~~Confidential~~

Helsinki, 14 April 2023

Addressees
Registrant(s) of Joint-TRISAMINO as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
11/10/2018

Registered substance subject to this decision ("the Substance")
Substance name: Trometamol
EC number: 201-064-4
CAS number: 77-86-1

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

DECISION TAKEN UNDER ARTICLE 42(1) OF THE REACH REGULATION

Under Article 42(1) of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***19 January 2026***.

Requested information must be generated using the Substance unless otherwise specified.

A. Information required from all the Registrants subject to Annex IX of REACH

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

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) by oral route, in one species (rat or rabbit)

Reasons for the request(s) are explained in the following appendix:

- Appendix entitled "Reasons common to several requests";
- Appendix entitled "Reasons to request information required under Annexes VII to IX of REACH", respectively.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

How to comply with your information requirements

To comply with your information requirements you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also update the chemical safety report, where relevant, including any changes to classification

and labelling, based on the newly generated information.

You must follow the general testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". In addition, you should follow the general recommendations provided under the Appendix entitled "General recommendations when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[1] under the authority of Mike Rasenberg, 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 Reasons common to several requests

1. **Assessment of your read-across approach under Annex XI, Section 1.5.**

You were requested to submit information derived with the analogue substance 2-amino-1,3-propanediol (APD) (EC no 208-584-0, CAS no 534-03-2) for

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

The original decision stated that you have provided information to demonstrate that it might be possible to predict the properties of your Substance from the data obtained from the analogue substance APD. The decision also stated that in the case where the tests performed in accordance with the present decision would not confirm the read-across and grouping hypothesis relied upon by you, this outcome shall not alter your obligation to meet the standard information requirements. Should the read-across approach be inadequate, it is your responsibility to ultimately submit reliable information or adaptations which is used in a way that does not underestimate hazards of the registered substance in relation to the relevant endpoints.

Following the provision on the newly generated data, ECHA has re-considered the scientific and regulatory validity of your grouping and read-across approach.

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 (addressed under 'Scope of the analogue approach'). 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 (addressed under 'Prediction for toxicological properties').

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

A. Scope of the analogue approach

In the original decision ECHA understood that you applied one-to-one or, in other words, analogue approach in the testing, i.e., you tested only one analogue to read-across to the Substance, even though in your registration dossier you have formed a group (category) of 'aminopropanediols'. In addition, in your read-across justification you clarify that analogue approach is used for e.g. repeated dose toxicity and developmental toxicity. You have provided a read-across justification document in IUCLID Section 13.

For the purpose of this decision, the following abbreviations are used for the group members:
[1] 2-amino-2-(hydroxymethyl)-1,3-propanediol (the Substance, CAS No. 77-86-1)
[2] 2-amino-2-ethyl-1,3-propanediol (AEPD, CAS No. 115-70-8)
[3] 2-amino-2-methyl-1,3-propane-diol (AMPD, CAS No. 115-69-5)
[4] 2-amino-1,3-propanediol (APD, CAS No. 534-03-2)

You provide the following reasoning for the read-across approach for the Substance: The similarities in molecular structures enables read-across of the available toxicological data to

fulfil specific information requirements under REACH for the target substance (the Substance). The potential analogues for the Substance are the sources AEPD, AMPD and ADP which share a common propane backbone with an amine group at 2-carbon position and primary alcohols at 1 and 3 positions. Further analogues differ in the length of the alkyl side-chain at position 2 so that the following sequence is obtained: from 0 carbon atoms (APD) through 1 (AMPD) to 2 (AEPD). You expected that the Substance and the source substances share similar physico-chemical properties, as well as properties in regard to environmental fate, environmental toxicology, and mammalian toxicology.

However, as indicated above in your read-across justification you clarify that analogue approach between the Substance and APD is used to fulfill the requirements of the repeated dose toxicity and developmental toxicity endpoints.

B. Prediction for toxicological properties

Read-across hypothesis contradicted by newly provided 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 [2] 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)/category members. The observation of differences in the toxicological properties among some members of a category 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.

As indicated above, your read-across hypothesis is that the structural similarity between the source substance(s) and your Substance is a sufficient basis for predicting the properties of your Substance.

In order to support the read-across hypothesis and category, you provided old non-GLP repeated dose toxicity studies (15, 30, 31 and 35 days) with the Substance. In those studies, no effects but also almost no parameters were reported, and correspondigly, the studies were assigned reliability 4. In addition, you have provided a reproduction/development screening test with the Substance (OECD TG 421).

Complete references to those studies in the order as they appear in the registration dossier, IUCLID Section 7.5.1. are:

1. [redacted] (the Substance), [redacted], 1966, [redacted], 30d, dog, reliability 4
2. [redacted] (the Substance), [redacted], 1966, [redacted] 15d, rat, reliability 4
3. Recherches Pharmacologiques Sur Le THAM (the Substance), Giroux and Beaulaton, 1961, Societe Pharmacie Montpellier. 21:206-217, 35d, rat, reliability 4
4. [redacted] (the Substance), [redacted], 1966, [redacted], 30d, rat, reliability 4
5. Reproduction/developmetal toxicity screening test, 2012, OECD TG 421, rat, reliability 1

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

Additionally, you refer in your read-across justification document to the results of a OECD TG 422 study performed with AEDP. However, you have not provided that study in your dossier. In your comments to the draft decision, you have summarised the results of the OECD TG 422 study based on source substance AEPD and indicated that this information can be included in the dossier. Based on the summary of the results provided by you in the comments to the draft decision, the study showed effects amongst others in heamatology (indications of anemia) in satellite group males, statistically significant increases in kidney weight in mid and high dose females and increases in thyroid weight in satellite group females.

None of the above listed effects were noted in the studies performed with the Substance.

In the newly provided OECD 408 study with the analogue substance APD tested at 62,5, 250 and 1000 mg/kg bw/day, following statistically significant effects were noted:

Increased absolute and relative liver weights in both sexes with histopathological correlates (centrilobular hepatocellular hypertorphy), increased absolute and relative kidney weights in both sexes with histopathological correlates (minimal to slight bilateral/unilateral focal/multifocal tubular vacuolation in the cortex/outer strip (medulla)), increased absolute and/or relative adrenal weights in both sexes, and decreased absolute and relative epididymides weights in males with histopathological correlate (bilateral vacuolation of the epithelial cells in the caput (proximal)).

None of the above listed effects were noted in the studies performed with the Substance.

In your comments to the draft decision, you have further introduced a new analogue substance, Aminomethyl propanol (AMP, CAS 124-68-5), which you consider is the worst case source substance. You have provided summary data from the AMP for showing no concern for developmental toxicity (rat and rabbit, according to OECD TG 414). However, publicly available information[3] based on repeated exposure shows notably differing toxicity with the new source substance AMP e.g. effects levels and target organs (e.g. dose related increase in post-implantation loss and complete or partial litter loss, OECD TG 421, 2005) indicating differing toxicity compared to the Substance and other source substances.

None of the above listed effects were noted in the studies performed with the Substance.

The available set of data on the target and source substance indicates differences in the toxicological properties of the substances. This contradicts your read-across hypothesis whereby the structurally similar target and source substances cause the same type of effect(s). Here this information shows differences not only in strength, but also in type of effects. Additionally, you have not demonstrated and justified that the properties of the source substance(s) and of the Substance are likely to be similar despite the observation of these differences.

As explained above, you have not established that relevant properties of the registered substance can be predicted from data on the analogue substance. Therefore, your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and your grouping and read-across approach is rejected.

[3] See ECHA's website at: https://echa.europa.eu/de/registration-dossier/-/registered-dossier/11767/7/9/2.

Appendix A: Reasons to request information required under Annex IX of REACH

1. Sub-chronic toxicity study (90-day)

A Sub-chronic toxicity study (90 day) is an information requirement under Annex IX to REACH.

As explained above in the Appendix entitled "Reasons common to several requests" your adaptation according to Annex XI, Section 1.5. is rejected.

On this basis, the information requirement is not fulfilled.

Specifications for 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 toxicityand the prefered rodent species is rat[4]. The sub-chronic toxicity study must be performed according to the OECD TG 408, in rats and with oral administration of the Substance.

2. Pre-natal developmental toxicity study in one species

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

As explained above in the Appendix entitled "Reasons common to several requests" your adaptation according to Annex XI, Section 1.5. is rejected.

On this basis, the information requirement is not fulfilled.

Specifications for the study design

A PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit as preferred species with oral[5] administration of the Substance.

[4] ECHA Guidance R.7a, Section R.7.5.6.3.2 and Table R.7.5-1
[5] ECHA Guidance R.7a, Section R.7.6.2.3.2

Appendix B: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. Test methods, GLP requirements and reporting

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

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

3. 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 on How to report robust study summaries[6].

B. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

1. Selection of the Test material(s)

   The Test Material used to generate the new data must be selected taking into account the following:
   - the variation in compositions reported by all members of the joint submission,
   - the boundary composition(s) of the Substance,
   - 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.

2. Information on the Test Material needed in the updated dossier
   - You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
   - The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[7].

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

Appendix C: Procedure

In the decision of 25 August 2016 ("the original decision"), ECHA requested you to submit information by 3 September 2018 in an update of your registration dossier.

In accordance with Article 42(1) of the REACH Regulation, the Agency examined the information submitted by you in consequence of that decision. The Agency considered that this information triggered the request for further information. Therefore, a new decision-making process was initiated under Article 41 of the REACH Regulation.

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

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 took into account your comments 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.

The deadline of the decision is set based on standard practice for carrying out OECD TG tests. It has been exceptionally extended by 12 months from the standard deadline granted by ECHA to take into account currently longer lead times in contract research organisations.

Appendix D: List of references - ECHA Guidance[8] 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)[9]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, 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.

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.

OECD Guidance documents[11]

[8] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[9] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[10] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316
[11] 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 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.

Appendix E: Addressees of this decision and the corresponding information requirements applicable to them

You must provide the information requested in this decision for all REACH Annexes applicable to you.

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.