~~Confidential~~

Helsinki, 12 January 2023

Addressees
Registrant(s) of JS_204-265-5 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
23/05/2018

Registered substance subject to this decision ("the Substance")
Substance name: Ethyl salicylate
EC number: 204-265-5

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 VII of REACH

1. Skin sensitisation (Annex VII, Section 8.3.; test method:)

   i. *in vitro/in chemico* skin sensitisation information on molecular interactions with skin proteins (OECD TG 442C), inflammatory response in keratinocytes (OECD TG 442D) and activation of dendritic cells (OECD TG 442E) (Annex VII, Section 8.3.1.); and

   ii. Only if the *in vitro/in chemico* test methods specified under point i.) are not applicable for the Substance or the results obtained are not adequate for classification and risk assessment, *in vivo* skin sensitisation (Annex VII, Section 8.3.2.; test method: EU B.42./OECD TG 429)

2. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method: EU C.2./OECD TG 202)

3. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: EU C.3./OECD TG 201)

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

Reasons related to the information under Annex VII of REACH 4

1. Skin sensitisation 4
2. Short-term toxicity testing on aquatic invertebrates 5
3. Growth inhibition study aquatic plants 6

References 8

Reasons related to the information under Annex VII of REACH

1. Skin sensitisation

1 Skin sensitisation is an information requirement under Annex VII, Section 8.3. Under Section 8.3., Column 1, the registrants must submit information allowing (1) a conclusion whether the substance is a skin sensitiser and (2) whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A).

1.1. Information provided

2 You have provided:

i. An in vivo Guinea Pig Maximization test (1986) with the Substance;
ii. A maximization test in human (1986) with the Substance.

1.2. Assessment of the information provided

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

1.2.1. Assessment whether the substance is a skin sensitiser

4 The provided study (i) does not meet the specifications of the test guideline(s). To fulfil the information requirement, and to enable concluding whether the Substance causes skin sensitisation, a study must comply with the EU Method B.6/OECD TG 406 (Article 13(3) of REACH). Therefore, the following specifications must be met:

a) a dose level selection rationale is provided;
b) the induction concentration is the highest causing mild-to-moderate irritation to the skin;
c) the appropriate number of animals is included in the study: minimum 10 in test group and 5 in control, if negative results 20 in test group and 10 in control group highly recommended;
d) positive control is included to establish the sensitivity and reliability of the experimental technique.

5 In study (i) described as a guinea pig maximisation test.

6 However, the following specifications are not according to the requirements of OECD TG 406:

a) no dose level selection rationale was provided;
b) the concentration used for induction did not cause mild-to-moderate irritation;
c) negative results but only 10 animals were used in the test group;
d) no information on positive control group was provided.

7 The information provided does not cover the specification(s) required by OECD TG 406 and does not allow to make a conclusion whether the Substance causes skin sensitisation.

1.2.1.1. Adequacy of the provided study ii. for hazard identification

8 A study must be adequate for the corresponding information requirement. According to the Guidance on IRs and CSA, Section R.4 (page 1), "*The evaluation of data quality includes assessment of adequacy of the information for hazard/risk assessment and C&L purposes*". The Guidance on IRs and CSA, Section R.4 (page 1) defines adequacy as "*the usefulness of*

data for hazard/risk assessment purposes". As a consequence, a study must be relevant for hazard assessment and for classification and labelling purposes.

9 You have provided a study according to the Human Maximization Test (HMT) (study ii.), and you consider that the Substance is not a skin sensitiser.

10 The study (ii.) appear to have been designed to establish safe levels for specific intended uses, rather than to investigate the intrinsic properties of the Substance as required for the purpose of hazard identification. In particular, the dose levels used in this study is far lower i.e. 12% than the doses expected to be used for hazard identification purposes. Moreover, the reporting of the study does not allow independent assessment of the study, as only concentration of the Substance is given and number of subjects, and is missing critical elements, such as treatment procedure (size of patch, duration of exposure, frequency of exposure etc.).

11 Therefore, the study is rejected and does not allow to make a conclusion whether the Substance causes skin sensitisation.

1.2.2. No assessment of potency

12 To be considered compliant and enable a conclusion in cases where the substance is considered to cause skin sensitisation, the information provided must also allow a conclusion whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A).

13 As the currently available data does not allow to conclude whether the Substance causes skin sensitisation (see section 1.2.1 above), this condition cannot be assessed.

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

1.3. Specification of the study design

15 To fulfil the information requirement for the Substance, information on molecular interaction with skin proteins and inflammatory response in keratinocytes and activation of dendritic cells (OECD TG 442C and OECD TG 442D and OECD TG 442E) must be provided. Furthermore, an appropriate risk assessment is required if a classification of the Substance as a skin sensitiser (Cat 1A or 1B) is warranted.

16 In case no conclusion on the skin sensitisation potency can be made for the Substance based on the existing data or newly generated in vitro/in chemico data, in vivo skin sensitisation study must be performed and the murine local lymph node assay (EU Method B.42/OECD TG 429) is considered as the appropriate study for the potency estimation.

2. Short-term toxicity testing on aquatic invertebrates

17 Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII to REACH (Section 9.1.1.).

2.1. Information provided

18 You have provided an acute immobilisation test to Daphnia magna (2001), according to OECD test guideline 202, with the Substance.

2.2. Assessment of the information provided

19 We have assessed this information and identified the following issue:

2.2.1. The provided study does not meet the information requirement

20 To fulfil the information requirement, a study must comply with OECD TG 202 (Article 13(3) of REACH). Therefore, the following specifications must be met:

a) analytical monitoring must be conducted. A reliable analytical method for the quantification of the test material in the test solutions with reported specificity, recovery efficiency, precision, limits of determination (i.e. detection and quantification) and working range must be available;
b) the concentrations of the test material are measured at least at the highest and lowest test concentration, at the beginning and end of the test;
c) the effect values can only be based on nominal or measured initial concentration if the concentration of the test material has been satisfactorily maintained within 20 % of the nominal or measured initial concentration throughout the test (see also Guidance on IRs and CSA, Section R.7.8.4.1).

21 Your registration dossier provides an OECD TG 202 study showing the following:

a) An analytical monitoring of the test concentrations was performed based on DOC-analysis. However, you did not report information on the limits of determination (limit of detection and limit of quantification) or on the working range of that method.
b) The concentrations of the test material were measured for all concentration levels and control, but only at the beginning of the test. Measured concentrations at the end of the test are not available.
c) The reported effect value is based on measured initial concentrations. However, you have not established that the concentrations of the test material at the end of the test were within ± 20 % of the nominal or measured initial concentration.

22 Based on the above, there are critical methodological deficiencies resulting in the rejection of the study results. More, specifically, measured concentrations at the end of the test are not available. Therefore, it cannot be established that the concentrations of the test material have been satisfactorily maintained within 20% of the nominal or measured initial concentration throughout the test. As indication, losses above 20% of the measured initial concentration were observed in the algae study (see request 3. below). Similarly, losses above 20% of the measured initial concentration cannot be ruled out for the Daphnia test.

23 Therefore, the requirements of OECD TG 202 are not met.

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

3. Growth inhibition study aquatic plants

25 Growth inhibition study on aquatic plants is an information requirement under Annex VII to REACH (Section 9.1.2.).

3.1. Information provided

26 You have provided an algal growth inhibition test (2017), according to OECD test guideline 201, with Pseudokirchneriella subcapitata and with the Substance.

3.2. Assessment of the information provided

27 We have assessed this information and identified the following issue:

3.2.1. The provided study does not meet the information requirement

28 To fulfil the information requirement, a study must comply with OECD TG 201 (Article 13(3) of REACH). Therefore, the following specifications must be met:

29 Validity criteria

a) the mean coefficient of variation for section-by-section specific growth rates (days 0-1, 1-2 and 2-3, for 72-hour tests) in the control cultures is ≤ 35%;
b) the coefficient of variation of average specific growth rates during the whole test period in replicate control cultures is ≤ 7% in tests with *Pseudokirchneriella subcapitata*.

30 Characterisation of exposure

c) the results can be based on nominal or measured initial concentration only if the concentration of the test material has been maintained within ±20 % of the nominal or measured initial concentration throughout the test. If the concentration of the test material has not been maintained within ±20 % of the nominal or measured initial concentration throughout the test, results must be based on the geometric mean of measured concentrations during exposure or on a model describing the decline of the concentration of the test material over the exposure period (e.g. time-weighted average).

31 Your registration dossier provides an OECD TG 201 study showing the following:

32 Validity criteria

33 You indicate that the study fulfils the validity criteria of the test guideline. However:

a) the mean coefficient of variation for section-by-section specific growth in the control is not reported and cannot be recalculated from the information provided;
b) the coefficient of variation of average specific growth rates during the whole test period in replicate control cultures is not reported and cannot be recalculated from the information provided.

34 Characterisation of exposure

c) Measured initial concentration are similar to nominal values. However, the concentrations measured in the old media (i.e. after 72 h) were in the range of < LOQ to 53% of the nominal values. Therefore, the concentration of the test material has not been maintained within ±20 % of the nominal or measured initial concentration throughout the test. You have expressed the effect values based on measured initial concentrations. Therefore, it does not correspond to either the geometric mean of measured concentrations during exposure or a model describing the decline of the concentration of the test material over the exposure period.

35 Based on the above,

- Some of the validity criteria of OECD TG 201 cannot be verified because of the the lack of reporting identified under points a) and b) above.
- There are critical methodological deficiencies resulting in the rejection of the study results. More specifically, you have derived the effect values based on measured initial concentrations whereas losses above 20% of the measured initial concentration were observed at the end of the test.

36 Therefore, the requirements of OECD TG 201 are not met.

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

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]

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[2].

(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[3].

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