Committee for Risk Assessment

RAC

Annex 3

Records

of the targeted consultation following the submission of further information to clarify the rate and relevance of hexyl salicylate hydrolysis for the oral route of exposure

Hexyl salicylate

EC Number: 228-408-6
CAS Number: 6259-76-3

CLH-O-0000007103-85-01/F

Adopted

18 March 2022

ANNEX 3 – RECORDS OF THE TARGETED CONSULTATION FOLLOWING THE SUBMISSION OF FURTHER INFORMATION TO CLARIFY THE RATE AND RELEVANCE OF HEXYL SALICYLATE HYDROLYSIS FOR THE ORAL ROUTE OF EXPOSURE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

The proposal for the harmonised classification and labelling (CLH) of Hexyl salicylate (EC 228-408-6; CAS 6259-76-3) was submitted by France and was subject to a consultation, from 08/02/2021 to 09/04/2021. The comments received by that date are compiled in Annex 2 to the opinion.

However, during its October meeting, the CLH working group for the Committee for Risk Assessment (RAC) asked for further information to clarify the rate and relevance of hexyl salicylate hydrolysis for the oral route of exposure. This information is needed to assess the relevance of toxicity data from structural analogues of this substance.

Comments provided during 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 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 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. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Substance name: Hexyl salicylate
EC number: 228-408-6
CAS number: 6259-76-3
Dossier submitter: France

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
12.01.2022	Netherlands		MemberState	1
Comment received				
The NLCA would like to thank France and ECHA for their (additional) efforts in gathering data and justifying the read across approach. The NLCA does not have additional toxicokinetic information other than presented in its previous SEv on hexyl salicylate and the information provided by France in the CLH report.				
RAC's response				
Thank you. Noted.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
12.01.2022	Netherlands		MemberState	2
Comment received				
NLCA view on the matter: Considering the new data and the original information from the CLH report, the proposed read-across and classification should be accepted based on the following:				

- The read across substances methyl salicylate (MeS) and ethylhexyl salicylate (EHS) have similar chemical properties compared to hexyl salicylate (HS). Although MeS is a bit more soluble and has less stearic hindrance, it is the opposite for EHS when compared to hexyl salicylate. EHS could be considered a worst case in comparison to hexyl salicylate as its properties will likely cause it to be less available for hydrolysis. Regardless, the chemical properties of hexyl salicylate seem to be in between those of MeS and EHS which should be sufficient for the read across.
- The presented QSARs support similar hydrolysis rates for these three salicylates.
- Both MeS and EHS cause developmental toxicity at doses around 100 mg/kg bw/day. The developmental toxicity is similar as compared to salicylic acid itself and this is a clear indication that sufficient salicylic acid is formed after oral uptake of MeS and EHS.
- In analogy with MeS and EHS it does not appear that for hexyl salicylate the availability of esterases to hydrolyze the substance would be a limiting factor. It seems unlikely hexyl salicylate is hydrolyzed slower and less complete than both MeS and EHS, and as a consequence would have a lower potency.
- Even a reduced uptake or hydrolyses of HS compared to MeS and EHS should not affect the classification for reproductive toxicity as this classification is not dependent upon potency but only on the potential to induce reprotoxic effects.

Overall based on the available data presented, the NL-CA considers it highly likely the formation of salicylic acid after oral exposure will be sufficient to cause developmental toxicity in vivo at relevant oral dose levels. This is considered sufficient to accept the read across and justify the classification of hexyl salicylate as repr. 2 H361d.

RAC's response

Thank you for your comment.

Date	Country	Organisation	Type of Organisation	Comment number
13.01.2022	Germany		MemberState	3

Comment received

Although the problem regarding the extent of hydrolysis of hexyl salicylate to salicylic acid after oral exposure compared to methyl salicylate is not solved, taking into account the data of ethylhexyl salicylate improves the read-across to other salicylate esters due its similarity with hexyl salicylate, and therefore strengthens the classification proposal. It can be taken from the comment from the registrants to the first consultation, that there are further studies available of potentially similar substances, namely benzyl salicylate (EC 204-262-9: OECD 421, OECD 414) and cyclohexyl salicylate (EC 400-410-3: OCED 414) not yet considered in the CLH-report. Both substances and the corresponding data are not mentioned and evaluated in the revised read across approach distributed for the ad hoc consultation.

An explanation would be helpful why data from ethyhexyl salicylate are considered in addition, but those from benzyl salicylate and cyclohexyl salicylate are not.

RAC's response

Thank you for your comment. The substances cyclohexyl salicylate and benzyl salicylate were discussed in RAC and it was decided that only the linear, non-cyclic molecules would be considered for the read-across approach to hexyl salicylate.

ANNEX 3 – RECORDS OF THE TARGETED CONSULTATION FOLLOWING THE SUBMISSION OF FURTHER INFORMATION TO CLARIFY THE RATE AND RELEVANCE OF HEXYL SALICYLATE HYDROLYSIS FOR THE ORAL ROUTE OF EXPOSURE

Date	Country	Organisation	Type of Organisation	Comment number
18.01.2022	Germany	Symrise AG	Company-Importer	4
Comment received				
Dear RAC Team, please find attached our comments in the attached pdf-document Best regards <confidential> ECHA note – An attachment was submitted with the comment above. Refer to public attachment Response to adhoc public consultation on CLH.pdf				
RAC's response				
Thank you. Please refer to our comment No. 5.				

Date	Country	Organisation	Type of Organisation	Comment number
17.01.2022	United Kingdom		Individual	5
Comment received				
Registrant comments for the ad hoc consultation launched on a CLH Dossier Substance name: Hexyl salicylate EC number: 228-408-6 CAS number: 6259-76-3 Introduction An ad hoc consultation has recently been conducted by RAC on the CLH dossier prepared by the French Competent Authority ('FR CA' or the 'Dossier Submitter') proposing harmonised classification and labelling (CLH) for hexyl salicylate (the 'Substance'). The CLH report proposed that the Substance be classified as Category 2 for reproductive toxicity and was submitted on 7 December 2020. The Ad hoc consultation follows the October 2021 meeting of the working group (WG) for the Committee for Risk Assessment (RAC) that considered the CLH dossier for the Substance. The WG-RAC notably, amongst other information requests, asked for further information to clarify the rate and relevance of hexyl salicylate hydrolysis for the oral route of exposure. This information is reported as needed to assess the relevance of toxicity data from structural analogues of the Substance. To address the information requests of the WG-RAC, the FR CA, as Dossier Submitter, submitted an Additional information report on 10 December 2021 The registrants would also like to point out that the Hexyl Salicylate REACH registration is currently ongoing, and the registrants submitted a testing proposal (Nov. 2020) to address data gaps within the dossier. ECHA has yet to respond to the registrants on the testing proposal, that include an 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) and an OECD TG 414 in the rat, via the oral exposure route (Prenatal Developmental Toxicity Study). Lastly an 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. The registrants of the Substance wish to highlight that neither the CLP Regulation, nor the				

ECHA's Guidance on the preparation of dossiers for harmonised classification and labelling, nor the RAC Framework Rules allow ad hoc consultations such as the Ad Hoc Consultation launched by RAC in October 2021, which contains a number of requests for further information from the Dossier Submitter to supplement the CLH report. Similarly there is no scope for an Additional information report, such as the one proposed by Dossier Submitter in December 2021, which contains additional information to that in the original CLH report. A CLH decision could not be lawfully adopted on the basis of this new information without a new CLH process being instigated. The registrants of the Substance will address those procedural issues more specifically in a separate communication.
Beyond those procedural issues, RAC and the Dossier Submitter concur with the Ad hoc consultation that the information in the CLH report of 7 December 2020 is not sufficient to allow a recommendation for a harmonized classification of the Substance as a reproductive toxicant to be made. Indeed, the generation and assessment of the information requested by RAC demonstrates that no conclusion can be reached on the read across which has been relied upon by the Dossier Submitter in order to arrive at its conclusion that the Substance should be subject to CLH as a Category 2 reproductive toxicant. The read across which forms the exclusive basis of the Dossier Submitter's conclusion has never undergone a proper evaluation. Therefore, without such an evaluation and without the information requested by the WG-RAC, no recommendation for a CLH on reproductive toxicity can be made by the Committee.
In the context of the Testing Proposals (TPs) made by the registrants and currently under review by ECHA, the registrants propose to generate the toxicokinetics information identified by WG-RAC as missing, and necessary for any recommendation to be made, as part of the two tests which are the subject of the TPs. This information would allow the preparation of a new CLH report, as the case may be. Such a CLH report would need to take into consideration all the information available in the registration dossier, as required by the CLP Regulation. In the meantime, based on the FR CA's CLH report of 7 December 2020, the RAC cannot recommend any CLH of the Substance for reproductive toxicity.
This document provides comments in direct relation to the subject of the Ad hoc consultation. The comments also detail testing proposals for hexyl salicylate which include toxicokinetic analysis to inform the rate and relevance of hexyl salicylate hydrolysis for the oral route of exposure.

Comments
The CLH report and the Additional information report for hexyl salicylate assess developmental study data on salicylic acid, sodium salicylate and methyl salicylate and exclusively rely on a read-across to justify the proposed classification. The salicylic acid and sodium salicylate data were not included in the hexyl salicylate REACH registration dossier, and the authors of the CLH report refer to the RAC opinion on salicylic acid as the source of this information. The RAC opinion and CLH report on methyl salicylate are also listed as data sources. The read-across relied upon has never undergone a thorough evaluation under the processes foreseen by the REACH Regulation and hence, the registrants never got an opportunity to be heard on the rationale followed for the CLH proposal.
The Registrants of hexyl salicylate have previously commented on the use of developmental study data on salicylic acid and sodium salicylate to justify the proposed classification for hexyl salicylate and presented arguments as to why read across from salicylic acid and sodium salicylate are considered appropriate to assess this health endpoint.
These comments were submitted to ECHA on 31 March 2021 as part of the Consultation on the CLH report and are presented in Appendix 1.
In the REACH registration dossier for hexyl salicylate, read across is applied from methyl

salicylate and cyclohexyl salicylate data to cover the endpoint 'Toxicity to reproduction'. While the relevant data on methyl salicylate did indicate developmental toxicity, the Prenatal Developmental Toxicity Study (OECD 414) performed with cyclohexyl salicylate did not show developmental toxicity up to and including the highest dose level tested. There are no reproduction toxicity data or developmental toxicity data for hexyl salicylate. In 2020 the Registrants of hexyl salicylate carried out a thorough review of the registration dossier to identify possible data gaps. This review was carried out in close cooperation with the International Fragrance Association (IFRA). In particular, the read across data used in the hexyl salicylate dossier for the endpoints 'Repeated dose toxicity' and 'Toxicity to reproduction' were re-assessed. Additionally, the new data on the structurally similar substance, benzyl salicylate, were also considered.

The benzyl salicylate data indicate that salicylates with differing side chains have differing systemic and reproductive toxicity hazard potentials. Consequently, a harmonised classification of Cat 2 Repro classification (H361d) for salicylates substances on the sole basis of a read across is not considered to be justifiable.

The Registrants' conclusion on the re-assessment of the hexyl salicylate registration dossier, therefore, is that it is necessary to generate new data on hexyl salicylate for the endpoints 'Repeated dose toxicity' and 'Toxicity to reproduction'.

On 27 November 2020, the Lead Registrant submitted an updated joint submission dossier to ECHA (submission number PX747848-81). This dossier includes testing proposals to ECHA for the following studies:

• 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.

It should be noted that to date, a final decision from ECHA on the testing proposals has not yet been received, because the Agency decided to suspend the evaluation process. The registrants question the soundness and regularity of such suspension.

The Committee for Risk Assessment (RAC) have recently acknowledged the need and asked for further information to clarify the rate and relevance of hexyl salicylate hydrolysis for the oral route of exposure. The registrants therefore propose to include the following toxicokinetic analyses within the OECD 421/OECD TG 408 combined study protocol, in the rat, via the oral exposure route:

• Days 1 and 91 blood samples (0.3 mL, via the jugular vein) will be taken from 3 rats/sex/test substance concentration as well as a positive control group dosed with salicylic acid at 6 time points (and at 2 time points from the negative (diet only) control toxicokinetic animals).

The additional sampling of blood to determine the plasma levels of hexyl salicylate and free salicylic acid will be useful additional information to assist in determining the degree of hydrolysis of the parent compound to salicylic acid and the respective alcohol. Pending such information, no recommendation for CLH on developmental toxicity can be made.

If the results showed that plasma salicylic acid levels were lower than the salicylic acid reproductive NOAEL, even at the maximum dose levels (or those that showed overt toxicity in females), this could confirm that a Cat 2 Repro classification (H361d) of hexyl salicylate is not justified. In this instance, the toxicokinetic data could be used in conjunction with the respective NOAELs from the OECD 421/408 and OECD 414 (rat and

potentially rabbit) hexyl salicylate studies, to inform on an overall weight of evidence with regards to classification for developmental toxicity. Additionally, a quantitative comparison of the toxicokinetic data for hexyl salicylate with the RAC (2016) proposed "hypothetical human threshold for malformations" of "around of 200 µg/mL of total salicylate in maternal serum" [i.e., free and protein-bound salicylic acid and salicylic acid anion] could also be made.

Conclusion
One of the recommendations made by the French Competent Authority in the Proposal for Harmonised Classification and Labelling is to classify hexyl salicylate as Repr. 2, H361d. This proposal is based on the RAC opinions for salicylic acid (2016) and methyl salicylate (2019), in which the classification of these two substances as Repr. 2, H361d was concluded. As read across with methyl salicylate to hexyl salicylate was applied in the hexyl salicylate dossier, the classification for methyl salicylate as Repr. 2 (H361d) would also apply to hexyl salicylate. However, the benzyl and cyclohexyl salicylate data indicate that salicylates with differing side chains have differing systemic and reproductive toxicity hazard potentials. Consequently, a harmonised classification of Cat 2 Repro classification (H361d) for salicylate substances on the sole basis of a read across is not considered to be justifiable.
The Registrants have submitted testing proposals for an OECD TG 421/OECD TG 408 combined study and OECD TG 414 studies in two species to ECHA and request that process for completing data gaps for the registration be completed first, to enable the data to be considered in the CLH proposal. By generating data on hexyl salicylate, the Registrants aim to provide important information regarding the (lack of) effects on reproductive toxicity that are specific to hexyl salicylate.
The registrants would also propose to conduct toxicokinetic analysis within the proposed OECD 421/OECD TG 408 combined study protocol for the registration. The purpose of such data would be to:
• Determine salicylic acid exposure levels.
• Use the salicylic acid exposure levels as part of the reproductive toxicity risk assessment for hexyl salicylate.
The proposed information would therefore be determinant in
i) filling the current data gaps identified by RAC and reported in the Ad hoc Consultation and
ii) providing information on the (lack of) effects on reproductive toxicity on hexyl salicylate itself.
According to ECHA's own words in the draft decision on the evaluation of the testing proposals, this information is considered "necessary".
The Registrants therefore call for the results of the proposed hexyl salicylate studies to be considered as part of any CLH process, when these become available, after which the complete data set can be assessed to determine the developmental toxicity potential of hexyl salicylate.

Submitted by the Registrants of hexyl salicylate:
Givaudan France SAS
International Flavors & Fragrances I.F.F. (Nederland) B.V.
Intertek Deutschland GmbH IEFC
ITS Testing Services (UK) Ltd
Synthite Ltd
Eternis Fine Chemicals UK Ltd

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments to CLH report hexyl salicylate_2022_01_17.DOCX
RAC's response
Thank you for your comment. The substances cyclohexyl salicylate and benzyl salicylate were discussed in RAC and it was decided that only the linear, non-cyclic molecules would be considered for the read-across approach to hexyl salicylate. However, RAC has no legal mandate to request new studies. Therefore, the assessement is based solely on the data available at submission of the CLH report.

PUBLIC ATTACHMENTS
1. Response to adhoc public consultation on CLH.pdf [Please refer to comment No. 4]
2. Comments to CLH report hexyl salicylate_2022_01_17.DOCX [Please refer to comment No. 5]