Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the 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/A2

Adopted

30 November 2012

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

ECHA has compiled the comments received via internet that refer to several hazard classes and entered them under each of the relevant categories/headings as comprehensive as possible. Please note that some of the comments might occur under several headings when splitting the given information is not reasonable.

Substance name: 2-ethylhexyl 10-ethyl-4,4-dimethyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate, DMT (EHMA)
EC number: 260-829-0
CAS number: 57583-35-4

General comments

Date	Country/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
26/03/2012	Germany/MSCA	The German CA thanks the France CA for preparing the dossier. In chapter 1.1 of the IUCLID file the type of substance is missing. Here mono-constituent and organometallic should be stated.	It has been added in the chapter 1.1 of the IUCLID file that it is a monoconstituent and an organometallic substance.	Noted
29/03/2012	Belgium/ MSCA	On page 16, in sections 4.2.4 and 4.2.5: H312 should be replaced by H302.	It has been corrected.	Noted
30/03/2012	Sweden/ MSCA	SE supports classification of DMT (EHMA) (Cas No 57583-35-4) as Acute Tox 4, H302 and STOT RE 1, H372 (with nervous system as main target organ) as specified in the proposal. SE agrees with the rationale for classification into the proposed sub category.	Thanks for your support	Noted
30/03/2012	Netherlands/ MSCA	As the classification proposal for DMT (EHMA) is based on the same set of information as DMTC, the same comments regarding the developmental tox classification are presented.	Ok	Noted

Carcinogenicity - no comments received
Mutagenicity - no comments received

Toxicity to reproduction

Date	Country/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
26/03/2012	Germany/MSCA	Editorial: The citation of the investigations of Noda, T. (2001) should be corrected from Nodal to Noda on page 9 and page 41.	It has been corrected.	Noted
		Page 9, second last paragraph: Please add to the signs of maternal toxicity listed in brackets also death and severe thymus atrophy.	It has been added.	Noted
		Please also consider our thoughts on Repro. 2 vs. 1B below.		
		Section 4.11.1 (Effects on fertility) In case that the reproductive organ system was investigated during repeat dose toxicity testing, then for the results please refer to section 4.7.	The reproductive organs were not investigated during repeated toxicity testing. It has been added on pages 17 (table 10), on pages 20, 22, 24 and on section 4.7.1.6.	Noted
		Section 4.11.2.1 (Table on pages 31-34): Please include in the description of maternal toxicity data from the study of Noda (2001) that also maternal thymus organ weight was clearly affected.	The description of maternal toxicity (with thymus weight reduction) has been included in the study of Noda.	Noted
		Furthermore information on and an evaluation of the available data on	The reproductive and	Noted

Date	Country/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		the reproductive toxicity of EHMA should be included in the dossier. ECHA has published registration data on EHMA (CAS 7659-86-1) on their website including a combined reproduction/developmental toxicity screening study. Section 4.11.5. Comparison with criteria: Based on the presentation of the available data base in the dossier, the proposal to classify DMTC as Repr. 2; H361d is supported. However, there are some remarks to make: 1. The cleft palates observed at the highest dose (20 mg/kg bw/d) (Noda, 2001, first study) seem to be an incidental finding. Severe maternal toxicity (mortality, clinical signs of toxicity (e.g. tremor and convulsion)) occurred at the high dose; there is no dose-response relationship and no reproducibility. 2. It is difficult to evaluate the developmental neurotoxic potential. Adversity of the behavioural test findings should be discussed in more detail. The significant reduction in brain weight seems to be more relevant to classify for developmental toxicity. Since there is no dose-response relationship in brain weight reduction, classification for Repr. 2 – H361d is sufficient. In addition, available information on the repeat-dose and reproductive toxicity of EHMA (CAS 7659-86-1/EC No. 231-626-4) – one of the gastric hydolysis products of DMT(EHMA) - should also be evaluated.	developmental screening test published on ECHA website (registration data) does not show any effects justifying classification for these endpoints. EHMA is not toxic for the organs for the reproduction and development. A sentence was added (on page 26), mentioning the non-classification of the EHMA, resulting from the data presented on ECHA website. So, there is no need to evaluate again the EHMA. 1. Although, the cleft palates occurred with severe maternal toxicity, this is such a rare and severe malformation in rats that it has to be taken into consideration. Besides, skeletal and visceral malformations are observed from the dose of 10 mg/kg bw, onward. These malformations support	The RAC supports classification for Repr. 2 (H361d). due to maternal toxicity and the contradictory neurotoxic effects.

Date	Country/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		For example, according to the registrant's summaries as published by ECHA, repeated administration of EHMA at and above 150 mg/kg already caused mortality (both in the OECD 421 and the repeat-dose toxicity studies published on ECHA's website), while this is not described in the study cited by ANSES in the present dossier. Also other effects, e.g. vasoactivity or narcosis are mentioned. Obviously, the proposal to classify DMT(EHMA) for developmental toxicity is based on read across to the corresponding toxic properties of DMTC. Therefore, the justification for the read-across between DMT(EHMA) and DMTC should be transferred from the DMTC classification proposal (there it is presented on page 36) to the classification proposal at hand. In addition, there is some uncertainty about whether the possible effects on reproduction and/or development resulting from simultaneous exposure towards DMTC and EHMA is correctly assessed by considering the toxicity of these compounds separately. Simple read-across from DMTC may be seen as likely to underestimate this risk. While conversely the available data may not suffice to put DMTC (EHMA) into Repr. 1B, we would suggest to at least add some text on the limitations and uncertainties of the evaluation.	the classification in Repr. 2. 2. Although it is very difficult to assess the neurotoxicity potential, we observe neurotoxic effects and propose to take those effects into account within the classification as Repro 2 H360d. The justification on the read across between DMTC and DMT(EHMA) has been transferred from the DMTC report to the DMT(EHMA) report. Indeed, there are not studies in literature on the substance DMT(EHMA), that is why the read across has been done from DMTC. Besides, EHMA has not been classified for the toxicity for the organs of the reproduction in the registration data published on ECHA website. So Repr. 1B is not adapted. A text has	Noted

Date	Country/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
			been added on page 27.	
29/03/2012	Belgium / MSCA	We support the classification proposal for reproductive toxicity as Repro.2 H361d for DMT(EHMA), based on read-across with DMTC.	Thanks for your support	
30/03/2012	Sweden/MSCA	We question the conclusion that the evidence is only sufficient to classify in Repro Cat 2. We think that it should be considered to classify in Repro Cat 1B based on the presence of cleft palate both at dose level 15 and 20 mg/kg/day (2.5 and 22.5 % respectively). Cleft palate was not detected in the second developmental study, however, this can be explained by the fact that the critical period for formation of the palate is around day 15.5 for rats. The three day dosing regime with dosing day 13-15 and day 16-17 could explain why no cleft palate was detected in the second study, either because concentrations high enough to cause damage in the fetus was not reached with only a three day dosing (not reaching high enough steady-state levels) or that dosing did not take place at the sensitive window of development.	We think that classification in Repro. 2 is more adapted because of maternal toxicity, absence of reproducibility and absence of dose-response relationship. We think that it would be too severe to classify in Repr. 1B. The information on the period for formation of the palate around day 15.5 for rats is interesting, but we think that the periods of day 13-15 and day 16-17 are very close to the day 15.5 and cannot explain totally the absence of cleft palate formation.	The RAC supports classification for Repr. 2 (H361d). due to maternal toxicity and the contradictory neurotoxic effects.
30/03/2012	Netherlands/ MSCA	The proposed classification for DMTC and DMT(EHMA) is Repr. Cat. 2 H361d and Repr. Cat 3, Xn R63) based on CLP and DSD, respectively. The substance is discussed in the TC C&L in 2006, and new information is presented by the dossier submitter. We want to share our doubts regarding the proposed classification. The main developmental effect (cleft palates) was observed only in the	Although cleft palate seems to appear with maternal toxicity, there are important skeletal and visceral malformations that occur at lower doses (5 and 10 mg/kg) without maternal toxicity and	The RAC supports this comment and the MSCA proposed C&L in Reprotox Cat. 2.

Date	Country/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		presence of (severe) maternal toxicity effects (20% mortality) and is therefore considered to be secondary to the maternal effects (CLP Annex I part 3.7.2.4.3). We agree that cleft palates are rare and serious malfomations. However, there is no knowledge on the occurrence of cleft palates in pups when the health of the dams is severely affected. The absence of cleft palates in the experiment with exposure during a limited interval of 2 days covering the same exposure window is a further indication that the effect may related to the maternal toxicity. It is acknowledged that DMTC can reach the foetal brains after administration to pregnant dams, and that brain weight reductions and histopathological lesions in the brain were shown in the developmental neurotoxicological study (exp. 1), although brain weight reductions were not decreased in a dose dependently way and the histopathological lesions are not statistically significantly different from controls. Moreover, these lesions were not reproduced in the second experiment. The effects on the brain such as reduced brain weight could also be related to the lower pup body weight. Maternal effects, other than body weights and food consumption, were not reported in this study. The foetal effects were observed at levels above the LOAEL in repeated dose studies. Further, pups may also be directly exposed to the test substance in the lactation period. This makes it unclear whether there is a specific effect on development or just the same effect as observed in the adult animals. Based on the above we wonder whether the neuropathological findings in the foetuses can be considered developmental effects.	there are neurotoxic developmental effects. So we think that classification in Repr. 2 is nevertheless necessary.	

Date	Country/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		Based on the presented information we propose not to classify the substance for developmental toxicity. Other organotin compounds Other organotin compounds such as dibutyltin have been classified as toxic to the development and others such as dioctyltin are under consideration for classification as toxic to the development. This is for dioctyltin based on positive results in other species. A read-across could be considered to strengthen the classification proposal for dimethyltin.	If read-across would have been included in the dossier, we think that it would be more appropriate to base a read across on MMTC (monomethyltintrichloride) classified Repro. 2 H360d, than on dibutyltin or dioctyltin. No read-across has been incorporated in the dossier,as the dossier concerns an hand-over substance: we therefore preferred to modify it minimally. Moreover, we think that there are sufficiently data to classify DMT EHMA as Repro 2 H360d.	The RAC supports the MSCA conclusion that there is sufficient information from DMTC to properly classify DMT (EHMA)

Respiratory sensitisation - no comments received

Other hazards and endpoints

Date	Country/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
26/03/2012	Germany/MSCA	Acute Toxicity, page 4 (Table 2) and page 10 (introduction to section 3): Please consider also proposing harmonised C&L for acute toxicity	We have not classified DMT(EHMA) for acute toxicity by dermal route	Noted and supported by RAC, because there is no indication

Date	Country/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		Justification: Based on more recent information than was available at the time the dossier was generated, notifiers to the C&L inventory (as of Feb 29, 2012) have in fact proposed different classifications for acute toxicity: - Acute Tox. 4 for oral AND dermal toxicity (56 notifiers) - Acute Tox. 4 for oral and Cat. 3 for dermal toxicity (4 notifiers) - Acute Tox. 4 for oral and no classification for dermal toxicity (5 notifiers)	and by inhalation because we have not found study on this substance by these exposure routes and a read across is not possible between DMTC and DMT(EHMA) by dermal route and by inhalation.	that DMT(EHMA) is sufficiently hydrolysed at the high ph values on the skin and the respiratory tract.
		It is also noted that ANSES in Table 2 proposes classification for acute oral toxicity, but does not propose classification for acute dermal toxicity (in contrast to 60/65 notifiers). The reason for this is not clear and should be explained.	We agree with you on the classification as Skin Sens1A because the GPMT study is in agreement with the criteria of the sub category 1A. It has been corrected.	Noted and further supported by thesensitizing potency of EHMA.
		Skin sensitisation, pages 4 (Table 2) and 17-19 : Please consider revising the justification for Skin Sens. 1B. Justification : The criteria for sub-categorising skin sensitisers are laid out in the 2nd ATP to the CLP regulation, while the corresponding update of the CLP guidance is still pending. Based on a GPMT, the criteria for sub-category 1A are met when > 30 % of the animals are sensitised following 0.1 % dilution. Thus Skin Sens. 1A could be assigned in the≤induction with a present case, where 40 % of the males and 70 (!) % of the females gave positive test results. Moreover, to our best knowledge, the 2nd ATP to the CLP regulation does not establish potency based on the severity of reaction, as proposed by ANSES, but only depending on the number of sensitised animals and the concentration of the test substance upon induction . On the other hand the classification as Skin sensitizer 1B can be supported for the following reasons:		

Date	Country/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		- the Maurer optimization test is not fully guideline compliant - the classification criteria are laid down for different test (i.e., the Guinea Pig Maximization Test), and - the Buehler test was negative.		
		Repeated dose toxicity: Page 20, table: Headline of second column: to be changed from 'dose mg/kg body weight, mg/kg diet' to 'dose, ppm in the diet (mg/kg body weight)'.	"dose, ppm in the diet (mg/kg body weight)" has been added.	Noted
		For the drinking water study as well as for the dietary study reported in chapter 4.7 it should be indicated which type of formulation of DMT (solid material or aqueous solution) has been used to create the finally administered test substance preparation.	We do not have this information.	Noted
		For both of the 13 week studies with DMTC, as well as for the 28-d study on EHMA (BIBRA 1998), it should be indicated, whether or not reproductive organs have been evaluated during these studies. If this was the case, information should be provided on the nature of the investigations performed. In addition, even in case of negative results, these should be reported in the table.	Reproductive organs have not been studied in BIBRA study. So effects on reproductive organs are not reported.	Noted
		Furthermore, the complete set of available data for EHMA (CAS 7659 86 1/EC No. 231-626-4) should be evaluated. ECHA has published registration data including summaries of a 7-day subacute test, a 28-d test, a dose range-finding test for an OECD 421 study and the OECD 421 study itself on their website. None of these study summaries are discussed in the present dossier, while a preliminary assessment suggests a higher level of toxicity than can be deduced from the BIBRA (1998) study.	Organs of the reproductive system have not been investigated. A sentence has been added on page 19 (table 10), page 20 and 22 and in	Noted
		Summary of repeated dose toxicity, section 4.7.1.6 (page 26/27): If organs of the reproductive system have been investigated and no		

Date	Country/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		effects were observed this should be reported as an additional result in section 4.7.1.6 (Summary and discussion of repeated dose toxicity). In general, we suggest to include a more comprehensive discussion, in particular on the repeat-dose toxicity of EHMA. The current discussion of EHMA in this section is now confusing to read and neither its intention nor possible conclusions are immediately evident: "The lowest dose (0.05% of EHMA, corresponding to 42 mg/kg/day of EHMA or 16.8 mg/kg/day of DMTC in the males and 45 mg/kg/day of EHMA or 18 mg/kg/day of DMTC in the females) leads to the little reduction in the amount of periportal fat in the livers from male and female rats and higher relative kidney weight for the males (at 42 mg/kg/day of EHMA or 16.8 mg/kg/day of DMTC)." While STOT RE 1 is supported for DMTC, the discussion whether to assign STOT RE 1 or 2 to DMT(EHMA) in our opinion is less straightforward and would need more argumentative backup. DMT moiety If the toxicity of EHMA is neglected then, as calculated by ANSES, it would take the 2.5fold amount of DMT(EHMA) to elicit the same toxicity as observed with DMTC. Thus, if 5.2 mg/kg bw/d is the relevant LOAEL for classification of DMTC, then extrapolation to DMT(EHMA) using a factor of 2.5 leads to a LOAEL of 13 mg/kg bw/d which is slightly higher than the relevant guidance value of 10 mg/kg bw/d for STOT RE 1 and would lead to classification with STOT RE 2. On the other hand, the guidance values are not limit values set in stone and allow for a certain flexibility in borderline cases. Here, exceedance	section 4.7.1.6 of summary and discussion. These data are new. Thank you for having informed us about the publication of the registration dossier of EHMA. Those information are not contradictory with those presented for the DMT(EHMA)) and would not modify our proposal. No new information on EHMA has been incorporated, as the dossier concerns an hand-over substance: we therefore preferred to modify it minimally. Moreover, we think that there are sufficiently data to classify DMT(EHMA) in STOT RE1.	Noted

Date	Country/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		of the guidance value is only small and without more detailed data on the dose response relationship such as effect size, group means and standard deviations, the uncertainty in the LOAEL cannot be evaluated. If ANSES has access to such data from the original study report, it is suggested to perform a BMD analysis which could provide insight in e.g. the ratio between BMD and BMDL. This would result in a more reliable assessment based on the whole dose-response relationship vs. reliance on only a point estimate. EHMA moiety In order to justify classification with STOT RE 1 vs. 2, also a thorough appraisal of the available data on EHMA appears helpful. As noted above, since the generation of the present dossier, registration data on EHMA (CAS No. 7659-86-1) have been published by ECHA. These are the LOAELs for effects potentially relevant for classification as provided by the registrant: 7-day oral study in SD rats (BG Chemie 1992): 200 mg/kg bw/d based on mortality 2-4 days after administration. 14-day oral study in rats (Author not given , 2005): 150 mg/kg bw/d based on mortality/severe toxicity. 14-day dermal study in guinea pigs (author not given, 1974): 0.58 mg/kg bw/d based on mortality after 7 days of treatment. 14-day dermal study in rats (author not given, 1974): 0.58 mg/kg bw/d based on mortality after 10 days of treatment. OECD 407 28-d study in SD rats (BG Chemie 1988): No relevant effects up to a dose level of 150 mg/kg bw/d.		

Date	Country/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		OECD 421 combined reproductive/developmental toxicity screening test in rats (author not given, 2005): 150 mg/kg bw/d based on mortality between days 4-22 of treatment. In addition, results of specific investigations also suggest narcotic effects and hypotension as possible results of EHMA administration. It is noted that for comparison with the guidance values for STOT RE classification, the LOAELs given above need to be extrapolated using Haber's law (e.g. for the 7-day study: divide by a factor of 13). While an independent assessment of these data is not available, they clearly point at a considerable potential of EHMA to cause severe toxicity, perhaps to a similar degree as the DMT moiety. The results also stand in contrast to the BIBRA study evaluated by ANSES in which no mortality was observed. Finally an additional argument for choosing STOT RE 1 over 2, could be that separating the action of both moieties conceptually does not take into account any potential combination effect.		
30/03/2012	Sweden/MSCA	In our opinion classification of DMT (EHMA) as a skin sensitizer in sub category 1A should be considered as we question the following reasoning and conclusion in 4.6.1.4 of the proposal: "With a concentration for intradermal induction of 0.1%, and an incidence sensitised guinea pigs of 55% (males and females), the potency calculated according to the table 3.4.2.3.4.2 in the guidance of the CLP criteria is considered as strong; so the classification in the sub-category 1B is justified." Guinea Pig Optimisation Test is an adjuvant test; thus a positive	I agree with you if you do not consider the sensitivity of the GPOT, according to the CLP criteria.So the classification in the sub-category 1A is more appropriate based on the strong effects observed.	The RAC supports classification in the subcategory 1A, which is further supported by the sensitizing potency of EHMA.

Date	Country/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		response of ≥ 30% of the animals will trigger classification according to the CLP. In the Optimisation Test any challenge reaction above an individual threshold value represent an allergic reaction, therefore also grade 1 is an allergic reaction. The Optimisation test is comparable to Guinea Pig Maximisation Test (GPMT) as regards the sensitivity of the test; therefore the criteria in the CLP for subcategorisation could be applied. Thus 55% sensitization with an induction concentration of 0.1% (≥ 30% responding at ≤ 0.1% intradermal induction dose) in the Optimisation Test would lead to a classification in sub category 1A. The result of the Buehler test (being a less sensitive test) is inconclusive as similar responses appeared in the test group and the control group.		

ATTACHMENTS RECEIVED: None