Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

tetrakis(2,6-dimethylphenyl)-*m*-phenylene biphosphate; tetrakis(2,6-dimethylphenyl) 1,3-phenylene bis(phosphate)

EC Number: 432-770-2
CAS Number: 139189-30-3

CLH-O-0000001412-86-291/F

Adopted

13 June 2019

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL FOR TETRAKIS(2,6-DIMETHYLPHENYL)-*M*-PHENYLENE BIPHOSPHATE; TETRAKIS(2,6-DIMETHYLPHENYL) 1,3-PHENYLENE BIS(PHOSPHATE)

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Substance name: tetrakis(2,6-dimethylphenyl)-*m*-phenylene biphosphate; tetrakis(2,6-dimethylphenyl) 1,3-phenylene bis(phosphate)
EC number: 432-770-2
CAS number: 139189-30-3
Dossier submitter: United Kingdom

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
02.12.2018	Japan		Individual	1
Comment received				
No general comments.				
Dossier Submitter's Response				
Noted, thank you.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
27.11.2018	Germany		MemberState	2
Comment received				
In the weight of evidence approach we agree with the final outcome of UK CA to remove the harmonized classification "Skin Sens. 1" for PX-200. The actual and updated experimental data presented in the CLH Report support "no classification" for PX-200.				
Dossier Submitter's Response				
Thank you for the support.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
02.12.2018	Japan		Individual	3
Comment received				
Based on the test results submitted by the notifier, this substance is not classified as corrosive or irritant to skin. I think the proposal is reasonable.				
Dossier Submitter's Response				
Thank you for the support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
07.12.2018	France		MemberState	4
Comment received				
FR agrees that no classification is required.				
Dossier Submitter's Response				
Thank you for the support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
27.11.2018	Germany		MemberState	5
Comment received				
No evidence of an irritant effect in animal and human reports.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
02.12.2018	Japan		Individual	6
Comment received				
Since the decision of the classification as "skin sensitization" under Directive 67/548/EEC, many new tests, including human volunteer testing have been conducted, and none of them indicates the skin sensitization of this substance. Although the reason of the positive response with the GPMT is not known, I think, using the weight-of-evidence approach, this substance is suggested to be a "Not-sensitizing substance". I think the proposal of the change of the classification is reasonable.				
Dossier Submitter's Response				
Thank you for the support.				

RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
07.12.2018	France		MemberState	7

Comment received

Based on the limitations described in the CLH report, the in chemico and in vitro studies are not considered reliable to conclude on sensitizing properties of PX-200. In addition, the human study seems not sensitive enough to detect any sensitizing properties of PX-200. In particular, the dose tested seems too low, in the light of the maximisation assay showing positive results only at high concentrations. Similarly, the Buehler protocol is not sufficiently sensitive to detect weak or moderate sensitizer, in particular considering the few animals tested in the available study.

Therefore, at the end, only the Maximisation assay (positive) and the LLNA (negative) are judged relevant for classification purpose.

However, the negative results obtained in the LLNA could be due to insufficiently high tested concentrations. Indeed, only concentrations up to 25% were used in the pre-screen test without producing any irritation and in the main test, the maximal concentration was limited to 50%. Is there any justification why a higher concentration had not been tested? This is an essential information considering that the positive results obtained in the Maximisation occurred with challenge doses of 50% and 75%.

Dossier Submitter's Response

The GPMT and the LLNA were conducted using different vehicles. In the LLNA, AOO was used (i.e., one of the solvents recommended in the test guideline OECD 442B). The GPMT was conducted using Arachis oil. Our understanding is that this was the preferred solvent used by the testing laboratory, and the one for which they had the most historical data for that study type.

Regarding the doses, the criteria for dose setting are different for each test system, therefore the validity of the doses for each test should be considered independently. According to test guideline OECD 406, the GPMT, the concentration of test substance used for each induction exposure should be well-tolerated systemically, and should be the highest to cause mild-to-moderate skin irritation. For the LLNA (OECD 442B), the highest concentration should maximise exposure while avoiding systemic toxicity and/or excessive local skin irritation. In other words, there is no specific 'aim' in the LLNA to induce a certain level of irritiation.

The dose selection strategy of the LLNA is described in a peer review report, and is normally 3 to 5 concentrations from the following:

100%, 50%, 25%, 10%, 5%, 2.5%, 1.0%, 0.5%, 0.25%, 0.1% (ICCVAM, 1999)

In the case of PX-200 (a solid), 50% was the maximum concentration that could be achieved in AOO. No lymphocyte proliferation was detected up to a concentration of 50%.

Importantly, the LLNA assay appears to have been conducted at appropriate doses in accordance with the test guideline, and the result is considered to be reliable.

ICCVAM (1999) The Murine Local Lymph Node Assay: A Test Method for Assessing the Allergic Contact Dermatitis Potential of Chemicals/Compounds. Results of an Independent Peer Review Evaluation Coordinated by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and the National Toxicology Program Interagency Centre For the Evaluation of Alternative Toxicological Methods (NICEATM). NIH Publication No. 99-4494. Research Triangle Park, NC: National Institute of Environmental Health Sciences.

RAC's response

Thank you for the comments and clarifications regarding the vehicles and doses used in the studies. RAC agrees with the DS that the LLNA assay appears to have been conducted at appropriate doses in accordance with the test guideline.

Date	Country	Organisation	Type of Organisation	Comment number
27.11.2018	Germany		MemberState	8

Comment received

Weight of evidence indicates that PX-200 is not sensitizing.

Dossier Submitter's Response

Thank you for the support.

RAC's response

Noted.