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Helsinki, 12 January 2023

Addressees
Registrant(s) of JS_RM isopentyl salicylate as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
09/06/2020

Registered substance subject to this decision ("the Substance")
Substance name: Reaction mass of 2-methylbutyl salicylate and isopentyl salicylate
EC number: 904-908-6

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 ***17 October 2024***.

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)

2. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: EU C.1./OECD TG 203)

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.

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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.

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

3 Therefore, the information requirement is triggered.

1.1. Information provided

4 You have adapted this information requirement by using Column 2 of Annex VIII, Section 8.6.1. To support the adaptation, you have provided following information on the basis of a read-across adaptation:

(i) an *in vivo* mammalian somatic cell study: cytogenicity / erythrocyte micronucleus (1989) with the source substance 25485-88-5 / 607-733-0; cyclohexyl salicylate
(ii) a justification document for cyclohexylsalicylate in section 13 of IUCLID.

You provide the following reasoning for the prediction of this information requirement: *"[…the two substances share structural similarities and also 'mechanistic action' similarities which are both general and endpoint specific (key physical chemical parameters and toxicological data available for both substances) …]* and you conclude that *[…"the results from the Source Substance are anticipated to be comparable to that of the Target Substance and are considered to be suitable for both classification and labelling and any required risk assessment."…]*

5 ECHA understands that you predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects. The properties of your Substance are predicted to be quantitatively equal to those of the source substance.

1.2. Assessment of the information provided

1.2.1. The provided adaptation does not meet the criteria of Annex VIII, Section 8.4.3., column 2

6 Under Annex VIII, Section 8.4.3., column 2, the study may be omitted if adequate data from a reliable in vivo mammalian gene mutation test are available. The Guidance on IRs and CSA, Section R.7.7.6.3. clarifies that the in vivo study must be a Transgenic Rodent Somatic and Germ Cell Gene Mutation Assay (TGR), performed according to the OECD TG 488. This test investigates gene mutations using reporter genes.

7 The study (ii) is described as in vivo mammalian erythrocyte micronucleus tests (OECD TG 474) and is not Transgenic Rodent Somatic and Germ Cell Gene Mutation Assays.

8 Therefore, the requirements of Annex VIII, Section 8.4.3., column 2 are not met and your adaptation is rejected.

1.2.2. Read-across adaptation

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

10 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.

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

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

12 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).

13 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.

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

15 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.

16 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 dose 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).

17 This other substance is a closer structural analogue of the Substance than the source substance that you have identified because it contains the same branched ester and does as well not contain a cyclic moiety. 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.

18 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.

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

1.2.2.2. Conclusion on the read-across approach

20 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.

1.2.3. Conclusion on the adaptations

21 On this basis, the information requirement is not fulfilled.

1.3. Specification of the study design

22 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.

2. Short-term toxicity testing on fish

23 Short-term toxicity testing on fish is an information requirement under Annex VIII to REACH (Section 9.1.3.).

2.1. Information provided

24 You have adapted this information requirement by using Column 2 of Annex VIII, Section 9.1.3. To support the adaptation, you have provided the following justification:

25 "The study does not need to be conducted because the substance is highly insoluble in water, hence indicating that aquatic toxicity is unlikely to occur".

2.2. Assessment of the information provided

2.2.1. The provided adaptation does not meet the criteria of Annex VIII, Section 9.1.3., Column 2

26 Under Annex VII, Section 9.1.3., Column 2, first indent, the study may be omitted if aquatic toxicity is unlikely, for instance if the Substance is highly insoluble in water. Guidance on IRs and CSA, Section R.7.8.5 explains that there is no scientific basis to define a cut off limit for solubility below which toxicity is unlikely. Therefore, the justification must demonstrate very low water solubility and low likelihood to cross biological membranes. For the latter, the indicators used for low likelihood of a high bioaccumulation potential (Guidance on IRs and CSA, Figure R.11-4) must be considered, including:

- physico-chemical indicators of hindered uptake due to large molecular size (*e.g.* average maximum diameter of the molecule (D_{max}) > 17.4 Å and molecular weight (MW) > 1100 g/mol or maximum molecular length (MML) > 4.3 nm) or high octanol-water partition coefficient (log K_{ow} > 10) or low potential for mass storage (octanol solubility (mg/L) < 0.002 x MW), and
- supporting experimental evidence of hindered uptake (no chronic toxicity for mammals and birds, no chronic ecotoxicity, no uptake in mammalian toxicokinetic studies, very low uptake after chronic exposure).

27 Your registration dossier provides:

- information on the solubility of the Substance in water (4.2 mg/L based on OECD TG 105);
- a repeated-dose toxicity (90 days) in rodents, showing systemic effects.

28 The following contradicts your justification:

- for the two main constituents of the Substance, Dmax << 17.4 Å, MW << 1100 g/mol, MML << 4.3 nm, log Kow << 10, which do not support the hypothesis of hindered uptake[2];
- systemic effects were observed in the repeated-dose toxicity study (NOAEL: 47 mg/kg bw/d (500 ppm); NOEL: 4.7 mg/kg bw/d (50ppm)) which demonstrate systemic exposure and significant uptake in mammals.

29 Therefore, you have not demonstrated that toxicity is unlikely to occur and your adaptation is rejected.

30 Therefore, the information requirement is not fulfilled.

[2] Calculated by software Catalogic: Dmax 12.379 Å (1.24 nm) for the main constituent (isopentyl salicylate), and 12.164 Å (1.22 nm) for the other main constituent (2-methylbutyl salicylate). For both constituents, MW: 208.26 g/mol.

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 6 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]

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[3].

(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[4].

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