we could have included more information on this hydrolysis product. 2-EHA has been evaluated under the substance evaluation process by Spain. Spain wanted to clarify suspected risks about CMR (reproductive toxicity – fertility), wide dispersive use, consumer use, high tonnage and high RCR. After an ECHA decision the registrant submitted two new studies (EOGRTS and 90-day repeat dose study) and the evaluating MSCA concluded that the concerns had been clarified and neither further				

information nor additional classification was required following this substance evaluation. The substance evaluation report (2017)[3] states however that all human health hazard endpoints were reviewed. The evaluation report has extensively reported all studies submitted by the registrant and the evaluating MSCA has also searched for other literature available. The evalution of the substance did not reveal any other concerns on human health endpoints.

Based on the findings in the new studies submitted by the registrant, Spain submitted a classification proposal only for reproductive toxicity.

We have included below information on the substance's mutagenic and repeat dose toxicity.

Concerning dibutyltin bis(EHMA): We agree that it was unnecessary to include information on dibutyltin bis(EHMA) as it turns out to be rather irrelevant to the dossier. It was included as the studies were included in the registration of DBTE.

RAC's response

Thank you for your comment. RAC agrees with the dossier submitter that the formation of 2-EHA in this case does not alter the proposed classification, but thanks the Swedish national authorities for raising this point.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Sweden		MemberState	5

Comment received

Based on the available information in the current CLH-proposal we find it difficult to support classification for germ cell mutagenicity only based on read-across data from the dibutyltin category. 2-EHA is a hydrolysis product of DBTE of toxicological significance, and not of low toxicological significance (as is the case for the other member substances in the category), but toxicity data for 2-EHA are not included and discussed in the current proposal for mutagenicity. We think that this is necessary to be able to conclude if 2-EHA contributes (or not) to additional toxicity and the resulting classification.

Dossier Submitter's Response

Thank you for your comment.

We see that we could have included more information on the hydrolysis product 2-EHA in our dossier.

<u>In the substance evaluation report Spain concludes as follows on mutagenicity:</u>
"The mutagenicity of 2-EHA has been investigated in several experimental test systems reported in the IUCLID and in the literature. The results obtained in bacteria assays indicated that 2-EHA is not mutagenic in any of the tested strains, with or without metabolic activation system (S9 mix). Clastogenicity was negative in a chromosome aberration test using rat lymphocytes, with and without metabolic activation. Negative results were also obtained in two gene mutation tests (mouse lymphoma assay and hprt test) in the presence and absence of metabolic activation system. Some papers reviewed included positive data for several in vitro studies. However, this activity is not expressed in vivo in somatic cells. 2-EHA was not clastogenic in a mouse micronucleus assay. No

[3] Substance evaluation report, 2017: https://echa.europa.eu/documents/10162/2e474208-618e-b9c9-67f5-0784779998d7

studies in germ cells were reported. Overall, based on the collective evidence on genotoxicity, especially in the negative in vivo results, the eMSCA considers that 2-EHA has not mutagenic activity." We therefore find that 2-EHA is not of toxicological significance when it comes to the endpoint mutagenicity and that the proposal for classification as Muta 2 is valid.
RAC's response
Thank you for your comment. RAC agrees with the dossier submitter that the formation of 2-EHA in this case does not alter the proposed classification, but thanks the Swedish national authorities for raising this point.

Date	Country	Organisation	Type of Organisation	Comment number
21.11.2019	Austria		MemberState	6
Comment received				
AT CA supports the classification proposal for Muta. 2, although there is very limited information for DBTE itself. There are convincing arguments that the compound meets the criteria to be part of the category approach – the compound has also labile ligands - and thus read across to category members is supported.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your comment.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Sweden		MemberState	7
Comment received				
The SE CA supports the proposed harmonised classification of DBTE as Repr. 1B, H360FD based on a category approach. As reproductive toxicity has been assessed (no other hazard classes were addressed) recently by Spain for 2-EHA, one of the hydrolysis product of DBTE, concluding on Repr. 2 H361d we can support the proposal of Repr. 1B H360FD based on read-across from (mainly) DBTC since we can assume that available data on 2-EHA would not contribute to classification in category 1A for this hazard class.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
21.11.2019	Austria		MemberState	8
Comment received				
AT CA supports the classification proposal for Repr. 1B, DF. 2-Ethylhexanoic acid, a hydrolysis product of DBTE, is itself classified for Repr. 2. Thus, DBTE is somehow different to other category members. It is, however, very plausible that under gastric				

conditions DBTC (or derivates thereof) is formed, likewise seen with other category members.
Dossier Submitter's Response
Thank you for your support.
RAC's response
Thank you for your comment.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Sweden		MemberState	9
Comment received				
Based on the available information in the current CLH-proposal we find it difficult to support classification for specific organ toxicity only based on read-across data from the dibutyltin category. 2-EHA is a hydrolysis product of DBTE of toxicological significance, and not of low toxicological significance (as is the case for the other member substances in the category), but toxicity data for 2-EHA are not included and discussed in the current proposal for this hazard class. We think that this is necessary to be able to conclude if 2-EHA contributes (or not) to additional toxicity and the resulting classification.				
Dossier Submitter's Response				
Thank you for your comment. We see that we could have included more information on the hydrolysis product 2-EHA in our dossier. <u>In the substance evaluation report Spain concludes as follows on repeat dose toxicity:</u> "Information on the effects of repeated exposure to 2-EHA has been obtained from subacute and subchronic repeated oral exposure studies in rats and mice. Observed clinical signs of toxicity were highly similar in both species and throughout all the studies. In two subchronic (90 days) toxicity studies, NOAELs of 300 and 200 mg/kg bw/d were established for rats and mice, respectively. The main observed effects were associated with growth retardation, decreases in body weight, increases in absolute and relative liver weights and hepatocyte hypertrophy. A NOAEL for general toxicity of 4615 ppm (corresponding to at least 248 mg/kg bw/d for males and 308 mg/kg bw/d for females) was established in a recent OECD 422 study, based on the effects on body weights, food consumption, organ weights, haematology, clinical chemistry and zinc and metallothionein concentrations observed at the highest dose. No concern regarding repeated exposure to 2-EHA is identified by the eMSCA." We therefore find that 2-EHA is not of toxicological significance when it comes to the endpoint repeat dose toxicity and that the proposal for classification as STOT RE 1 is valid.				
RAC's response				
Thank you for your comment. RAC agrees with the dossier submitter that the formation of 2-EHA in this case does not alter the proposed classification, but thanks the Swedish national authorities for raising this point.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON DIBUTYLTIN BIS(2-ETHYLHEXANOATE)

Date	Country	Organisation	Type of Organisation	Comment number
21.11.2019	Austria		MemberState	10
Comment received				
AT CA supports the classification for STOT RE1 (immune system). No studies are carried out with DBTE itself – the category approach has been applied. Although there is less information on hydrolytic behaviour of DBTE than for other category members, it seems very likely that DBTE reacts in a similar manner under gastric conditions, therefore the category approach is supported.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your comment.				