~~Confidential~~

Helsinki, 12 June 2023

Addressees
Registrant(s) of JS_218-451-9 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
19/10/2022

Registered substance subject to this decision ("the Substance")
Substance name: Dibutyl itaconate
EC/List number: 218-451-9

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 ***19 June 2026***.

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

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

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

2. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: EU C.47./OECD TG 210)

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

Reasons related to the information under Annex IX of REACH

1. Long-term toxicity testing on aquatic invertebrates

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

1.1. Information provided in the dossier

2 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:

3 "According to Column 2 of REACH Annex IX (section 9.1), long-term toxicity testing on invertebrates is not proposed by the registrant as the CSA indicates no need to investigate further the effects on aquatic organisms. Based on the currently available data, the substance is not classified as hazardous for the environment, the substance is not poorly water soluble and the substance is readily biodegradable".

1.2. Assessment of the information provided in the dossier

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

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

5 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).

6 Your adaptation is therefore rejected.

1.3. Information provided in the comments to the draft decision

7 In the comment to the draft decision, you disagree to perform the long-term toxicity test on aquatic invertebrates.

8 You state that the Decision of the Board of Appeal in case A-011-2018 was specific to a potentially persistent substance with data gaps for short term toxicity to fish and aquatic invertebrates, whereas your Substance is readily biodegradable and has short term aquatic toxicity data for three trophic levels.

9 In addition, you present a weight of evidence approach (Annex XI, section 1.2) based on the following pieces of information:

- Available ecotoxicological data for the Substance:
  - i. Short-term toxicity study in fish (OECD 203),
  - ii. Short-term toxicity study in aquatic invertebrates (OECD 202),
  - iii. Toxicity to aquatic algae and cyanobacteria (OECD 201),
- Available ecotoxicological data for analogue substance dimethyl itaconate:
  - iv. Short-term toxicity study in fish (OECD 236),

v. Short-term toxicity study in aquatic invertebrates (pre-test for OECD 211, comparable to OECD 202),

vi. Toxicity to aquatic plant other than algae (OECD 221),

vii. Long-term toxicity study in aquatic invertebrates (OECD 211),

- Available ecotoxicological data for hydrolysis product itaconic acid:

viii. Short-term toxicity study in fish (EU Method C.1),

ix. Short-term toxicity study in aquatic invertebrates (EU Method C.2),

x. Toxicity to aquatic algae and cyanobacteria (EU Method C.3),

- Available ecotoxicological data for hydrolysis product butanol:

xi. Short-term toxicity study in fish (OECD 203),

xii. Short-term toxicity study in aquatic invertebrates (OECD 202),

xiii. Toxicity to aquatic algae and cyanobacteria (OECD 201),

xiv. Long-term toxicity study in aquatic invertebrates (OECD 211).

1.4. Assessment of the information provided in the comments to the draft decision

1.4.1. The decision of the Board of Appeal in case A-011-2018 was not specific to a substance

10 The Board of Appeal's interpretation of the second column of Annex IX Section 9.1 in its decision in case A-011-2018 was not limited to a specific substance, and it has been confirmed also in a more recent decision for another substance in case A-010-2019.

11 The study information set out in Annex IX, Section 9.1.5, Column 1 ('Long-term toxicity testing on invertebrates') is a standard information requirement under Annex IX. It is independent of the information on short-term aquatic toxicity or on biodegradability. The specific rule for adaptation in Annex IX, Section 9.1.5, Column 2 concerns testing other than the tests referred to in points 9.1.5 and 9.1.6.

1.4.2. Your weight of evidence approach is not reliable

12 Annex XI, Section 1.2. states that there may be sufficient weight of evidence from several independent sources of information enabling, through a reasoned justification, a conclusion on the information requirement, while the information from each single source alone is insufficient to fulfil the information requirement.

13 The justification must have regard to the information that would otherwise be obtained from the study that must normally be performed for this information requirement.

14 According to ECHA Guidance R.4, a weight of evidence adaptation involves an assessment of the relative values/weights of the different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance and coverage of the information for the given regulatory information requirement. Subsequently, relevance, reliability, coverage, consistency, and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude on the corresponding information requirement.

15 To fulfil the information requirement of Annex IX, Section 9.1.5., information on long-term toxicity study in aquatic invertebrates must normally be obtained according to OECD TG

211. OECD TG 211 requires the study to investigate the concentrations of the test material leading to no observed effect (NOECs) on the following key parameters:

- the reproductive output of Daphnia sp. expressed as the total number of living offspring produced at the end of the test (i.e. 21 days), and
- the survival of the parent animals during the test.

16 Only sources of information (vii) and (xiv) provide information on the key parameters of OECD TG 211. On this basis, only sources of information (vii), on analogue substance dimethyl itaconate, and (xiv), on hydrolysis product butanol, may be relevant for the information requirement.

17 However, the validity of those two sources of information is not demonstrated to support the weight of evidence, for the following reasons.

1.4.2.1. Read-across from analogue substance dimethyl itaconate

18 You explain that analogue substance dimethyl itaconate and the registered Substance are both aliphatic linear esters of itaconic acid, but with different chain length, that could be hydrolysed back to itaconic acid and the corresponding alcohol (respectively methanol and butanol for the analogue substance and the registered Substance). By comparing the results from the available short-term toxicity studies for the analogue substance and the registered Substance, you claim that both substances have comparable ecotoxicological profiles.

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

20 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.

21 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).

22 ECHA understands that you intend to 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, i.e. dimethyl itaconate.

23 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.).

24 The observation of differences in the 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 substance(s). An explanation why such differences do not affect the read-across hypothesis must be provided and supported by scientific evidence.

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

26 You note that the results from the available short-term aquatic toxicity studies are of the same order of magnitude between the source substance and the registered Substance. On this basis, you claim that both substances have comparable ecotoxicological profiles also for long-term exposure.

27 However, ECHA notes that the available short-term results for the Substance (i.e. studies (i), (ii) and (iii)) indicate a systematically higher short-term aquatic toxicity of the Substance compared to the source substance (i.e. studies (iv), (v) and (vi)).

28 For long-term exposure, results for the Substance can be expected to show even higher toxicity and to diverge even more than those for the source substance. The Substance has longer chain lengths and is more lipophilic than the source substance (log Kow of 3.8 for the Substance vs. log Kow of 0.86 for the source substance). As such, the Substance can reach a higher internal concentration within the organisms after long-term exposure compared to the source substance. The registered Substance could not only disrupt to a higher extent the cellular membranes (baseline toxicity due to narcotic effect), but also affect more easily any other potential biomolecular toxicity targets within the organisms. Therefore, the Substance is expected to cause higher long-term aquatic toxicity compared to the source substance.

29 This contradicts your read-across hypothesis whereby the Substance and the source substance cause the same type of effect, and you have not supported and scientifically justified why such differences between the two substances do not affect your read-across hypothesis.

30 Therefore, the proposed read-across approach cannot be considered a reliable source of information that could contribute to your weight of evidence approach.

1.4.2.2. Read-across from hydrolysis product butanol

31 You explain that butanol is one of the expected hydrolysis products of the registered Substance.

32 ECHA understands that you intend to predict the properties of the Substance using a read-across hypothesis which is based on the formation of hydrolysis products.

33 We have assessed this information and identified the following issues:

34 As indicated above, your read-across hypothesis is based on the (bio)transformation of the Substance into hydrolysis products. In this context, information characterising the rate and extent of that (bio)transformation is necessary to confirm the formation of the proposed hydrolysis products and to assess the impact of the exposure to the parent compounds. Furthermore, data on long-term toxicity to aquatic invertebrates must be provided for all the hydrolysis products. Finally, you must demonstrate that the information on long-term toxicity to aquatic invertebrates for the hydrolysis products is relevant for predicting the long-term toxicity of the Substance.

35 You explain that the Substance could be (bio)transformed into two hydrolysis products: itaconic acid and butanol.

36 You do not provide details on the rate and extend of that (bio)transformation reaction.

37 You provide data on long-term toxicity data for aquatic invertebrates for butanol, but not for itaconic acid.

38 ECHA notes that:

- you have not provided any experimental information about the rate and extent of that (bio)transformation reaction;

- no information on long-term toxicity to aquatic invertebrates is provided for itaconic acid. Information on long-term toxicity of butanol to aquatic invertebrates is, alone, not sufficient to assess the long-term toxicity to aquatic invertebrates of the two hydrolysis products;
- The comparison between available short-term information for butanol (sources of information (xi), (xii) and (xiii)) and itaconic acid (sources of information (viii), (ix) and (x)) and available short-term information for the Substance (sources of information (i), (ii) and (iii)) suggests that the short-term toxicity of the two hydrolysis products is far lower than for the Substance. Therefore, as indicated in your comments, the toxicity of the Substance is not expected to be caused by the hydrolysis products but by the Substance as such.

39 Therefore, the read-across hypothesis is not demonstrated and cannot be considered a reliable source of information that could contribute to your weight of evidence approach.

1.4.2.3. Conclusion on the weight-of-evidence

40 In summary, only sources of information (vi), on analogue substance dimethyl itaconate, and (xiv), on hydrolysis product butanol, provide information relevant for the information requirement on long-term toxicity to aquatic invertebrates. However, you did not demonstrate that the requirements for read-across from the information on dimethyl itaconate or butanol are met, as described above, and cannot reliably contribute to the conclusion on the information requirement.

41 Therefore, it is not possible to conclude, based on any source of information alone or considered together, on the information requirement for long-term toxicity to aquatic invertebrates.

1.5. Conclusion

42 Based on the information provided in your dossier and in your comments to the draft decision, the information requirement is not fulfilled.

2. Long-term toxicity testing on fish

43 Long-term toxicity testing on fish is an information requirement under Annex IX to REACH (Section 9.1.6.).

2.1. Information provided in the dossier

44 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:

45 "According to Column 2 of REACH Annex IX (section 9.1), long-term toxicity testing on fish is not proposed by the registrant as the CSA indicates no need to investigate further the effects on aquatic organisms. Based on the currently available data, the substance is not classified as hazardous for the environment, the substance is not poorly water soluble and the substance is readily biodegradable".

2.2. Assessment of the information provided in the dossier

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

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

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

48 Your adaptation is therefore rejected.

2.3. Information provided in the comments to the draft decision

49 In the comment to the draft decision, you disagree to perform the long-term toxicity test on fish.

50 You state that the Decision of the Board of Appeal in case A-011-2018 was specific to a potentially persistent substance with data gaps for short term toxicity to fish and aquatic invertebrates, whereas your Substance is readily biodegradable and has short term aquatic toxicity data for three trophic levels.

51 In addition, you present a weight of evidence approach (Annex XI, section 1.2) based on the following pieces of information:

- Available ecotoxicological data for the Substance:
  - i. Short-term toxicity study in fish (OECD 203),
  - ii. Short-term toxicity study in aquatic invertebrates (OECD 202),
  - iii. Toxicity to aquatic algae and cyanobacteria (OECD 201),
- Available ecotoxicological data for analogue substance dimethyl itaconate:
  - iv. Short-term toxicity study in fish (OECD 236),
  - v. Short-term toxicity study in aquatic invertebrates (pre-test for OECD 211, comparable to OECD 202),
  - vi. Toxicity to aquatic plant other than algae (OECD 221),
  - vii. Long-term toxicity study in aquatic invertebrates (OECD 211),
- Available ecotoxicological data for hydrolysis product itaconic acid:
  - viii. Short-term toxicity study in fish (EU Method C.1),
  - ix. Short-term toxicity study in aquatic invertebrates (EU Method C.2),
  - x. Toxicity to aquatic algae and cyanobacteria (EU Method C.3),
- Available ecotoxicological data for hydrolysis product butanol:
  - xi. Short-term toxicity study in fish (OECD 203),
  - xii. Short-term toxicity study in aquatic invertebrates (OECD 202),
  - xiii. Toxicity to aquatic algae and cyanobacteria (OECD 201),
  - xiv. Long-term toxicity study in aquatic invertebrates (OECD 211).

2.4. Assessment of the information provided in the comments to the draft decision

2.4.1. The decision of the Board of Appeal in case A-011-2018 was not specific to a substance

52 As already explained in section 1.4.1 above, the Board of Appeal's interpretation of the second column of Annex IX Section 9.1 in its decisions in case A-011-2018, or later in case

A-010-2019, was not limited to a specific substance. The information requirement for Section 9.1.6. ('Long-term toxicity testing on fish') is independent of the information on short-term aquatic toxicity or on biodegradability.

2.4.2. Your weight of evidence approach is not reliable

53 To fulfil the information requirement of Annex IX, Section 9.1.6., information on long-term toxicity study in fish must normally be obtained according to OECD TG 210. OECD TG 210 requires the study to investigate the survival and development of fish in early life stages from the stage of fertilized egg until the juvenile life-stage following exposure to the test substance are measured, including the following key parameters:

- the stage of embryonic development at the start of the test, and
- hatching of fertilized eggs and survival of embryos, larvae and juvenile fish, and
- the appearance and behaviour of larvae and juvenile fish, and
- the weight and length of fish at the end of the test.

54 None of the sources of information (i) to (xiv) provide information on the key parameters of OECD TG 210. Therefore, none of the sources of information you provided are relevant for the information requirement.

55 Therefore, it is not possible to conclude, based on any source of information alone or considered together, on the information requirement for long-term toxicity to fish.

2.5. Conclusion

56 Based on the information provided in your dossier and in your comments to the draft decision, the information requirement is not fulfilled.

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

2.6. Study design and test specifications

58 To fulfil the information requirement for the Substance, the Fish, Early-life Stage Toxicity Test (test method OECD TG 210) is the most appropriate (Guidance on IRs and CSA, Section R.7.8.2.).

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 17 November 2021.

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

In your comments, you requested an extension of deadline. Your request was supported by a letter from a testing laboratory. The deadline has been exceptionally extended by 24 months from the standard deadline granted by ECHA, to take into account the 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 Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;

Registrant Name	Registration number	Highest REACH Annex applicable to you
[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