COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

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

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.

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.				

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.				

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.

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.				

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.				

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.				

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.

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.				