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 di(acetate)

EC Number: 213-928-8
CAS Number: 1067-33-0

CLH-O-0000006851-71-01/F

Adopted

17 September 2020

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON DIBUTYLTIN DI(ACETATE)

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 di(acetate)
CAS number: 1067-33-0
EC number: 213-928-8
Dossier submitter: Norway

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	France		MemberState	1
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. Inclusion of DBTA in the category is supported by a toxicokinetic study showing metabolisation of DBTA into species similar to DBTC. Characteristic developmental effects of DBTA similar to DBTC and other dibutyltin compounds are also demonstrated in several studies and support toxic properties similar to DBTC. For mutagenicity, the existing data on DBTA (negative Ames study) does not contradict the overall database that detect a genotoxic effects in vivo. 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 DBTA 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 for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
19.11.2019	Germany		MemberState	2

Comment received

The present CLH proposal for dibutyltin di(acetate) (DBTA) is based on a category approach and a limited number of studies with DBTA itself. The category approach is based on the common hydrolytic behavior and comparable toxicity of the category members. This approach is plausible and has been accepted by RAC for classification of several dibutyltin compounds.
Therefore, the proposed classification of DBTA as Muta 2 (H341), Repr.1B (H360FD), and STOT RE1 (immune system) is supported.

SID
In section 1.1. the IUPAC name is stated as "Dibutylstannanebis(ylium) diacetate". This is not 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.
Therefore we suggest the following IUPAC-name: "Diacetoxy(dibutyl)stannane".

Phys Chem
In section 7 the vapour pressure is reported as 0.32 Pa at 20 °C. The value is taken from a study that is included in the registration dossier. The toxicology data network (Toxnet) reports a value of 1.3 mmHg (173 Pa) at 20 °C.

https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@na+DIBUTYLTIN%20DIACETATE
https://www.cdc.gov/niosh/docs/81-123/pdfs/0614.pdf?id=10.26616/NIOSHPUB81123

The reliability of the value last mentioned cannot be assigned.
However, if the difference between those values is significant for the dossier we suggest a closer evaluation of the vapour pressure.

Dossier Submitter's Response

Thank you for your support for the classification proposal.

- IUPAC name: we see that the registrants proposal for IUPAC name (Dibutylstannanebis(ylium) diacetate) is not correct and we agree to change it to your suggested name Diacetoxy(dibutyl)stannane.

- Phys-chem: we are aware of the other vapour pressure value, which is also mentioned in the registration. We considered however, that the 0.32 Pa value is more reliable as the study is said to be performed according to current guideline EU Method A.4, using the dynamic method. The other value of 1.3 mmHg seems to date from at least 1978 (as dated in the the cdc.gov-link above) and we have no information on how the study was performed. We therefore consider it less reliable than the 0.32 Pa-value. In addition we cannot see that the vapour pressure should have any bearing on the classification proposal. We propose to keep the 0.32 Pa value.

RAC's response

Thank you for your comment.

Date	Country	Organisation	Type of Organisation	Comment number
22.11.2019	Sweden		MemberState	3
Comment received				
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 DBTA in this report.				
Dossier Submitter's Response				
Thank you for your comment. 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 DBTA.				
RAC's response				
Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
21.11.2019	Germany	BNT Chemicals GmbH	Company-Manufacturer	4
Comment received				
The Norwegian Competent Authority drafted a Proposal for Harmonized Classification and Labelling for Dibutyltin diacetate (DBTAc). 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 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 DBTAc 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 (Hansen. 2019) it was shown that DBTAc hydrolysed at pH 1.2 /37 °C/ 4 h solely to the dimeric distannoxane [(DBTC)2O]2. No traces DBTC could be indentified by 119-Sn-NMR spectroscopy.				

Historical results
In older studies the formation of DBTC has been reported under comparable conditions for DBTM, DBTO and DBTL. Since the analytical method (GC-FMP) used in the studies included a derivatization step of the hydrolysate, the structural information about the dibutyltin compound was destroyed at this point. In other words the formation of the ([DBTC)2O]2 as a potential low pH hydrolysis product would have produced the same analytical finding as the postulated DBTC.

Low pH hydrolysis of DBTC
In a more recent study (Naßhan 2016) is was shown that DBTC itself forms at pH 1.2 /37 °C/ 4 h aprox. 90 % of the dimeric distannoxane [(DBTC)2O]2.

Dimeric structure of the distannoxanes
The distannoxane formed by low pH hydrolysis exists only in dimeric form (Davies 2004). The dimerization is stabilizing the electronic deficit of the tin atoms in the monomer. Only few examples of monomeric distannoxanes are described – in solid phase with very bulky ligands. An equilibrium between the monomeric and dimeric form of stannoxanes does not exist. Such an equilibrium would be visible in the 119Sn-NMR spectra of the distannoxanes. The most common structure of the dimeric distannoxanes, which besides the 119Sn-NMR data are confirmed by X-Ray diffraction includes a Sn-O-Sn-O 4 membered ring with exocylic tin atoms coordinated via the ring oxygen. All tin atoms are 5 fold coordinated which shows in the in the low chemical shift if the of the tin atoms. The two exocylclic tin atom absorb at -91 ppm whereas the two endocylcic tin atoms appear at -138 ppm.
A potential monomer with two equivalent 4 fold coordinated tin atoms would be expected to absorb at lower field (higher chemical shift)
Based on the 119Sn-Spectra and literature data it can be unequivocaly concluded that the main products of the low pH hydrolysis of DBTC and DBTAc are the dimeric distannoxane [(DBTC)2O]O and that no monomeric form of this distannoxane can be identified.

Bioavailability
The dimeric distannoxane [(DBTC)2O]2 formed as main product in the low pH hydrolysis of DBTAc as well as DBTC has a molecular weight of > 1100 Dalton. It cannot pass biological membranes and thus is not bioavailable. No serious hazard assessment can be carried out based on these circumstances. In other words: the human toxicity after oral exposure cannot be assessed by reading across to data resulting from DBTC feeding studies.

Differences in toxicology / kinetic considerations
It is a valid question why the toxicity of DBTAc should differ significantly from that of DBTC although both seem to demonstrate comparable chemical behavior in a mammalian gastric environment.
When DBTAc is exposed to the gastric fluid the non bioavailable dimeric hydrolysis product of DBTAc will be formed quantitatively in less than 4 hours. Until that state is reached , DBTAc may pass the gastric mucosa. The same principle is valid for the Exposure towards DBTC. Until DBTC is transferred by the gastric juice into a non bioavailable metabolite is still can be resorbed by the stomach.
This concept of a concurring speed of resorption of the substance itself versus the speed of metabolism is supported by firstly the difference in acute toxicity and secondly by the differences in teratogenicity of DBTC compared to DBTAc
Compared to other Dibutyltin caboxylates the LD50 of DBTC is 5-10 times lower.
Furthermore an OECD 414 study on DBTAc (Noda et. al) reports teratogenic effects only in dose levels of serve maternal toxicity. Which is different from the teratogenic

properties of DBTC.
Another explanation of the high toxicity of DBTC compared to the other category members would be to consider the 10 % remaining DBTC as toxic enough to cause the severe toxicity. This underlines that in the case of oral exposure toward DBTC there will always DBTC available for ressoption wheras in the case of DBTAc it newer is formed.
Other category members
The concept of concurring resorption speed versus speed of metabolism is valid as well for those substances where the low pH hydrolysis showed the formation of minor amounts of DBTC.
It is obvious that here the small amounts of DBTC have to be formed out of the thermodynamically far more stable metabolite, wheras DBTC when administered orally is always available in concentrations > 10 % for direct resorption via the gastric mucosa.

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 substanciated by studies on the individual members. 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.
Proposal
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.
DBTAc/DBTL/DBTM
A group of DBTAc, DBTL, DBTM shows comparable in-vitro metabolism. The formation of traces of DBTC are not considered as relevant. This could be verified by e.g. a repeated dose toxicity study or7and teratogenicity study on DBTL (since it formed the highest amount of DBTC)
DBTO
Currently there is no 119Sn-NNR data on DBTO. DBTO has no organic acid ligands and has a polymeric structure. Thus is should not belong to the group
However all of the category members (except DBTC) are manufactured out of DBTO, which would qualify DBTO for the category. Furthermore recently new data got available on DBTO replacing DBTC data, which will in any case be of value.
Meaningfulness / boundaries of studies.
A key information for the scope of the category are results from low pH value hydrolysis studies which have been conducted using 119Sn-NMR spectroscopy to identify the structure of the metabolites.
These in vitro studies provide qualitatively very important and valid information on a substance's chemical behavior in a mammalian gastric environment. The main products will be formed in vivo as well as they are formed in vitro. If the same side products are formed in an vitro environment in the same quantities as they are formed in vitro can be questioned since there are indeed differences in physiological conditions compared to a laboratory condition.

Summary
Based on the results of a recent in-vitro metabolism study on DBTAc the formation of

DBTC under simulated mammalian gastric conditions can be excluded.
The main products of the gastric hydrolysis is the dimeric distannoxane [(DBTC)2O]2. It is the also formed under comparable conditions out of DBTC. They Hydrolysis product is always dimer, no equilibria with the monomeric form exists and has a molecular weight > 1100 Da. It cannot pass the gastric mucosa and is thus not bioavailable.
Reading across from DBTC to DBTAc is for the above mentioned reasons not appropriate.
The dossier submitter has addressed this fact in a dossier update removing all inappropriate read across data concentrating on the data on the substance itself which have been already in the dossier (update november 2019)

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Hansen, Gastric hydrolysis Dibutyltin diacetate.pdf

Dossier Submitter's Response

Thank you for your comments.

Thank you also for the new study you have sent us. We agree that this, and other new hydrolysis studies (Naßhan, 2016[1]; Ghobrial et al, 2019[2]), sheds 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.
- You write yourself that DBTC also has such a dimeric metabolite. So, in other words, a read-across is valid since the metabolites are identical.
- Although the dimeric distannoxanes are of high molecular weight it is quite clear that the category members are present in some bioavailable form, to some degree, since they produce a number of clear toxic effects.
- One reason for this may be that the toxic substances are absorbed before the dimeric structures are created, as you yourself propose above, or that there is an equilibrium that is created between the monomer and the dimer and that the monomer is absorbed and drives the reaction in the direction of the monomer.
- You write above that "The distannoxane formed by low pH hydrolysis exists only in dimeric form (Davies 2004)". We do not agree however that that is a correct interpretation of the Davies (2004) study. Davies writes that the monomer variant is disfavoured, which however does not mean that the monomer does not exist. Although the metabolites may mainly be present in the dimeric form, as long as there is a certain proportion that exists in the monomeric form, the reaction may be driven toward the monomer if this portion is continuously absorbed in the gut.
- Concerning the toxic effects seen in the category members we certainly agree that "the category should be more substanciated by studies on the individual members", as you write above. However, for DBTA there are some studies and these in fact show that the same toxic effects are seen in animals exposed to DBTA as for those exposed to DBTC. In fact, the LOAEL's seen in the teratogenicity studies are quite similar for these two

[1] Naßhan H (2016). Dibutyltin dichloride [DBTC] CAS number: 683-18-1. In-vitro Metabolism Study. Galata Chemicals GmbH, Chemiestrasse 22, 68623 Lampertheim, 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.

substances (DBTA LOAEL range:5-28 mg/kg bw/day; DBTC LOAEL range:2.5-50 mg/kg bw/day) further establishing the category approach as a correct way to classify these substances.
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.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
21.11.2019	Austria		MemberState	5
Comment received				
AT CA supports the classification proposal for Muta 2. The gene mutation study available with DBTA carried out with bacteria is negative. However, the applied category approach is plausible and thus same mutagenic effects as for DBTC are expected for DBTA. DBTC shows mutagenic effects in in vitro and in vivo tests. The compound is harmonised classified as Muta. 2.				
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
22.11.2019	Sweden		MemberState	6
Comment received				
The SE CA supports the proposed harmonised classification of DBTA 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 comment.				

Date	Country	Organisation	Type of Organisation	Comment number
21.11.2019	Germany	BNT Chemicals GmbH	Company-Manufacturer	7
Comment received				
the only study on the substance itself produce any mutagenic effects. The read acoross from Dibutyltin dichloride was considered as not valid; see attached study ECHA note – An attachment was submitted with the comment above. Refer to public attachment Hansen, Gastric hydrolysis Dibutyltin diacetate.pdf				
Dossier Submitter's Response				
Thank you for your comment. As explained in our response to your comments above we consider the read across valid.				

RAC's response
Thank you for your comment.

TOXICITY TO REPRODUCTION

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, FD. The category approach for dibutyltin compounds with liable ligands is well documented. No sexual function and fertility studies are available with DBTA. Relevant studies are performed with DBTC. Four developmental toxicity studies with DBTA show teratogenic effects on the offspring of the rat. These effects are also observed in several studies with category members, most of the studies are carried out with DBTC.				
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
22.11.2019	Sweden		MemberState	9
Comment received				
The SE CA supports the proposed harmonised classification of DBTA 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 comment.				

Date	Country	Organisation	Type of Organisation	Comment number
21.11.2019	Germany	BNT Chemicals GmbH	Company-Manufacturer	10
Comment received				
in the clh proposal only a review is cited, whitch did not consider maternal toxicity. the primary source of the review quoted by norway it is reported that maternal toxicity occoury at 1.7 mg/kg - thymus athropy; (30% reduction of thymus @1.7 mg/kg, 55% reduction of thymus @5 mg/kg) . Therefore we consider no teratogenic effects caused by the substance The read acoross from Dibutyltin dichloride was considered as not valid; see attached study ECHA note – An attachment was submitted with the comment above. Refer to public attachment Hansen, Gastric hydrolysis Dibutyltin diacetate.pdf				
Dossier Submitter's Response				
Thank you for your comment. Firstly we would like to note that you had self-classified DBTA as Rep1B, until november 2019, due to malformations in the foetuses.				

We suppose that it is the study by Noda et al (1992b in the reference list of the classification proposal) that you are referring to above since this is the only study we have included with these dose levels. The study has reported a reduction in thymus weight in the mothers. The reduction is significant from 5 mg/kg. External and skeletal malformations also increased at ≥5 mg/kg bw/d (mainly cleft mandible, cleft lower lip, ankyloglossia and schistoglossia). We did not comment on this reduced thymus weight in our CLH-dossier, which we might have done. However, we do not see that there is an obvious causal relationship between the reduced weight in thymus in the mothers and the malformations seen in the foetuses. Other maternal effects did not appear before higher doses and the authors of the study themselves, Noda and co-workers, did not either see that the reduced thymus weight had any relevance to the malformations seen in the foetuses. On the contrary, they quite clearly state that DBTA is teratogenic. There are four studies that show that DBTA has teratogenic effects in the rat. In addition, the same effects are seen in several studies with other substances in the dibutyltin-category, mostly DBTC, which consistently show that these substances have the potential to cause foetal malformations. Concerning the read-across to other category members, please see comments above.
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
21.11.2019	Austria		MemberState	11
Comment received				
AT CA supports the classification proposal for STOT RE 1 (immune System). No studies are carried out with DBTA. The applied category approach for this endpoint is supported. DBTC (source compound) exposure demonstrates a clear and consistent effect on the thymus at dose levels which warrant classification into STOT RE1 (immune system).				
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
22.11.2019	Sweden		MemberState	12
Comment received				
The SE CA supports the proposed harmonised classification of DBTA 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 comment.				

Date	Country	Organisation	Type of Organisation	Comment number
21.11.2019	Germany	BNT Chemicals GmbH	Company-Manufacturer	13
Comment received				
Allready self-classified based on serve thymus effects ECHA note – An attachment was submitted with the comment above. Refer to public attachment Hansen, Gastric hydrolysis Dibutyltin diacetate.pdf				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your comment.				

PUBLIC ATTACHMENTS
1. Hansen, Gastric hydrolysis Dibutyltin diacetate.pdf [Please refer to comment No. 4, 7, 10, 13]