Decision number: TPE-D-2114340870-53-01/F Helsinki, 25 August 2016

DECISION ON TESTING PROPOSALS SET OUT IN A REGISTRATION PURSUANT TO ARTICLE 40(3) OF REGULATION (EC) NO 1907/2006

For trometamol, EC No 201-064-4 (CAS No 77-86-1), registration number: [redacted]

Addressee: [redacted]

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

I. Procedure

Pursuant to Article 40(1) of the REACH Regulation, ECHA has examined the following testing proposals submitted as part of the registration dossier in accordance with Articles 10(a)(ix) and 12(1)(d) thereof for trometamol, EC No 201-064-4 (CAS No 77-86-1), submitted by [redacted] (Registrant).

- 90-day oral toxicity study (OECD 408) in rats, oral route using the analogue substance 2-amino-1,3-propanediol (APD).
- Developmental toxicity study (OECD 414) in rats, oral route using the analogue substance 2-amino-1,3-propanediol (APD).

This decision is based on the registration as submitted with submission number [redacted], for the tonnage band of 100 to 1000 tonnes per year.

This decision does not take into account any updates after **18 January 2016**, i.e. 30 calendar days after the end of the commenting period.

This decision does not imply that the information provided by the Registrant in his registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the registration at a later stage.

ECHA received the registration dossier containing testing proposals for further examination pursuant to Article 40(1) on 30 May 2013. The registration was subsequently updated on 3 February 2014 containing the above-mentioned testing proposals.

ECHA held a third party consultation for the testing proposals from 17 June 2014 until 1 August 2014. ECHA did not receive information from third parties.

On 11 November 2015 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision.

On 7 December 2015 ECHA received comments from the Registrant agreeing to ECHA's draft decision. ECHA took the comments into account and did not amend the request(s). On 3 March 2016 ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals for amendment of the draft decision within 30 days of the receipt of the notification.

Subsequently, proposals for amendment to the draft decision were submitted.

On 8 April 2016 ECHA notified the Registrant of the proposals for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on the proposals for amendment within 30 days of the receipt of the notification.

The ECHA Secretariat reviewed the proposals for amendment received and did not amend the draft decision.

On 18 April 2016 ECHA referred the draft decision to the Member State Committee.

By 10 May 2016, in accordance to Article 51(5), the Registrant provided comments on the proposals for amendment. The Member State Committee took the comments of the Registrant on the proposals for amendment into account.

After discussion in the Member State Committee meeting on 14-15 June 2016, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 15 June 2016.

ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Testing required

The Registrant has requested to carry out the required tests using the analogue substance as part of a read-across and grouping approach, in accordance with Annex XI, 1.5. ECHA emphasises that any final determination on the validity of the read-cross, including the grouping approach proposed by the Registrant, would be premature at this point in time. The eventual validity of the read-across hypothesis and grouping approach will be reassessed once the requested information is submitted. In the meantime, based on the information currently submitted, ECHA considers that the read-across approach proposed by the Registrant might be plausible. In the light of this assessment ECHA has taken the following decision:

A. Tests required pursuant to Article 40(3)

The Registrant shall carry out the following proposed tests pursuant to Article 40(3)(a) and 13(4) of the REACH Regulation using the indicated test methods and the analogue substance 2-amino-1,3-propanediol (APD) (EC no 208-584-0, CAS no 534-03-2):

1. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26/OECD 408) in rats; It is at the Registrant's discretion to perform the intended additional examinations during the testing program.

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31/OECD 414) in rats or rabbits, oral route.

Note for consideration by the Registrant:

The Registrant may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring to and conforming with the appropriate rules in the respective Annex, and an adequate and reliable documentation.

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

B. Deadline for submitting the required information

Pursuant to Articles 40(4) and 22(2) of the REACH Regulation, the Registrant shall submit to ECHA by **3 September 2018** an update of the registration dossier containing the information required by this decision, including, where relevant, an update of the Chemical Safety Report. The timeline has been set to allow for sequential testing as appropriate.

III. Statement of reasons

The decision of ECHA is based on the examination of the testing proposals submitted by the Registrant for the registered substance proposed to be performed with the analogue substance 2-amino-1,3-propanediol (APD) (CAS no 534-03-2) and on the submitted read-across justification. ECHA has considered first the scientific validity of the proposed read-across and grouping approach (Section III.0, below), before assessing the testing proposed (Sections III.1. and III.2.).

Article 13(1) of the REACH Regulation requires information on intrinsic properties of substances on human toxicity to be generated whenever possible by means other than vertebrate animal tests, including from information from structurally related substances (grouping or read-across), "*provided that the conditions set out in Annex XI are met*".

According to Annex XI, 1.5 there needs to be structural similarity among the substances within a group or a category and furthermore, it is required that the relevant properties of a substance within the group can be predicted from the data for reference substance(s) by interpolation, and the data should be adequate for the purpose of classification and labelling and/or risk assessment. The following analysis presents the Registrant's justification for the proposed read-across approach and hypothesis, together with ECHA's analysis.

0. Grouping of substances and read-across approach

a. Introduction of the grouping approach and read-across hypothesis proposed by the Registrant

The Registrant has proposed to cover the standard information requirements for a sub-chronic toxicity study (90-day; Annex IX, Section 8.6.2.) and a pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) by performing the test with an analogue substance 2-amino-1,3-propanediol (APD) (CAS no 534-03-2).

The Registrant has provided the following justification:

"Potential analogues for the substance 2-amino-2-(hydroxymethyl)-1,3-propanediol (TROMETAMOL, CAS No. 77-86-1) are other 2-amino-1,3-propanediols, i.e. substances that share with the target substance a common propane backbone with an amine group at 2-carbon position and primary alcohols at 1 and 3 positions. Candidate source substances are thus members of the aminopropanediol category: 2-amino-2-ethyl-1,3-propanediol (AEPD, CAS No. 115-70-8), 2-amino-2-methyl-1,3-propane-diol (AMPD, CAS No. 115-69-5) and 2-amino-1,3-propanediol (APD, CAS No. 534-03-2). The only structural difference between TROMETAMOL and AEPD is a replacement of a hydroxyl group with a methyl group. 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). There are no other functional groups present in these molecules. It is expected that the target substance and the source substances share similar physico-chemical properties, as well as properties in regard to environmental fate, environmental toxicology, and mammalian toxicology. Their class with respect to the mode of action in the environment can be characterised as narcotic aliphatic amines. If TROMETAMOL is absorbed in-vivo, it is not metabolised and rapidly excreted via urine. The available data support this hypothesis and underpin the read-across between target and source substances to fill data gaps while minimising additional animal testing where possible."

b. Information submitted by the Registrant to support the grouping and read-across hypothesis

In order to support its testing proposals, the Registrant has provided a grouping and read-across justification document (Analogue Approach Justification Documentation) in which data on the following aminopropanediol category members has been provided:

- 2-amino-2-(hydroxymethyl)-1,3-propanediol (TROMETAMOL, CAS no 77-86-1), the substance subject to the present decision (hereinafter referred to as the registered substance),
- 2-amino-2-ethyl-1,3-propanediol (AEPD, CAS no 115-70-8),
- 2-amino-2-methyl-1,3-propanediol (AMPD, CAS no 115-69-5), and
- 2-amino-1,3-propanediol (APD, CAS no 534-03-2), the analogue substance.

In the grouping and read-across justification document, the Registrant has provided structures of the category members, an assessment of the physico-chemical and toxicological properties of the substances, a data matrix presenting physico-chemical properties, QSAR profiling results with respect to mammalian toxicity, the results of experimental studies for mammalian toxicity, the classification of the substances and a PBT and vPvB assessment. In the technical dossier and CSR the Registrant has provided information from experimental studies for human health endpoints.

c. ECHA analysis of the grouping approach and the read-across hypothesis of the Registrant in light of the requirements of Annex XI, 1.5

According to the Registrant, the substance subject to the present decision can be grouped with other substances in a category for the purpose of read-across.

ECHA understands that the grouping approach is based on similar structures, i.e. substances belong to an aminopropanediol category and have a common propane carbon chain that has an amine group at carbon 2 and primary alcohols at carbons 1 and 3. The structural differences are related to the substituent at carbon 2: there is a ethyl-hydroxyl group in the registered substance Trometamol, a ethyl group in AEDP, a methyl group in AMPD and no substituent in APD, the analogue substance. The Registrant explains that APD has *"a basic molecular structure"* as it does not contain a substituent at carbon 2, and is therefore the most appropriate source substance.

ECHA notes that the Registrant has not explained whether the different substituents at carbon 2 may impact the chemical reactivity, toxicokinetics and toxicological profiles of the substances. However, there seems to be no chemical reason to prefer one substance over the others in this category. In addition, based on the data provided, the substances have similar physico-chemical properties and toxicological profiles, which indicate that the different substituents may not affect the toxicity.

Based on the toxicokinetic assessment the Registrant concludes that the substances are absorbed poorly via the oral route. ECHA notes that there are differences in the pKa values: Trometamol (8.22), APD (8.51), AMPD (8.76) and AEPD (9.03). An uncertainty is that these differences can result in different degrees of expected passive absorption at pH 8. ECHA further notes, that other absorption mechanisms, such as active transport, may occur. ECHA notes that similar results obtained in the available toxicological studies indicate that even if absorption differs it does not seem to impact the toxicity of the substances.

Based on several scientific publications, the structure of the substance and OECD QSAR Toolbox v.2.0 (2010) modelling, the Registrant concludes that the registered substance does not metabolise. Similarly, based on the structures and on the OECD QSAR Toolbox predictions, the other category members APD and AEPD are not expected to metabolise. No predictions have been provided for AMPD. ECHA notes that the Registrant has not provided (robust) study summaries on the scientific publications he is referring to and therefore, ECHA is not able to evaluate the reliability and adequacy of the studies. ECHA cannot therefore confirm if there are no differences in predicted metabolism. However, similar results obtained in the experimental studies suggest that even if metabolism occurs is does not seem to impact the toxicity of the substances.

The Registrant has provided acute oral and dermal toxicity, skin and eye irritation, repeated dose toxicity (15, 31 and 35 days), and reproduction/development toxicity screening (OECD 421) studies conducted with the registered substance, and skin sensitisation, Ames test, *in vitro* mammalian cell gene mutation, and *in vitro* mammalian chromosome aberration studies conducted with AEPD. In addition, in the individual registration dossiers, the Registrant has provided results of acute oral (APD, AEPD and AMPD) and dermal (APD and AEPD) toxicity studies and a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD 422) (AEPD), a non-guideline developmental screening study with *in vitro* limb bud micromass assay (AMPD) and skin irritation studies (APD and AEPD).

ECHA notes that all substances show low acute toxicity via oral and dermal route (LD50 values > 2000 mg/kg bw), are not skin irritants and are not genotoxic. AEPD and APD are self-classified as eye irritants. No systemic adverse effects and reproductive/ developmental effects were observed in the repeated dose toxicity and/or screening studies conducted with the registered substance, AEPD and AMPD (NOAELs > 1000 mg/kg bw/day). The *in vitro* limb bud micromass assay with AMPD did not indicate developmental toxicity of the substance. Based on the data provided, ECHA concludes that the substances show similar toxicological profile.

It is noted that no information from the repeated dose toxicity and screening/pre-natal developmental toxicity studies is available for the analogue substance APD, preventing ECHA to conclude on the similarity of the toxicological profile of APD and registered substance on these endpoints.

In a proposal for amendment, the similarity chemical reactivity was questioned. In his comments on the proposal for amendment, the Registrant provided the following arguments for similar chemical reactivity between the substances:

- *"Each amine will have similar steric restrictions, and internal hydrogen bonding capability"* and *"all the compounds have the ability to have the same internal hydrogen bonding with both the amine and other hydroxyls present"*;
- Alkyl moieties are inert and *"their presence is not going to significantly change the reactivity of the other, reactive, amine or hydroxyl groups"*;
- The hydroxylmethyl group in Trometamol does not *"open up new chemical transformations or hydrogen bonding that the others don't have"*;
- The hydroxylmethyl group in Trometamol *"does not open any new oxidative mechanisms"*;
- No relevant metabolites from any of the substances were predicted using the OECD QSAR toolbox v.2.0 (2010) and therefore, P450 mediated in vivo metabolism is not expected;
- *"The pKa of the four molecules increases from Trometamol (8.22) to APD (8.51) to AMPD (8.76) to AEPD (9.03) with an almost constant increment from one to the next of 0.25 pKa unit. This is a narrow range and reflects similar chemical reactivity of the amine group"* and *"this base strength increase is also in agreement with the increasing irritating properties of these four molecules"* which is also reflected in the increasing irritating properties of the substances.

ECHA acknowledges the further explanation of the Registrant.

ECHA notes that although the Registrant in the Analogue Approach Justification Documentation refers to "aminopropanediol category", he intends to apply a one-to-one read-across approach.

d. Conclusion on the read-across approach

ECHA concludes that, notwithstanding the uncertainties addressed above, the Registrant has provided information to demonstrate that the approach proposed might be plausible and may provide basis to predict the properties of the registered substance from the data obtained from the analogue substance 2-amino-1,3-propanediol (APD, CAS no 534-03-2).

In the case where the tests performed in accordance with the present decision would not confirm the read-across and grouping hypothesis relied upon the Registrant, this outcome shall not alter the obligation of the Registrant to meet the standard information requirements. Should the read-across approach be inadequate, it is the responsibility of the Registrant 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.

In any case, following the update of the dossier submitting the information required in the present decision, ECHA will determine whether the documentation provided is sufficient to satisfactorily address the information requirement of Annex IX. If, upon further consideration, the proposed approach does not satisfy the conditions set out in Annex XI, Section 1.5., ECHA reserves the right to request the information necessary to fulfil the information requirements for the substance subject to the present decision.

Tests required pursuant to Article 40(3)

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

a) Examination of the testing proposal

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.

A sub-chronic toxicity study (90 day) is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

The Registrant has submitted a testing proposal for a sub-chronic toxicity study (90 day) in rats via the oral route (EU B.26/OECD 408) to be performed with the analogue substance 2-amino-1,3-propanediol (APD) (EC no 208-584-0, CAS no 534-03-2).

ECHA considers that the proposed study via the oral route is appropriate to fulfil the information requirement of Annex IX, Section 8.6.2. of the REACH Regulation because the proposed route is the most appropriate route of administration having regard to the likely route of human exposure due to the following reasons.

The Registrant proposed testing by the oral route. The test is proposed to be conducted with the analogue substance APD. In light of the physico-chemical properties of APD [solid with non-inhalable particles (< 0.0828 % of the particles < 100 µm)], ECHA considers that testing by the oral route is most appropriate.

The Registrant proposed testing in rats. According to the test method EU B.26/OECD 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

The Registrant proposed testing with the analogue substance 2-amino-1,3-propanediol (APD) (EC no 208-584-0, CAS no 534-03-2). ECHA considers the read-across approach plausible as explained in section III.0. above.

The Registrant proposed to extend the sub-chronic toxicity study (90 day) with extended reproduction parameters, including additional sperm motility parameters and extra attention for reproductive organs/tissues in all groups. ECHA notes, that it is at the Registrant's discretion to perform the intended additional examinations during the testing program and use the results to ensure the safe use of the substance.

However, the Registrant is reminded that, if the condition of Annex IX, Section 8.7.3., Column 1 is fulfilled, the proposed extension of the study presently requested does not fulfil the standard information requirement in the registration dossier for reproductive toxicity set out in Annex IX, Section 8.7.3.

b) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is requested to carry out the proposed study with the analogue substance 2-amino-1,3-propanediol (APD) (EC no 208-584-0, CAS no 534-03-2): Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26/OECD 408).

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

a) Examination of the testing proposal

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.

A pre-natal developmental toxicity study for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

The Registrant has submitted a testing proposal for a pre-natal developmental toxicity study in rats according to EU B.31/OECD 414 to be performed with the analogue substance 2-amino-1,3-propanediol (APD) (EC no 208-584-0, CAS no 534-03-2).

ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

The Registrant proposed testing in rats by the oral route. According to the test method EU B.31/OECD 414, the rat is the preferred rodent species, the rabbit the preferred non-rodent species and the test substance is usually administered orally. ECHA considers these default parameters appropriate and testing should be performed by the oral route with the rat or the rabbit as a first species to be used.

The Registrant proposed testing with the analogue substance 2-amino-1,3-propanediol (APD) (EC no 208-584-0, CAS no 534-03-2). ECHA considers the read-across approach plausible as explained in section III.0. above.

b) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is requested to carry out the proposed study with the analogue substance 2-amino-1,3-propanediol (APD) (EC no 208-584-0, CAS no 534-03-2): Pre-natal developmental toxicity study in rats or rabbits, oral route (test method: EU B.31/OECD 414).

IV. Adequate identification of the composition of the tested material

The process of examination of testing proposals set out in Article 40 of the REACH Regulation aims at ensuring that the new studies meet real information needs. Within this context, the Registrant's dossier was sufficient to confirm the identity of the substance to the extent necessary for examination of the testing proposal. The Registrant must note, however, that this information, or the information submitted by other registrants of the same substance, has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation.

In relation to the information required by the present decision, the sample of the substance used for the new test(s) must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants. It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new test(s) is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new test(s) must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.

In case the required test(s) are conducted with an analogue substance in the context of a read-across approach, the identity of the test material used to perform the test should be specified in line with the ECHA's Practical Guide 6 "How to report on read-across". This is required to demonstrate that the test material is representative of the analogue substance identified in the read-across approach and used to predict the properties of the registered substance.

V. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Article 51(8) of the REACH Regulation. Such appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on the ECHA's internet page at http://www.echa.europa.eu/regulations/appeals . The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

Authorised[1] by Leena Ylä-Mononen, Director of Evaluation

[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.