EUROPEAN CHEMICALS AGENCY

Helsinki, 21 January 2021

Addressees
Registrant(s) of JS_Calcium dibenzoate as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
18/05/2018

Registered substance subject to this decision ("the Substance")
Substance name: Calcium dibenzoate
EC number: 218-235-4
CAS number: 2090-05-3

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 the deadline of ***28 April 2022***.

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

A. Information required from all the Registrants subject to Annex VII of REACH

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: EU B.13/14. /OECD TG 471)

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

1. If negative results are obtained in test performed for the information requirement of Annex VII, Section 8.4.1. then: In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490)

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

Reasons for the request(s) are explained in the following appendices:

- Appendices entitled "Reasons to request information required under Annexes VII to VIII of REACH", respectively.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

- 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;

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 testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

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 Christel Schilliger-Musset, Director of Hazard Assessment

[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 A: Reasons to request information required under Annex VII of REACH

1. In vitro gene mutation study in bacteria

An *in vitro* gene mutation study in bacteria is a standard information requirement in Annex VII to REACH.

You have adapted this information requirement according to Annex XI 1.5 (grouping of substances and read-across) of REACH.

You have provided a key study and supporting studies made with the analogue substance benzoic acid:

i. Key bacterial reverse mutation study (1979a) with the strains, TA 98, TA 100, TA 1535 and TA 1537 which all gave negative results
ii. Supporting bacterial reverse mutation study (1979b) with the strains, TA 97, TA 98, TA 100, TA 1535 and TA 1537 which all gave negative results
iii. Supporting bacterial reverse mutation study (1975) with the strains, TA 98, TA 100, TA 1535 and TA 1537 which all gave negative results
iv. Supporting bacterial reverse mutation study (1977) with the strains, TA 98, TA 100, TA 1535 and TA 1537 which all gave negative results
v. Supporting bacterial reverse mutation study (1983a) with the strains, TA 92, TA 94, TA 98, TA 100, TA 1535 and TA 1537 which all gave negative results
vi. Supporting bacterial reverse mutation study (1983b) with the strain TA 100 which gave negative result

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

According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across must have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3).

To fulfil the information requirement, the study has to meet the requirements. The key parameters of the applicable test method, OECD TG 471 (1997), include:

a) The test must be performed with 5 strains: four strains of *S. typhimurium* (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101)
b) The mean number of revertant colonies per plate must be reported for the treated doses and the controls.

The reported data for the studies you have provided did not include:

a) results for the required fifth strain, S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101).
b) data on the number of revertant colonies per plate for the treated doses and the controls.

In your comments to draft decision you indicate your intention to update your dossier with regard to data on the number of revertant colonies for the treated doses and the controls. ECHA acknowledges your partial agreement to the draft decision but notes that this information was not provided and thus cannot be taken into account. You are responsible to provide the necessary information to comply with the decision by the set deadline.

However, you also state in your comments to draft decision that conducting further testing with a required fifth strain is scientifically not justified due to structural considerations. More specifically, you consider the Substance "*is not a highly reactive agent and is therefore not expected to be a cross-linking agent and is no hydrazine*" and that "*from its structure, it is*

also not expected to have oxidizing properties." You claim that large scale DNA damage caused by any oxidative properties of the Substance would have been detectable in currently negative clastogenicity assays provided in the dossier. ECHA notes that you have not provided any legal basis for this adaptation and it does not appear related to any existing legal basis under REACH, and that you have, in any case, made allegations without substantiation, and that to fulfil the information requirement, the study has to meet the above OECD TG 471 requirements.

Therefore, the information requirement is not fulfilled.

To fulfil the information requirement for the Substance, the *in vitro* gene mutation study in bacteria (OECD TG 471) is considered suitable.

Appendix B: Reasons to request information required under Annex VIII of REACH

1. In vitro gene mutation study in mammalian cells

An *in vitro* gene mutation study in mammalian cells is a standard information requirement in Annex VIII to REACH in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test.

Your dossier contains (i) negative results for *in vitro* and *in vivo* cytogenicity studies in mammalian cells, and (ii) inadequate data for *in vitro* gene mutation study in bacteria.

You have provided no data on an *in vitro* gene mutation study in mammalian cells in accordance with OECD TG 476 or OECD TG 490.

The *in vitro* gene mutation study in bacteria provided in the dossier is rejected for the reasons provided in section 1 of Appendix A.

The result of the request for information in section 1 of Appendix A will determine whether the present requirement for an *in vitro* mammalian cell gene mutation study in accordance with Annex VIII, Section 8.4.3 is triggered.

In your comments to draft decision you argue that, with reference to the negative in vivo dominant lethal test and the negative results of the bacteria gene mutation tests, an additional in vitro gene mutation study in mammalian cells is not justified.

This endpoint is, however, a standard information requirement.

You argue also that, although dominant lethality is generally a consequence of structural and/or numerical chromosomal aberrations, gene mutations and toxic effects cannot be excluded, and that a negative in vivo dominant lethal test is therefore also indicative of a missing gene mutation activity.

To adapt this information requirement, there must be adequate data from a reliable *in vivo* mammalian gene mutation test.

ECHA acknowledges that the dominant lethal test identifies substances that cause dominant lethal (DL) mutations in germ cells causing embryonic or fetal death that are the result of gross chromosomal aberrations, and that gene mutations cannot be excluded in case of positive results. ECHA notes however that dominant lethal test or gene mutation study in bacteria does not investigate, and is thus not appropriate for, gene mutation (detection and quantification of gene mutations) in mammalian cells. Therefore the in vitro gene mutation study in mammalian cells cannot be adapted by an in vivo dominant lethal test or a gene mutation test in bacteria, and the information requirement is not fulfilled.

Consequently, you are required to provide information for this endpoint, if the *in vitro* gene mutation study in bacteria provide a negative result.

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

2. Screening for reproductive/developmental toxicity

A Screening for reproductive/developmental toxicity study (test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) is a standard information requirement under Annex VIII to

REACH, if there is no evidence from analogue substances, QSAR or *in vitro* methods that the Substance may be a developmental toxicant. There is no information available in your dossier indicating that your Substance may be a developmental toxicant.

You have adapted this information requirement according to Annex XI 1.5 (grouping of substances and read-across) of REACH.

You have submitting the following study:

a) Multi-generation reproductive toxicity in rat, with analogue substance benzoic acid (EC 200-618-2). No guideline (1960)

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

According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across must have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3).

In this case the study has to cover the key parameters of OECD TG 421 or 422, which include at least three dose levels, mating and fertility/duration of gestation or information on parturition, investigations for thyroid hormone assessment (P0 and F1), investigations for stillbirths and live births, gross abnormalities, anogenital distance, number of nipples, and areolae in male pups, monitoring of oestrus cycles.

The study you have provided deviated from the OECD TG 421 or 422 in the following ways:

- it was conducted with two dose levels instead of three;
- it did not include investigations for thyroid hormone assessment (P0 and F1);
- it did not report the duration of gestation or give information on parturition;
- oestrus cycles were not monitored;
- investigations for stillbirths and live births, gross abnormalities, anogenital distance, number of nipples, and areolae in male pups were not reported.

In your comments to draft decision you state that you can add information from a developmental toxicity study in rats with sodium benzoate to cover the endpoint developmental toxicity. It is in your discretion to generate and provide the necessary supporting information in order to justify your read-across adaptation. ECHA considers read-across between benzoic acid and simple salts (Na, K, Ca) to be plausible in principle. Nonetheless, you are responsible for demonstrating the fulfilment of the requirements of Section 1.5 of Annex XI to REACH, especially regarding the quality and documentation of the source study. You remain responsible for complying with this decision by the set deadline.

Based on the above, the information you provided does not fulfil the information requirement.

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 with oral[2] administration of the Substance.

[2] ECHA Guidance R.7a, Section R.7.6.2.3.2.

Appendix C: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. 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].

B. 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

Appendix D: 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 9 July 2019.

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

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend the requests.

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 E: List of references - ECHA Guidance[5] and other supporting documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)[6]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[7]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

[5] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[6] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[7] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316

OECD Guidance documents[8]

Guidance Document on aqueous–phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

[8] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Appendix F: Addressees of this decision and the corresponding information requirements applicable to them

You must provide the information requested in this decision for all REACH Annexes applicable to you.

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

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.