EUROPEAN CHEMICALS AGENCY

Helsinki, 10 February 2020

Addressees
Registrants of Di-Pentaerythritol listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
13 June 2016

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: 2,2,2',2'-tetrakis(hydroxymethyl)-3,3'-oxydipropan-1-ol
EC number: 204-794-1
CAS number: 126-58-9

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 deadlines provided.

A. Requirements applicable to 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: Bacterial reverse mutation test, EU B.13/14. / OECD TG 471) with the Substance; using one of the following strains: *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102;

B. 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;

C. Requirements applicable to all the Registrants subject to Annex X of REACH

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method OECD TG 414) in a second species (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 Annex VII of REACH, if you have registered a substance at 1-10 tonnes per annum (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;

- you have to comply with the requirements of Annexes VII and VIII of REACH, if you have registered a substance at 10-100 tpa;
- 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 Appendices state the reasons for the requests for information to fulfil the requirements set out in the respective Annexes 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 point B.1 above in an updated registration dossier by ***18 May 2021***, and the information requested in points A.1, C.1 above by ***15 November 2021***.

You must 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 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 VII of REACH

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

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)

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

You have provided a key study in your dossier conducted with the Substance according to the test guideline OECD 471 (Bacterial Reverse Mutation Assay) with the following strains, *S. typhimurim* TA 98, TA 100, TA 1535, TA 1537 and TA 1538 which all gave negative results ([redacted] 1992).

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

To fulfil the information requirement, the study has to meet the requirements of OECD TG 471 (1997). One of the key parameters of this test guideline includes that 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).

The reported data for the study you have provided includes information obtained from the following five *S. typhimurim* strains: TA 98, TA 100, TA 1535, TA 1537 and TA 1538.

The study you have provided does not include results from a strain capable of detecting oxidising mutagens and cross-linking agents, i.e. *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101). Due to the missing data from thisstrain the information provided does not cover one of the key parameters required by OECD TG 471. Therefore, the information requirement is not fulfilled.

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

Information on the study design

To fulfil the information requirement for the Substance, the *in vitro* gene mutation study in bacteria (OECD TG 471) should be performed using one of the following strains: *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102.

Appendix B: 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.

While an adaptation was not specifically indicated by you, ECHA has evaluated the provided information according to Annex XI, Section 1.2.

You have provided the following information on the Substance:

i. 14-day range-finding study conducted in rats via the oral route ([redacted] (1992));
ii. Combined repeated dose toxicity study with the reproduction / developmental toxicity screening test according to the OECD TG 422 conducted in rats via the oral route ([redacted] (1992));
iii. Pre-natal developmental toxicity study according to the OECD TG 414 conducted in rats via the oral route [redacted] (2016)).

Annex XI, Section 1.2 states that there may be sufficient weight of evidence from several independent sources of information leading to assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

According to ECHA Guidance R.4.4, 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 of the information for the given regulatory endpoint. Subsequently, relevance, reliability, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the (dangerous) property investigated by the required study.

Annex XI, section 1.2 requires that adequate and reliable documentation is provided to describe your weight of evidence approach.

Based on the presented sources of information, you argue that the available data gives sufficient information to conclude on the sub-chronic toxicity of the Substance because: "*Low toxicity was seen in both the OECD 422 ([redacted] 1992) and OECD 407 ([redacted] 1992) (i.e. NOAEL ≥ 1000 mg/kg bw/day in both studies). Furthermore also the OECD 414 study showed low toxicity (NOAEL 1000 mg/kg bw/day). Based on these results, a Repeated Dose 90-Day Oral Toxicity Study in Rodents (OECD 408) is not considered necessary, and is not justified on animal welfare grounds*".

However, you have not submitted any explanation why the sources of information provide sufficient weight of evidence leading to the assumption that the substance has or has not a particular dangerous property investigated by the required study.

Irrespective of the above mentioned deficiencies on the documentation, which in itself could lead to the rejection of the adaptation, ECHA has assessed the provided sources of information.

The sources of information must provide sufficient weight of evidence to conclude that the information requirements for sub-chronic toxicity are fulfilled by integrating and weighing the evidence, e.g. the following aspects are covered: information on the health hazards after repeated exposure over 13 weeks.

ECHA has assessed to what extent the sources of information submitted enables a conclusion on these dangerous properties and identified the following deficiencies:

A. Information on the health hazards after repeated exposure over 13 weeks

The sources of information (i. and iii.) provide partly relevant information for the property investigated, sub-chronic toxicity:

- The study (i.) is a dose-range finding study and investigates a limited set of parameters related to systemic toxicity with the objective to inform on the doses to be used in a subsequent 28-day study.
- The study (iii.) is a pre-natal developmental toxicity study and is not primarily designed to investigate toxicity after repeated exposure. However the investigations conducted as part of this study inform on some female reproductive organs toxicity after repeated exposure gestation days 6 and 19.

Therefore even though the results from both of these studies are not intended to provide a basis for deriving definitive conclusions on the systemic toxicity of the Substance, they provide partly relevant information on the property investigated.

The study (ii.) provides relevant information for the property investigated, sub-chronic toxicity.

However, all these sources of information have the following deficiencies affecting their weight in a weight of evidence adaptation:

To enable concluding whether the Substance has dangerous properties and supports the determination of the No-Observed Adverse Effect Level (NOAEL), the information provided has to meet the requirements of the OECD TG 408, including, among others, dosing of the Substance daily for a period of 90 days until the scheduled termination of the study.

The studies you have provided do not have the required exposure duration of 90 days as required in OECD TG 408.
The duration of exposure in study (i.) is limited to 14 days. The study (ii.) (OECD TG 422) has an exposure period of 7 weeks for males and 9 weeks for females. Dams were dosed for 13 days, between gestation days 6 and 19 in study (iii.) (OECD TG 414).

Based on the assessment above, none of the information provided as part of your weight of evidence adaptation has the required exposure duration of 90 days as required in OECD TG 408).

Taken together, sources of information as indicated above, provide information on the systemic toxicity of the Substance but they lack information of essential key investigation(s) relating to the duration of the exposure period. This information is essential because it is one aspect of the sub-chronic toxicity and cannot be covered by or derived from any of the

available sources of information and, therefore it is necessary for a conclusion on the sub-chronic toxicity of the Substance.

It is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 408 study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

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

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 although the Substance is reported to occur as a solid with a significant proportion (>1% on weight basis) of particles of inhalable size (MMAD < 50 µm) and the information indicate that human exposure to the Substance by the inhalation route is likely, there is no concern for severe local effects following inhalation exposure (e.g. substance is water soluble and not irritating/corrosive to skin and eyes).

Therefore the sub-chronic toxicity study must be performed according to the OECD TG 408, in rats and with oral administration of the Substance.

Appendix C: Reasons for the requests to comply with Annex X of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier at a tonnage abve 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to REACH.

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species

Pre-natal developmental toxicity (PNDT) studies (OECD TG 414) in two species is a standard information requirement under Annex X, Section 8.7.2. to REACH.

You have provided a study conducted with the Substance according to the test guideline OECD TG 414 (Prenatal Developmental Toxicity Study) in the rat as a first species ([redacted] 2016).

In order to be compliant and enable concluding if the Substance is a developmental toxicant, information provided has to meet the requirements of the OECD TG 414 in two species.

You have not provided any information on the pre-natal developmental toxicity of the Substance in a second species.

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

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

Information on study design

Species

The test in the first species was carried out by using a rodent species (rat). A PNDT study according to the test method OECD TG 414 must be performed in rabbit as preferred non-rodent species.

Route of administration

The study shall be performed with oral[2] administration of the Substance.

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

Appendix D: 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 2 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 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 adopted the decision under Article 51(3) of REACH.

Appendix E: 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'[3].

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

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

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"[4].

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

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)[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.

OECD Guidance documents[7]

[4] https://echa.europa.eu/manuals
[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] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

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.

Appendix F: 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.