COMPILED COMMENTS ON CLH CONSULTATION

Comments provided during consultation are made available in the table below as submitted through the web form. Please note that the comments displayed below may have been accompanied by attachments which are listed in this table and included in a zip file if non-confidential. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Last data extracted on 01.02.2021

Substance name: Dibutyltin oxide
CAS number: 818-08-6
EC number: 212-449-1
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				

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				

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.

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.				

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				

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				

Date	Country	Organisation	Type of Organisation	Comment number
27.01.2021	Luxembourg	Chemservice S.A.	Company-Importer	7

		(acting as OR)		
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				

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.				

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

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				

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.				

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.				

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.				

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

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

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				

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				

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

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				

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.				

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.				

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.				

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

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

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				

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				

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

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				

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.				

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).				

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.				

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				

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				

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				

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				

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				

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				

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.				

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 da-ta. 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.

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				

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				

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

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				

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.				

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				

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

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				

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.				

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 ef-fects 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.				

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

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				

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				

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				

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

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				

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.				

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.				

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.				

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				

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

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

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

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]