~~Confidential~~

Helsinki, 12 January 2023

Addressees
Registrant(s) of Hexyl Salicylate as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
29/03/2021

Registered substance subject to this decision ("the Substance")
Substance name: Hexyl salicylate
EC number: 228-408-6

Decision number: Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/F)

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***22 April 2025***.

Requested information must be generated using the Substance unless otherwise specified.

Information required from all the Registrants subject to Annex VIII of REACH

1. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490)

Information required from all the Registrants subject to Annex IX of REACH

2. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: EU C.20./OECD TG 211)

The reasons for the decision(s) are explained in Appendix 1.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you in accordance with Articles 10(a) and 12(1) of REACH. The addressees of the decision and their corresponding information requirements based on registered tonnage band are listed in Appendix 3.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

How to comply with your information requirements

To comply with your information requirements, you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also **update the chemical safety report, where** relevant, including any changes to classification and labelling, based on the newly generated information.

You must follow the general requirements for testing and reporting new tests under REACH, see Appendix 4.

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[1] under the authority of Mike Rasenberg, Director of Hazard Assessment

Appendix 1: Reasons for the decision
Appendix 2: Procedure
Appendix 3: Addressees of the decision and their individual information requirements
Appendix 4: Conducting and reporting new tests under REACH

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix 1: Reasons for the decision

Contents

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Reasons related to the information under Annex VIII of REACH

1. In vitro gene mutation study in mammalian cells

1 An in vitro gene mutation study in mammalian cells is an information requirement under Annex VIII, Section 8.4.3., in case of a negative result in the in vitro gene mutation test in bacteria and the in vitro cytogenicity test.

1.1. Triggering of the information requirement

2 Your dossier contains negative results for both an Ames test and an in vitro cytogenicity study.

3 Therefore, the information requirement is triggered.

1.2. Information provided

4 You provide a read-across justification document in IUCLID Section 13.

5 For the purpose of this decision, the following abbreviations are used for the category members:

[target]	Hexylsalicylate, EC no. 228-408-6
[1]	Cyclohexyl Salicylate, EC No. 400-410-3 and EC 607-733-0
[2]	Methylsalicylate EC no. 204-317-7
[3]	Isoamyl salicylate, EC No. 201-730-4
[4]	Ethyl Hexyl Salicylate. EC No. 204-263-4

1.2.1.1. Description of the grouping

6 You justify the grouping of the substances as: *"This category is defined based on two factors:*

Structural similarity: the category members are alkyl esters of salicylic acid

Similar metabolism: the category members are metabolised to the common metabolite, salicylic acid".

7 You furthermore state: *"Due to the structural and metabolic similarity of the category substances, systemic exposure to the unchanged parent substances will be minimal. Systemic exposure will be largely or exclusively to the metabolites; namely salicylic acid and an alcohol generated from the side chain. The toxicity of the category members will be due to salicylic acid rather than the parent substance or the alcohol metabolite."*

8 You define the applicability domain as:"alkyl esters of salicylic acid".

9 We have identified the following issue(s) with the proposed scope of the grouping:

1.2.1.1. Incomplete description of the applicability domain of the category

10 A category (grouping) hypothesis should address "the set of inclusion and/or exclusion rules that identify the ranges of values within which reliable estimations can be made for category members for the given endpoint" (Guidance on IRs and CSA, Section R.6.2.4.1.). Particularly, "the applicability domain of a (sub)category would identify the structural requirements and ranges of physico-chemical, environmental fate, toxicological or

ecotoxicological properties within which reliable estimations can be made for the (sub)category members" (Guidance on IRs and CSA, Section R.6.2.1.2.). Therefore, to reliably predict properties within a category the applicability domain should be described including the borders of the category, for which chemicals the category does not hold and a justification for the inclusion and/or exclusion rules.

11 You describe the applicability domain of the substances covered by the grouping as: " alkyl esters of salicylic acid". ECHA observes that potential source salicylic acid compounds contain saturated, branched and unbranched and cyclic side chains.

12 This applicability domain does not introduce unambiguous inclusion/exclusion criteria which would identify the structural requirements and ranges of physico-chemical, environmental fate, toxicological or ecotoxicological properties within which reliable estimations can be made for the (sub)category members.

13 Despite of the above issue(s), ECHA understands that this is the applicability domain of the grouping and your predictions are assessed on this basis.

1.2.1.2. Description of the prediction

14 You predict the properties of the Substance from information obtained from the following source substance(s):

- Cyclohexyl salicylate, **[1]**, EC No. 400-410-3; by providing the following study: An *in vitro* gene mutation study in mammalian cells (1994);

15 You provide the following reasoning for the prediction of toxicological properties: concerning the endpoints mutagenicity: "Studies available for the salicylates almost all report negative results. Salicylic acid is not considered to be genotoxic and the alcohol metabolites are similarly considered not to be genotoxic. [redacted] (2007) conclude that this group of substances is without genotoxic activity."

16 ECHA understands that your read-across hypothesis assumes that different compounds have the same type of effects. You predict the properties of your Substance to be quantitatively equal to those of the source substance.

1.3. Assessment of the information provided

17 We have assessed this information and identified the following issue(s):

1.3.1. Read-across adaptation rejected

18 Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group.

19 Additional information on what is necessary when justifying a read-across approach can be found in the Guidance on IRs and CSA, Chapter R.6. and related documents (RAAF, 2017; RAAF UVCB, 2017).

20 We have identified the following issue(s) with the prediction of toxicological properties:

1.3.1.1. Bias of the prediction from the selection of source substance(s)

21 In order to make an accurate prediction of toxicological properties all relevant information must be considered in the prediction. If not all information is considered in the read-across

approach, bias can be introduced in the predictions which may result in an over/underestimation in the prediction (RAAF, 2017; Chapter 4.5.1.5.). Bias may be caused by incorrect/incomplete selection of source substance(s); or due to a particular selection of study(ies) performed on the source substance(s).

22 To justify the selection of source substances, you must provide documentation how the source substance(s) have been chosen, for example, what methods/tools have been used to map the field of potential source substance(s), which other substances have been considered and why they have been discarded (RAAF, 2017, Chapter 4.4.1.5/4.5.1.5). If there are structural analogue(s) not used as source substances and data show significantly different results for the properties to be predicted without any justification for setting aside these different results, then the proposed prediction are considered biased.

23 You report information from the following source substances: cyclohexyl salicylate [1] (for (for in vitro mutagenicity in mammalian cells). You have not provided any justification on the selection of this substance used to predict the properties of the Substance.

24 Another substance (Reaction mass of 2-methylbutyl salicylate and pentyl salicylate EC no 911-280-7) has the following structure: pentyl- and 2-methylbutylester of salicylic acid. The substance contains around [redacted] of pentylsalicylate (and therefore a linear component).

25 The following study is available on that substance showing the following effects: OECD Guideline 414 (Prenatal Developmental Toxicity Study), 2020, showing at 333 mg/kg bw/d increased postimplantation loss (early resorption), in utero-growth retardation and increased visceral and skeletal malformations. Those effects were not observed in an equivalent OECD TG 414 study performed with the source substance cyclohexylsalicylate up to a does level of 360 mg/kg bw/d (No symptoms of toxicity nor embryotoxic or teratogenic potential up to a dose level of 360 mg/kg bw/d).

26 This other substance is a closer structural analogue of the Substance than the source substance that you have identified because its main constituent is a linear ester with pentylsalicylate and thereby only differing in one carbon in length from the Substance. Since the rate of hydrolysis can be affected by the cyclic structure of the source substance, this is likely to result in lower levels of free salicylate available, which are considered to cause the adverse effect.

27 The available data on this substance indicates significantly different results showing higher concern than the studies on the source substance which you use to draw a conclusion on the endpoint. In the absence of information on comparative hydrolysis rates of all substances under discussion here, this concern is relevant for other endpoints as well. You have not justified why this source substance has not been considered. Furthermore, an opinion on harmonised classification for Methylsalicylate[2] and hexylsalicylate[3] have been adopted in 2019 and 2020, respectively. This is supporting the outcome of the developmental toxicity study, listed above, on substance 911-280-7 **[11]** and differing from the outcome of the developmental toxicity study on cyclohexylsalicylate, thereby supporting the fact that cyclohexylsalicylate is not a suitable source substance.

28 Therefore, your predictions are biased and may underestimate the hazards of the Substance.

1.3.1. Conclusion on the information provided and the read-across approach

29 As explained above, you have not established that relevant properties of the Substance can be predicted from data on the source substance(s). Therefore, your read-across approach under Annex XI, Section 1.5. is rejected and the information requirement is not fulfilled.

[2] https://echa.europa.eu/documents/10162/ea33d742-d73f-a7a7-8bca-be3679b713e0
[3] https://echa.europa.eu/documents/10162/f477d9a0-f05a-d06d-4cba-695ba6c11f5b

1.4. Specification of the study design

30 To fulfil the information requirement for the Substance, either the in vitro mammalian cell gene mutation tests using the hprt and xprt genes (OECD TG 476) or the thymidine kinase gene (OECD TG 490) are considered suitable.

Reasons related to the information under Annex IX of REACH

2. Long-term toxicity testing on aquatic invertebrates

31 Long-term toxicity testing on aquatic invertebrates is an information requirement under Annex IX to REACH (Section 9.1.5.).

2.1. Information provided

32 You have adapted this information requirement by using Column 2 of Annex IX, Section 9.1. To support the adaptation, you have provided the following information:

> "*Long-term Daphnia toxicity testing as described in Annex IX is not considered to be necessary as the chemical safety assessment demonstrates safe use of the material. In addition hexyl salicylate is readily biodegradable, with rapid mineralisation to CO_2 occurring in aerobic aquatic systems*".

2.2. Assessment of the information provided

2.2.1. Annex IX, Section 9.1., Column 2 is not a valid basis to omit the study

33 Annex IX, Section 9.1., Column 2 does not allow omitting the need to submit information on long-term toxicity to aquatic invertebrates under Column 1. It must be understood as a trigger for providing further information on aquatic invertebrates if the chemical safety assessment according to Annex I indicates the need (Decision of the Board of Appeal in case A-011-2018).

34 Your adaptation is therefore rejected.

35 Therefore, the information requirement is not fulfilled.

2.3. Study design and test specifications

36 The Substance is difficult to test due to its adsorptive properties (log Kow of 5.5.) OECD TG 211 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 211. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solution.

References

The following documents may have been cited in the decision.

Guidance on information requirements and chemical safety assessment (Guidance on IRs & CSA)

Chapter R.4 Evaluation of available information; ECHA (2011).
Chapter R.6 QSARs, read-across and grouping; ECHA (2008).
Appendix to Chapter R.6 for nanoforms; ECHA (2019).
Chapter R.7a Endpoint specific guidance, Sections R.7.1 – R.7.7; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Chapter R.7b Endpoint specific guidance, Sections R.7.8 – R.7.9; ECHA (2017).
Appendix to Chapter R.7b for nanomaterials; ECHA (2017).
Chapter R.7c Endpoint specific guidance, Sections R.7.10 – R.7.13; (ECHA 2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Appendix R.7.13-2 Environmental risk assessment for metals and metal compounds; ECHA (2008).
Chapter R.11 PBT/vPvB assessment; ECHA (2017).
Chapter R.16 Environmental exposure assessment; ECHA (2016).

Guidance on data-sharing; ECHA (2017).

All Guidance on REACH is available online: https://echa.europa.eu/guidance-documents/guidance-on-reach

Read-across assessment framework (RAAF)

RAAF, 2017 Read-across assessment framework (RAAF), ECHA (2017)
RAAF UVCB, 2017 Read-across assessment framework (RAAF) – considerations on multi- constituent substances and UVCBs), ECHA (2017).

The RAAF and related documents are available online:
https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

***OECD Guidance documents* (OECD GDs)**

OECD GD 23 Guidance document on aquatic toxicity testing of difficult substances and mixtures; No. 23 in the OECD series on testing and assessment, OECD (2019).
OECD GD 29 Guidance document on transformation/dissolution of metals and metal compounds in aqueous media; No. 29 in the OECD series on testing and assessment, OECD (2002).
OECD GD 150 Revised guidance document 150 on standardised test guidelines for evaluating chemicals for endocrine disruption; No. 150 in the OECD series on testing and assessment, OECD (2018).
OECD GD 151 Guidance document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test; No. 151 in the OECD series on testing and assessment, OECD (2013).

Appendix 2: Procedure

This decision does not prevent ECHA from initiating further compliance checks at a later stage on the registrations present.

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The compliance check was initiated on 05 July 2021.

ECHA notified you of the draft decision and invited you to provide comments.

ECHA did not receive any comments within the commenting period.

The deadline of the decision is set based on standard practice for carrying out OECD TG tests. It has been exceptionally extended by 12 months from the standard deadline granted by ECHA to take into account currently longer lead times in contract research organisations.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix 3: Addressees of this decision and their corresponding information requirements

In accordance with Articles 10(a) and 12(1) of REACH, the information requirements for individual registrations are defined as follows:

- the information specified in Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa;
- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;
- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.

Appendix 4: Conducting and reporting new tests for REACH purposes

1. Requirements when conducting and reporting new tests for REACH purposes

1.1. Test methods, GLP requirements and reporting

(1) Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.

(2) Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

(3) Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[4].

(4) Under the introductory part of Annexes VII/VIII/IX/X to REACH, where a test method offers flexibility in the study design, for example in relation to the choice of dose levels or concentrations, the chosen study design must ensure that the data generated are adequate for hazard identification and risk assessment.

1.2. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

(1) Selection of the Test material(s)
The Test Material used to generate the new data must be selected taking into account the following:
- the variation in compositions reported by all members of the joint submission,
- the boundary composition(s) of the Substance,
- the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

(2) Information on the Test Material needed in the updated dossier
- You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
- The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[5].

[4] https://echa.europa.eu/practical-guides
[5] https://echa.europa.eu/manuals