Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

2-ethylhexyl 10-ethyl-4,4-dimethyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate

EC Number: 260-829-0

CAS Number: 57583-35-4

CLH-O-0000001412-86-10/F

Adopted

30 November 2012

Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu

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CLH-O-0000001412-86-10/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:

Chemical name:	**2-ethylhexyl 10-ethyl-4,4-dimethyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate**
EC Number:	**260-829-0**
CAS Number:	**57583-35-4**

The proposal was submitted by **France** and received by the RAC on ***14 February 2012***

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).

The proposed harmonised classification

	CLP	**DSD**
Current entry in Annex VI of CLP Regulation (EC) No 1272/2008	**Not included in Annex VI, Table 3.1**	**Not included in Annex VI, Table 3.2 (CLP)**
Proposal by dossier submitter for consideration by the RAC	Repr. 2 - H361d Acute Tox.4 - H302 Skin Sens.1B - H317 STOT RE1 - H372 (nervous system)	Repr. Cat. 3; R63 T; R48/25 Xn; R22 R43
Resulting harmonised classification (future entry in Annex VI of CLP Regulation) as proposed by dossier submitter	Repr. 2 - H361d Acute Tox.4 - H302 Skin Sens.1B - H317 STOT RE1 - H372 (nervous system))	Repr. Cat. 3; R63 T; R48/25 Xn; R22 R43

PROCESS FOR ADOPTION OF THE OPINION

France 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 **14/02/2012.** Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **30/03/2012**.

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by the RAC: **Helmut Greim**

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 **30 November 2012***,* 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 **2-ethylhexyl 10-ethyl-4,4-dimethyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate** should be classified and labelled as follows:

Classification and labelling in accordance with CLP

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard state-ment Code(s)	Pictogram, Signal Word Code(s)	Hazard state ment Code(s)	Suppl. Hazard statement Code(s)		
050-028-00-2	2-ethylhexyl 10-ethyl-4,4-dimethyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate	260-829-0	57583-35-4	Repr. 2 Acute Tox.4 Skin Sens. 1A STOT RE 1	H361d H302 H317 H372(nervous system, immune system)	GHS07 GHS08 Dgr	H361d H302 H317 H372(Nervous system, immune system)			

Classification and labelling in accordance with the criteria of DSD

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
050-028-00-2	2-ethylhexyl 10-ethyl-4,4-dimethyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate	260-829-0	57583-35-4	Repr. Cat. 3; R63 T; 48/25 Xn; R22 R43	T R: 22-43-48/25-63 S: (1/2-)-36/37-45-46		

SCIENTIFIC GROUNDS FOR THE OPINION

Acute toxicity

Summary of the Dossier submitter's proposal

The CLH report includes one acute oral toxicity study, done according to OECD 401 with no reported deviations (Morton International, 1996). The combined LD_{50} for both sexes was established at 1150 mg/kg and the dossier submitter proposed a classification of Acute Tox. 4 –H302 according to the CLP regulation and Xn R22 according to Directive 67/548/EEC.

Comments received during public consultation

Comments were received from two Member States during public consultation. One was in agreement with the proposed classification while another argued for additional classification of DMT(EHMA) for acute toxicity by the dermal and inhalation route. Further details can be found in the RCOM.

Assessment and comparison with the classification criteria

In an oral acute toxicity study, five rats of ten (one male and four females) died at the dose of 1250 mg/kg bw and the acute oral LD_{50} was determined at 1150 mg/kg bw. At the dose of 880 mg/kg bw four out of five females died indicating that the LD_{50} for females is between 625 and 880 mg/kg bw. The LD_{50} for either females or combined sexes are therefore between 300 and 2000 mg/kg bw, which according to the CLP regulation warrants a classification as Acute Tox. 4, H302. Falling between 200 and 2000 mg/kg bw, this therefore warrants a DSD classification of Xn; R22). The RAC agrees with the proposal by the DS.

The RAC did not evaluate acute dermal or inhalation toxicity or skin irritation, since the dossier submitted did not address these endpoints.

Skin sensitisation

Summary of Dossier submitter's proposal

The CLH report includes two studies on skin sensitisation, one Guinea pig Maurer Optimization test (CIBA-GEIGY, 1975) and a modified Buehler test (Dow, 1989). The guinea pig optimization test showed a response in 55% of animals while the modified Buehler test showed no response. The dossier submitter proposes a classification of Skin Sens. 1B – H317 according to the 2nd ATP to the CLP regulation and DSD.

Comments received during public consultation

Two Member States submitted comments on skin sensitisation during public consultation. Both argued that given the strong positive reaction seen in the guinea pig optimization test, classification for Skin Sens. 1A – H317 should be considered. The dossier submitter agreed with the comments received and the changes can be seen in a revised version of the CLH report, supplied as an appendix to the RCOM.

Assessment and comparison with criteria

In the Maurer Guinea pig optimization test, 10 animals per sex were injected intra-dermally with 0.1 ml of the 0.1% test substance in saline. A total of 6 injections were applied during the 3 weeks of induction. Two weeks after the last injection, 0.1 ml of the test substance was applied intra-dermally. The reaction was assessed 24 hours later and a strong positive response was observed (Draize score 1 in 4/10 males and 7/10 females). A Buehler test in Guinea pigs revealed negative results.

A strong reaction was observed in the Guinea pig optimization test where 55% of animals showed an erythema score of 1 (Draize) 24 hours after removal of dressing. Although the Maurer optimization test is not guideline compliant, the RAC considers that the Draize scores from this test may be used in the same way as those arising from the guideline compliant tests. Since ≥ 30% of animals responded after a ≤ 0,1% intradermal induction dose, the criteria for Skin Sens 1A - H317 according to CLP (DSD:Xi, R43) are met.

Repeated dose toxicity (DSD) and specific target organ toxicity (CLP) – repeated exposure (STOT RE)

Summary of Dossier submitter's proposal

No repeated dose toxicity studies are available on DMT(EHMA). The dossier submitters presented the results of a simulated gastric hydrolysis study, which demonstrated the rapid hydrolysis of DMT(EHMA) to dimethyltin dichloride (DMTC) and 2-ethylhexyl mercaptoacetate (EHMA). The DS therefore proposes to use read-across from DMTC to classify for DMT(EHMA). Two repeated dose toxicity studies on DMTC are presented in the CLH report, one 90-day oral (drinking water) repeated dose study in rats similar to OECD 408 and OECD 424 (neurotoxicity in rodents) (Rohm and Haas, 1999) and one 90-day oral (diet) repeated dose study in rats similar to OECD 408 (Elf Atochem , 1996). In addition, one 28-day repeated dose study using EHMA was included (BIBRA. 1998). The DS concludes that the DMT moiety is of greater toxicological concern than EHMA and proposes classification as STOT RE 1 according to the CLP Regulation (DSD: T; R48/25 .

Comments received during public consultation

Two comments from Member States were received during public consultation. One supported the classification proposal while another argued that the effects were seen at dose levels which are borderline between STOT RE 1 and STOT RE 2 and requested further analysis on the EHMA moiety. Further details can be found in the RCOM.

Assessment and comparison with criteria

Since no studies on DMT(EHMA) are available, the DS refered to the studies on DMTC and EHMA. In an *in vitro* study (ORTEP 2000) a concentration of 2 µg/mL DMT(EHMA) (80% with 20% MMT(EHMA)) was tested at a pH of approximately 1-2 (0.07 N HCl) at 37°C in order to simulate the possible hydrolytic action on mammalian gastric contents. The degree of hydrolysis was studied by determination of the DMTC content in the water fraction after extraction of DMT(EHMA) in heptane. The conversion of DMT(EHMA) to DMTC was rapid. The calculated percentage of hydrolysis was 103% after 0.5 hours. This supports the use of data from DMTC to evaluate DMT(EHMA). It is estimated that approximately 1mg of DMTC is released from every 2.5 mg of DMT(EHMA)

In the two oral 90-day studies on DMTC the main target organ was the nervous system. Deaths and severe neurological signs occurred from 75 ppm (5.2/6.7 mg/kg/day) in Rohm and Haas (1999), as evidenced by moderate vacuolisation in the brain and spinal cord tissue and ventricular dilation and neuronal necrosis at highest doses. At 25 ppm (equivalent to 1.6 and 2.2 mg/kg/day for males and females, respectively), no mortality occurred and treatment-related findings were limited to reduced food (males only) and water intake and neuropathological lesions with moderate vacuolization in brain and spinal cord tissue. The NOAEL was considered to be less than 25 ppm. In the Elf Atochem (1996) study deaths and severe neurological signs occurred at 200 ppm (16.81/17.31 mg/kg/day), with similar lesions to those found in the Rohm and Haas (1999) study. Histopathology was not performed at lower doses. The overall NOAEL for neuropathology was 0.6 mg/kg bw/day for the dimethyltin dichloride component of the mixture.

The critical effects (death and histopathological lesions in the brain) identified in the 90-day studies occurred between 1.6 and 6.7 mg/kg bw/day DMTC, which corresponds to 4 and 16.75 mg/kg bw/day of DMT(EHMA).

The RAC notes that absolute and relative weights of the thymus have been reduced in a 90-day oral study, with effect levels at about 5 mg/kg bw/day in males (Rohm and Haas, 1999), and in another 90-day oral study about 15 mg/kg bw/day in both sexes (including histopathological lesions) (Elf Atochem 1996). Since no histochemical analysis has been performed at the lower dose of 1 mg/kg/day in the latter study it remains unclear whether effects on the thymus at this dose can be excluded, and the effect on the thymus at 5 mg/kg/day in the 90 days oral Roehm and Haas (1999) study is considered to be relevant for a hazard statement.
Reduced thymus weights have also been observed in the two developmental studies (Noda, 2001) on day 20 of gestation at 15 and 20 mg/kg/day. The effects observed on the thymus are consistent with a class effect of organotins on the immune system.
The threshold level for classification as toxic under DSD is 5 mg/kg/day. A classification of T; R48/25 according to Directive 67/548/EEC is therefore supported.

Substances that cause significant and/or severe toxic effects of relevance to human health at ≤ 10 mg/kg/day in a 90-day study shall be classified under CLP in Category 1. Since effects are seen below that level, classification as **STOT RE 1- H372** is warranted. The main target organs identified are the central nervous system and the immune system, therefore **nervous system and immune system** should be added as target organs to the hazard statement. A specific concentration limit is not warranted, because the effective dose level or concentration is not 10 times below the guidance value of ≤ 10 mg/kg according to the CLP.

Reproductive toxicity

Summary of Dossier submitter's proposal

No reproductive toxicity studies on DMT(EHMA) are available so the DS applied read-across from DMTC. Please see section on repeated dose toxicity for further details. Two prenatal developmental studies in rats (gavage) similar to OECD 414 (with some deviations on group size and exposure) were evaluated in the CLH report (Noda *et al*., 2001). In addition, two developmental neurotoxicity studies in rats (drinking water) similar to EPA OPPTS 870.6300 were presented (Ehman, 2007). One supporting study (Noland, 1983) is included to demonstrate transfer of DMTC to blood and brain of foetuses from exposed mothers during gestation. Based on effects seen in the prenatal development and neurotoxicity studies, the DS proposed a classification of Repr. 2 – H361d according to the CLP Regulation (DSD: Repr. Cat. 3; R63). Effects on fertility were not examined in the CLP report.

Comments received during public consultation

Comments were received from four Member States during public consultation. Two member states supported the proposal while one suggested considering classification as Repr. 1B – H360D. The fourth Member State suggested no classification was warranted. Further details, including the dossier submitter's response, can be found in the RCOM.

Assessment and comparison with criteria

No data regarding developmental toxicity are available for DMT(EHMA). The RAC considers read-across from DMTC to be acceptable; please see section on repeated dose toxicity for further details.

Evaluation of toxicity for reproduction of DMT(EHMA) is based on the two prenatal development studies (both published in Noda, 2001) and two developmental neurotoxicity studies (both in Ehman, 2007). In the first study of Noda (2001) (oral treatment on days 7-17 of gestation at 0, 5, 10, 15, and 20 mg/kg bw/day), severe maternal toxicity occurred at the high dose of 20 mg/kg/day. These clinical signs of toxicity were vaginal bleeding, tremors and convulsions (30%), ataxia and other signs of toxicity (severe thymus atrophy) (100%) and they generally appeared after the 15th day of gestation. Oral administration of DMTC at 20 mg/kg/day resulted in the death of two pregnant rats (20%). At this dose, total absorption was observed in one of eight living pregnant rats, which exhibited all these clinical signs of toxicity in the late stages of gestation. DMTC at 20 mg/kg/day also caused cleft palate in 21 foetuses (22%). The teratogenicity of DMTC occurred in the presence of severe maternal toxicity at this dose level. Mean body weight in living foetuses of both sexes decreased in a dose-dependent manner with statistical significance at 15 and 20 mg/kg/day.
In the second study of Noda (2001), shorter periods of DMTC treatment (two or three consecutive days at one of four different periods of gestation) and daily doses of 20 or 40 mg DMTC/kg bwt were chosen in order to reduce maternal toxicity. The highest dose (40 mg/kg/day) caused slight maternal toxicity as indicated by the reductions of the adjusted body weight gain and the thymus weight. No significant increase in the incidence of external, skeletal or visceral malformations were observed at either dose in any treatment period group, and no cleft palate was found. Foetal body weight was also unaffected.

In the developmental neurotoxicity studies (Ehman, 2007) the effect of DMTC in drinking water was evaluated in two experiments. In the first, female Sprague-Dawley rats were exposed via drinking water to 0, 3, 15, and 74 ppm DMTC daily before mating and throughout gestation and lactation. Reduced maternal weight gain occurred at the highest dose. In the offspring, decreased brain weight, decreased apoptosis and mild vacuolation in the brain of adult offspring, and slower learning in the water maze have been observed. In a second study, DMTC via drinking water has been provided from gestational day 6 to weaning. The high concentration depressed maternal weight gain, decreased offspring birth weight and pre-weaning growth, and decreased brain weight. Learning deficits were observed in the runway at postnatal day 11 at 15, 74 ppm and again in the adult offspring in the water maze at 15 ppm, although the latter has not been seen at the highest concentration. However, these effects occurred either in one study only, had no dose response relationship or, occurred in the presence of maternal toxicity.

During public consultation one Member State recommended to evaluate the Reprotoxicity studies on EHMA, which are described in the published registration data. After reviewing these data the DS concluded that the reproductive and developmental screening test published on the ECHA website (registration data) does not show any effects justifying classification for these endpoints. The RAC agreed with this conclusion. In the OECD 421

screening assay male and female rats received 0, 10, 50 and 150 mg EHMA/kg bwt. No test article-related effects on male and female mating indices, male copulation or female conception index were shown. There were no effects on gestation length or on numbers of corpora lutea or implantation sites at the lower doses. Slight reductions in the mean numbers of corpora lutea and implantation sites and decreased numbers of pups born corresponded to reduced maternal body weight gain late in gestation. Since these effects were attributed primarily to a single female with only 6 corpora lutea the effects have not been considered test article-related. The decreased viability and growth of F1 animals through post-partum day 4 also occurred at the 150 mg/kg bwt/day dose at which maternal toxicity occurred.

In conclusion

- DMTC induced cleft palates in the foetuses at 20 mg/kg/day, in presence of severe maternal toxicity at this high dose level (Noda, 2001, first study). No significant increase in the incidence of cleft palates or other external, skeletal or visceral malformations were observed in a second study at similar or higher dose levels although the substance was administered for shorter durations but covering the whole embryogenesis period. Maternal toxicity and malformations were not observed in the Ehman (2007) studies, which may be due to lower dosage (high dose between 4 and 12 mg/kg). Therefore, considering the absence of reproducibility in both studies in Noda (2001) and since no skeletal malformations seen in the Ehman (2007) studies, the occurrence of cleft palate in one study in the presence of severe maternal toxicity is not considered sufficient to place the substance in category 1B.

- DMTC induced a decrease in foetal body weight at 15 and 20 mg/kg (Noda, 2001, first study). At these doses, maternal toxicity was also observed but the magnitude of foetal weight decrease (-17% and -37% in male pups and -15% and -34% in female pups) exceeded the magnitude of maternal weight decrease (-5% and -24%). These effects did not occur in the second study at similar or higher dose levels although the substance induced significant decrease in maternal adjusted body weight gain. In Ehman (2007), a decrease in foetal body weight was observed only at high dose (7-12 mg/kg) in the second experiment during lactation when maternal weight was also significantly decreased. The link between foetotoxicity and maternal toxicity is therefore likely and cannot be totally excluded. Therefore, the evidence is not considered sufficient to place the substance in category 1B.

- DMTC showed developmental neurotoxic potential in Ehman (2007). The absence of reproducibility of the effects observed in the runaway and water maze tests does not permit a clear conclusion to be drawn. Besides, the studies are not consistent with guideline requirements, which raises further uncertainties on the significance of the results. Due to these uncertainties, the evidence is not considered sufficient to place the substance in category 1B.

The effects reported above support classifying DMTC as a reproductive toxicant for effects seen on development. Due to the inconsistencies in these effects, the RAC agrees with the DS proposal and considers classification of DMT(EHMA) in category Repr. 2 - H361d justified (DSD: Repr. Cat 3 Xn R63).

As the dossier submitted did not address the fertility endpoint, the RAC did not evaluate this aspect of reproductive toxicity.

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 the 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).