Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Thixatrol® MAX

(Reaction mass of N,N'-ethane-1,2-diylbis(hexanamide) and 12-hydroxy-N-[2-[(1-oxyhexyl)amino]ethyl]octadecanamide and N,N'-ethane-1,2-diylbis(12-hydroxyoctadecanamide))

EC NUMBER: 432-430-3

CAS NUMBER: NOT ASSIGNED

ECHA/RAC/CLH-O-0000002529-68-01/A2

Adopted
3 May 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: Thixatrol® Max (Reaction mass of N,N'-ethane-1,2-diylbis(hexanamide) and 12-hydroxy-N-[2-[(1-oxyhexyl)amino]ethyl]octadecanamide and N,N'-ethane-1,2-diylbis(12-hydroxyoctadecanamide))
CAS number: not assigned
EC number: 432-430-3

General comments

Date	Country / Person / Organisation /MSCA	Comment	MSCA Response to comment	RAC response to comment
2011/10/14	France / Member State	France agrees with the removal of the skin sensitisation classification.	No comment, no further action required by the dossier submitter.	Noted
2011/10/14	United Kingdom / UK CLP CA / HSE / Member State	The UK CA would like to emphasise that this CLH proposal was submitted by the UK CA in accordance with Article 37(6) of CLP. This proposal was produced by Elementis UK Limited and reflects their opinions on the classification and labelling of this substance. However, the UK is in agreement with the proposal to remove Skin Sens 1 (H317) from the current Annex VI entry for Thixatrol Max.	No comment, no further action required by the dossier submitter.	Noted
2011/10/10	Sweden / Ing-Marie Olsson / Member State	Part B, 1 Identity of the substance Information on Name and identifiers of the substance, Composition of the substance and Physico/chemical properties of Thixatrol Max is missing. Parameters such as molecular formula, molecular weight range, structural formula, impurities, solubility and partition coefficient may be useful when considering the methodology used in the studies referred to in the proposal. Please add.	Substance i.d. is available in the confidential sections of the IUCLID dossier. However as the CLH report will be publically available, this information has been removed	Noted

Date	Country / Person / Organisation /MSCA	Comment	MSCA Response to comment	RAC response to comment
			from Part B as CBI. The water solubilities of the main components were determined at pH 5.14 as: Constituent 1 = 147 mg/l Constituent 2 = < 0.499 mg/l Constituent 3 = 0.104 mg/l (Method 92/69/EEC, A6 (Flask method)) The log Pow was determined to be >6.2 for all the main constituents of the substance. Method 92/69/EEC, A8 (HPLC)	Water solubility and log Pow are not listed in the IUCLID5 dossier
2011/10/06	Germany / Jan Averbeck / Member State	The German CA supports the proposed removal of the harmonised classification for skin sensitisation. However, we suggest some minor corrections: - The study results of LLNA in mice conducted on Thixatrol Max should be reported	The summary	Noted We agree with

Date	Country / Person / Organisation /MSCA	Comment	MSCA Response to comment	RAC response to comment
		and discussed in the CLH report. The testing results from the structural analogue (Thixatrol Plus) are supporting data.	of the LLNA data for Thixatrol Max are provided and discussed in the CLH report.. It is not clear what other information is required.	the dossier submitter.
		- The summary table of relevant study results (p. 13ff, Table 15) is confusing. Testing data from the structural analogue (Thixatrol Plus) should be deleted in the table to avoid redundancies.	If this is the preferred approach then data on Thixatrol Plus could be removed from the report. However, these data were included to provide the full background to the previous classification of this substance.	We agree that data on Thixatrol Plus could be removed from the report.
		- The detailed presentation of the Thixatrol Plus GPMT data and results of LLNA in mice conducted on Thixatrol Max reported in section "4.5.1.3 summary" (p. 18ff) should be described in section "4.5.1.1 Non-human information".	We note this comment. However, all data that are relevant to the classification	Noted

Date	Country / Person / Organisation /MSCA	Comment	MSCA Response to comment	RAC response to comment
			discussion have been included and we can not amend the dossier at this stage.	

Carcinogenicity

Date	Country / Person / Organisation / MSCA	Comment No comments received	MSCA Response to comment	RAC response to comment

Mutagenicity

Date	Country/ Person/ Organisation/ MSCA	Comment No comments received	MSCA Response to comment	RAC response to comment

Toxicity to reproduction

Date	Country / Person / Organisation / MSCA	Comment No comments received	MSCA Response to comment	RAC response to comment

Respiratory sensitisation

Date	Country / Person / Organisation / MSCA	Comment No comments received	MSCA Response to comment	RAC response to comment

Other hazards and endpoints

Date	Country / Person / Organisation / MSCA	Comment	MSCA Response to comment	RAC response to comment
2011/10/10	Sweden / Ing-Marie Olsson / Member State	Skin sensitization Part B, 4 Human Health hazard Assesssment The study by Sanders A (2009) is regarded as a key study and is taken as evidence of no sensitizing properties of Thixatrol-Max. However, the CLH report of the study does not clarify certain important aspects of the methodology used, which raises doubts on the reliability of the study. Therefore the following needs clarifications: - The choice of 25% as the highest test concentration has not been justified adequately. The highest test concentration should be maximized, and according to OECD TG 429 "….the highest concentration maximizes exposure whilst avoiding systemic toxicity and excessive local skin irritation….". Such information on toxicity and skin irritation to support the choice of the highest test concentration needs to be provided in the report. - The maximum test concentration was 25%. A higher test concentration was considered "unsuitable" (page 24). Please explain why. - It appears from the report that the test of the positive control α-HCA in 1% Pluronic L92 was not conducted at the same time as that of the test material. This is a weakness of the methodology. - The identity of the vehicle Pluronic L92 should be provided. - The studies by Aitchison G (2003) and Driscoll R (2009) have deficiencies and are not reliable. Therefore we do not agree that they can be used as supportive evidence in a weight of evidence evaluation of non-sensitising properties as stated in e.g. Table 15 and page 25.	A detailed response to these comments is provided at the end of this table.	We agree with SE comment and thank the dossier submitter for the clarifying response following the RCOM table. We agree with SE that the timing of the positive control study is a weakness. We agree, but note that it is freely available online We agree with SE

Date	Country / Person / Organisation / MSCA	Comment	MSCA Response to comment	RAC response to comment
2011/10/06	Germany / Jan Averbeck / Member State	Skin sensitisation: The German CA supports the proposed removal of the harmonised classification for skin sensitisation of Thixatrol MAX. The existing classification is based upon read-across to a structural analogue (Thixatrol Plus, EC Number 430-050-2). Based on the results of GPMT studies on Thixatrol Plus, Thixatrol MAX was classified as a skin sensitiser. There is information available demonstrating the need to revise the existing entry in Annex VI as Skin Sens. 1 H317 (May cause an allergic skin reaction)/ Xi; R43 (May cause sensitisation by skin contact). Thixatrol MAX was tested in three LLNA in mice. In the LLNA using 1 % Pluronic L92 in distilled water as vehicle Thixatrol MAX gave a maximum stimulation index of 0.94. Stimulation index of 8.14, 2.37, and 1.3 were determined with the positive control test substance α-hexylcinnamaldehyde when formulated in the same vehicle at concentrations of 25 %, 10 % and 5 % (2009). On the basis of a stimulation index below 3 Thixatrol MAX is not considered to be a skin sensitiser and does not require classification.	No comment, no further action required by the dossier submitter.	Noted
2011/10/14	Ireland / Health & Safety Authority / Member State	MSCA comments, which are based on the impurity profile of the substance which is not publically available. The Irish CA agrees that the result of the LLNA study (Sanders, 2009) conducted with Thixatrol Max supports the proposal to remove the classification for skin sensitisation. However, we note that Thixatrol Max contains an impurity, which is classified as a sensitiser. The impurity is present at a concentration which would trigger classification. Therefore, under current CLP criteria, the Thixatrol Max would require classification for sensitisation if the concentration of this impurity is ≥1 %.	It is our understanding that, other than for CMR properties, test data on the substance containing the impurity would take precedence over a classification derived from a calculation. The data on Thixatrol Max	We note the support. Regarding the content of impurities we refer to guidance provided by CARACAL (Doc. CA/87/2009) on

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			itself do not appear to meet the criteria for classification as a skin sensitiser. If the RAC agree with this interpretation the harmonised entry should be amended accordingly. The applicant is revising the REACH registration dossier to reflect the current typical level of the impurity of concern, which is below 0.02%. Hence, classification based on the presence of this impurity is adjusted accordingly.	Classification of substances containing an identified impurity, additive or individual constituent classified as a carcinogen, germ cell mutagen or reproductive toxicant (CMR) at a concentration above its specific or above the generic concentration limit. Reference is also made to Doc. CA/61/2011.

Response to Swedish CA comments on Local Lymph Node Assays conducted on Thixatrol Max

Responses prepared by the test facility responsible for conducting the study – 21 November , 2011

Skin sensitization
Part B, 4 Human Health hazard Assesssment

The study by Sanders A (2009) is regarded as a key study and is taken as evidence of no sensitizing properties of Thixatrol-Max. However, the CLH report of the study does not clarify certain important aspects of the methodology used, which raises doubts on the reliability of the study. Therefore the following needs clarifications:

- The choice of 25% as the highest test concentration has not been justified adequately. The highest test concentration should be maximized, and according to OECD TG 429 "….the highest concentration maximizes exposure whilst avoiding systemic toxicity and excessive local skin irritation….".
Such information on toxicity and skin irritation to support the choice of the highest test concentration needs to be provided in the report.

Response:
The test item, Thixatrol Max, was found to be poorly soluble in all vehicles recommended for use in OECD Test Guideline 429, Local Lymph Node Assay, i.e. acetone: olive oil (4:1), dimethyl formamide, methyl ethyl ketone, propylene glycol and dimethyl sulphoxide. The test item either formed suspensions that were unsuitable for application to the mouse ear (due to separation of the test item and vehicle phases) or that could be prepared only at concentrations lower than 25% (as in the case when using propylene glycol as vehicle). A non-standard vehicle, corn oil was used in the study of Driscoll (2009) but was found to be unsuitable due to failure of the known skin sensitizer α-HCA to produce a satisfactory positive response in the LLNA when diluted in this vehicle. When diluted in 1% aqueus Pluronic L92 for the study of Sanders (2009), it was possible to prepare suspensions of Thixatrol Max up to a concentration of 25%, that were suitable for application to the ears of mice. This concentration of test item produced no evidence of skin irritation or systemic toxicity in any mice in the study. Before commencing the study, attempts were made to prepare higher concentrations of the test item in 1% aqueous Pluronic L92, but the preparations were found to be unsuitable for application to the mouse ear. The concentration of 25% in 1% aqueous Pluronic L92 was therefore found to be the maximum that could be applied to the ears of the mice in the LLNA and hence provide maximum exposure to the test item.

- The maximum test concentration was 25%. A higher test concentration was considered "unsuitable" (page 24). Please explain why.

Response
Before commencing the study, attempts were made to prepare formulations of the test item in 1% aqueous Pluronic L92 at concentrations higher than 25%, but these were found to be unsuitable for application to the mouse ear. This was due to the physical nature of the test item, such that formulations of greater than 25% were neither a suspension nor a solution, the particles of test item becoming swollen and non-cohesive.

- It appears from the report that the test of the positive control α-HCA in 1% Pluronic L92 was not conducted at the same time as that of the test material. This is a weakness of the methodology.

Response
Before conducting a LLNA on Thixatrol Max using 1% aqueous Pluronic L92 as vehicle, a positive control study was conducted on the known skin sensitizer α-HCA to demonstrate the suitability of this vehicle and appropriate performance of the test by the test facility. This study was conducted between July 8 and July 14, 2009 and a satisfactory sensitization response was obtained. The LLNA on Thixatrol Max was then conducted between September 2 and September 15, 2009 (i.e. two months later). It was considered unnecessary to conduct another positive control study on α-HCA in 1% Pluronic L92, i.e. at the same time as the study on Thixatrol Max. The test facility had also conducted nine other LLNA positive control studies within the six months prior to the study on Thixatrol Max, using various other vehicles, and in each case obtained a satisfactory response.

- The identity of the vehicle Pluronic L92 should be provided.

Response
Pluronic® L92 is a polyoxypropylene-poloxyethylene block copolymer non-ionic surfactant. It is used at the concentration of 1% in water to improve the wettability of the mouse ears by the formulated test item in LLNAs.

- The studies by Aitchison G (2003) and Driscoll R (2009) have deficiencies and are not reliable. Therefore we do not agree that they can be used as supportive evidence in a weight of evidence evaluation of non-sensitising properties as stated in e.g. Table 15 and page 25.

Response
The studies by Aitchison G (2003) and Driscoll R (2009) do have deficiencies but the results do not contradict the results of the valid LLNA conducted on Thixatrol Max diluted in the vehicle 1% aqueous Pluronic L92 (Sanders, 2009)