Committee for Risk Assessment

RAC

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/F

Adopted

5 December 2013

5 December 2013

CLH-O-0000003769-59-03/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemicals name: Tributyltin compounds, with the exception of those specified elsewhere in this annex

EC number: -

CAS number: -

The proposal was submitted by **Germany** and received by the RAC on **6 June 2013.**

In this opinion, all classifications are given firstly in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonised System (GHS) and secondly, according to the notation of 67/548/EEC, the Dangerous Substances Directive (DSD).

PROCESS FOR ADOPTION OF THE OPINION

Germany has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation*** on **6 June 2013**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **22 July 2013**.

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by RAC: **Benjamin Piña**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation.

The RAC opinion on the proposed harmonised classification and labelling was reached on **5 December 2013** and the comments received are compiled in Annex 2.

The RAC Opinion was adopted by **consensus**.

OPINION OF THE RAC

The RAC adopted the opinion that **tributyltin compounds** should be classified and labelled as follows:

Classification and labelling in accordance with the CLP Regulation

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	050-008-00-3	tributyltin compounds, with the exception of those specified elsewhere in this annex	-	-	Acute Tox. 3 * Acute Tox. 4 * STOT RE 1 Eye Irrit. 2 Skin Irrit. 2 Aquatic Acute 1 Aquatic Chronic 1	H301 H312 H372** H319 H315 H400 H410	GHS06 GHS08 GHS09 Dgr	H301 H312 H372** H319 H315 H410	-	* STOT RE 1; H372: C ≥ 1 % STOT RE 2; H373: 0,25 % ≤ C < 1 % Skin Irrit. 2; C ≥ 1 % Eye Irrit. 2; C ≥ 1 % M=10	A1
Dossier submitters proposal	050-008-00-3	tributyltin compounds, with the exception of those specified elsewhere in this annex			**Modify** Acute Tox. 3 Acute Tox. 3 **Add** Repr. 1B	**Modify** H301 H311 **Add** H360Fd		**Modify** H301 H311 **Add** H360Fd			
RAC opinion	050-008-00-3	tributyltin compounds, with the exception of those specified elsewhere in this annex			**Retain** Acute Tox. 4* **Modify** Acute Tox. 3 **Add** Repr. 1B	**Retain** H312 **Modify** H301 **Add** H360FD		**Retain** H312 **Modify** H301 **Add** H360FD			
Resulting Annex VI entry if agreed by	050-008-00-3	tributyltin compounds, with the exception of those specified elsewhere in			Repr. 1B Acute Tox. 3 Acute Tox. 4 * STOT RE 1	H360FD H301 H312 H372**	GHS06 GHS08 GHS09 Dgr	H360FD H301 H312 H372**	-	* STOT RE 1; H372: C ≥ 1 %	A1

COM		this annex			Eye Irrit. 2 Skin Irrit. 2 Aquatic Acute 1 Aquatic Chronic 1	H319 H315 H400 H410		H319 H315 H410		STOT RE 2; H373: 0,25 % ≤ C < 1 % Skin Irrit. 2; C ≥ 1 % Eye Irrit. 2; C ≥ 1 % M=10	

Classification and labelling in accordance with the DSD

	Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
Current Annex VI entry	050-008-00-3	tributyltin compounds, with the exception of those specified elsewhere in this annex	-	-	T; R25-48/23/25 Xn; R21 Xi; R36/38 N; R50-53	T; N R: 21-25-36/38-48/23/25-50/53 S: (1/2-)36/37/39-45-60-61	T; R25: C ≥ 2,5 % Xn; R22: 0,25 % ≤ C < 2,5 % Xn: R21: C ≥ 1 % T; R48/23/25: C ≥ 1 % Xn; R48/20/22: 0,25 % ≤ C < 1 % Xi; R36/38: C ≥ 1 % N; R50-53: C ≥ 2,5 % N; R51-53: 0,25 % ≤ C < 2,5 % R52-53: 0,025 % ≤ C < 0,25 %	A1
Dossier submitters proposal	050-008-00-3	tributyltin compounds, with the exception of those specified elsewhere in this annex			**Add** Repr. Cat. 2; R60 Repr. Cat. 3; R63	**Add** T; R60-63		
RAC opinion	050-008-00-3	tributyltin compounds, with the exception of those specified elsewhere in this annex			**Add** Repr. Cat. 2; R60-61	**Add** T; R60-61 S:53		
Resulting Annex VI entry if agreed by COM	050-008-00-3	tributyltin compounds, with the exception of those specified elsewhere in this annex			Repr. Cat. 2; R60-61 T; R25-48/23/25 Xn; R21 Xi; R36/38 N; R50-53	T; N R: 21-25-36/38-48/23/25-50/53-60-61 S: 45-53-60-61	T; R25: C ≥ 2,5 % Xn; R22: 0,25 % ≤ C < 2,5 % Xn: R21: C ≥ 1 % T; R48/23/25: C ≥ 1 % Xn; R48/20/22: 0,25 % ≤ C < 1 % Xi; R36/38: C ≥ 1 % N; R50-53: C ≥ 2,5 % N; R51-53: 0,25 % ≤ C < 2,5 % R52-53: 0,025 % ≤ C < 0,25 %	A1

SCIENTIFIC GROUNDS FOR THE OPINION

RAC general comment

In the CLH report, the dossier submitter noted that the current Annex VI entry includes the anionic substituents of tri-n-butyltin (TBT) compounds such as halides, alkoxylates or carboxylates, and that since all of them have a common feature of metabolic hydroxylation and dealkylation, the rationale for the assessment of reproductive toxicity is based on the existing toxicity data for bis(tri-n-butyltin) oxide, tri-n-butyltin chloride, and tri-n-butyltin acetate.

During public consultation, a member state (NL) raised the issue of the applicability of the present dossier to all "tributyltin compounds, with the exception of those specified elsewhere in this Annex" (stated in the existing entry in Part 3 of Annex VI of the CLP Regulation). In response, the dossier submitter (DS) argued that the tri-n-butyltin compounds which are used in industry (TBTX, X = oxygen, halogen or carboxylate) do not differ substantially in their toxic effects and that the anions attached to the TBT molecule are less relevant to their cellular interactions (see the RCOM for details). The DS also argued that following oral uptake, the TBT compounds dissociate in the gastric juices to form a hydrated TBT cation and the corresponding anion to yield the corresponding TBT chloride. Therefore the TBT species used in the submitted studies are suitable representatives for reproductive toxicity of the whole group of TBT derivatives with the general formula TBTX.

RAC noted that the data in the dossier only refer to tributyltin chloride (TBT-Cl, EC no 215-958-7), tributyltin acetate (TBT-Ac, EC no 200-269-6) and tributyltin oxide (TBTO, EC no 200-268-0), and the read-across for other compounds depends on the extent to which the 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. Bearing these considerations in mind, RAC none-the-less considered that the proposed read-across is justified and that there was no need to change the scope of the current Annex VI entry.

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.

HUMAN HEALTH HAZARD ASSESSMENT

RAC evaluation of acute toxicity

Summary of the Dossier submitter's proposal

The current acute toxicity classification for TBT is Acute Tox. 3* (H301) and Acute Tox. 4* (H312), with the asterisk (*) denoting a minimum classification. Following re-assessment of the available data, the DS proposed Acute Tox. 3 (H301) and R25 (under DSD) based on oral LD_{50} values of 101 and 127 mg/kg in rats. The DS also proposed Acute Tox. 3 (H311) and R21 (DSD) based on a dermal LD_{50} value of 500 mg/kg in rabbits, but also commented that this was based on a note in a registration update (without any reference).

Comments received during public consultation

No comments were received on acute toxicity during public consultation

Assessment and comparison with the classification criteria

The oral LD_{50} values were within the range 50 to 300 mg/kg, therefore classification as Acute Tox. 3 (H301) as proposed by the DS is warranted (R25 under DSD). However, RAC considered that there was insufficient evidence to change the classification for acute dermal toxicity and therefore the current minimum classification as Acute Tox. 4* (H312) should be maintained.

RAC evaluation of reproductive toxicity

Summary of the Dossier submitter's proposal

The proposed classification is based exclusively on animal studies, mainly in rodents. Fertility effects were found in both males and females. In female rats, implantation failure at relatively high doses of TBT-Cl (30-60 mg/kg/d) was the most significant effect on reproduction and could not be explained as a secondary effect resulting from food deprivation and/or maternal body weight loss. TBTO (50 mg/kg/d) resulted in significantly reduced sperm head counts, failure of seminiferous tubule organisation, and in vacuolisation of Sertoli cells in male mice. Rats showed reductions in homogenisation-resistant spermatid counts after exposure to TBTCl in the absence of other toxic effects.

There is evidence of significant toxic effects on development in the offspring in rats and mice. Studies with rats and mice showed that TBTO or TBT salts induced embryo-/foetal lethality, foetal growth retardation, and structural abnormalities as well as impairment of postnatal viability and development following pre- or postnatal exposure. All effects on pre- and postnatal development occur concurrently with significant maternal toxicity (maternal death, maternal weight loss and/or reduction in maternal weight gain). However, maternal mortality was less than 10% and was not considered to be excessive; irreversible effects on developmental toxicity were not considered to be a secondary consequence of maternal toxicity.

Comments received during public consultation

Comments were received from four Member States (MS). Three MS agreed with the proposed classification. One MS (NL) put forward the issue of the read across of toxicological data to other TBT compounds.

Assessment and comparison with the classification criteria

No human data were provided, therefore Repr. 1A is not appropriate.

The CLH report provided convincing data for adverse effects on fertility (especially in females) occurring with only limited other toxic effects in rats and mice. This corresponds to Repr. 1B (H360F) based on the CLP criteria and Repr. Cat 2 (R60) under the DSD.

The effects on the development of offspring were somewhat masked by the moderate to severe maternal toxicity observed in all the developmental toxicity studies summarised in the CLH report.

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 foetuses (e.g. cleft palate), seen in multiple studies in both rats and mice, are not secondary to maternal toxicity. Spontaneous cleft palates are rare in rats, suggesting a specific MoA for this effect.

Cleft palates are mentioned in the RAC opinion for Dioctyltin bis(2-Ethylhexyl mercaptoacetate) (http://echa.europa.eu/documents/10162/5266b444-9e22-4051-86ec-e0c59a95649b), which concluded that classification of the substance as Repr. 1B (H360D) according to the CLP Regulation was appropriate. A potential metabolite of TBT, dibutyltin dichloride also has a harmonised classification as Repr. 1B (H360FD). Although these considerations represent only indirect support for the Repr. 1B classification, they do suggest that developmental defects, including cleft palates, are intrinsic, adverse effects specifically associated with some organotin compounds.

RAC therefore considers that these effects warrant classification as Repr. 1B – H360D for developmental toxicity (Repr. Cat. 2 (R61) under the DSD). No data suggest that the observed effects may not be relevant to humans.

Combining the toxicological data for both development and fertility, the RAC considered that the appropriate resulting classification was Repr. 1B (H360FD) under the CLP Regulation and Repr. Cat. 2; R60-61 according to DSD.

ANNEXES:

Annex 1 Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in RAC boxes.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and rapporteurs' comments (excl. confidential information).