ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 9 December 2019

Addressees
The registrants of JS_701-230-0 listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
18 February 2019

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Reaction products of butane-1,4-diol and 1-chloro-2,3-epoxypropane, esters with acrylic acid
EC number: 701-230-0
CAS number: NS

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

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of ***16 March 2022***.

A. Requirements applicable to all the Registrants subject to Annex IX of REACH

1. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method OECD TG 408) in rats with the Substance

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method OECD TG 414) in a first species (rat or rabbit), oral route with the Substance

Conditions to comply with the requests

Each addressee of this decision is bound by the requests for information corresponding to the REACH Annexes applicable to their own registered tonnage of the Substance at the time of evaluation of the jointly submitted dossier.

To identify your legal obligations, please refer to the following:

- you have to comply with the requirements of Annexes VII, VIII and IX of REACH, if you have registered a substance at 100-1000 tpa;

Registrants are only required to share the costs of information that they must submit to fulfil the information requirements for their registration.

The Appendix on general considerations addresses common arguments that are applicable throughout the present decision while the other Appendices state the endpoint specific reasons for the requests for information.

The test material used to perform the required studies must be selected and reported in accordance with the specifications prescribed in the Appendix entitled Observations and technical guidance.

You must submit the information requested in this decision by the deadline indicated above in an updated registration dossier and also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information. The timeline has been set to allow for sequential testing where relevant.

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 Schillinger-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 on general considerations

Assessment of the Grouping of substances and read-across approach, in light of the requirements of Annex XI, Section 1.5.

You seek to adapt the following standard information requirements by applying a read-across approach in accordance with Annex XI, Section 1.5:

- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

ECHA has considered the scientific and regulatory validity of your read-across approach in general before assessing the specific standard information requirements in the following appendices.

Grouping of substances and read-across approach

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 the ECHA RAAF document.[2]

You have provided a read-across justification for the relevant endpoints in the Chemical Safety Report.

You read across to the Substance from the structurally similar substance, (1-methyl-1,2-ethanediyl) bis[oxy(methyl-2,1-ethanediyl)] diacrylate, EC No. 256-032-2 (CAS No. 42978-66-5; i.e. the source substance).

You have provided the following reasoning for the prediction of toxicological properties: you state that both substances are structurally similar, they are liquids that have a similar molecular weight and a comparable partition coefficent, and they have similar toxicological properties.

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 prediction of toxicological properties.

1. Lack of a read-across hypothesis on why predictions as a result of structural similarity is possible

A read-across hypothesis needs to be provided, establishing why a prediction for a toxicological or ecotoxicological property is reliable. This hypothesis should be based on

[2] The ECHA Guidance documents referred to in this decision are listed in Appendix C of this decision.

recognition of the structural similarities and differences between the source substance(s) and your Substance[3]. It should explain why the differences in the chemical structures should not influence the toxicological/ecotoxicological properties or should do so in a regular pattern.

Your read-across hypothesis states that both substances are similar in structure and in some physical-chemical properties and have similar toxicological properties.

You do not provide a read-across hypothesis, which would explain the structural similarities and differences between the source substance(s) and the Substance and which would further establish why the differences in the chemical structures should not influence the toxicological/ecotoxicological properties.

2. Characterisation of the composition of the source substance

The substance characterisation of the source substance(s) need to be sufficiently detailed in order to assess whether the attempted prediction is not compromised by the composition and/or impurities. In ECHA's Practical Guide on "How to use alternatives to animal testing to fulfil your information requirements" (chapter 4.4), it is recommended to follow the ECHA *Guidance for identification and naming of substances under REACH and CLP* (version 2.1, May 2017) also for the source substances. This ensures that the identity of the source substance and its impurity profile allows an assessment of the suitability of the substances for read-across purposes.

Furthermore, the provided information for categories consisting of UVCB (Unknown or Variable composition, Complex reaction products or of Biological materials) substances needs to include qualitative compositional information of the individual constituents of the category members; as well as quantitative characterisation in the form of information on the concentration of the individual constituents of these substances; to the extent that this is measurable.[4]

However, you have described the source substance only by EC and CAS numbers. You have not provided a detailed comparison of the composition of the source substance with the Substance. In the absence of this information, ECHA considers that it is not possible to assess whether the attempted predictions are compromised by the composition of the source substance.

3. Similar toxicological properties

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[5] 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 Substance and the source substance is a warning sign. An explanation for such a difference resulting in a contradiction between the similarities in properties claimed in the read-across hypothesis and the observation of different properties needs to be provided and supported by scientific evidence.

[3] Echa Guidance R.6, Section R.6.2.1
[4] Echa Guidance R.6, Section R.6.2.5.5.
[5] ECHA Guidance R.6, Section R.6.2.2.1.f

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

You have provided the following studies to support your hypothesis:

With the Substance:

(i) Screening for reproduction/development toxicity study in rats, oral-gavage (key study, according OECD TG 422, GLP compliant, assigned reliability score of 1; [redacted] 2013). Doses: 50, 150, 500 mg/kg bw/day (up to day 5), 300 (mg/kg bw/day from day 6). NOAEL systemic (male) = 50 mg/kg bw/day based on mortality, decrease in body weight and body weight gain; LOAEL local (M/F) = 50 mg/kg bw/day based on erosion/ulcers in the stomach

With the source substance

(ii) Sub-chronic (90-day) dermal toxicity study in rats (key study, no guideline, no GLP, assigned reliability score of 2; publication: EPA, 1982). Doses: 20, 66.7, 200 mg/kg b.w.). NOAEL systemic (male) = 66.7 mg/kg bw based on reduced body weight; LOAEL local (M/F) = 20 mg/kg bw/day based on dermal irritation.

However, the available set of data on the Substance and source substance indicates qualitative differences in the toxicological properties of the substances from different routes of administration. In particular, the data demonstrates that the oral route shows more severe effects (mortality) compared to those of the source substance (decreased body weight). This contradicts your read-across hypothesis where you claim the Substance and source substance cause the same type of effect(s). Therefore you have not demonstrated and justified that the properties of the source substance and your Substance are likely to be similar despite the aforementioned observed differences.

Conclusions on the read-across approach

As explained above, your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. Therefore, your adaptation is rejected and it is necessary to perform testing on your Substance.

Further, specific considerations are addressed under the individual endpoints.

Appendix A: Reasons for the requests to comply with Annex IX of REACH

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII-IX to the REACH Regulation.

1. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)

A Sub-chronic toxicity study (90 day) is a standard information requirement in Annex IX to REACH.

You have adapted the standard information requirement in accordance with Annex XI, section 1.5. to REACH. For the reasons explained in the Appendix on General considerations above your adaptation is rejected.

Regarding the information on the Substance, the Screening for reproduction/development toxicity study which is further specified in point 3 of the Appendix on general considerations above, ECHA moreover finds the following:

To be considered compliant and enable concluding whether the Substance has dangerous properties and supports the determination of the No-Observed Adverse Effect Level (NOAEL), a study has to meet the requirements of OECD TG 408. The following key parameter(s) of this test guideline include, among others:

- dosing of the Substance daily for a period of 90 days until the scheduled termination of the study
- At least 10 female and 10 male animals should be used at each dose level (including control group)

The Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) does not have the required exposure duration of 90 days as required in OECD TG 408, because the exposure duration of the screening test is approximately 63 days (for females) and 28 days (for males). Furthermore the organ weight and histopathological investigations in OECD TG 422 are only conducted using 5 animals per sex per group and not 10 per sex per group as in OECD TG 408.

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

Information on the study design

Following the criteria provided in Annex IX, Section 8.6.2, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity. The sub-chronic toxicity study must be performed according to the OECD TG 408, in rats and with oral administration of the Substance. Although the information in the registration dossier indicates that human exposure to the Substance by the inhalation route is likely, ECHA considers that the potential inhalation-specific effects are already addressed by deriving a long-term DNEL for inhalation, local effects.

In your comments to the draft decision you agreed to perform the requested study.

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

A Pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is a standard information requirement in Annex IX to REACH.

You have adapted the standard information requirement in accordance with Annex XI, section 1.5. to REACH by providing the justification discussed in the Appendix on general considerations above and the following study record with the source substance:

> Pre-natal developmental toxicity study in rats, via oral-gavage (key study, no guideline, no GLP, assigned reliability score of 2, publication: EPA, 1987). Dose: 250 mg/kg bw/day, treatment: 5-16 GD. LOAEL maternal toxicity = 250 mg/kg bw/day; NOAEL embrio/fetal toxicity = 250 mg/kg bw/day.

As explained in the Appendix of general considerations, your adaptation in accordance with Annex XI, section 1.5. is rejected.

In addition, ECHA has identified the following issues regarding the adequacy and reliability of the source study.

According to Annex XI, Section 1.5., in all cases the results to be read across should:
- be adequate for the purpose of classification and labelling and/or risk assessment;
- have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3);
- cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter.

To fulfil the information requirements of OECD TG 414, the study has to provide, among others, reliable and adequate information on the following key parameters:
- testing of at least three dose levels and a concurrent control,
- examination of the dams for weight and histopathology of the thyroid gland, thyroid hormone measurements, and
- examination of the foetuses for sex and body weight, number of resorptions and or live foetuses, measurement of anogenital distance in live rodent foetuses.

However, the source study you have reported does not provide adequate and reliable coverage of the above key parameters, because
- it was conducted with only one dose, and lower than the limit dose of 1000 mg/kg bw/day according to the OECD TG 414,
- the weight and histopathology of the thyroid gland, thyroid hormone measurements, have not been examined in the dams, and
- the sex ratio, the number of resorptions and or live foetuses, measurement of anogenital distance in live rodent foetuses have not been examined.

Moreover, the study does not have a required exposure duration. The animals were exposed during GD 5-16, while the exposure duration required in OECD TG 414 is from implantation until the day prior to scheduled caesarean section.

Therefore ECHA concludes that the source study does not not meet the requirements of Annex XI, Section 1.5 also for these reasons.

Consequently it is necessary to provide information for this endpoint.

Information on the study design

A PNDT study according to the test method OECD TG 414 should be performed in rat or rabbit as preferred species with oral[6] (dietary/gavage/drinking water) administration of the Substance.

In your comments to the draft decision you agreed to perform the requested study.

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

Appendix B: Procedural history

This decision does not take into account any updates of registration dossiers after the date on which you were notified the draft decision according to Article 50(1) of the REACH Regulation.

The compliance check was initiated on 16 January 2019.

ECHA notified you of the draft decision and invited you to provide comments within 30 days of the notification.

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend the request(s).

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Appendix C: Observations and technical guidance

1. This compliance check decision does not prevent ECHA from initiating further compliance checks at a later stage on the registrations present.

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of the Member States.

3. Test guidelines, GLP requirements and reporting

   Under Article 13(3) of REACH, all new data generated as a result of this decision needs to be conducted according to the test methods laid down in a European Commission Regulation or according to international test methods recognised by the Commission or ECHA as being appropriate.

   Under Article 13(4) of REACH ecotoxicological and toxicological tests and analyses shall be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

   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: 'How to report robust study summaries[7]'.

4. Test material

   Selection of the test material(s) for UVCB substances

   The registrants of the Substance are responsible for agreeing on the composition of the test material to be selected for carrying out the tests required by this decision. The test material selected must be relevant for all the registrants of the Substance, i.e. it must take into account the variation in compositions reported by all members of the joint submission. The composition of the test material(s) must fall within the boundary composition(s) of the Substance.

   While selecting the test material you must take into account 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. Any constituents that have harmonised classification and labelling according to the CLP Regulation (Regulation (EC) No 1272/2008) must be identified and quantified using the appropriate analytical methods.

   The OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, Number 11 [ENV/MC/CHEM(98)16] requires a careful identification of the test material and description of its characteristics. The Test Methods Regulation (EU) 440/2008, as amended by Regulation (EU) 2016/266, requires that "*if the test method is used for the testing of a [...] UVCB [...] sufficient information on its composition should be made*

[7] https://echa.europa.eu/practical-guides

available, as far as possible, e.g. by the chemical identity of its constituents, their quantitative occurrence, and relevant properties of the constituents".

In order to meet this requirement, all the constituents of the test material used for each test shall be identified as far as possible. For each constituent the concentration value in the test material must be reported in the Test material section of the endpoint study record.

Technical Reporting of the test material for UVCB substances

The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and their concentration values. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

Technical instructions are available in the manual "How to prepare registration and PPORD dossiers" on the ECHA website[8].

5. List of references of the ECHA Guidance and other guidance/ reference documents[9]

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 in this decision.

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 in this decision.

ECHA Read-across assessment framework (RAAF, March 2017)[10]

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.

[8] https://echa.europa.eu/manuals
[9] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[10] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

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.

OECD Guidance documents[11]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD23.
Guidance Document on Mammalian Reproductive Toxicity Testing and Assessment – No 43, referred to as OECD GD43.

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

Appendix D: List of the registrants to which the decision is addressed and the corresponding information requirements applicable to them

Registrant Name	Registration number	(Highest) Data requirements to be fufilled
[redacted]	[redacted]	[redacted]