EUROPEAN CHEMICALS AGENCY

Helsinki, 25 June 2020

Addressees
Registrants of TMPTA_JS listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
12/10/2017

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: 2-ethyl-2-[[(1-oxoallyl)oxy]methyl]-1,3-propanediyl diacrylate; 2,2-bis(acryloyloxymethyl)butyl acrylate; trimethylolpropane triacrylate
EC number: 239-701-3
CAS number: 15625-89-5

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 ***30 September 2021***.

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;

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;
- you have to comply with the requirements of Annexes VII to X of REACH, if you have registered a substance at above 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 A states the reasons for the requests for information to fulfil the requirements set out in Annex IX of REACH.

The Appendix entitled Observations and technical guidance addresses the generic approach for the selection and reporting of the test material used to perform the required studies and provides generic recommendations and references to ECHA guidance and other reference documents.

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.

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 for the requests to comply with Annex IX of REACH

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

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 provided in your dossier:

i. a key study by [redacted] (2005) corresponding to a dermal sub-chronic toxicity study (no guideline) with the Substance;
ii. a key study by [redacted] (2012) corresponding to a dermal 2-year study study, similar to OECD TG 453, with the Substance.
iii. a key study by [redacted] (2015) corresponding to an oral combined repeated dose and reproduction/ developmental screening study, according to OECD TG 422, with the Substance;
iv. Four additional dermal studies of shorter duration (less than 90 days);
v. *in vitro* dermal absorption study according to OECD TG 428 ([redacted], 2015).

We have assessed this information and identified the following issues:

A. As stated in Annex IX, Section 8.6.2. Column 2 of REACH, testing by the dermal route is appropriate if, among others, the following criteria are fulfilled:
   (1) the physicochemical properties suggest a significant rate of absorption through the skin; and
   (2) one of the conditions set out in column 2 (3) is met, i.e *in vitro* tests indicate significant dermal absorption, or significant dermal toxicity.

   The above-mentioned studies i., ii. and iv. were assessed against the above criteria. You have also provided toxicokinetic and dermal absorption data for the Substance:

   (1) in the summary of IUCLID section 7.1.1, you conclude on the *"absorptions rates [will] be used for humans for CSA:*
   oral : 50% (default value used for route to route extrapolation),
   inhalation: 100% (default value used for route to route extrapolation) and,
   dermal: 0.6% "

   (2) In section "7.1.2 Dermal absorption", for the study v. ([redacted], 2015), you conclude that *"the mean total absorption, defined as the compound-related radioactivity present in the receptor fluid, the receptor compartment wash and the skin membranes (excluding tape strips) was 0.32 ± 0.12% of the applied dose. The mean potentially absorbed dose, which is defined as the compound-related radioactivity present in the receptor fluid, the receptor compartment wash, the skin membranes and the stratum corneum (except for the first 2 tape strips) was 0.60 +/- 0.26 % of the applied dose."*

   In your comments to the draft decision you indicated that data from studies using dermal application, that is i. and ii. above [redacted] is considered appropriate for evaluation of the hazard properties of the Substance. You also claimed that the Substance is only used in industrial settings.

According to ECHA guidance Chapter R.7.a, section R.7.5.4.3.2, the oral route is the default route for repeated dose toxicity testing, because it is assumed to maximise systemic availability. The provided studies do not indicate that the Substance has a significant absorption rate through the skin, because a value of 0.6% for the rate of absorption is not considered to be significant. Therefore you have failed to fulfil the above condition A.(1), nor have you fulfilled any of the conditions under A.(2).

Moreover, ECHA notes that widespread uses by professional workers are also reported in your dossier (PROCs 1, 3, 10). Thus, you cannot conclude that "*only exposure to workers is considered relevant*". Additionally, exposure based arguments are not listed as criteria under column 2 of this endpoint to justify testing by the dermal route.

Therefore, the dermal route cannot be considered as the most appropriate route of administration.

B. 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 criteria of this test guideline include, among others:
   (1) the highest dose level should aim to induce some systemic toxicity, but not death or severe suffering.
   (2) dosing of the Substance daily for a period of 90 days until the scheduled termination of the study;

The above-mentioned studies i., ii. and iii. were assessed against the above criteria:

(1) Concerning the highest dose to induce systemic toxicity

- The chosen doses in the study i. ([redacted], 2005) do not help to demonstrate any systemic adverse effects, because you concluded that *"No adverse dose related systemic effect could be observed up to and including a dosage of 12mg/kg bw. Local repeated dose dermal effects could be observed at 1.5mg/kg bw".*

- The same lack of systemic toxicity was observed in the study ii. ([redacted], 2012), as you stated that *"Survival and mean body weights of all dosed groups were similar to those of the vehicle control groups. Local effects on skin was observed at 0.3 mg/kg/d in female rats (LOAEL), whereas 0.3 mg/kg/d in mice was found as a NOAEL."*

The difference of the route of exposure (dermal vs oral) has most likely influenced the rate of absorption of the substance with regard to systemic toxicity.

(2) Concerning the exposure duration

- The study iii. ([redacted], 2015) does not have the required exposure duration of 90 days as you indicated an exposure duration of 29 days for males (i.e. 2 weeks prior to mating, during mating, and up to the day prior to scheduled necropsy) and of 41-55 days for females (from 2 weeks prior to mating, mating, post-coitum, and up to at least 4 days of lactation).

In your comments to the draft decision, you refer again to the studies available in the dossier, that have been addressed above (i, ii and iii). Based on these studies you consider that there is "*adequate existing data*" to fulfil the data requirement for classification, DNEL derivation

and ensure safe occupational handling of the Substance. However, ECHA notes that based on the issues identified above, the information you provided does not fulfil the information requirement.

Information on the design of the study to be performed

Referring to 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, because the Substance is a liquid with low vapour pressure (0.1 Pa at 20 °C).

Therefore the sub-chronic toxicity study must be performed according to the OECD TG 408 (oral route) in rats and with the Substance.

Furthermore ECHA considers that for irritating substances, the dietary route may allow higher systemic dosing with less local irritation than by gavage administration: the local effects manifested via dermal administration of the Substance did not allow choosing a dose high enough to exert systemic effects at the top dose. Hence the local were the leading effets. When comparing these effects with the ones observed in the oral OECD TG 422 study, the local effects could be minimised with the administration of a higher dose via the oral route, allowing the evaluation of systemic toxicity effects.

OECD TG 408 also requires that "*where necessary, the test material is dissolved in a suitable solvent/ vehicle. It is recommended the use of aqueous solution to be considered first, followed by consideration of a solution/ emulsion in oil (e.g. corn oil) and then by possible solution in other vehicles.*" In addition, according to ECHA Guidance R.7a, "*It is to be noted that:*

(a) corrosive or highly irritating substances should be tested preferentially via the oral route. [...] For some substances dietary administration may allow adequate dosing without irritation compared with oral gavage."

(b) *[...] the vehicle should be chosen to minimise gastrointestinal irritation. In certain cases, testing of neutral salts of alkaline or acidic substances may be appropriate and allows investigation of intrinsic properties at adequate dose levels."*

Therefore administration of the Substance must be performed (a) via the feed or drinking water throughout the day, and (b) using of the most appropriate solvent/ test material form, to minimise the irritation and observe any systemic effects.

ECHA notes that the evaluating Member State performing a Substance Evaluation on the Substance, noted that for study iii. above, "*the choice of the solvent used (PEG 400) is rather unusual. Considering that TMPTA is soluble in organic solvents, it is not clear why a more common solvent had not been used (e.g. corn oil, as recommended in the OECD guideline). PEG 400 is also known for its anti-inflammatory or anti-oxidant properties. In addition, some publications report interactions with other substances affecting their systemic absorption or reducing their adverse effects. In particular, pegylation is used ... in order to improve the tolerability of medicine. In this context, it cannot be ruled out that in the absence of PEG 400, TMPTA may have induced effects at lower doses than the NOAELs set in the OECD guideline 422 study.*"

In your comments on the draft decision you state that: "*Regarding the comments on the use of vehicle (PEG 300) in the OECD 422 study using oral gavage application, PEG 300 was chosen due to good trial formulations performed at* [redacted] *in connection with initial evaluations performed in relation to a dose range finding study. TMPTA was not soluble in corn oil and water. PEG 300 was also well accepted by the animals used in the control group (no adverse reactions) using a dose volume of 5 mL/kg. The use of PEG is*

generally accepted in regulatory toxicity studies and is also used at [redacted] *on a regular basis (see attached statement from* [redacted]*).*"

ECHA acknowledges your clarifications on the choice of vehicle for the OECD 422 study. Additionally you also provided comments on "pegylation", indicating that it is normally used to improve tolerability of medicine, however you consider that the use of PEG 300 in the OECD 422 study could have had a shielding effect of the local irritative properties of the Substance thereby allowing for higher dosing and higher systemic uptake. You are reminded that according to OECD TG 408 you must provide a justification for the choice of vehicle (other than water).

If needed, a dose range finding study must first be conducted to ensure that the requirements above are addressed and that the highest dose is set to exhibit some toxic effects as per OECD TG 408 requirements.

Appendix B: Procedural history

For the purpose of the decision-making, 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 REACH.

The compliance check was initiated on 07 May 2019.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

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

ECHA took into account your comments and did not amend the request.

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. The information requirement under Section 8.7.3. of Annex IX/ X to REACH (Extended one-generation reproductive toxicity study, EOGRTS) is not addressed in this decision, because the information from the Sub-chronic toxicity study (90-day), requested in the present this decision, is relevant for the design of the EOGRTS.

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

3. 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.

4. 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'[2].

5. Test material

   Selection of the test material(s)

   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 the present decision. The test material selected must be relevant for all the registrants of the Substance, i.e. it takes 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.

   Technical reporting of the test material

   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.

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

Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[3].

6. List of references of the ECHA Guidance and other guidance/ reference documents[4]

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)[5]

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.

OECD Guidance documents[6]
Guidance Document on Mammalian Reproductive Toxicity Testing and Assessment – No 43, referred to as OECD GD43.

[3] https://echa.europa.eu/manuals
[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] 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]

Note: where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas the decision is sent to the actual registrant.