Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Hexyl salicylate

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

CLH-O-0000007103-85-01/F

Adopted

18 March 2022

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

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
29.03.2021	Germany		MemberState	1
Comment received				
Formal note: In table 3 in subsection 2.1 "Proposed harmonised classification and labelling according to the CLP criteria" should be in the column "Pictogram, Signal Word Code(s)" instead of the word "Warning" there is the corresponding coding "Wng".				
Dossier Submitter's Response				
Thank you for your comment and for noticing. However, it is not possible to modify the CLH report at this step of the CLH process anymore.				
RAC's response				
Thank you for you comment.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
29.03.2021	Germany		MemberState	2
Comment received				
The read-across hypothesis is based on the metabolism of hexyl and methyl salicylate to the common product salicylic acid, which mediates the properties of the salicylates. However, there remain uncertainties regarding the read-across hypothesis, although extensive metabolism of hexyl salicylate to salicylic acid by human skin esterases was observed in an in vitro dermal absorption test. While one reference indicates that carboxyl esterases with respect to hydrolysis of methyl salicylate show extensive tissue distribution, the data do not provide any experimental evidence of the hydrolysis of hexyl salicylate in other tissues, e.g. in the liver. Therefore, it is not possible to conclude that hydrolysis of hexyl salicylate in the body would occur as				

extensively as for methyl salicylate. Finally, it is not possible to decide if the same level of toxicologically effective salicylic acid can be reached with hexyl salicylate compared to methyl salicylate, taking into account the differences in solubility and Log Pow between hexyl and methyl salicylate

Dossier Submitter's Response

The read-across hypothesis is based on the biotransformation of hexyl salicylate and structural analogues (methyl salicylate and sodium salicylate) to the common compound salicylic acid. Although, as you mentioned, no data is available regarding distribution and kinetics of biotransformation of hexyl salicylate, that may raise some uncertainties regarding this hypothesis, an *in vitro* dermal absorption test still confirmed that hexyl salicylate is biotransformed into salicylic acid by human skin esterases. On the basis of this result and in the absence of other data, the read-across hypothesis was considered adequate, as a conservative option . Moreover, although extensive tissue distribution of carboxyl esterases is only indicated with respect to hydrolysis of methyl salicylate, these esterases are highly expressed in the epithelia of most metabolic organs including liver, intestine and kidney in humans. Thus, hydrolysis of hexyl salicylate is also likely to occur extensively.

Although no experimental data is available regarding distribution of hexyl salicylate, this substance is likely to distribute into cells based on log Pow > 0 according to REACH guidance document 7c.

RAC's response

Thank you. RAC will take the comment into account when making the decision.

Date	Country	Organisation	Type of Organisation	Comment number
31.03.2021	United Kingdom	Tennants Fine Chemicals	Company-Manufacturer	3

Comment received

On 8 February 2021, ANSES (on behalf of the French Member State Competent Authority) submitted a Proposal for Harmonised Classification and Labelling for hexyl salicylate. This proposal includes the classification for reproductive toxicity Category 2, H361d (detailed on page 30 of the proposal). The proposal on classification and labelling for reproductive toxicity refers to the classification Repr. 2, H361d proposed for salicylic acid and methyl salicylate as the justification for concluding that hexyl salicylate should be classified for reproductive toxicity.

A response by the Registrants* for hexyl salicylate is attached which details the following:
- There are relevant data available on benzyl salicylate that were not considered in the CLH proposal, which does not show developmental toxicity effects in the rat.
- 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. 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 are concerned that the CLH process will need to be repeated following the availability of new data on hexyl salicylate. This would lead to a considerable additional effort in preparing and reviewing a new CLH report.
- In view of this concern, the Registrants call for the results of the proposed hexyl salicylate studies to be considered as part of the CLH process when these become available, after which the complete data set can be assessed to determine the developmental toxicity potential of hexyl salicylate.

* Registrants are: Givaudan France SAS International Flavors & Fragrances I.F.F. (Nederland) B.V. Intertek Deutschland GmbH IEFC ITS Testing Services (UK) Ltd Sensient Fragrances, S.A.U. Symrise AG Synthite Ltd Tennants Fine Chemicals Ltd (Lead Registrant) ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments to CLH report hexyl salicylate_2021-03-23.docx
Dossier Submitter's Response
- Regarding the new data on benzyl salicylate, as mentioned by the Registrants in the public attachments, it could not have been taken into account in the CLH report as data were not yet available at that time. The Reproduction/Developmental Toxicity Screening Test (OECD TG 421) conducted with benzyl salicylate in Sprague-Dawley rats did not show any effect. However, the doses tested were low, which raises questions about the acceptability of this test. The results of the Prenatal Developmental Toxicity Study (OECD TG 414) conducted with benzyl salicylate at 0, 1000, 3000 and 4000 ppm in Sprague-Dawley rats are difficult to interprete in the absence of the complete study report. Higher incidence of some developmental variations (14th rudimentary rib(s), bent rib(s)) were observed in the foetuses exposed to the two highest doses (3000 and 4000 ppm)). Nevertheless, the proportion of these variations is not indicated, except that they are statistically significant, which does not allow extent robust assessment of these effects in comparison to the control group. Moreover, on the ECHA website, it is indicated that dosage selection for the study was based on a previous range-finding rat embryo/fetal developmental toxicity study in which benzyl salicylate was administered at exposure levels of 0, 750, 1500, 3000, and 6000 ppm in the diet. The highest dose caused decreased body weight gain and food consumption in the female rats as well as decreased uterine weights, decreased viable fetuses, decreased fetal weights (male, female, and combined), increased early resorptions and increased postimplantation loss. In the present Prenatal Developmental Toxicity Study and based on these previous results, doses should also have been tested up to 6000 ppm. - Regarding the testing proposals for an OECD TG 421/OECD TG 408 combined study and OECD TG 414 studies in two species submitted by the Registrants, they are not yet accepted by ECHA. Due to the widespread uses of hexyl salicylate by consumers, professional and industrial workers, EU regulatory risk management with the implementation of harmonised classification for reprotoxicity and skin sensitisation is needed in the short-term. Nevertheless, when the results of these testing proposals (if accepted) will be available, they could be taken into account if needed.
RAC's response
Thank you for your comment.

PUBLIC ATTACHMENTS
1. Comments to CLH report hexyl salicylate_2021-03-23.docx [Please refer to comment No. 3]