~~Confidential~~

Helsinki, 18 April 2023

Addressees
Registrant(s) of JS_431-090-3 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
26/04/2021

Registered substance subject to this decision ("the Substance")
Substance name: 2-hydroxybenzoic acid 2-butyloctyl ester
EC/List number: 431-090-3

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 ***24 July 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. Long-term toxicity testing on aquatic invertebrates (triggered by Annex VII, Section 9.1.1., column 2; test method: EU C.20./OECD TG 211)

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

2. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) by oral route, in rats

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 request(s)
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 request(s)

Contents

Reasons related to the information under Annex VII of REACH

1. Long-term toxicity testing on aquatic invertebrates

1 Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII to REACH (Section 9.1.1.). However, long-term toxicity testing on aquatic invertebrates must be considered (Section 9.1.1., Column 2) if the substance is poorly water soluble.

1.1. Triggering of the information requirement

2 Poorly water soluble substances require longer time to reach steady-state conditions. As a result, the short-term tests do not give a true measure of toxicity for this type of substances and the long-term test is required. A substance is regarded as poorly water soluble if, for instance, it has a water solubility below 1 mg/L or below the detection limit of the analytical method of the test material (Guidance on IRs and CSA, Section R.7.8.5).

3 In the provided OECD TG 105 (1998), the saturation concentration of the Substance in water was determined to be 0.0284 mg/L. You also provided a study on short-term toxicity to aquatic invertebrates (Daphnia magna, 1999) of the Substance where measured concentrations of the test material at 0 and at 48 hours were below the limit of quantification (5 ug/L).

4 Therefore, the Substance is poorly water soluble and information on long-term toxicity on aquatic invertebrates must be provided.

1.2. Information provided and its assessment

5 You have provided no information on long-term toxicity on aquatic invertebrates.

6 Therefore, the information requirement is not fulfilled.

1.3. Study design and test specifications

7 The Substance is difficult to test due to the low water solubility (0.0284 mg/L) and adsorptive properties: log kow >6.2. 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 solutions.

8 In your comments to the draft decision, you acknowledge that the information requirement is not fulfilled for this endpoint and you agree to perform the requested study.

Reasons related to the information under Annex VIII of REACH

2. Screening for reproductive/developmental toxicity

9 A screening for reproductive/developmental toxicity study (OECD 421 or OECD 422) is an information requirement under Annex VIII, Section 8.7.1., if there is no evidence from analogue substances, QSAR or *in vitro* methods that the substance may be a developmental toxicant.

2.1. Information provided

10 You have adapted this information requirement by using Annex XI, Section 1.5. (Grouping of substances and read-across approach) based on experimental data from the following substances:

(i) three-generation reproductive toxicity study (1971) with the source substance methyl salicylate, EC number 204-317-7;
(ii) OECD TG 421 study (2012) with the source substance 2-ethylhexyl salicylate, EC number 204-263-4.

11 You provide the following reasoning for the prediction of this information requirement: "To address some of the toxicological endpoints as part of the REACH registration of 2-Hydroxybenzoic acid, 2-Butyloctyl ester (CAS 190085-41-7) (target substance), it is proposed to read across to methyl salicylate (CAS 119-36-8) (source substance) […]. Both the above mentioned substances share similar chemical structures. As mentioned, both substances have identical functionality, they are both esters of salicylic acid. The only difference in the two substances is in the alcohol portion of the ester group".

12 Although you did not provide any justification for the use of the source substance 2-ethylhexyl salicylate (EC number 204-263-4), ECHA assumes that you applied a similar reasoning.

13 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.

2.2. Assessment of the information provided

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

2.2.1. Read-across adaptation rejected

15 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.

16 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).

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

2.2.1.1. Inadequate read-across hypothesis

18 Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must include an explanation why the properties of the Substance may be predicted from other substances in the group, i.e. a read-across hypothesis. This hypothesis should be based on recognition of the structural similarities and differences between the substances (Guidance on IRs and CSA, Section R.6.). It should explain why the differences in the chemical structures should not influence the toxicological properties or should do so in a regular pattern, taking into account that variations in chemical structure can affect both toxicokinetics (uptake and bioavailability) and toxicodynamics (e.g. interactions with receptors and enzymes) of substances (Guidance on IRs and CSA, Section R.6.2.1.3).

19 Your read-across hypothesis is only based on the structural similarity between the source substance(s), which you consider a sufficient basis for predicting the properties of the Substance. However, your hypothesis does not explain why the structural differences between the substances do not influence the toxicological properties or do so in a regular pattern.

20 While structural similarity is a prerequisite for applying the grouping and read-across approach, it does not necessarily lead to predictable or similar toxicological properties. You have not provided a well-founded hypothesis to establish a reliable prediction for a toxicological property, explaining why the structural differences do not influence toxicokinetics and toxicodynamics of the substances, and thus why the properties of the Substance may be predicted from information on the source substance(s).

21 In the comments to the draft decision, you acknowledge the lack of experimental and qualitative data to support your read-across justification.

2.2.1.2. Missing supporting information to compare the properties of the substances

22 Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide supporting information to scientifically justify the read-across explanation for prediction of properties. The set of supporting information should strengthen the rationale for the read-across in allowing to verify the crucial aspects of the read-across hypothesis and establishing that the properties of the Substance can be predicted from the data on the source substance(s) (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.).

23 Supporting information must include (bridging) studies to compare properties of the source substances.

24 As indicated above, your read-across hypothesis is based on the assumption that the structurally similar source substance(s) cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the source substance(s) is necessary to confirm that the substances cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and of the source substance(s).

25 For the source substance, you provide the study used in the prediction in the registration dossier. Apart from that study, your read-across justification or the registration dossier does not include any robust study summaries or descriptions of reproductive and developmental toxicity data for the Substance that would confirm that both substances cause the same type of effects.

26 In the comments to the draft decision, you acknowledge the lack of experimental and qualitative data to support your read-across justification.

27 In the absence of such information, you have not established that the Substance and the source substance(s) are likely to have similar properties. Therefore you have not provided sufficient supporting information to scientifically justify the read-across.

2.2.1.3. Read-across hypothesis contradicted by existing data

28 Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide supporting information to scientifically justify the read-across explanation for prediction of properties. The set of supporting information must strengthen the rationale for the read-across in allowing to verify the crucial aspects of the read-across hypothesis and establishing that the properties of the Substance can be predicted from the data on the source substance(s) (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.).

29 The observation of differences in the toxicological properties between the source substance(s) and the Substance would contradict the hypothesis that the properties of the Substance can be predicted from the data on the source substances. An explanation why such differences do not affect the read-across hypothesis must to be provided and supported by scientific evidence.

30 As indicated above, your read-across hypothesis is based on the assumption that the structurally similar Substance and source substance(s) cause the same type of effect(s).

31 You predict the properties of the Substance from studies (i) and (ii) and conclude that they do not support classification of the source or target substances for fertility or developmental toxicity effects.

32 However, based on study (i) and other studies with the source substance methyl salicylate (EC number 204-317-7), ECHA's Committee for Risk Assessment (RAC) adopted an opinion on 20 September 2019 supporting a proposal for harmonised classification and labelling at EU level of this substance as Repr. 2 for developmental toxicity effects.

33 Moreover, study (ii) shows reproductive and developmental toxicity effects such as changes in gestational length, increased post-implantation losses, reduced litter size, and reduced body weight of offspring. These effects were considered by ECHA as of concern and sufficient to trigger a request for an EOGRTS at Annex IX in its compliance check decision of 13 March 2018 for the source substance 2-ethylhexyl salicylate (EC number 204-263-4).

34 This contradicts your read-across hypothesis whereby the Substance and source substances cause the same type of effects and do not need classification for fertility or developmental toxicity effects. However, you have not provided any justification for this contradiction.

35 In your comments to the draft decision you acknowledge the above studies and the reproductive and developmental toxicity properties of the source susbtances and the harmonised classification of the source substance methyl salicylate (EC number 204-317-7).

2.2.1.4. Source studies not adequate for the information requirement

36 Under Annex XI, Section 1.5., the study to be read across must have an adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this case EU B.63/OECD TG 421 or EU B.64/OECD TG 422. Therefore, the following specifications must be met:

a) body weights are measured at least weekly;
b) food consumption is measured at least weekly;
c) the nature, severity, and duration of clinical signs observed daily are reported;
d) thyroid hormone levels are measured;
e) terminal organ and body weights are reported;

f) gross pathology of reproductive organs is performed, and the presence or absence, incidence and severity of abnormalities is evaluated;
g) histopathology of reproductive organs and tissues is performed, and the presence or absence, incidence and severity of abnormalities is evaluated;
h) oestrous cycles are monitored;
i) offspring parameters such as number and sex of pups, anogenital distance, nipple retention in male pups are reported.

37 In study (i) described as a three-generation reproductive toxicity study:

a) data on body weights, body weight changes are missing;
b) data on food consumption are missing;
c) data on clinical signs, including their nature, severity, and duration, are not reported;
d) thyroid hormone levels were not measured;
e) terminal organ weights and organ/body weight ratios are not reported;
f) data on gross pathology findings, including incidence and severity of abnormalities, are not reported, except for the F3 generation;
g) data on histopathology findings, including incidence and severity of abnormalities, are not reported, except for the liver and kidney. In particular, investigations of the reproductive organs are missing.
h) data on oestrous cycles is missing;
i) data on number and sex of pups, anogenital distance, nipple retention in male pups is missing.

38 In study (ii) described as a screening study for reproductive/developmental toxicity:

a) thyroid hormone levels were not measured;
b) data on oestrous cycles is missing;
c) data on anogenital distance, nipple retention in male pups is missing.

39 The information provided does not provide an adequate and reliable coverage of the specifications required by the OECD TG 421/422.

40 Based on the above, the studies (i) and (ii) are not an adequate basis for your read-across predictions.

2.2.2. Conclusion on the read-across adaptation

41 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.

42 In the comments to the draft decision, you present a strategy relying on the generation of additional supporting information on the Substance and on analogue substances and you propose to:

i. perform developmental toxicity studies in zebrafish embryos and also human cell lines *in vitro* to demonstrate similarity of effects between the Substance and source substances.

43 You also intend to:

ii. investigate the Substance and source substances for their stability in simulated gastric and intestinal fluid media,

iii. investigate their *in vitro* metabolism using human and/or rat liver hepatocytes, and,

iv. if considered as necessary, investigate their oral bioavailability by performing an *in vitro* Caco-2 permeability assay or *ex vivo* everted rat gut study.

44 ECHA acknowledges your intention to improve the (eco)toxicological profile of the Substance and your plans to refine your read-across approach. In order to provide input for your further reflection, ECHA observes that, for the above aspects:

i. the proposed *in vitro* studies could be useful to establish toxicological similarity if (adverse) effects are observed and this is the basis for predicting the hazardous property of the Substance. If the prediction is aimed at predicting absence of effects, the investigations in zebrafish embryos and de-differentiated human cell lines may be limited in their predictive capacity for being useful as supporting evidence.

ii. to iv., the proposed approach may be useful for establishing similarity in toxikokinetic properties and to support a read-across approach that is based on similar toxicity profiles. However, the approach may have severe limitations for (bio)transformation approaches, because those approaches generally aim at demonstrating an *absence* of the parent compound from systemic circulation.

45 For this decision, ECHA points out that this strategy relies essentially on data which is yet to be generated. No conclusion on the compliance can currently be made, as this is work in progress.

2.3. Specification of the study design

46 A study according to the test method EU B.63/OECD TG 421 or EU B.64/OECD TG 422 must be performed in rats.

47 The study must be conducted with oral administration of the Substance (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

48 Therefore, the study must be conducted in rats with oral administration of the Substance.

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).
Guidance for monomers and polymers; ECHA (2012).
Guidance on intermediates; ECHA (2010).
All guidance documents are 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 14 September 2021.

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

ECHA took into account your comments and did not amend the requests or the deadline.

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]

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