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Symrise AG · Muehlenfeldstrasse 1 · 37603 Holzminden · Germany

Dr. [redacted]
Director Global Substance Registration
Global Product Compliance
—
[redacted]@symrise.com
Tel [redacted]

European Chemical Agency

Holzminden, January 18, 2022

Dear requesting authority

Response to the adhoc public consultation of the RAC on the CLH dossier of Hexylsalicylate (CAS# 6259-76-3, EC#228-408-6)

Symrise welcomes the scientific work of the Risk Assessment Committee of ECHA. In your October meeting you have identified a data gap with regard to the toxicokinetics of hexyl salicylate which you consider essential for the assessment of its hazardous properties and a respective conclusion for Classification and Labelling based on analogue considerations. The assumption that hexyl salicylate might be a possible CMR2 candidate is based on read-across to salicylic acid and the metabolism of methyl salicylate to salicylic acid. 1)

We fully agree that for a proper assessment and a comparison and potential read across to other salicylic esters or the hydrolysis product Salicylic acid, the kinetic of the hydrolysis of hexyl salicylate is essential. Without such data a hazard assessment and a respective classification on a read across/analogue approach on the Toxicity on Reproduction is premature, as the release of the critical molecule (salicylic acid) and its kinetic is key for potential effects of such esters. The hazard assessment and the respective classification proposal for Methyl salicylate was based on a fast hydrolysis and the assumption that the effects are triggered by the hydrolysis product Salicylic acid. For Hexyl salicylate there are no data available at the moment to support such an approach and the longer C-chain of hexyl (compared to methyl) can have a significant impact on the hydrolysis kinetics and release of salicylic acid.

The concern of insufficient data was already picked up by the registrants of hexyl salicylate. Since end of November 2020 there is still an open testing proposal, requesting:

- OECD 421/OECD TG 408 combined study protocol, in the rat, via the oral exposure route (OECD TG 421: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and OECD TG 408: Repeated dose 90-day oral toxicity study in rodents).

- OECD TG 414 in the rat, via the oral exposure route (Prenatal Developmental Toxicity Study).

- OECD TG 414 in the rabbit, via the oral exposure route (Prenatal Developmental Toxicity Study) – this study will be carried out in a sequential manner, if required, following the results of the previous tests

These studies aim to provide a reliable data basis for the endpoint of reproductive toxicity. Therefore, the outcome should be awaited before any conclusion is drawn, especially based on a not substantiated read across. We therefore highly appreciate the action taken by RAC before concluding on a hazard assessment and the respective classification and labelling of this substance.

Symrise made an opt-out from these studies' due to animal welfare reasons and the fact that the CLH activity had already started. The proposed studies will not be finalized by the end of the current CLH public consultation. Consequently, they cannot be taken into consideration by the RAC due to procedural constraints.

Since there is now an opt-out in the Dossier for hexyl salicylate for the above-mentioned study proposals, ECHA is formally obliged to start a dossier evaluation to identify potential data gaps, assess if the proposed studies are the right ones to be performed, or request different studies.

It is our understanding that the deadline for adopting a RAC opinion on 8th June 2022 cannot be postponed. We therefore wonder if a possible way forward would be to accept for the time being that the data is insufficient to classify the substance with regard to reproductive/developmental toxicity as a read across cannot be substantiated with the data at hand and respective in vivo studies for Hexyl salicylate itself, allowing an assessment and conclusion regarding reprotoxicity, are not available either.

The discussion could restart when the respective data are available.

[1] CLH report, Proposal for Harmonised Classification and Labelling, Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2, Page 30
"Based on a read-across with salicylic acid and methyl salicylate, the same approach was undertaken for hexyl salicylate. Therefore, considering the RAC opinions for these substances as Repr. 2 for development, hexyl salicylate should also be classified as Repr. 2 –H361d."

Yours sincerely,

[redacted]

[redacted]

i.V. Dr. [redacted]
Director Global Substance Registration
Global Product Compliance

i.V. Dr. [redacted]
Senior Vice President Global Marketing
Aroma Molecules Division