Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Dibutylbis(pentane-2,4-dionato-O,O')tin

EC Number: 245-152-0
CAS Number: 22673-19-4

CLH-O-0000001412-86-184/F

Adopted
5 December 2017

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON DIBUTYLBIS(PENTANE-2,4-DIONATO-O,O')TIN

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public 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 public 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 public 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: dibutylbis(pentane-2,4-dionato-O,O')tin
EC number: 245-152-0
CAS number: 22673-19-4
Dossier submitter: Sweden

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
09.02.2017	Germany		MemberState	1
Comment received				
We support the CLH proposal from Sweden for dibutylbis(pentane-2,4-dionato-O,O')tin as Repr. 1B, H360FD and STOT RE1 with thymus as target organ.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted				

Date	Country	Organisation	Type of Organisation	Comment number
06.02.2017	Norway		MemberState	2
Comment received				
CLH report for dibutylbis(pentane-2,4-dionato-O,O')tin - Comments from Norway Norway would like to thank Sweden for the proposal for harmonised classification and labeling of dibutylbis(pentane-2,4-dionato-O,O')tin, CAS no. 22673-19-4. We support the classification of dibutylbis(pentane-2,4-dionato-O,O')tin with Repr 1B; H360FD and STOT RE 1; H372 based on a read-across approach from DBTC and other dibutyltin substances, justified on the basis of hydrolytic and toxicokinetic behaviour and toxicological data. A similar approach was used in the CLH report for DBTL which was accepted by RAC in 2014.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				

Noted

Date	Country	Organisation	Type of Organisation	Comment number
09.02.2017	Germany	TIB Chemicals AG	Company-Manufacturer	3

Comment received

sorry, in first submission the wrong attachemet (CLHP_22673-19-4_20170209) was attached instead of CLHP_22673-19-4_20170209(1)

ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLHP_22673-19-4_20170209 (1).pdf

Dossier Submitter's Response

We thank TIB Chemicals AG for their comments on the read-across approach.

On the basis of the in vitro hydrolysis studies the reaction rates, leading to the bridged distannoxane, for both dibutylbis(pentane-2,4-dionato-O,O')tin and DBTC seem to be fast. Dibutylbis(pentane-2,4-dionato-O,O')tin is reported to form the bridged stannoxane in close to 100% yield in two hours. No further data points are given. The DBTC is reported to form the same bridged stannoxane in 85% after 1h and 90% after 4 hours. On the basis of this data, one can only conclude that both reactions are relatively rapid.

We agree that, under specific experimental conditions involving isolation of the formed "metabolite", the observed species (by 119Sn-NMR) may differ and depend on experimental conditions and auxiliary ligands. This is also stated in the dossier for the dialkyltin compounds based on the thioglycolate ligands (section 9.2.1). For both DBTC and dibutylbis(pentane-2,4-dionato-O,O')tin, however, the same hydrolysis product is formed which support the read-across approach. For the other dibutyltin compounds in the category, the dossier submitter did not have access to the gastric hydrolysis studies referred to in the comment.

Importantly, in a comparative rat developmental study of all category members the findings demonstrate similar characteristic external and skeletal foetal malformations largely affecting the jaw/skull.

Taken together, all available data in a weight-of-evidence approach support the read-across strategy for the classification of dibutylbis(pentane-2,4-dionato-O,O')tin.

RAC's response

Noted.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
23.01.2017	France		MemberState	4

Comment received

Read-across approach

Although there are some uncertainties in the read-across, overall, we agree with the classification proposal. The following points would need further clarification:

- Purity/impurities (p. 15)
It is stated that, in general, dibutyltin compounds may contain monobutyltin and

tributyltin compounds as impurities. It should not be disregarded that dibutyltin dichloride (DBTC) may also be a potential impurity. The presence of DBTC even at low concentration (above 0.3%) may impact developmental toxicity of the dibutyltin compound and it would be very useful to have such information.

- Physico-chemical properties
Although it seems not to impact the behaviour of the substance at low pH, the difference in oxidative state between dibutylbis(pentane-2,4-dionato-O,O')tin and the other dibutyltin present in the category is not discussed in the dossier.

- Chemical similarities and toxicokinetic properties (p. 15-17)
Recent gastric hydrolysis studies suggest that both DBTC and dibutylbis(pentane-2,4-dionato-O,O')tin form rapidly the distannoxane ClBu2SnOSnBu2Cl. It is not clear why DBTL, DBTM, DBTO hydrolyse to DBTC and not further to this distannoxane ClBu2SnOSnBu2Cl. Could you please clarify whether this possibility was investigated in the study of Schilt&Zondervan van Beuken, 2004 and if the same method was used in the Naβhan, 2016 study?

Moreover, differences in results have been obtained with DBTC in the simulated gastric hydrolysis and in vivo in the rat. It is unclear how differences between in vitro and in vivo conditions may be extrapolated to dibutylbis(pentane-2,4-dionato-O,O')tin and consequently its toxic potency.

Dossier Submitter's Response

We thank the FR MSCA for the support for the classification proposal. Specific responses to the comments are given below:

Purity/impurities: There are no indications from the existing data that DBTC is present as impurity. Even so, the formation of common intermediates for dibutylbis(pentane-2,4-dionato-O,O´)tin and DBTC at low pH, which is the basis for the read-across approach, makes a discussion on the potential presence of DBTC less valid. In fact, DBTC is part of the general equilibria and, as stated in the dossier, also detected as a rxn product in the hydrolysis of dibutylbis(pentane-2,4-dionato-O,O´)tin (minor amount).

Physico-chemical properties: It is not clear to us what is meant by the comment. The formal oxidation state of the tin (Sn) in all substances in the category is Sn(IV), on the basis of an ionic binding model. It is also stated in the CLH dossier in Table 10.

Chemical similarities and toxicokinetic properties: As thoroughly discussed in the CLH dossier, the study design for the Schilt study and the Naβhan studies are very different, both in terms of concentration and most importantly in the analysis technique. The Schilt study does not allow positive identification of the formed species, only indirect detection. One can therefore not conclude on the actual species formed in the Schilt study, only come to the conclusion that DBTL, DBTM, DBTO as well as DBTC seems to form identical products under the experimental conditions. Whether DBTL, DBTM and DBTO also form the distannoxane has not been examined.

The *in vitro* simulated gastric hydrolysis study only gives information of the initial hydrolysis product, and thus the metabolites formed in vivo are not adressed in this test. The results can therefore not be directly compared to data from the in vivo metabolism study in rat administered intraperitoneally.

Overall, the data support the classification of dibutylbis(pentane-2,2-dionato-O,O´)tin and the differences for *in vitro* and *in vivo* data for DBTC do not influence the validity of the read-across approach.
RAC's response
Noted

Date	Country	Organisation	Type of Organisation	Comment number
06.02.2017	Norway		MemberState	5
Comment received				
We support the classification of dibutylbis(pentane-2,4-dionato-O,O')tin with Repr 1B; H360FD based on a read-across approach from DBTC and other dibutyltin substances, justified on the basis of hydrolytic and toxicokinetic behaviour and toxicological data. A similar approach was used in the CLH report for DBTL which was accepted by RAC in 2014.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted				

Date	Country	Organisation	Type of Organisation	Comment number
09.02.2017	Germany	TIB Chemicals AG	Company-Manufacturer	6
Comment received				
see attachment ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLHP_22673-19-4_20170209 (1).pdf				
Dossier Submitter's Response				
Please see response to comment no. 3.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
09.02.2017	Germany		MemberState	7
Comment received				
Regarding the argumentation for the classification of dibutylbis(pentane-2,4-dionato-O,O')tin as STOT RE 1 with thymus as target organ we have some doubts, whether the study of Gaunt et al. (1968) should be referred to as key study for this endpoint. The proposed classification of dibutylbis(pentane-2,4-dionato-O,O')tin is based on the effects on the thymus weight described in the studies of Seinen & Vos, 1977 and Penninks & Seinen, 1982. In these studies a reduction of the organ weight was found in male and female rats of 55/52 % at 50 ppm and of 72/68 % at 150 ppm. In the study of Gaunt et al. (1968) no effects on the thymus of the rats were identified. In our view this study				

should not be cited as key study but rather be taken into account as additional information.
Dossier Submitter's Response
We agree that the study of Gaunt et al. (1968) does not support classification in STOT RE 1 for effects on thymus since no effects either on weights or histopathology were observed and no LOAEL could be derived from this study (LOAEL >80 ppm, NOAEL ≥ 80 ppm). The proposed classification of dibutylbis(pentane-2,4-dionato-O,O')tin in STOT RE 1 is based on read-across from data on the source substance DBTC that already has a harmonised classification in STOT RE 1. Effects on the thymus were described in the studies by Seinen & Vos, 1977; Penninks & Seinen, 1982 and also in the reproductive/developmental toxicity studies of the source substance. The classification (R48) of DBTC was concluded by the the former TC C&L and was included in Annex I of Directive 67/548/EEC via ATP 30, published in 2008. All of the studies included in the current dossier for assessment of STOT RE 1 were available prior to 2008 (most recent study from 2005) and presumable the basis for the decision of harmonised classification by the TC C&L.
RAC's response
Noted

Date	Country	Organisation	Type of Organisation	Comment number
06.02.2017	Norway		MemberState	8
Comment received				
We support the classification of dibutylbis(pentane-2,4-dionato-O,O')tin with STOT RE 1; H372 based on a read-across approach from DBTC and other dibutyltin substances, justified on the basis of hydrolytic and toxicokinetic behaviour and toxicological data. A similar approach was used in the CLH report for DBTL which was accepted by RAC in 2014.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted				

PUBLIC ATTACHMENTS
1. CLHP_22673-19-4_20170209 (1).pdf [Please refer to comment No. 3, 6]