Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

2-ethylhexyl 10-ethyl-4-[[2-[(2-ethylhexyl)oxy]-2-oxoethyl]thio]-4-methyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate / (MMT(EHMA))

ECHA/RAC/CLH-O-0000001981-71-01/A2

Adopted

14 September 2011

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-[[2-[(2-ethylhexyl)oxy]-2-oxoethyl]thio]-4-ethyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate(MMT (EHMA))
CAS number: 57583-34-3
EC number: 260-828-5

General comments

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comment
24/02/2011	UK / MSCA	The classification of EHMA is based on read-across to MMTC, which was agreed previously by TC C&L. We support this approach.	Noted.	RAC has re-evaluated the data on mutagenicity of MMTC and concluded that the proposed C&L as Muta 2 (GHS) is not warranted
28/02/2011	Germany / Jan Averbeck / MSCA	The German CA agrees with the proposed classifications. However, there are some general comments: P3, PP5-9, IUCLID Section 1.2 "Composition": The substance identity of MMT (EHMA) is not consistent throughout the report and technical dossier. The concentration range is given as >= 20 - <= 90 % w/w (IUC) for the main constituent 2-ethylhexyl 10-ethyl-4-[[2-[(2-ethylhexyl)oxy]-2-oxoethyl]thio]-4-methyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate. This composition does not match the criteria for mono-constituent substances but could be any kind of substance (Mono/multi-constituent substances or UVCB substances). Moreover, there are impurities stated in the composition without any concentration given. DE wonders whether these are hypothetically occurring impurities resulting from production process or whether they are confirmed for substance identity by analysis. However, the substance identity	Noted Information from the registration dossier on composition has been included in the revised CLH dossier as confidential information (in IUCLID 5). Available information confirms that MMT(EHMA) is a mono-constituant substance. RSS from the registration dossiers have been included in the IUCLID 5 dossier. For studies for which no RSS was available, additional information has been added in the revised CLH report.	See above. Other comments noted.

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		should be clarified in accordance with RIP3.10 and the documents should be revised accordingly. Additionally, several molecular weight values are not correct or not consistent throughout the report and technical dossier. In addition, we ask the dossier submitter to provide Robust Study Summaries of all relevant toxicological studies in IUCLID 5. This is necessary because the presentation of the study results in the CLH report is not clearly arranged and thus difficult to read. General editorial comments: P8, classification of MMTC: replace "Muta. 2; H361d" by "Muta. 2; H341" P8, classification of MMTC: replace "Repr. 2; H330" by "Repr. 2; H361d" P13, 5.2.1: replace "LD50 (mg/l)" by "LD50 (mg/kg)" P14, 5.2.3: replace "LD50 (mg/l)" by "LD50 (mg/kg)" P19, table, 2nd row: Give number of animals per sex and dose P24, table: Give number of animals per sex and dose P29, table, 2nd row: Give number of animals per sex and dose	Noted. The comments have been considered in the revised CLH report.	
03/03/2011	Sweden / Ing-Marie Olsson / MSCA	In absence of any new data Sweden supports the proposed classification and labelling for 2-etylhexyl 10-etyl-4-[[2-[(2-ethylhexyl)oxy]-2-oxoetyl]thio]-4-methyl-7-oxo-8-oxa-3,5-dithia-4- stannatetradecanoate / (MMT (EHMA))(CAS Number: 57583-34-3), as agreed by the Technical Committee on Classification and Labelling (Directive 67/548/EEC) ('TC C&L').	Noted.	See above.

Carcinogenicity

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comment

Mutagenicity

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteur's comment
28/02/2011	Germany / Jan Averbeck / MSCA	We support the Submitter's conclusion	Noted.	RAC has re-evaluated the data on mutagenicity of MMTC and concluded that the proposed C&L as Muta 2 (GHS) is not warranted
03/03/2011	Ireland / Health and Safety Authority	The Irish CA is in agreement with the proposed classification Muta Cat 3; R68 (Muta 2- H341) as previously agreed by the TC C&L in 2006.	Noted.	RAC has re-evaluated the data on mutagenicity of MMTC and concluded that the proposed C&L as Muta 2 (GHS) is not warranted

Toxicity to reproduction

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comment
24/02/2011	UK / MSCA	We note that the classification is based on read-across from MMTC. As for MMTC, we consider the case for classification with Repro Cat 3; R63 to be borderline, based on the following observations: In the reproductive/screening study (Appel; 2004), conducted in Wistar rat, an increase in "post-implantation" loss (43 %) was observed in the high dose group (measured by subtracting the number of live foetuses from the number of implantation sites; no information on resorptions was provided). In addition, 30 of the 48 pups born alive were reported 'missing' by PND 4 and	In the study by Appel (2004), the test substance has a purity of ca. 84% MMTC and contains ca. 10% of DMTC. The available data on DMTC suggests that DMTC is foetotoxic with a NOAEL of 10 mg/kg in rat (see DMTC CLH report). In the Appel 2004 study, the effects are seen at the highest dose of ca. 50 mg/kg of test substance, which contains around 5 mg/kg of DMTC. The effects can therefore not be attributed to DMTC. No information is	RAC agrees that the case for classification with Repro Cat 2 (GHS) of MMTC is borderline. Although the interpretation of the available study has deficits and is difficult to interpret it cannot be ruled out that MMTC induces post implantation losses. RAC concludes therefore that classification with Repro Cat 2 (GHS) is warranted.

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		one was found dead. Given the magnitude of the effects, it appears unlikely that the effect on post-implantation loss/post-natal survival is a chance finding related to the low group sizes employed. However, there are a number of unknowns: • It is not known whether the post-implantation loss was due to increased embryo/foetal death in utero or increased pup death around the time of birth. If pups died and were cannibalised prior to group size determination this will bias the value derived for post-implantation loss • It is not known whether the pups went 'missing' owing to a developmental effect that resulted in their cannibalisation, whether the pups became ill and died through administration of the test substance via the milk or whether the dams cannibalised their pups because of a neurotoxic effect of the substance on the dams. • The test substance administered was a mixture of 83/ 9% MMTC/DMTC. The composition of the remaining 8 % of the test substance is not clear in the CLH report. It is also not clear if the presence of ~ 9 % DMTC (classified as repr Cat 3; R63 for foetotoxicity) contributed in some way to the effects observed. In addition, no effects on litter size or pup viability were observed in either of the two Moser developmental neurotoxicity studies, conducted in Sprague-Dawley rats at similar dose levels, using a purer form of the test substance (97 % purity). In these studies, the test substance was administered via the drinking water. We can see no reason why this route of administration should produce dramatically different results from dietary administration. We note that in the first Moser study, of the 30 dams selected/group, only 10-12 of them from each group (including the controls) delivered litters, which may reduce confidence in this study. However, in the second Moser study, which employed a higher dose, most of the dams successfully delivered litters.	available on the developmental toxicity of the other impurities. Their identity and concentration is presented in an additional confidential appendix I to the CLH report. No information is therefore available to show that the effect can be attributed to an impurity. We agree that cannibalisation of the pups in Appel 2004 introduces uncertainties in the analyses of the study results, both regarding post-natal effects as well as regarding what was identified as post-implantation loss in the high-dose group. However, cannibalisation was also observed in the other test and control groups although to a much lesser extent (respectively 16%, 25%, 3% and 62% of missing pups at 0, 30, 150 and 750 ppm). It is therefore difficult to fully explain cannibalisation by the neurotoxicity of the test substance. The magnitude of the effects observed in the high-dose group (43% of post-implantation loss and 65% of pups lost between PND 1 and PND4) raise strong concern on foetotoxicity of MMTC. CLP criteria states that "If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification". Overall and recognising the uncertainties due to postnatal cannibalisation by the dams, classification in category 2 is therefore considered appropriate. In Moser 2005 that was designed to assess more specifically	

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		Given the number of uncertainties associated with the screening study and the lack of effects observed in the Moser studies, we do not feel that there is a strong case for classification with Repr cat 3; R 63. However, we appreciate the decision is borderline. In addition, for the Appel study, please express the mg/kg diet values as ppm. At the moment, the tables give the impression that higher doses were achieved than actually were (i.e. the achieved intake in the developmental study at 750 mg/kg diet was only 49/53 mg/kg/day in males/females).	developmental neurotoxicity, no foetotoxic effect was identified when substance was administered in water. In absence of data on the influence of vehicle (water vs diet) it is not possible to either confirm or exclude that it may have impacted the ADME of the substance and its toxicity. The effect seen in the study by Appel cannot be fully dismissed. Doses in the Appel study have been expressed in ppm in the revised CLH report.	
28/02/2011	Germany / Jan Averbeck / MSCA	We support the Submitter's conclusion	Noted	Noted
03/03/2011	Ireland / Health and Safety Authority	The Irish CA is in agreement with the proposed classification Repr. Cat 3; R63 (Repr. 2- H361d) as previously agreed by the TC C&L in 2007.	Noted	Noted

Respiratory sensitisation

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comment

Other hazards and endpoints – Acute toxicity

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comment

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comment
24/02/2011	UK / MSCA	Page 16. Acute toxicity Although we appreciate this endpoint is not proposed for harmonisation, please note that there is a discrepancy between the acute oral LD50 value reported in the table and in the summary text.	The information has been checked and corrected in the summary text of the revised CLH report.	Noted
03/03/2011	Ireland / Health and Safety Authority	The Irish CA notes that the classification agreed by TC C&L in 2006/7 for acute toxicity (Xn; R21/22) has not been proposed for harmonisation, even though data justifying classification has been included in the Annex VI dossier.	Acute toxicity data are reported to provide information on the toxicological profile of MMTC but harmonisation is not proposed in agreement with article 36 (1) of CLP.	Noted

Other hazards and endpoints – Repeated dose toxicity

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comment
24/02/2011	UK / MSCA	Page 23. Repeat Dose As for MMTC, it was agreed at the October 2006 TC C&L meeting not to classify for repeat dose toxicity. We note neurotoxicological effects were observed at the top dose level (49/50 mg/kg/day) in the 90-day study. Given the change in boundary for repeated dose toxicity under CLP (100 mg/kg/day), the available data may support a classification for STOT-RE. Although on page 40 it is stated that data on repeat dose toxicity is provided for information only, might it be possible to justify harmonisation of this hazard class at a Community level?	Significant effects after 90 days at this dose are consistent with a classification STOT-RE in category 2. Besides, C&L notifications by industry indicate that classification STOT RE 2 – H373 is currently applied by all notifiers as shown in the CL inventory report that has been added to the revised CLH dossier as Appendix II (confidential). As this classification was not included in the CLH report submitted to comments in public consultation, it is not clear whether a harmonisation can be proposed for this endpoint.	Noted