EUROPEAN CHEMICALS AGENCY

Helsinki, 07 February 2020

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

Date of submission for the jointly submitted dossier subject of this decision
01/08/2017

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Reaction products of di-, tri- and tetra-propoxylated propane-1,2-diol with ammonia
EC number: 618-561-0
CAS number: Not specified

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 ***17 May 2021***.

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), using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102 with the Substance;

B. Requirements applicable to all the Registrants subject to Annex VIII of REACH

1. In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method OECD TG 473) or in vitro micronucleus study (Annex VIII, Section 8.4.2., test method OECD TG 487) with the Substance;

2. Only if a negative result in [Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2.] is obtained, In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or OECD TG 490), 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 (rat), 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 Appendix on general considerations addresses issues relevant for several requests while the other 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 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 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.

EUROPEAN CHEMICALS AGENCY

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, for *in vitro* gene mutation in bacteria (1982) with negative results.

We have assessed this information and identified the following issue:

To fulfil the information requirement, the study has to meet the requirements of OECD TG 471 (1997), which indicates that the test should 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).

You have provided an Ames test with the following strains, TA 98, TA 100, TA 1535, TA 1537, and TA 1538, which all gave negative results.

The study you have provided was not conducted with the appropriate 5 strains as it does not include results in the required fifth strain, *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101).

Therefore, the information provided does not cover a key parameter required by OECD TG 471.

In your comments on the draft decision, you acknowledge that the information requirement is not fulfilled for this endpoint and you agree to perform the requested study.

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 VIII of REACH

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

1. **In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)**

An *In vitro* cytogenicity study in mammalian cells or an *In vitro* micronucleus study is a standard information requirement in Annex VIII to REACH.

You provided the following key *in vivo* study with the Substance: Mammalian erythrocyte micronucleus test (according to OECD TG 474, GLP compliant, 2010) with negative results. Although you did not explicitly claim such an adaptation, ECHA understands that the information provided was submitted in order to meet the required information by way of adaptation under column 2, section 8.4.2.

We have reviewed this information and identified the following deficiencies:

To fulfil this adaptation, the study must qualify as "*adequate data from an in vivo cytogenicity test*". [2]

To be considered adequate, the study has to meet the requirements of OECD TG 474, and the key parameters of this test guideline include, among others the determination and reporting of the proportion of immature erythrocytes among total erythrocytes and of the mean number of micronucleated immature erythrocytes for each group of animals.

As indicated in the draft decision, the reported data for the *in vivo* study you submitted did not include information on the proportion of immature erythrocytes among total erythrocytes and the mean number of micronucleated immature erythrocytes for each group of animals.

In your comments on the draft decision you disagree with ECHA's assessment in the draft decision that the *in vivo* study with the Substance is deficient. You claim that the reported data for the *in vivo* study submitted did include information on the proportion of immature erythrocytes among total erythrocytes and the mean number of micronucleated immature erythrocytes for each group of animals. To support this, you provided the full study report.

ECHA agrees that the reported data in the full study report include information on the proportion of immature erythrocytes among total erythrocytes and the mean number of micronucleated immature erythrocytes for each group of animals.

Therefore, ECHA considers that the existing study would be adequate to fulfill the information requirement by way of an adaption under Annex VIII, Section 8.4.2, Column 2 of the REACH Regulation. However, in order to address the request, the information must be included in a dossier update in the form of a robust study summary by the deadline of this decision.

Based on the above, ECHA notes that the information provided in the dossier does not meet the condition of the adaptation and therefore, the information requirement is still not fulfilled.

[2] ECHA Guidance R.7a, Table R.7.7-3, p.558

You can fulfill this information requirement for the Substance either by providing a valid adaptation under Annex VIII, Section 8.4.2, Column 2 of the REACH Regulation or by submitting either an *In vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method OECD TG 473) or an *in vitro* micronucleus study (Annex VIII, Section 8.4.2., test method OECD TG 487).

2. Only if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. is obtained, In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or OECD TG 490)

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 in mammalian cells or the *in vitro* micronucleus study.

Your dossier contains data for an in vitro gene mutation study in bacteria, and an adaptation for an in vitro cytogenicity study in mammalian cells or in vitro micronucleus study.

The information for the in vitro gene mutation study in bacteria and for the in vitro cytogenicity study in mammalian cells provided in the dossier are rejected for the reasons provided in sections A1 and B1.

The result of the requests for information in sections A1 and B1 will determine whether the present requirement for an *in vitro* gene mutation study in mammalian cells in accordance with Annex VIII, Section 8.4.3 is triggered

You have provided a key study in your dossier: In vitro gene mutation in mammalian cells (equivalent to OECD TG 476, not GLP compliant; 1982). Negative results with and without bioactivation.

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

To fulfil the information requirement, the in vitro gene mutation study on mammalian cells has to meet the requirements of OECD TG 476 or OECD TG 490. The key parameter(s) of these test guidelines include, among others the determination and reporting of the cytotoxicity and the mutation frequency for the treated and control cultures.

As indicated in the draft decision, the reported data for the *in vitro* study you submitted did not include information on the cytotoxicity and the mutation frequency for the treated and control cultures.

In your comments on the draft decision you disagree with ECHA's assessment in the draft decision that the *in vitro* study is deficient. You claim that the reported data for the *in vitro* study submitted did include information on the cytotoxicity and the mutation frequency for the treated and control cultures. To support this, you provided the full study report.

ECHA agrees that the the reported data in the full study report include information on the the cytotoxicity and the mutation frequency for the treated and control cultures.

Therefore, ECHA considers that the existing study would be adequate to fulfil the information requirement of Annex VIII, Section 8.4.3. However, in order to address the request, the information must be included in a dossier update in the form of a robust study summary by the deadline of this decision.

Based on the above, ECHA notes that the information provided in the dossier still does not fullfill the information requirement.

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.

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 to REACH..

You have provided a PNDT study in a first species (rabbit; *2016*) and an adaptation of the PNDT study in a second species. In your justification for this adaptation, you claim that the PNDT study in a second species would not provide additional information. You based your claim on the lack of adverse effects in an OECD TG 421 study in rats and in an OECD TG 414 study in rabbits as well as lack of adverse effects in reproductive tissues in an OECD TG 411 study in rats. Furthermore, you claim that the rabbit is described as a sensitive and relevant species to predict effects in humans regarding reproduction and development.

Although you did not explicitly claim such an adaptation, ECHA understands that the information provided aims to adapt the standard information requirement according to Annex XI, Section 1.2. (Weight of evidence) of the REACH Regulation.

Annex XI, Section 1.2 states that there may be sufficient weight of evidence (WoE) 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.

In order to allow concluding on the asbence of prenatal developmental toxicity in two species for the Substance in a weight of evidence adaptation, the justification must cover the key elements (parameters) foreseen to be investigated in an OECD TG 414 study in two species. The key parameter(s) of this test guideline include, among others: external, skeletal and soft tissue alterations (variations and malformations).

We have assessed to what extent the information submitted enables a conclusion of hazardous properties for prenatal developmental toxicity and identified the following deficiencies:

The OECD TG 421 and OECD TG 411 rat studies are the only pieces of information from a rodent studies included in your weight-of-evidence approach. In these studies key parameters on external, skeletal and soft tissue alterations (variations and malformations) are not investigated as required in the pre-natal developmental toxicity study (OECD TG 414). Therefore, these provided piece(s) of information in rodents cannot be used as part of weight of evidence adaptation intended to conclude on the prenatal developmental toxicity of the Substance in a second species. Since this information does not address the key parameters foreseen to be investigated in an OECD TG 414 study in a second species, there is an information gap.

Therefore, your adaptation is rejected and the information requirement is not fulfilled.

In your comments on the draft decision, you acknowledge that the information requirement is not fulfilled for this endpoint and you agree to perform the requested study.

Information on study design

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

Administration route

The study shall be performed with oral[3] administration of the Substance.

[3] 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 09 April 2019.

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

ECHA took into account your comments 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: 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'[4].

4. Test material

   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. In addition, 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 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 must be identified as far as possible.

   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

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

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 (https://echa.europa.eu/manuals).

5. 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]

[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.