Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Tributyltin compounds, with the exception of those specified elsewhere in Annex VI

EC number: -
CAS number: -

CLH-O- 0000003769-59-03/A2

Adopted

5 December 2013

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON TRIBUTYLTIN COMPOUNDS

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in this table as submitted by the webform. Please note that some attachments received may have been copied in the table below. The attachments received have been provided in full to the dossier submitter and RAC.

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Substance name: tributyltin compounds
EC number: -
CAS number: -
Dossier submitter: Germany

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2013	Norway		MemberState	1
Comment received				
Norway would like to thank Germany for the proposal for harmonised classification and labeling of tributyltin compounds, with the exception of those specified elsewhere in this Annex, Index Number 050-008-00-3. We support the proposal to classify tributyltin compounds for reproductive toxicity with Repr. 1B - H360Fd based on studies with tributyltin salts (TBTCl, TBT acetate and TBTO) and the toxic properties of DBT compounds as DBT derivates appear to be important in vivo metabolites of TBT compounds.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted. However, RAC considers Repr. 1B - H360FD to be more appropriate (see below).				

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2013	Netherlands		MemberState	2
Comment received				
The Netherlands are of the opinion that it is difficult to draw the conclusion that the classification for reproduction and developmental toxicity is valid for the whole group of tributyltin compounds. This is due to the fact that the applicability domain of 'tributyltin compounds' is not well defined and the fact that a hydrolysis step is part of the mode of action of the reproductive toxicity of tributyltin compounds. Since the group of tributyltin compounds is not well defined, it is difficult to extrapolate whether all substances in the group will hydrolyse to the extent that classification for reproduction toxicity is justified.				
Dossier Submitter's Response				
The tri-n-butyltin compounds which are used in industry (TBTX, X = oxygen, halogen or carboxylate) do not differ substantially in the toxic effects they produce either after single or after repeated administration (The MAK Collection for Occupational Health and Safety: Tri-n-butyltin compounds, 1989; n-Butylzinnverbindungen, 2007). The anions attached to the TBT molecule are of less relevance to the cellular interactions, because, when absorbed, TBT compounds will be present in the form of the cations di-n-butyltin^{++} and tri-n-butyltin^{+} (DBT and TBT respectively), a salt (chloride, carbonate, acetate, sulfate), or bound to proteins at sulfhydryl or histidine groups (Benya 1997). TBTO and various TBT carboxylates can be readily extracted as TBT chloride in essentially 100 % yield from 1N hydrochloric acid (MAK 1989). After oral uptake the TBT compounds				

dissociate in the gastric juice to form a hydrated TBT cation and the corresponding anion to finally yield the corresponding TBT chloride. Thus the same species, assumed to be TBTCl, will be absorbed from the gastrointestinal tract after ingestion of various TBT compounds (MAK 1989, 2007). Bis(tri-n-butyltin) oxide (TBTO), tri-n-butyltin acetate and tri-n-butyltin chloride (TBTCl) are therefore representatives for reproductive toxicity of the whole group of TBT derivatives with the general formula TBTX that are
registered: tributyltin chloride,
pre-registered: tributyltin acetate, tributyltin hydroxide, tributyltin bromide, tributyltin fluoride,
notified: tributyltin phenylsulphide, tributyltin 10-undecenylate, tributyltin laurate, tributyltin trichloroacetate, tributyltin 8-quinolinolate, tributyltin oxide, tributyltin 2,4,5-trichlorophenolate (ECHA),
used in synthesis: tributyltin azide (Saito, S. *Tetrahedron Letters* **30**: 4153, 1989),
used in industry: tributyltin benzoate, tributyltin linoleate, tributyltin methacrylate, tributyltin naphthenate (MAK 1989, 2007), and
listed in data bases: tributyltin oleate, tributyltin abietate, tributyltin ethanolate, tributyltin iodide, tributyltin methanolate, tributyltin phosphate (GESTIS: http://gestis.itrust.de/nxt/gateway.dll?f=templates&fn=default.htm&vid=gestisdeu:sdbdeu)
Furthermore, the reproductive toxicity of dibutyltin compounds supports the classification of TBT compounds since DBT compounds are in vivo metabolites of TBT compounds (Appel 2004; Benya 1997).

RAC's response

The read-across of the toxicological data for TBT-Cl, TBT-Ac and TBTO depends indeed on the extent to which other derivatives (which fall within the dossier submitter's proposed Annex VI entry) can decompose to a common, active product. As such, TBT does not form salts with organic or inorganic acids, but instead it forms complexes bound by covalent bonds. TBT-Cl can decompose to hydroxide complexes, TBT-OH and others (PubChem), and in organic fluids it is expected to be stable only at low pH, the TBT-OH conjugates being the predominant forms (Foti et al., (2004) Marine Chemistry 85;157–167). This is the likely fate of the three compounds included in the report, and it can be inferred that this will be the case for many of the TBT derivatives listed by the DS. However, it is conceivable that a particular TBT derivative may not be decomposable to the hydroxide or other similar complexes, and therefore its bioavailability and toxicity may differ significantly from those considered here.

RAC agrees that there is no need to change the scope of the current Annex VI entry for tributyltin compounds. In the event that a manufacturer, importer or downstream user of a 'tributyltin compound' covered by this classification considers that the harmonised classification should not apply to their substance, they may submit a proposal (via a member state) for a specific classification for that substance.

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2013	France		MemberState	3
Comment received				
Fr agrees with the classification proposal as Repr.1B H360Fd.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted. However, RAC considers Repr. 1B - H360FD to be more appropriate (see below).				

Date	Country	Organisation	Type of Organisation	Comment number

18.07.2013	Belgium		MemberState	4
Comment received				
Belgium supports the classification of Tributyltin Compounds as Reprotoxic 1B and we agree with the rationale presented in the CLH report Classification H360 F is justified by the fact that : • implantation failure in dose related manner were revealed from several rat studies and could not be explained as a secondary effect due to food deprivation and/or maternal body weight loss, • statistically significant spermatotoxicity has been shown in mice in absence of other toxic effects. Classification H360 d is justified by the fact that developmental effects were only induced at dosages that were associated with maternal toxicity. Since a specific maternally mediated mechanism has been demonstrated, classification in Category 2 is considered more appropriate than Category 1.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
RAC considers Repr. 1B - H360FD to be more appropriate. Whereas some of the observed effects in offspring (low weight, resorptions) could be linked to maternal toxicity, RAC considers that at least some of the serious adverse effects on fetuses (e.g., cleft palate), seen in multiple studies in both rats and mice, could not be explained by this maternal toxicity. RAC therefore considers that these effects warrant classification as Repr. 1B for developmental toxicity (Repr. Cat. 2 (R61) under the DSD).				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2013	Netherlands		MemberState	7
Comment received				
The Netherlands agree with the classification of TBT compounds as H360d. An additional argument for classification in Category 2 (instead of in Category 1B) is that the postnatal developmental toxicity may be due to postnatal exposure, e.g. via lactation. According to 3.7.1.4 of the CLP legal text, developmental toxicity is exclusively defined as adverse effects induced due to prenatal exposure. In view of the uncertainty that the effects may be induced postnatal, Category 2 for the developmental effects is considered the appropriate classification for developmental toxicity. Specific comments: Page 22 and 23, study of Harazono (1998b) We are of the opinion that the way of presenting the increase or decrease in food consumption and body weight gain is not very clear. Please provide additional data for clarification, e.g. by presenting the increases and decreases in the way it is presented in study of Harazono (1998a).				
Dossier Submitter's Response				
Thank you for your support. Specific comments: **TBTCl treated group (16.3 mg /kg/d) (I):** decreased maternal food consumption during days 0-8 (19 % of the controls) mat. body weight loss during days 0-8 (of 17 %) **feed restricted group (II):**				

restricted maternal food consumption during days 0-8 (6 % of the controls) mat. body weight loss during days 0-8 (of 19 %)
RAC's response
Noted. However, RAC considers Repr. 1B - H360FD to be more appropriate. RAC considers that cleft palates cannot be attributed to maternal toxicity or lactation effects (they are observed in fetuses).

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2013	France		MemberState	8
Comment received				
We agree with the justification of the read across for tributyltin compounds. Classification of dibutyltin compounds for reproduction as Repr. 1B H360FD support the classification of TBT compounds since DBT compounds are in vivo metabolites of TBT compounds. We agree with the classification proposal for fertility (H360F), based on the implantation failure in females and spermatotoxic effects in males. For developmental toxicity, a classification as H360d is appropriated based on embryo/fetal lethality, fetal growth retardation and induction of structural abnormalities associated with maternal toxicity.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted. However, RAC considers Repr. 1B - H360FD to be more appropriate, based on the presence of specific skeletal abnormalities, such as cleft palates. This classification would be consistent with that considered appropriate for dibutyltin compounds.				