Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

Dioctyltin bis(2-Ethylhexyl mercaptoacetate)

EC Number: 239-622-4

CAS Number: 15571-58-1

ECHA/RAC/CLH-O-000000243-78-01/F

Adopted

8 June 2012

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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 Regulation (EC) No 1272/2008 (CLP Regulation), the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling of

Substance Name: Dioctyltin bis(2-Ethylhexyl mercaptoacetate)

EC Number: 239-622-4

CAS Number: 15571-58-1

The proposal was submitted by industry **ARKEMA, on behalf of ETINSA** and received by RAC on **25 March 2011**.

The proposed harmonised classification:

	CLP Regulation (EC) No 1272/2008	**Directive 67/548/EEC**
Current entry in Annex VI to CLP Regulation	-	-
Proposal by dossier submitter for consideration by RAC	Repr. 2 (H361d)	Repr. Cat. 3; R63
Resulting harmonised classification (future entry in Annex VI to CLP Regulation) based on the proposal by the dossier submitter	Repr. 2 (H361d)	Repr. Cat. 3; R63

PROCESS FOR ADOPTION OF THE OPINION

ARKEMA, on behalf of ETINSA, 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/consultations/harmonised_cl/harmon_cl_prev_cons_en.asp*** on **25 March 2011**. Parties concerned and MSCAs were invited to submit comments and contributions by **9 May 2011**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Agnes Schulte**

Co-rapporteur, appointed by RAC: **Bert-Ove Lund**

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

The RAC opinion on the proposed harmonised classification and labelling has been reached on **8 June 2012,** in accordance with Article 37 (4) of the CLP Regulation; giving parties concerned the opportunity to comment. Comments received are compiled in Annex 2.

The opinion of RAC was adopted by **consensus**.

OPINION OF RAC

RAC adopted the opinion that **Dioctyltin bis(2-Ethylhexyl mercaptoacetate)** should be classified and labelled as follows:

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008[1])

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)		
	Dioctyltin bis(2-ethylhexyl mercaptoacetate)	239-622-4	15571-58-1	Repr. 1B	H360D	GHS08 Dgr	H360D	-	-	-

Classification and labelling in accordance with the criteria of Directive 67/548/EEC

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
-	Dioctyltin bis(2-ethylhexyl mercaptoacetate)	239-622-4	15571-58-1	Repr. Cat 2; R61	T R: 61 S: 45-53	-	

[1] It is the view of RAC that hazard statement H360D is the most appropriate, given the available toxicological profile of Dioctyltin bis(2-ethyhexyl mercaptoacetate), but RAC recognized that H360 could be applied if the available criteria are applied strictly.

SCIENTIFIC GROUNDS FOR THE OPINION

The opinion relates only to those hazard classes that have been reviewed in the proposal for harmonised classification and labelling by the Dossier Submitter.

HEALTH HAZARDS

Toxicity to reproduction

Summary of Dossier Submitter's proposal

The CLH report presents five studies relevant for the assessment of reproductive toxicity. Although more detailed information would have been beneficial, the data give clear evidence of developmental toxicity in three different species.

The findings of developmental effects include:

- reduction in fetal body weight in rabbits and mice
- increased post-implantation losses in rats, rabbits and mice
- abortions in rabbits
- increased number of stillbirths in rats
- increased rates of pup mortalities in rats (PND 4 > PND 1, reduced lactation index (PND 21))
- increased incidences of minor visceral anomalies, skeletal head anomalies, and skeletal variations in rabbits
- increased incidences of skeletal variations, skeletal abnormalities, cleft palate, and exencephaly in mice
- reduced thymus weights in F1 pups (indicative for developmental immunotoxicity ≥60 ppm (4.4 mg/kg bw/day, 2-gen study, rat))
- reduced T-cell mitogen response (indicative for an immunosupressive effect) in directly dosed weanlings (rats) from PND 3-24, indicating that weanlings are more sensitive than young adults

The effects occur at daily doses of 23-100 mg/kg bw/day, and for some of the effects with clear dose-response. At these dose levels, there are signs of maternal thymotoxicity in some of the studies (signs in rats and in mice (mice are based on a LOAEL comparison 50-fold less sensitive than rats), no signs in rabbits), and the maternal toxicity caused by these dose levels can therefore according to RAC be characterised as slight.

The Dossier Submitter proposed that the maternal thymotoxicity should be characterised as moderate maternal toxicity, and that the developmental effects could have been secondary to the maternal toxicity, warranting classification for developmental toxicity in Repr. Cat. 2 (H361d) (CLP) and Repr. Cat 2; R63 (DSD). Visceral abnormalities in rabbits were considered to be related to fetal growth retardation.

Comments received during public consultation

No new information was received during the public consultation. Six Member States questioned that the maternal thymotoxicity is moderate and that the developmental effects could have been secondary to the maternal toxicity, and were rather of the opinion that the substance should be classified in Repr. Cat. 1B (H360D) (CLP) and Repr. Cat 2; R61 (DSD). More details on the studies reported and an overview table on substances used for testing were added by the Dossier Submitter in a revised version of the CLH report submitted after public consultation. This version can be found attached to the RCOM.

There were also requests for more detailed data from the studies, discussion on developmental immunotoxicity and effects on fertility. The thymus is clearly a target organ in the developing animal as well as in adults, and there is some evidence to suggest that young animals are more sensitive than adults. However, the available data do not allow RAC to make a firm conclusion on this.

Outcome of RAC assessment - comparison with the criteria and justification

The major difference in the assessment made by the Dossier Submitter and RAC concerns whether the developmental effects could have been secondary to the observed maternal (thymo-)toxicity.

In agreement with comments received during public consultation, RAC also finds that the signs of maternal thymotoxicity are rather to be characterised as slight. Furthermore, RAC notes that the developmental toxicity studies are rather short (10-13 days), with some effects (post-implantation losses) likely to have occurred after just a few days of exposure, and that the maternal thymotoxicity may not have been implemented as functional effects on the immune system after such short exposure periods. In addition, there is no plausible link between the thymotoxicity and the different types of developmental effects observed in three species. The strongest thymocytic (T-cell suppressive) effect was observed in the rat, however higher level of evidence for developmental toxicity came from mice and rabbits, which were much less sensitive to maternal thymotoxicity.

To clarify the potential contribution of maternal toxicity the following observations are informative: In mice (Faqi *et al*., 2001) that received a mixture (80:20%) of DOT(IOMA) (diisooctyl 2,2'-[(dioctylstannylene)bis(thio)]diacetate, CAS No. 26401-97-8, EC no 247-660-0) and MOT(IOMA) (triisooctyl 2,2',2''-[(octylstannylidyne)tris(thio)]triacetate, CAS no. 26401-86-5, EC no. 247-665-5) on GD 6-17, skeletal variations were significantly increased at dose levels (≥20 mg/kg bw/day) below those causing thymus weight effects (45 mg/kg bw/day). Significant increases of skeletal abnormalities were seen at ≥67 mg/kg bw/d while no signs of maternal toxicity were recorded except decreased liver weight and one dead dam at 100 mg/kg bw/day. Significant maternal toxicity was also absent in rabbits at doses where abortions, fetolethality and skeletal /visceral abnormities were seen (Battenfeld, 1992). RAC is therefore of the opinion that the maternal thymotoxicity has no bearing on the reproductive toxicity observed in these species, and supports the view expressed by the six Member States during public consultation on this issue.

According to RAC, there is clear evidence of developmental toxicity in three different species, while there are no or only slight signs of maternal (thymo-)toxicity. The observed developmental toxicity is not considered to be a secondary non-specific consequence of the (thymo-)toxicity. Additionally, there is no mechanistic information that raises doubt about the relevance of the developmental effects for humans. Classification as Repr. 1B (H360D) according to the CLP criteria is therefore appropriate. The corresponding classification under DSD is Repr. Cat. 2; R61.

Repr. 1A is not appropriate in view of the lack of human data. Repr. 2 should be chosen if there is only some evidence or the quality of evidence is less convincing. In this case, there is clear evidence of developmental toxicity occurring in three different species, where the evidence comes from convincing studies.

Regarding effects on fertility, the available data indicate that all toxic effects occur post-implantation; however RAC noted that the proposal was targeted at developmental effects. It is concluded that data may not be sufficiently detailed or complete for a comprehensive evaluation for the endpoint fertility. Thus no decision is taken with regard to this endpoint.

RAC remarks on read-across and category approach to a common metabolite

None of the studies of concern for reproductive toxicity were conducted on the DOT(2-EHMA) (Dioctyltin bis(2-ethyhexyl mercaptoacetate), which is proposed for classification. The key studies referred to in the proposal used Dioctyltin bis(IOMA) [CAS no. 26401-97-8]:Octyltin tris(IOMA) [CAS no. 26401-86-5] mixture (≥80:<20%) (two rat studies, one study in rabbits, one study in mice) and DOTC (Dioctyltin dichloride, EC no. 222-583-2, CAS no. 3542-36-7))(one rat study).

The Dossier Submitter's view in the original CLH dossier was that DOTC is an appropriate surrogate for the mammalian toxicity of the corresponding thioesters DOT(2-EHMA/(IOMA) due to its 100% hydrolysis in simulated mammalian gastric contents within 30 min, and RAC shares this view.

Reproductive findings from the DOTC study are consistent with findings on DOT(IOMA) in rats (no comparison possible for other species). This indicates that these structurally similar substances either have the same inherent reproductive toxicity or form a common hydrolysis product (e.g. DOTC) which is a reproductive toxicant.

This category concept is internationally accepted for the oral route (see OECD SIAR on dioctyltin compounds http://webnet.oecd.org/Hpv/UI/SIDS_Details.aspx?id=FA10501B-95AD-42C8-8873-42AC7BB34E9E).

In conclusion DOTC is considered by RAC as the active moiety causing developmental effects in mammalian species. DOTC is a hydrolysis product of DOT(2-EHMA) and of DOT (IOMA), which are structurally similar and which immediately form DOTC at comparable hydrolysis rates after oral administration Therefore read-across from DOT(IOMA) and DOTC to DOT(2-EHMA) appears to be justified.

In absence of any reasons that may indicate significantly (significant in the meaning of qualitative difference) lower toxicity of DOT(2-EHMA) than of the other members of this dioctyl tin group, similar reproductive effects are expected for DOT(2EHMA) as for the tested substances. Thus, the read across to DOT(2EHMA) is fully justified.

If in future, new data may show that there are quantitative differences in the potency of DOTC, DOT(IOMA) and DOT(2-EHMA), these might be relevant when considering specific concentration limits (when agreed and adopted) for this endpoint but not for classification.

RAC recommendations

While the present CLH dossier proposes classification of DOT(2-EHMA) only, RAC encourages a Member State to consider the preparation of classification dossiers on DOTC and DOT(IOMA) in order to achieve a consistent classification of these category members.

ANNEXES

Annex 1 Background Document (BD)[1]

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excl. confidential information). A revised version of the CLH report, submitted after public consultation by the Dossier Submitter as part of the RCOM, is included in Annex 2, section 2.

[1] The Background Document (BD) gives 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.