~~Confidential~~

Helsinki, 09 September 2021

Addressees
Registrant listed in the last Appendix of this decision

Date of submission of the dossier subject of a decision
05/06/2018

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Reaction mass of bisisopropyl peroxydicarbonate and bis-sec-butyl peroxydicarbonate and isopropyl-sec-butylperoxydicarbonate
List number: 931-536-1
CAS number: NS

Decision number: Please refer to the REACH-IT message which delivered this communication (in format TPE-D-XXXXXXXXXX-XX-XX/F)

DECISION ON TESTING PROPOSAL(S)

Based on Article 40(3)(d) of Regulation (EC) No 1907/2006 (REACH), the testing proposal listed below is rejected:

A. Testing proposal under Annex VII to REACH

1. *In vivo* mammalian alkaline comet assay (OECD TG 489) using the analogue substance bisisopropyl peroxydicarbonate (IPP), EC number 203-317-4.

The reasons for the rejection are explained in Appendix A.

For references used in this decision, please consult the Appendix entitled "List of references – ECHA Guidance and other supporting documents".

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Approved[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 for the decision

This decision is based on the examination of the testing proposal you submitted.

A. Reasons to reject testing proposal under Annex VII to REACH

1. In vivo mammalian alkaline comet assay

Under Annex VII Section 8.4., column 2 of REACH, further mutagenicity studies must be considered in case of a positive result in an *in vitro* gene mutation study in bacteria.

1.1. Information provided

Your dossier does not contain positive results for the *in vitro* gene mutation study in bacteria.

You have submitted a testing proposal for an *In vivo* mammalian alkaline comet assay to be performed with the analogue substance bisisopropyl peroxydicarbonate (IPP), (EC no. 203-317-4).

ECHA requested your considerations for alternative methods to fulfil the information requirement for Genetic toxicity *in vivo*. You provided your considerations and you applied read-across to fulfil the respective information requirement, but you considered that no other alternative methods were available. ECHA has taken these considerations into account.

1.2. No information required

As noted above, further mutagenicity studies must be considered in case of a positive result in an *in vitro* gene mutation study in bacteria. The generation of new information should be tailored to real information needs, and unnecessary animal testing should be avoided.

On the basis of the information in your dossier, and in particular the absence of positive *in vitro* mutagenicity results, ECHA considers that no further *in vivo* study needs to be performed at this point in time to further investigate the mutagenic properties of the Substance. As explained in section 1.3., also your read-across documentation does not further support the generation of new *in vivo* data.

1.3. Grouping of substances and read-across approach

In your testing proposal you proposed testing with an analogue substance thereby using the *Grouping of substances and read-across approach* under Annex XI, Section 1.5.

We have assessed the information you provided and identified the following issues:

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.

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance R.6 and related documents.

You have provided a read-across justification document in IUCLID Section 13.

You predict the properties of the Substance from the following structurally similar substances, which are the constituents and the stabiliser of this multi-constituent Substance:

i. Isopropyl sec-butyl peroxydicarbonate (hereafter 'IBP'), EC no. 278-901-5;
ii. bisisopropyl peroxydicarbonate (hereafter 'IPP'), EC no. 203-317-4;
iii. di-sec-butyl peroxydicarbonate (hereafter 'SBP') EC no. 243-424-3; and
iv. diallyl 2,2'- oxydiethyldicarbonate (hereafter 'stabilizer') EC no. 205-528-7.

You have provided the following reasoning for the prediction of the genotoxicity (toxicological) properties:

"The available Ames test with the stabilizer is negative without metabolic activation and ambiguous with metabolic activation, the overall conclusion for the stabilizer is negative for mutagenicity. The Ames test with SBP is negative and an MLA is ongoing. IPP is positive with metabolic activation in the Ames test and the MLA. […]"

"[…] Based on the available information, the multi-constituent substance is concluded not to be a mutagen pending the outcome of the proposed Comet assay. SBP has a negative In vivo micronucleus assay. IPP and the stabilizer have negative In vitro micronucleus assays (Appendix 1). Based on the structural similarities of IBP the same outcome is expected."

"Therefore, it can be concluded that the multi-constituent substance is not a clastogen and no further testing is required. The robust summaries for the In vitro studies are unfortunately not available to the registrant at the time of dossier submission."

Based on the above you propose to perform the *in vivo* comet assay with one of the source substances (IPP) due to the positive results obtained with IPP in the *in vitro* gene mutation studies in bacterial cells and mammalian cells (OECD TG 471 and 490, respectively). As explained above, we note that these positive results are not available in the dossier.

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.

ECHA notes the following shortcomings with regards to the predictions of toxicological properties.

a) Missing supporting information

Annex XI, Section 1.5 of the REACH Regulation states that "*physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s)*". For this purpose "*it is important to provide supporting information to strengthen the rationale for the read-across*"[2]. The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substance(s).

As indicated above, your read-across hypothesis is based on the assumption that the structurally similar substances cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the Substance and

[2] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.2.1.f

of the source substance(s) is necessary to confirm that the substances cause the same type of effects.

However, in the read-across justification document you do not account for all the source substances, which are the constituents and the stabiliser of the multi-constituent Substance. In particular, for IBP you do not provide any information as you claim that it only exists as a constituent of the Substance and is not found as a pure substance. For the two minor constituents IPP and SBP, and the stabiliser, though you provide information in the justification document, you fail to provide relevant, reliable and adequate information in the dossier that allows comparison of the properties of the Substance and the source substances. More specifically, you have not provided any *in vitro* mutagenicity data with the Substance and the source substances.

Furthermore we note that you propose testing with IPP, which is only one of the minor constituents of the Substance (about [redacted]% (w/w) of the Substance). The multi-constituent Substance is mostly composed of the stabiliser (about [redacted]% (w/w)) and IBP (about [redacted]% (w/w)). In your justification you did not consider the impact of the presence of these main constituents on the properties of the Substance.

As explained above, the lack of this data does not allow us to compare the properties between the substances and the possibility to determine whether IPP can be used to predict the genotoxicity property for the Substance.

In the absence of such information, you have not established that the Substance and the source substance(s) are likely to have similar properties.

b) Read-across hypothesis contradicted by existing data

Annex XI, Section 1.5. provides that "substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances. The ECHA Guidance[3] indicates that "*it is important to provide supporting information to strengthen the rationale for the read-across*". The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substance(s). 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 needs to be provided and supported by scientific evidence.

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

Based on the information provided in the justification document the results on mutagenicity obtained with the source substances vary. Specifically, positive results are observed in the *in vitro* bacterial study conducted with one of the source substances (IPP) while negative results are reported for equivalent studies conducted for the other source substances. Moreover, no data is available with one of the constituents (IBP).

The data matrix in the justification document indicates differences in the toxicological properties of the substances. This contradicts your read-across hypothesis whereby the

[3] Guidance on information requirements and chemical safety assessment (version 6.0, July 2017), Chapter R.6, Section R.6.2.2.1.f

structurally similar target and source substances cause the same type of effect(s). Therefore, you have not demonstrated and justified that the properties of the source substances and of the Substance are likely to be similar despite the observation of these differences.

Conclusions on the read-across approach

As explained above, you have not established that relevant properties of the Substance can be predicted from data on the analogue substance(s). Therefore, you have not provided sufficient supporting information to strengthen the rationale for the read-across justifying the need for testing.

1.4. Outcome

Your testing proposal is rejected under Article 40(3)(d) of REACH.

Appendix B: Procedure

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 20 July 2020.

ECHA held a third party consultation for the testing proposal(s) from 24 August 2020 until 8 October 2020. ECHA did not receive information from third parties.

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

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

ECHA did not receive any comments within the commenting period.

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 C: List of references - ECHA Guidance[4] 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)[5]

RAAF - considerations on multi-constituent substances and UVCBs (RAAF UVCB, March 2017)[6]

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.

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

OECD Guidance documents[7]
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.

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

Appendix D: Addressees of this decision

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.