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 oxide

EC Number: 212-449-1
CAS Number: 818-08-6

CLH-O-0000007033-84-01/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 oxide
EC number: 212-449-1
CAS number: 818-08-6
Dossier submitter: Austria

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
29.01.2021	Switzerland	SONGWON Industrial Group	Company-Manufacturer	1
Comment received				
The validity of using DBTC as a read across substance for DBTO needs closer examination as a result of more recent published information on the transformation of DBTO and other substances which previously were thought to form DBTC in the gastric system. If DBTC is not an appropriat read across substance, several of the proposed classifications need to be re-considered. At several points in relation to acute toxicity the CLH proposal gives relatively less weight to reliable and more current GLP studies in favour of less reliable/less appropriate studies that indicate more severe effects. While precaution is at times prudent in the absence of good information, this is not the case when looking at the acute toxicity and skin corrosivity information. There is solid, current and reliable information that can be used for classification of these end points. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Songwon CLH Consultation DBTO.docx				
Dossier Submitter's Response				
In the comment several endpoints and aspects were addressed. Please find below a response on all endpoints. <u>Acute oral toxicity</u> For this endpoint several studies are available and in the registration dossier limited reliability was given to most of the studies except Anonymous, 2019 (reliability of 1) and Anonymous, 1980b (reliability of 2).				

The key study Anonymous (1983) is a well documented OECD 401 study (including detailed information on the animal model, the housing conditions, vehicle used, dosing scheme, statistics, detailed results). As documented on ECHA dissemination site registrants assigned a reliability of 4 based on insufficient information on the test material, which is described as "dibutyltin oxide, liquid". However, the study was rated as "valid without restriction" (reliability 1) in the OECD SIDS Dossier for DBTO (2008). Therefore the results of this study were considered as relevant and used for classification purpose.
Also the acute oral toxicity studies Anonymous (1978) and Anonymous (1971) were evaluated in the OECD SIDS Dossier and a reliability of 2 (valid with restriction) was assigned to both of them.

Information on purity of the test substance is missing for all studies and evaluation of the studies has been done according to the guidance on the application of CLP criteria (ECHA, 2017). In general, classification has to be based on the lowest ATE value available in the most sensitive appropriate species tested. The results from the most recent studies have been taken into consideration but the evidence shown in other available studies, showing toxicity at lower concentrations, cannot be dismissed based on the information given.

Reference:
OECD SIDS Dossier for DBTO (2008): OECD's Work on Co-operating in the Investigation of High Production Volume Chemicals - Chemical Detailed Results

Skin corrosion
In the dossier it is clearly described that the results of the OECD 404 study indicate a classification as Skin Irrit 2, H315. However, there is strong evidence from additional studies, both in rabbits and rats, for corrosivity. In general the rat skin is considered to be less sensitive compared to rabbit skin and only in case of evidence of skin corrosivity (as opposed to irritation) in a rat dermal toxicity test the substance can be classified as Skin Corrosive Category 1 (Guidance on the application of CLP criteria, 2017). Based on this a classification as Skin Corr 1 has been proposed.

Muta. 2, H341, Repr. 1B, H360FD, STOT RE 1, H372

Category approach:

We consider DBTO as category member, since it is substantiated with analytical data that the category members (including DBTC, DBTM, DBTL, DBTP, DBTA) after oral administration behave in a similar manner and identical intermediates are formed, moreover toxicological information supports the read across. As also highlighted in your comment, data from recent simulated gastric hydrolysis studies with category members (DBTC, DBTP and DBTM) demonstrate that identical metabolites/intermediates – DBDTC distannoxane dimers (CAS 33194-92-2) - are formed. Like DBTC also DBTO forms DBDTC distannoxane dimers (citations: Munschi et al, 2010, Patel et al., 2009). The same formed intermediates support the read across hypothesis between DBTC and DBTO.

DBTC hydrolyses under the simulated gastric conditions (HCl, pH 1.2, 4 h, 37°C) to DBDTC distannoxane dimers to an extent of 90%, and with 10% DOTC unreacted (Naßhan, 2016). We do not think that only remaining 10% DBTC is responsible for the toxicological properties of DBTC, but think that also dimeric structures might contribute. The argument that DBDTC distannoxane dimers (CAS 33194-92-2) are large molecules and thus not

bioavailable is not supported by toxicological data. There is evidence that DBTO itself is bioavailable, because it provokes toxicological effects (Unpublished report, 2017; Noda et al., 1993). The new submitted prenatal development toxicity study (OECD TG 414) demonstrates that DBTO has an adverse impact on thymus integrity, which is a target organ for category members. In the study reduced thymus weights were observed (relative and absolute, up to - 38-44%) (see also CLH report Table 52). in a dose dependent manner and also an increased incidence of small thymus was observed in dams at the highest dose applied. Also, the comparative study by Noda et al. (1993) indicates that category members, including those for which hydrolysis data show DBDTC distannoxane dimers formation, have a negative impact on reproductive toxicity endpoints (Noda et al., 1993).

We agree that monomeric distannoxanes XR2SnOSnR2X structures are only present in solid state and only when the groups R are very bulky (Davies, 2004). In other cases monomeric distannoxane structures exhibit their character as both Lewis acids and Lewis bases by dimerising to give an SnOSnO 4-membered ring as given in CLH report, figure 3 (CAS 33194-92-2) (DBDTC distannoxane dimer) (depicted in the CLH report). This is supported by the study of Umweltbundesamt (Ghobrial et al, 2019), which indicated that DBTM was converted to DBDTC distannoxane dimers (CAS 33194-92-2) in a gastric hydrolysis study. Nevertheless, it cannot be ruled out that under other conditions dissociation to monomeric distannoxanes might occur, however, monomeric distannoxanes (e.g. CAS 10428-19-0) were not observed under reported reaction conditions of the study of Ghobrial et al. (2019).

It is important to consider, that the gastric hydrolysis studies conducted with DBTC, DBTM, DBTP mimic only the acidic conditions in the stomach and do not provide a full toxicokinetic analysis. We do not have information on *in vivo* transformation in the stomach and on metabolites systemically available and responsible for toxic effects.

In summary, the available information indicates that common metabolite/intermediate are formed *in vivo*, and affect common biological targets, which supports the applicability of a read across from category members (e.g. DBTC) to DBTO for oral toxicity studies and for following endpoints: mutagenicity, toxicity to reproduction, specific target organ toxicity repeated exposure, specific target organ toxicity single exposure.
We conclude, based on available information, that the read across is robust and it is valid to consider data of category members to read across between these endpoints.

We noted that further studies (e.g. OECD 422, *in vitro* mutagenicity) will be submitted, to further address reproductive toxicity, mutagenicity and repeated dose toxicity.

References:

Davies A. G. (2004). Difunctional distannoxanes, XR2SnOSnR2X. J. Chem. Res. 309-314.

Ghobrial et al. (2019). Conversion of organotin compounds in the gastric environment. Vienna, 2019; Reports, Band 0709 ISBN: 978-3-99004-529-9. (link:https://www.umweltbundesamt.at/aktuell/publikationen/publikationssuche/publikationsdetail/?pub_id=2308)

Munschi P et al. (2010) Tuning catalyst solubility in CO2 by changing molar volume. Green Chem. Lett. and Rev., p. 319–328, 2010

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

Noda T, Morita S & Baba A (1993). Teratogenic effects of various di-n-butyltins with different anions and butyl(3-hydroxybutyl)tin dilaurate in rats. Toxicology 85: 149-60.

RAC (2018). Committee for Risk Assessment. Opinion proposing harmonised classification and labelling at EU level of dioctyltin dilaurate dioctyltin dilaurate; [1] stannane, dioctyl-, bis(coco acyloxy) derivs. [2] EC Number: 222-883-3 [1] 293-901-5 [2] CAS Number: 3648-18-8 [1] 91648-39-4 [2]; CLH-O-0000001412-86-223/F

Unpublished report (2017). Dibutyltin Oxide: an oral prenatal developmental toxicity study in rats

RAC's response

Thank you for your comment. On the category approach, RAC agrees with the explanation provided by the dossier submitter and considers the proposed read-across approach valid.

Regarding the acute toxicity studies, RAC agrees with the DS that the limitations in reporting on the test material are insufficient to discard the outcome of the Anonymous, 1983, study. In all other parameters the study was well reported and showed a very consistent pattern over the entire dose range.

For skin corrosion/irritation RAC considers that Category 2 is more appropriate, as explained in the reply to comment No. 39.

Date	Country	Organisation	Type of Organisation	Comment number
29.01.2021	Germany	TIB Chemicals AG	Company-Importer	2

Comment received

We disagree with the proposed classification, please see detailed comments in the attached document.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment TIB Comment on DBTO CLH Proposal_29-01-2021_Redacted.pdf

Dossier Submitter's Response

Please see response to comment No 1.

RAC's response

Please see response to comment No 1.

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2021	France		MemberState	3

Comment received

We agree with the proposed category approach. DBTO belongs to the dibutyltin compounds ((DBTC, DBTL, DBTO, DBTA). As DBTL and DBTM, there are information that the substance DBTO 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	4
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.				

Date	Country	Organisation	Type of Organisation	Comment number
28.01.2021	Ireland	Exponent International Engineering and Scientific Consulting Limited	Company-Importer	5
Comment received				
In summary it can be said the use of old to very old studies and the current knowledge of certain impurities and the re-evaluation of the hydrolysis of organotins clearly argue against a read-across to DBTC. The studies performed so far in connection with DBTO must be critically evaluated along with the new studies that are being performed to reach any appropriate conclusions on classification. This is especially true for the studies on hydrolysis and the occurrence of dimers and in considering the human health toxicity/classification of the substance ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH_DBTO_Comments_Final.docx				
Dossier Submitter's Response				
Please see response to comment No. 1.				
RAC's response				
Please see response to comment No. 1.				

Date	Country	Organisation	Type of Organisation	Comment number
27.01.2021	Germany	Galata Chemicals GmbH	Company-Downstream user	6
Comment received				
In summary, it can be said that the use of old to very old studies and the current knowledge of certain impurities clearly argue against a read-across to DBTC. The studies performed so far in connection with DBTO must be critically evaluated and the new studies are to be preferred here. This is especially true for the studies on hydrolysis and the occurrence of dimers.				

ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH_DBTO_Comments_Galata_Redacted.pdf
Dossier Submitter's Response
Please see response to comment No. 1.
RAC's response
Please see response to comment No. 1.

Date	Country	Organisation	Type of Organisation	Comment number
27.01.2021	Luxembourg	Chemservice S.A. (acting as OR)	Company-Importer	7
Comment received				
It seems that read-across data from other (inappropriate) substances receive a higher rating and importance than current and valid GLP studies, which have been performed in the light of enhancing the dossier quality and robustness. In summary, it can be said that the use of old to very old studies and the current knowledge of certain impurities clearly argue against a read-across to DBTC (Dibutyltin chloride). The studies performed so far in connection with DBTO must be critically evaluated and the new studies are to be preferred here. This is especially true for the studies on hydrolysis and the occurrence of dimers. One additional comment unrelated to the above: We have registered the substance as OR. Why can "Only Representative" not be selected from the "type-of-Organisation" Button? ORs are good for 25% of the REACH registered substances and should therefore be considered in parallel to importers and manufacturers. ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH_DBTO_Comments to proposal_CSL.pdf				
Dossier Submitter's Response				
Please see response to comment No. 1.				
RAC's response				
Please see response to comment No. 1.				

Date	Country	Organisation	Type of Organisation	Comment number
27.01.2021	Sweden	ChemSec	International NGO	8
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 Rep 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 comment and your support on the category approach.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
29.01.2021	Switzerland	SONGWON Industrial Group	Company-Manufacturer	9
Comment received				
Data is not sufficient to propose Mutagenicty 2 (H341). As shown on Table 21 the mutagenicity classification relies on the use of a read across from dibutyltin dichloride (DBTC). Chapter 9 (Toxicokinetics) of the CLH proposal contains information which is claimed by the Environmental Agency Austria to support this approach. However we must question the assumption that DBTO is hydrolyzed in the gastric system to DBTC. A 2019 publication by UBA-Austria [Conversion of organotin compounds in the gastric environment – Introduction, Ghobrial et al, 2019] looked at dibutyltin maleate (DBTM) another potential read across subtance and found no evidence of formation of DBTC. Instead, the DBTM formed bis(dibutylchlorotin) oxide dimer (DBTDC dimer) in quantitative amounts. This is in line with previous hydrolysis studies on DBTC and DBTO showing DBDTC distannoxane dimer is formed under similar conditions [P. MUNSCHI ET AL. Tuning catalyst solubility in CO2 by changing molar volume. Green Chem. Lett. and Rev., p. 319–328, 2010 and Y. PATEL ET AL. Effect of lipophilicity of catalyst in cyclic carbonate formation by transesterification of polyhydric alcohols. Greenchem., p. 1056–1060, 2009]. Sp the This study by [Ghobrial et al, 2019] demonstrates that DBTM forms hydrolysis products identical to DBTO and therefore gives important information about the substances, but importantly it confirms that the breakdown of these two substances is not to DBTC. Without DBTC as a read across there is no information on which to propose a Category 2 Mutagenicity classification. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Songwon CLH Consultation DBTO.docx				
Dossier Submitter's Response				
Please see response to comment No. 1.				
RAC's response				
Please see response to comment No. 1.				

Date	Country	Organisation	Type of Organisation	Comment number
29.01.2021	Germany	TIB Chemicals AG	Company-Importer	10
Comment received				
We disagree with the proposed classification, please see detailed comments in the attached document. ECHA note – An attachment was submitted with the comment above. Refer to public attachment TIB Comment on DBTO CLH Proposal_29-01-2021_Redacted.pdf				
Dossier Submitter's Response				
Please see response to comment No. 1.				

RAC's response
Please see response to comment No. 1.

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2021	France		MemberState	11
Comment received				
We agree with the DS's proposal to classify DBTO 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
29.01.2021	Sweden		MemberState	12
Comment received				
The SE CA supports the proposed harmonised classification of DBTO 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.				

Date	Country	Organisation	Type of Organisation	Comment number
21.01.2021	Germany		MemberState	13
Comment received				
The addition of the harmonised classification as Muta. 2; H341: Suspected of causing genetic defects is supported. Although only one negative bacterial reverse mutation assay according to OECD TG 471 with DBTO itself is presented, the result is in line with results of category members. Overall, more studies from category members are positive (9) than negative (6). According to the category approach, for the group overall available data can be used for a read-across approach con-cerning mutagenic effects.				
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
28.01.2021	Ireland	Exponent International Engineering and Scientific Consulting Limited	Company-Importer	14
Comment received				
Please see attached document for details ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH_DBTO_Comments_Final.docx				
Dossier Submitter's Response				
Please see response to comment No. 1.				
RAC's response				
Please see response to comment No. 1.				

Date	Country	Organisation	Type of Organisation	Comment number
27.01.2021	Germany	Galata Chemicals GmbH	Company-Downstream user	15
Comment received				
Muta. 2, H341, Repr. 1B, H360FD, STOT RE 1, H372 It is not appropriate to base these proposed classifications for these end points on study data from dibutyltin dichloride (DBTC). Recent work has shown that DBTC is not a scientific correct read across molecule. Simulated Gastric Hydrolysis studies using a more accurate NMR analytical technique, have shown that dibutyltin dichloride (DBTC) is not an appropriate metabolite. We would like to refer to a publication by Umweltbundesamt GmbH, Austria [Conversion of organotin compounds in the gastric environment – Introduction, Ghobrial et al, 2019], which investigated the simulated gastric hydrolysis of Dibutyltin Maleate (DBTM, CAS 78-04-6). The study shows that DBTM was quantitatively converted to bis(dibutylchlorotin) oxide dimer (DBTDC) dimer in a simulated gastric environment (0.1 mol of aqueous HCl, 72h, 40 °C). Other potential metabolites such as DBTC were not detected. It has been demonstrated previously that upon hydrolysis of category members such as DBTC and DBTO, DBDTC distannoxane dimer is formed under similar conditions [P. MUNSCHI ET AL. Tuning catalyst solubility in CO2 by changing molar volume. Green Chem. Lett. and Rev., p. 319–328, 2010 and Y. PATEL ET AL. Effect of lipophilicity of catalyst in cyclic carbonate formation by transesterification of polyhydric alcohols. Greenchem., p. 1056–1060, 2009]. This study by [Ghobrial et al, 2019] demonstrates that DBTM forms hydrolysis products identical to DBTO and therefore gives important information about the substances, but importantly it confirms that the breakdown of these two substances is not to DBTC. In the 119Sn spectra no DBTC was detected. It was concluded, that DBTC was below the detection limit of the 119Sn NMR (according UBA approx. 3 %). This was also demonstrated under similar conditions, industry studies show that the LOQ was much below 3%. The formation of Tetrabutlydichlorodistannoxane by reaction of DBTO with hydrochloric acid is described in the literature [Alwyn G. Davies, JOURNAL OF CHEMICAL RESEARCH 2004 MAY, 309–314]. It also is described, that the molecules in solution are always at least dimers. A monomer could only be determined in just one case - in solid and with very bulky				

ligands. The most common structure of the dimer is a ladder structure including 2 endo- and 2 exocyclic tin atoms. In the 119Sn-NMR spectrum they appear at a chemical shift of -91.4 and -140.3 ppm. Equilibria between the monomer and the dimer are not determined. Also, an equilibrium between the dimeric distannoxane and DBTC does not occur. Both equilibria would easily be able to be determined as additional signals in the 119Sn-NMR spectra.

The dimeric structure, which is the only metabolite of the gastric hydrolysis has a molecular weight of 1089.4 Dalton. With this high molecular weight, the dimeric distannoxane is by far too heavy to be biologically active and have a low reaction potential because the molecules are too large to pass through biological membranes, limiting their bioavailability. A recent GLP guideline OECD TG 414 study with DBTO in rats, which was conducted in 2017 [MPI Research], was shared for the CLH procedure with Umweltbundesamt GmbH. Unfortunately, at this stage without information from the additional OECD 422 that is shortly to be conducted on DBTO it is not considered possible to provide a result for the reproduction end point and a definitive overall reproductive classification for the substance. However, it could be confirmed that no teratogenic effects were observed in the new OECD 414 study.

It has been noted in the comments added into the appropriate "End Point Summaries" of the EU REACH dossier, our intention to perform new testing due to the fact, that the previous read across is no longer being appropriate and to indicate the intention to remove the DBTC data once the new studies are available. Classification for mutagenicity, reproduction and specific organ toxicity – repeated will be reassessed by the lead registrant once this new data on DBTO is available.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH_DBTO_Comments_Galata_Redacted.pdf

Dossier Submitter's Response
Please see response to comment No. 1.
RAC's response
Please see response to comment No. 1.

Date	Country	Organisation	Type of Organisation	Comment number
27.01.2021	Luxembourg	Chemservice S.A. (acting as OR)	Company-Importer	16

Comment received
We disagree with the proposed classification, please refer to the attached document. ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH_DBTO_Comments to proposal_CSL.pdf
Dossier Submitter's Response
Please see response to comment No. 1.
RAC's response
Please see response to comment No. 1.

Date	Country	Organisation	Type of Organisation	Comment number
26.01.2021	Netherlands	PMC Vlissingen BV	Company-Importer	17
Comment received				
The category approach for classification of chronic hazards which is described in detail in Chapter 9.2 of the CLH Report is not appropriate for this substance. Please see detailed comments in the attached document. ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH_DBTO_Comments to proposal_PMC.pdf				
Dossier Submitter's Response				
Please see response to comment No. 1.				
RAC's response				
Please see response to comment No. 1.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
29.01.2021	Switzerland	SONGWON Industrial Group	Company-Manufacturer	18
Comment received				
Comments in the "Mutagenicity" section regarding the relevance of the use of DBTC data as read across to DBTO for classification purposes also apply here. More recent data indicates that DBTC is not expected to be a transformation product of DBTO in the gastric system. Therefore the references and use of DBTC read across form the basis of the classification should be removed. As the developmental effects conclusions are based predominantly on studies using DBTC as the read across, the classification H360D is not appropriate. This is supported by the results of the OECD 414 study performed using DBTO which showed the absence of teratogenic effects. The registrants support the conduct of an OECD 422 study which will more fully examine the reproductive and developmental effects of DBTO. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Songwon CLH Consultation DBTO.docx				
Dossier Submitter's Response				
Please see response to comment No. 1.				
RAC's response				
Please see response to comment No. 1.				

Date	Country	Organisation	Type of Organisation	Comment number
29.01.2021	Germany	TIB Chemicals AG	Company-Importer	19
Comment received				
We disagree with the proposed classification, please see detailed comments in the attached document. ECHA note – An attachment was submitted with the comment above. Refer to public attachment TIB Comment on DBTO CLH Proposal_29-01-2021_Redacted.pdf				

Dossier Submitter's Response
Please see response to comment No. 1.
RAC's response
Please see response to comment No. 1.

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2021	France		MemberState	20
Comment received				
We agree with the DS's proposal to classify DBTO 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
29.01.2021	Sweden		MemberState	21
Comment received				
The SE CA supports the proposed harmonised classification of DBTO as Repr. 1B, H360FD based on a category approach. For adverse effects on the development of offspring there is also substance specific data from an OECD TG 414 in rat that provides further support to the classification proposal as part of a weight of evidence.				
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	22
Comment received				
The addition of the harmonised classification "Repr. 1B; H360FD: May damage fertility. May damage the unborn child" is supported. One PNDT according to OECD TG 414 with DBTO itself is presented, showing only statistically non significant visceral variations, while foetal malformations were observed for all category members - including DBTO of unknown impurity - in a single dose comparative study. Furthermore, increased incidence of post-implantation loss was detected in the PNDT (OECD TG 414) with DBTO. These results together with adverse effects from data of the category members can be used for a read-across approach concerning reproductive effects.				
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
28.01.2021	Ireland	Exponent International Engineering and Scientific Consulting Limited	Company-Importer	23
Comment received				
Please see attached document for details ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH_DBTO_Comments_Final.docx				
Dossier Submitter's Response				
Please see response to comment No. 1.				
RAC's response				
Please see response to comment No. 1.				

Date	Country	Organisation	Type of Organisation	Comment number
27.01.2021	Germany	Galata Chemicals GmbH	Company-Downstream user	24
Comment received				
Muta. 2, H341, Repr. 1B, H360FD, STOT RE 1, H372 It is not appropriate to base these proposed classifications for these end points on study data from dibutyltin dichloride (DBTC). Recent work has shown that DBTC is not a scientific correct read across molecule. Simulated Gastric Hydrolysis studies using a more accurate NMR analytical technique, have shown that dibutyltin dichloride (DBTC) is not an appropriate metabolite. We would like to refer to a publication by Umweltbundesamt GmbH, Austria [Conversion of organotin compounds in the gastric environment – Introduction, Ghobrial et al, 2019], which investigated the simulated gastric hydrolysis of Dibutyltin Maleate (DBTM, CAS 78-04-6). The study shows that DBTM was quantitatively converted to bis(dibutylchlorotin) oxide dimer (DBTDC) dimer in a simulated gastric environment (0.1 mol of aqueous HCl, 72h, 40 °C). Other potential metabolites such as DBTC were not detected. It has been demonstrated previously that upon hydrolysis of category members such as DBTC and DBTO, DBDTC distannoxane dimer is formed under similar conditions [P. MUNSCHI ET AL. Tuning catalyst solubility in CO2 by changing molar volume. Green Chem. Lett. and Rev., p. 319–328, 2010 and Y. PATEL ET AL. Effect of lipophilicity of catalyst in cyclic carbonate formation by transesterification of polyhydric alcohols. Greenchem., p. 1056–1060, 2009]. This study by [Ghobrial et al, 2019] demonstrates that DBTM forms hydrolysis products identical to DBTO and therefore gives important information about the substances, but importantly it confirms that the breakdown of these two substances is not to DBTC. In the 119Sn spectra no DBTC was detected. It was concluded, that DBTC was below the detection limit of the 119Sn NMR (according UBA approx. 3 %). This was also demonstrated under similar conditions, industry studies show that the LOQ was much below 3%. The formation of Tetrabutlydichlorodistannoxane by reaction of DBTO with hydrochloric acid is described in the literature [Alwyn G. Davies, JOURNAL OF CHEMICAL RESEARCH 2004 MAY, 309–314]. It also is described, that the molecules in solution are always at least dimers. A monomer could only be determined in just one case - in solid and with very bulky				

ligands. The most common structure of the dimer is a ladder structure including 2 endo- and 2 exocyclic tin atoms. In the 119Sn-NMR spectrum they appear at a chemical shift of -91.4 and -140.3 ppm. Equilibria between the monomer and the dimer are not determined. Also, an equilibrium between the dimeric distannoxane and DBTC does not occur. Both equilibria would easily be able to be determined as additional signals in the 119Sn-NMR spectra.

The dimeric structure, which is the only metabolite of the gastric hydrolysis has a molecular weight of 1089.4 Dalton. With this high molecular weight, the dimeric distannoxane is by far too heavy to be biologically active and have a low reaction potential because the molecules are too large to pass through biological membranes, limiting their bioavailability. A recent GLP guideline OECD TG 414 study with DBTO in rats, which was conducted in 2017 [MPI Research], was shared for the CLH procedure with Umweltbundesamt GmbH. Unfortunately, at this stage without information from the additional OECD 422 that is shortly to be conducted on DBTO it is not considered possible to provide a result for the reproduction end point and a definitive overall reproductive classification for the substance. However, it could be confirmed that no teratogenic effects were observed in the new OECD 414 study.

It has been noted in the comments added into the appropriate "End Point Summaries" of the EU REACH dossier, our intention to perform new testing due to the fact, that the previous read across is no longer being appropriate and to indicate the intention to remove the DBTC data once the new studies are available. Classification for mutagenicity, reproduction and specific organ toxicity – repeated will be reassessed by the lead registrant once this new data on DBTO is available.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH_DBTO_Comments_Galata_Redacted.pdf

Dossier Submitter's Response
Please see response to comment No. 1.
RAC's response
Please see response to comment No. 1.

Date	Country	Organisation	Type of Organisation	Comment number
27.01.2021	Luxembourg	Chemservice S.A. (acting as OR)	Company-Importer	25

Comment received
We disagree with the proposed classification, please refer to the attached document. ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH_DBTO_Comments to proposal_CSL.pdf
Dossier Submitter's Response
Please see response to comment No. 1.
RAC's response
Please see response to comment No. 1.

Date	Country	Organisation	Type of Organisation	Comment number
26.01.2021	Netherlands	PMC Vlissingen BV	Company-Importer	26
Comment received				
The category approach for classification of chronic hazards which is described in detail in Chapter 9.2 of the CLH Report is not appropriate for this substance. Please see detailed comments in the attached document. ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH_DBTO_Comments to proposal_PMC.pdf				
Dossier Submitter's Response				
Please see response to comment No. 1.				
RAC's response				
Please see response to comment No. 1.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
29.01.2021	Switzerland	SONGWON Industrial Group	Company-Manufacturer	27
Comment received				
The acute oral toxicity data base is considerable. Ten studies, all in rats are cited in the proposal. The reliablility of many of these studies is poor (Klimisch 4). The proposed Category 3 acute toxic relies on a 1983 study which found an LD50 of 172mg/kg bw and was among the studies assigned as being poorly reliable. There is reference to a highly reliable (Klimisch 1) study found in the current REACH dossier {GLP OECD 423 study (Bioneeds; 2019)]. This study along with a supporting (reliability 2) earlier study (Biodynamics 1980) indicates that the LD 50 is clearly above the 300mg/kg bw cut off for Cat 3 Acute Oral toxicity classification. The EAA proposal does not provide any explanation why these studies more reliable were not used for classification purposes other than the remark "Based on the lowest LD50 value available". The reader is left to wonder why they ignored and did not use the most reliable (and current) study. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Songwon CLH Consultation DBTO.docx				
Dossier Submitter's Response				
For this endpoint several studies are available and in the registration dossier limited reliability was given to most of the studies except Anonymous, 2019 (reliability of 1) and Anonymous, 1980b (reliability of 2). Anonymous (1983) is a well documented OECD 401 study (including detailed information on the animal model, the housing conditions, vehicle used, dosing scheme, statistics, detailed results). As documented on ECHA dissemination site registrants assigned a reliability of 4 based on insufficient information on the test material, which is described as "dibutyltin oxide, liquid". However, the study was rated as "valid without restriction" (reliability 1) in the OECD SIDS Dossier for DBTO (2008). Therefore the results of this study were considered as relevant and used for classification purpose. Also the acute oral toxicity studies Anonymous (1978) and Anonymous (1971) were evaluated in the OECD SIDS Dossier and a reliability of 2 (valid with restriction) was assigned to both of them.				

Information on purity of the test substance is missing for all studies and evaluation has been done according to the guidance on the application of CLP criteria (ECHA, 2017). In general, classification has to be based on the lowest ATE value available in the most sensitive appropriate species tested. The results from the most recent studies have been taken into consideration but the evidence shown in other available studies, showing toxicity at lower concentrations, cannot be dismissed based on the information given.

Reference:
OECD SIDS Dossier for DBTO (2008): OECD's Work on Co-operating in the Investigation of High Production Volume Chemicals - Chemical Detailed Results

RAC's response
RAC agrees with the DS that the limitations in reporting on the test material are insufficient to discard the outcome of the Anonymous, 1983, study. In all other parameters the study was well reported and showed a very consistent pattern over the entire dose range.

Date	Country	Organisation	Type of Organisation	Comment number
29.01.2021	Germany	TIB Chemicals AG	Company-Importer	28
Comment received				
We disagree with the proposed classification, please see detailed comments in the attached document. ECHA note – An attachment was submitted with the comment above. Refer to public attachment TIB Comment on DBTO CLH Proposal_29-01-2021_Redacted.pdf				
Dossier Submitter's Response				
See response to comment No 27.				
RAC's response				
See response to comment No 27.				

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2021	France		MemberState	29
Comment received				
Based on the results of the acute toxicity study in rats (Anonymous, 1983), we agree that DBTO warrants to be classified as Acute Tox. 3 with the proposed ATE.				
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	30
Comment received				
The SE CA supports the proposed harmonised classification of DBTO as Acute Tox. 3, H301 based on the lowest available LD50 value from an OECD TG 401 oral acute toxicity study				

in rat at 172 mg/kg bw (m/f). Since there was not any apparent trend in sensitivity between sexes, we also support to set the ATE at 172 mg/kg bw (m/f).
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	31

Comment received

The proposed non-classification for Acute Tox, dermal is supported.

The proposed non-classification for Acute Tox, inhalation is supported.

To add the harmonised classification as Acute Tox. 3, H301 is supported.
In general, classification for Acute Tox. 3, H301 can be comprehended.
It remains unclear, however, why the guideline-compliant study by Anonymous (1983), con-ducted according to OECD 401, was assigned a reliability of 4 (= "not assignable") and then nevertheless used to derive the ATE. It should therefore be specified in more detail, why the study is relevant for the classification despite a reliability of 4. If only the studies with a reli-ability of 1 or 2 were considered, a different classification (Acute Tox. 4, H302) would result.

Dossier Submitter's Response

Thank your for your support.

Anonymous (1983) is a well documented OECD 401 study (including detailed information on the animal model, the housing conditions, vehicle used, dosing scheme, statistics, detailed results). As documented on ECHA dissemination site the registrants assigned a reliability of 4 based on insufficient information on the test material, which is described as "dibutyltin oxide, liquid". However, the study was rated as "valid without restriction" (reliability 1) in the OECD SIDS Dossier for DBTO (2008). Therefore the results of this study were considered as relevant and used for classification purpose.

Also the acut oral toxicity studies Anonymous (1978) and Anonymous (1971) were evaluated in the OECD SIDS Dossier and a reliability of 2 (valid with restriction) was assigned to both of them.
A description of the purity of the test material is missing for all studies listed in Table 12 of the CLH dossier.

Reference:
OECD SIDS Dossier for DBTO (2008): OECD's Work on Co-operating in the Investigation of High Production Volume Chemicals - Chemical Detailed Results

RAC's response

Thank you for your comment. RAC agrees with the dossier submitter that the Anonymous, 1983, study is of sufficient quality to be used as key study for classification.

Date	Country	Organisation	Type of Organisation	Comment number
28.01.2021	Ireland	Exponent International Engineering and Scientific Consulting Limited	Company-Importer	32
Comment received				
Please see attached document for details ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH_DBTO_Comments_Final.docx				
Dossier Submitter's Response				
See response to comment No 27.				
RAC's response				
See response to comment No. 27.				

Date	Country	Organisation	Type of Organisation	Comment number
27.01.2021	Germany	Galata Chemicals GmbH	Company-Downstream user	33
Comment received				
A GLP study conducted according to the standardised method OECD Guideline 423 [Bioneeds] was completed in February 2019 and added to the dossier. The results of this new GLP study along with one other reliable supporting study from 1980 [Biodynamics, 1980b] performed to an equivalent or similar to guideline to OECD 401 were submitted, showing that DBTO has an Acute Oral toxicity classification of category 4. Several other existing studies are available which assess the acute oral toxicity of the test material with a widely varying range of results, from 164 mg/kg bw to > 10 000 mg/kg bw. After a review of all available studies, the data used to determine Acute Tox. 3 should not be used. The reliability of these studies is questionable, with the general concern being the physical form of the substance that was tested and its purity and technical grade. In addition, lack of GLP, inadequate reporting of methods and lack of guidelines result in the existing data lacking reliability. ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH_DBTO_Comments_Galata_Redacted.pdf				
Dossier Submitter's Response				
See response to comment No. 27.				
RAC's response				
See response to comment No. 27.				

Date	Country	Organisation	Type of Organisation	Comment number
27.01.2021	Luxembourg	Chemservice S.A. (acting as OR)	Company-Importer	34
Comment received				
We disagree with the proposed classification, please refer to the attached document.				

ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH_DBTO_Comments to proposal_CSL.pdf
Dossier Submitter's Response
See resonse to comment No. 27.
RAC's response
See response to comment No. 27.

Date	Country	Organisation	Type of Organisation	Comment number
26.01.2021	Netherlands	PMC Vlissingen BV	Company-Importer	35
Comment received				
Based on appropriate GLP testing an acute toxicity classification Cat. 3 is not warranted. ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH_DBTO_Comments to proposal_PMC.pdf				
Dossier Submitter's Response				
See response to comment No. 27.				
RAC's response				
See response to comment No. 27.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
29.01.2021	Switzerland	SONGWON Industrial Group	Company-Manufacturer	36
Comment received				
The proposed Category 1 Skin Corrosion classification is not supported by the information provided in Section 10.4. This chapter references several skin irritation/corrosivity studies and the the EAA also drew information from two acute dermal toxicity studies found in Chapter 10.2 where dermal effects were noted. There were two GLP skin studies in rabbits which used semi-occlusive application of 0.5 gms of material for up to 4 hours and with suitable post exposure observation which did not give indication of corrosive effects. In addition one of the GLP studies followed the OECD 404 guideline and included 1 hour of occluded exposure and found no indication of corrosive effects. The only evidence of corrosive effects were reported in animals with occluded exposure periods of 24 hours in combination with moistened skin or a vehicle. However, it has to be considered that the exposure duration of 24 h is six times longer than the standard 4 hour exposure period used in the an OECD Guideline 404 – Acute dermal irritation/corrosion). Occlusive exposure combined with the extended duration of exposure in the acute dermal toxicity studies and in the dermal irritation/corrosivity study used by EAA far exceed the boundary conditions which have long been used to classify substances for their dermal corrosivity to skin. It should also be considered that the acute dermal studies use an applied dose that is 4 fold greater than an standard OECD 404 study. Therefore none of the cited studies should not be used as the basis for classification of dermal corrosvity. Instead the results from the 1994 GLP 404 study should be used as the basis for classification and and the GLP (OECD SIDS 2008) used as supporting information (as it also used a 3-4 hours duration of exposure).				

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Songwon CLH Consultation DBTO.docx
Dossier Submitter's Response
In the dossier it is clearly described that the results of the OECD 404 study indicate a classification as Skin Irrit 2, H315. However, there is strong evidence from additional studies, both in rabbits and rats, for corrosivity. In general the rat skin is considered to be less sensitive compared to rabbit skin and only in case of evidence of skin corrosivity (as opposed to irritation) in the rat dermal toxicity test the substance can be classified as Skin Corrosive Category 1 (Guidance on the application of CLP criteria, 2017). Based on this a classification as Skin Corr 1 has been proposed.
RAC's response
Please see response to comment No. 39

Date	Country	Organisation	Type of Organisation	Comment number
29.01.2021	Germany	TIB Chemicals AG	Company-Importer	37
Comment received				
We disagree with the proposed classification, please see detailed comments in the attached document. ECHA note – An attachment was submitted with the comment above. Refer to public attachment TIB Comment on DBTO CLH Proposal_29-01-2021_Redacted.pdf				
Dossier Submitter's Response				
See response to comment No. 36.				
RAC's response				
Please see response to comment No. 39				

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2021	France		MemberState	38
Comment received				
Based on the irreversible effects, skin burns and necrosis seen in rabbits, a classification of DBTO as Skin Corr. 1 is warranted as proposed. As the effects occurred following 4h exposure (Anonymous, 1994), sub-category 1C could be considered.				
Dossier Submitter's Response				
Thank you for your support. Anonymous (1994) documented slight erythema and edema after 4h of exposure which were not fully reversible within the observation periode of 14 days. However, the classification proposal is based on a primary skin irritation study and on acute dermal toxicity studies describing severe effects after 24h of exposure. Therefore no subcategorization was proposed.				
RAC's response				
RAC agrees with the DS that the effects seen in the study by Anonymous, 1994, does not warrant classification in subcategory 1C. Regarding the classification in Category 1 or 2, please see the response to comment No. 39.				

Date	Country	Organisation	Type of Organisation	Comment number
21.01.2021	Germany		MemberState	39
Comment received				
To add the harmonised classification as Skin Corr. 1, H314 is not supported. Instead, addition of the harmonised classification as Skin Irrit. 2, H315 is proposed. At least the classification as Skin Irrit. 2, H315 appears justified on basis of the available data. However, the indications of corrosivity in the study by Anonymous (1975), used by AT for the classification as Skin Corr. 1, H314 only occurred after 24-hour occlusive exposure, which is a significant deviation of the 4 h duration intended by the CLP regulation for the assess-ment of corrosive effects. Moreover, the acute dermal toxicity study (Anonymous, 1980) considered in addition, also used 24-hour exposure. Therefore no classification as Skin Corr. 1, H314 but as Skin Irrit. 2, H315 is proposed.				
Dossier Submitter's Response				
Based on the results of the OECD 404 study a classification as Skin Irrit 2, H315 is indicated. However, there is strong evidence from additional studies (with an exposure periode of 24h), both in rabbits and rats, for corrosivity. In general the rat skin is considered to be less sensitive compared to rabbit skin and only in case of evidence of skin corrosivity (as opposed to irritation) in the rat dermal toxicity test the substance can be classified as Skin Corrosive Category 1 (Guidance on the application of CLP criteria, 2017). Based on this a classification as Skin Corr 1 has been proposed.				
RAC's response				
RAC agrees with the comment that the effects observed in studies with only scoring after 24-h exposure cannot be used as key studies to evaluate skin corrosivity. In addition there is a secondary source that noted severe effects after 4 h, but information on this study was too limited to use for classification. RAC concludes that Skin Irrit. 2 is more appropriate than Skin Corr. 1.				

Date	Country	Organisation	Type of Organisation	Comment number
28.01.2021	Ireland	Exponent International Engineering and Scientific Consulting Limited	Company-Importer	40
Comment received				
Please see attached document for details ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH_DBTO_Comments_Final.docx				
Dossier Submitter's Response				
See response to comment No. 36.				
RAC's response				
Please see response to comment No. 39				

Date	Country	Organisation	Type of Organisation	Comment number
27.01.2021	Germany	Galata Chemicals GmbH	Company-Downstream user	41
Comment received				
A GLP compliant OECD Guideline 404 (in vivo Acute Dermal Irritation/Corrosion) study [Wil Research Labs] from 1994 shows DBTO to be non-corrosive to skin. There was no evidence of corrosion following the three-minute, sixty-minute and four-hour exposures. No irritation greater than very slight to slight erythema and no edema was observed on any three or 60-minute exposure site at both 24- and 4-hours post-exposure. The test material induced very slight to moderate erythema and very slight to slight edema on all rabbits following the four-hour exposure. All sites had desquamation by day 11. There were no other dermal findings. Edema completely subsided within 72 hours. Very slight to slight erythema was present on all sites at study termination (day 14) for all 4-hour sites. There were no deaths or significant body weight changes during the study period. Therefore, a skin corrosion classification Cat. 1 is not warranted. The dossier was updated with skin corrosion classification Cat. 2. ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH_DBTO_Comments_Galata_Redacted.pdf				
Dossier Submitter's Response				
See response to comment No. 36.				
RAC's response				
Please see response to comment No. 39				

Date	Country	Organisation	Type of Organisation	Comment number
27.01.2021	Luxembourg	Chemservice S.A. (acting as OR)	Company-Importer	42
Comment received				
We disagree with the proposed classification, please refer to the attached document. ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH_DBTO_Comments to proposal_CSL.pdf				
Dossier Submitter's Response				
See response to comment No. 36.				
RAC's response				
Please see response to comment No. 39				

Date	Country	Organisation	Type of Organisation	Comment number
26.01.2021	Netherlands	PMC Vlissingen BV	Company-Importer	43
Comment received				
Based on appropriate GLP testing and human experience, a skin corrosion classification Cat. 1 is not warranted. ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH_DBTO_Comments to proposal_PMC.pdf				

Dossier Submitter's Response
See response to comment No. 36.
RAC's response
Please see response to comment No. 39

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
21.01.2021	Germany		MemberState	44
Comment received				
To add the harmonised classification as Eye Dam. 1, H318 is supported. A classification as Skin Corr. 1, H314, which would automatically trigger an additional classification as Eye Dam. 1, H318 appears not to be justified, as discussed above. Nevertheless classification as Eye Dam. 1, H318 is supported , since the available in vivo studies provide clear evidence for eye damaging effects.				
Dossier Submitter's Response				
Thank your for your support.				
RAC's response				
Thank your for your support.				

Date	Country	Organisation	Type of Organisation	Comment number
29.01.2021	Switzerland	SONGWON Industrial Group	Company-Manufacturer	45
Comment received				
We agree that the available toxicity data information supports the classification of Category 1 Eye Damage (H318) and stands on its own. However currently Chapter 10.5.3 also states "DBTO showed corrosive effects in skin irritation studies and is therefore proposed to be classified as Skin Corr. 1, H314 (see Chapter 9.6)". As indicated in our comments on skin irritation/corrosivity, refererencing DBTO as a Skin Corr. 1 H314 should be removed since the available information does not support this conclusion. Furthermore there is no Chapter 9.6 in the CLH proposal. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Songwon CLH Consultation DBTO.docx				
Dossier Submitter's Response				
Thank you for your support. See also response to comment No. 36. Additional remark: Thank you, the reference on page 34 should be "……see Chapter 10.4."				
RAC's response				
Thank your for your support.				

Date	Country	Organisation	Type of Organisation	Comment number
28.01.2021	Ireland	Exponent International Engineering and Scientific Consulting Limited	Company-Importer	46
Comment received				
Please see attached document for details ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH_DBTO_Comments_Final.docx				
Dossier Submitter's Response				
There is no specific comment on eye irritation. For further response see response to comment No 1.				
RAC's response				
Please see response to comment No. 1				

Date	Country	Organisation	Type of Organisation	Comment number
27.01.2021	Luxembourg	Chemservice S.A. (acting as OR)	Company-Importer	47
Comment received				
We disagree with the proposed classification, please refer to the attached document. ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH_DBTO_Comments to proposal_CSL.pdf				
Dossier Submitter's Response				
There is no specific comment on eye irritation. For further response see response to comment No 1.				
RAC's response				
Please see response to comment No. 1				

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2021	France		MemberState	48
Comment received				
Based on the rabbit study, we agree that a classification as Eye. Dam. 1 is warranted for DBTO.				
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	49

Comment received

To add the harmonised classification as STOT SE 1, H370: causes damage to the immune system is proposed.

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 expo-sure 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 effec-tive 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 Guid-ance. In this assessment, DBTO 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

Thank you for your comment. RAC has evaluated the two studies, but considers the weight of evidence insufficient for classification as STOT SE 1.

Date	Country	Organisation	Type of Organisation	Comment number
29.01.2021	Switzerland	SONGWON Industrial Group	Company-Manufacturer	50

Comment received

Comments in the "Mutagenicity" section regarding the relevance of the use of DBTC data as read across to DBTO for classification purposes also apply here. More recent data indicates that DBTC is not expected to be a transformation product of DBTO in the gastric system. Therefore the references to DBTC toxicity studies in Section 10.11 should be removed as they are not relevant to DBTO.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Songwon CLH Consultation DBTO.docx

Dossier Submitter's Response

See response to comment No. 1.

RAC's response

See response to comment No. 1.

Date	Country	Organisation	Type of Organisation	Comment number
26.01.2021	Netherlands	PMC Vlissingen BV	Company-Importer	51

Comment received

The category approach for classification of chronic hazards which is described in detail in Chapter 9.2 of the CLH Report is not appropriate for this substance. Please see detailed comments in the attached document.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH_DBTO_Comments to proposal_PMC.pdf

Dossier Submitter's Response

See response to comment No. 1.

RAC's response
See response to comment No. 1.

Date	Country	Organisation	Type of Organisation	Comment number
28.01.2021	Ireland	Exponent International Engineering and Scientific Consulting Limited	Company-Importer	52
Comment received				
Please see attached document for details ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH_DBTO_Comments_Final.docx				
Dossier Submitter's Response				
See response to comment No. 1.				
RAC's response				
See response to comment No. 1.				

Date	Country	Organisation	Type of Organisation	Comment number
27.01.2021	Luxembourg	Chemservice S.A. (acting as OR)	Company-Importer	53
Comment received				
We disagree with the proposed classification, please refer to the attached document. ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH_DBTO_Comments to proposal_CSL.pdf				
Dossier Submitter's Response				
See response to comment No. 1.				
RAC's response				
See response to comment No. 1.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
29.01.2021	Switzerland	SONGWON Industrial Group	Company-Manufacturer	54
Comment received				
Comments in the "Mutagenicity" section regarding the relevance of the use of DBTC data as read across to DBTO for classification purposes also apply here. More recent data indicates that DBTC is not expected to be a transformation product of DBTO in the gastric system. Therefore the references and use of DBTC read across form the basis of the classification of STOT RE Cat 1 (H372) should be removed. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Songwon CLH Consultation DBTO.docx				

Dossier Submitter's Response
See response to comment No. 1.
RAC's response
See response to comment No. 1.

Date	Country	Organisation	Type of Organisation	Comment number
29.01.2021	Germany	TIB Chemicals AG	Company-Importer	55
Comment received				
We disagree with the proposed classification, please see detailed comments in the attached document. ECHA note – An attachment was submitted with the comment above. Refer to public attachment TIB Comment on DBTO CLH Proposal_29-01-2021_Redacted.pdf				
Dossier Submitter's Response				
See response to comment No. 1.				
RAC's response				
See response to comment No. 1.				

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2021	France		MemberState	56
Comment received				
We agree with the DS's proposal to classify DBTO as STOT RE 1 (immune system) based on the study with DBTO and read-across with 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	57
Comment received				
The SE CA supports the proposed harmonised classification of DBTO as STOT RE 1, H372 (immune system) based on a category approach and on supportive findings on the thymus from the OECD TG 414 in rat in a weight of evidence assessment.				
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	58
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
28.01.2021	Ireland	Exponent International Engineering and Scientific Consulting Limited	Company-Importer	59
Comment received				
Please see attached document for details ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH_DBTO_Comments_Final.docx				
Dossier Submitter's Response				
See response to comment No. 1.				
RAC's response				
See response to comment No. 1.				

Date	Country	Organisation	Type of Organisation	Comment number
27.01.2021	Germany	Galata Chemicals GmbH	Company-Downstream user	60
Comment received				
Muta. 2, H341, Repr. 1B, H360FD, STOT RE 1, H372 It is not appropriate to base these proposed classifications for these end points on study data from dibutyltin dichloride (DBTC). Recent work has shown that DBTC is not a scientific correct read across molecule. Simulated Gastric Hydrolysis studies using a more accurate NMR analytical technique, have shown that dibutyltin dichloride (DBTC) is not an appropriate metabolite. We would like to refer to a publication by Umweltbundesamt GmbH, Austria [Conversion of organotin compounds in the gastric environment – Introduction, Ghobrial et al, 2019], which investigated the simulated gastric hydrolysis of Dibutyltin Maleate (DBTM, CAS 78-04-6). The study shows that DBTM was quantitatively converted to bis(dibutylchlorotin) oxide dimer (DBTDC) dimer in a simulated gastric environment (0.1 mol of aqueous HCl, 72h, 40 °C). Other potential metabolites such as DBTC were not detected. It has been demonstrated previously that upon hydrolysis of category members such as DBTC and DBTO, DBDTC distannoxane dimer is formed under similar conditions [P. MUNSCHI ET AL. Tuning catalyst solubility in CO2 by changing molar volume. Green Chem. Lett. and Rev., p. 319–328, 2010 and Y. PATEL ET AL. Effect of lipophilicity of catalyst in cyclic carbonate formation by transesterification of polyhydric alcohols. Greenchem., p. 1056–1060, 2009]. This study by [Ghobrial et al, 2019] demonstrates that DBTM forms hydrolysis products identical to DBTO and therefore gives important information about the substances, but importantly it confirms that the breakdown of these two substances is not to DBTC. In the 119Sn spectra no DBTC was detected. It was concluded, that DBTC was below the detection limit of the 119Sn NMR (according UBA approx. 3 %). This was also demonstrated under similar conditions, industry studies show that the LOQ was much below 3%.				

The formation of Tetrabutlydichlorodistannoxane by reaction of DBTO with hydrochloric acid is described in the literature [Alwyn G. Davies, JOURNAL OF CHEMICAL RESEARCH 2004 MAY, 309–314]. It also is described, that the molecules in solution are always at least dimers. A monomer could only be determined in just one case - in solid and with very bulky ligands. The most common structure of the dimer is a ladder structure including 2 endo- and 2 exocyclic tin atoms. In the 119Sn-NMR spectrum they appear at a chemical shift of -91.4 and -140.3 ppm. Equilibria between the monomer and the dimer are not determined. Also, an equilibrium between the dimeric distannoxane and DBTC does not occur. Both equilibria would easily be able to be determined as additional signals in the 119Sn-NMR spectra. The dimeric structure, which is the only metabolite of the gastric hydrolysis has a molecular weight of 1089.4 Dalton. With this high molecular weight, the dimeric distannoxane is by far too heavy to be biologically active and have a low reaction potential because the molecules are too large to pass through biological membranes, limiting their bioavailability. A recent GLP guideline OECD TG 414 study with DBTO in rats, which was conducted in 2017 [MPI Research], was shared for the CLH procedure with Umweltbundesamt GmbH. Unfortunately, at this stage without information from the additional OECD 422 that is shortly to be conducted on DBTO it is not considered possible to provide a result for the reproduction end point and a definitive overall reproductive classification for the substance. However, it could be confirmed that no teratogenic effects were observed in the new OECD 414 study. It has been noted in the comments added into the appropriate "End Point Summaries" of the EU REACH dossier, our intention to perform new testing due to the fact, that the previous read across is no longer being appropriate and to indicate the intention to remove the DBTC data once the new studies are available. Classification for mutagenicity, reproduction and specific organ toxicity – repeated will be reassessed by the lead registrant once this new data on DBTO is available. ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH_DBTO_Comments_Galata_Redacted.pdf
Dossier Submitter's Response
See response to comment No. 1.
RAC's response
See response to comment No. 1.

Date	Country	Organisation	Type of Organisation	Comment number
27.01.2021	Luxembourg	Chemservice S.A. (acting as OR)	Company-Importer	61
Comment received				
We disagree with the proposed classification, please refer to the attached document. ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH_DBTO_Comments to proposal_CSL.pdf				
Dossier Submitter's Response				
See response to comment No. 1.				
RAC's response				
See response to comment No. 1.				

Date	Country	Organisation	Type of Organisation	Comment number
26.01.2021	Netherlands	PMC Vlissingen BV	Company-Importer	62
Comment received				
The category approach for classification of chronic hazards which is described in detail in Chapter 9.2 of the CLH Report is not appropriate for this substance. Please see detailed comments in the attached document. ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH_DBTO_Comments to proposal_PMC.pdf				
Dossier Submitter's Response				
See response to comment No. 1.				
RAC's response				
See response to comment No. 1.				

PUBLIC ATTACHMENTS
1. Songwon CLH Consultation DBTO.docx [Please refer to comment No. 1, 9, 18, 27, 36, 45, 50, 54]
2. TIB Comment on DBTO CLH Proposal_29-01-2021_Redacted.pdf [Please refer to comment No. 2, 10, 19, 28, 37, 55]
3. CLH_DBTO_Comments_Final.docx [Please refer to comment No. 5, 14, 23, 32, 40, 46, 52, 59]
4. CLH_DBTO_Comments_Galata_Redacted.pdf [Please refer to comment No. 6, 15, 24, 33, 41, 60]
5. CLH_DBTO_Comments to proposal_CSL.pdf [Please refer to comment No. 7, 16, 25, 34, 42, 47, 53, 61]
6. CLH_DBTO_Comments to proposal_PMC.pdf [Please refer to comment No. 17, 26, 35, 43, 51, 62]