~~Confidential~~

Helsinki, 2 February 2022

Addressees
Registrant of JS_85702-79-0_X2 as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
26/07/2019

Registered substance subject to this decision ("the Substance")
Substance name: tris(2-hydroxyethyl)ammonium 6-(3,5,5-trimethylhexanamido)hexanoate
EC number: 701-138-0
CAS number: 242482-67-3

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***9 August 2023***.

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, modified to include urinalysis and immuno-histochemical investigation of renal pathology allowing the determination of whether the pathology is mediated by alpha-2u globulin nephropathy.

2. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: EU C.20./OECD TG 211)

3. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: OECD TG 210)

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

- Appendix entitled "Reasons to request information required under Annex IX of REACH".

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.

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". 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 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 a standard information requirement under Annex IX to REACH.

You have provided adaptations according to Annex XI, Section 1.2. and Section 1.5. in your dossier.

In support of your adaptations, you have provided the following sources of information:

(i) an experimental study (28-day study) according to OECD TG 407 (2012) with the Substance; NOAEL 500 mg/kg bw/day;

(ii) an experimental study (28-day study) according to OECD TG 407 (2002) with the source substance 3,5,5-trimethylhexanoic acid (EC 221-975-0); NOAEL 50 mg/kg bw/day.

Based on the presented sources of information and to justify of your adaptation according to Annex XI Section 1.2. (weight of evidence), you argue that the available data gives sufficient information to conlude on the sub-chronic toxicity because:

- The Substance or the source substance did not cause lethal effects after administration of a single oral doses of >= 2000 mg/kg or in tests for acute toxicity in rats;
- The Substance showed no irritating effects;
- The source substance does not have to be classified as skin sensitizing based on the negative findings in a test with guinea pigs;
- There are two reliable 28-day oral toxicity studies in rats available for the Substance as well the source substance. Only effects observed were species specific effects on the liver as well as species and gender specific effects on the kidney (these effects were fully reversible within recovery period of 14 days). Similar findings were seen in 7-day dose range oral studies available for the Substance and one other source substance. These effects were not attributed as adverse for human (as not relevant for human risk assessment). The incorporation of an uncertainty factor of three for the effect-extrapolation from subacute to subchronic conditions (i.e. 500 mg/kg bw in subacute condition -> 167 mg/kg bw in subchronic condition) would not lead to classification with respect to the endpoint repeated dose toxicity;
- No concern with respect to the bioaccumulation can be derived;

You conclude: *"Based on all the available data, there is sufficient weight of evidence leading to the conclusion that the substance has no intrinsic hazardous toxic activity relevant to humans by repeated exposure. An improvement in toxicological hazard characterization is not expected from further repeated dose toxicity data. Hence, further testing on vertebrate animals is unjustified and should be omitted considering scientific as well as animal welfare reasons".*

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

Weight of evidence

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, 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 and coverage of the information for the given regulatory information requirement. Subsequently, relevance, reliability, coverage, 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 adaptation.

However, your justification does not include an adequate and reliable (concise) documentation as to why the sources of information provide sufficient weight to conclude that the Substance has or has not the 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.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.6.2 at Annex IX includes, at general level, information on systemic toxicity in intact, non-pregnant and young adult males and females from: 1) in-life observations, 2) blood chemistry, 3) organ and tissue toxicity. Information should address effects on the following physiological systems: circulatory system, digestive/excretory system, endocrine system, immune system, integumentary system, musculoskeletal system, nervous system, renal/urinary system, reproductive system, and respiratory system.

Both sources of information (i. and ii.) provide relevant information on sub-chronic toxicity, but have deficiencies affecting their reliability. Studies on acute toxicity, irritation or skin sensitisation do not provide relevant information on sub-chronic toxicity.

Regarding the deficiencies affecting reliability, ECHA notes the following deficiencies with regards to prediction of sub-chronic toxicity:

Exposure duration

The conditions of exposure in accordance with the OECD TG 408 specifies that dosing of the Substance is performed daily for a period of 90 days until the scheduled termination of the study.

You have provided two 28-day inhalation toxicity studies (i, ii). These studies do not have the exposure duration of 90 days as required in OECD TG 408.

This condition of exposure is essential, as the effects observed in a sub-chronic study might be considerably more pronounced compared to a shorter study duration such as a 28-day study. Furthermore effects may only occur after 90 days of exposure that have not been observed after shorter times of exposure. You have not demonstrated that the effects of the Substance generated over the exposure of 90 days will not be different to that over the exposure of 28 days. Therefore, these studies (i) and (ii) do not inform on the properties of the Substance after a longer exposure than 28 days.

In your comments on the initial draft decision, you stated that information on sub-chronic toxicity is available on the source substance 3,5,5-trimethylhexanoic acid (EC 221-975-0). This information is however not yet included in your dossier. Please note that this decision does not take into account updates of the registration dossiers after

the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation").

In the absence of reliable information on dosing of the substance for a period of 90 days, no conclusion can be drawn on sub-chronic toxicity as required by the information requirement.

Read-across

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. 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 'Assessment of prediction(s)').

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance R.6. and related documents[2,3].

A. Predictions for toxicological properties

You have provided a read-across justification document in IUCLID Section 13.

You read-across between the structurally similar substances, 3,5,5-trimethylhexanoic acid (EC 221-975-0) as source substance and the Substance as target substance.

You have provided the following reasoning for the prediction of toxicological properties: *"The underlying scientific rationale for the use of 3,5,5-trimethylhexanoic acid as source chemical is based on the metabolism consideration. Upon absorption, the target chemical is expected to undergo a degradation process, resulting in the systemic release of 3,5,5-trimethylhexanoic acid, thereby providing the justification for the read-across especially for the mid- and long term toxicities such as repeated dose toxicity and reproduction toxicity."*

ECHA understands that you predict the properties of the Substance using a read-across hypothesis which is based on the formation of common (bio)transformation products. The properties of your Substance are predicted based on a based on a worst-case approach.

Supporting information on the formation of common compounds

Annex XI, Section 1.5 of the REACH Regulation states that "*physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s)*". For this purpose "*it is important to provide supporting information to strengthen the rationale for the read-across*" (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.). The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish

[2] Read-Across Assessment Framework (RAAF). 2017 (March) ECHA, Helsinki. 60 pp. Available online: Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across)

[3] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 (March) ECHA, Helsinki. 40 pp. Available online: https://doi.org/10.2823/794394

that the properties of the Substance can be predicted from the data on the source substance(s).

Supporting information must include toxicokinetic information on the formation of the common compound.

As indicated above, your read-across hypothesis is based on the (bio)transformation of the Substance and of the source substance(s) to a common compound(s). In this context, information characterising the rate and extent of the (bio)transformation of the Substance and of the source substance(s) is necessary to confirm the formation of the proposed common (bio)transformation product and to assess the impact of the exposure to the parent compounds.

However, in your dossier you have not provided any experimental information about the (bio)transformation of the Substance to support your claims regarding formation of a common compound.

In your comments on the initial draft decision you provided:

- Study Summary: Metabolite investigation in the degradation samples of Zahn-Wellens-Test
- Study summary: Identification of 3,5,5-trimethylhexanoic acid as a metabolite in satellite animals of a PNDT study with the Substance.

The data you provided in your comments indicate that the source substance 3,5,5-trimethylhexanoic acid (EC 221-975-0) is a metabolite of the Substance. However, you did not provide (quantitative) data on all metabolites and compare the hazard properties of those with the source substance to support the worst-case approach. You also did not explain the impact on the prediction. Furthermore, you did not explain the impact of (potential) non-common/partial metabolites, nor their impact on the prediction.

In the absence of this information, you have not provided supporting evidence establishing that the proposed common (bio)transformation product is formed as assumed in your read-across hypothesis. Therefore, you have not provided sufficient supporting information to strengthen the rationale for the read-across. Please note that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation").

Therefore, the information on the analogue substance as source of information is not reliable to be used as part of weight-of-evidence adaptation for your Substance.

In the absence of reliable read-across from analogue substances, the properties of your Substance cannot be predicted from the data on the analogue substance(s). Therefore, the information from the analogue substance(s) submitted under your weight-of-evidence adaptation is not considered reliable and does not contribute to the weight of evidence adaptation.

B. Conclusions on the read-across approach

As explained above, you have not established that relevant properties of the 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.

Therefore, the pieces of information are not reliable.

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.

Information on the design of the study to be performed

Referring to the criteria provided in Annex IX, Section 8.6.2, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity, because the substance is a viscous liquid.

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

Additional parameters

The studies you submitted showed that adverse effects were observed in the kidneys of male rats *("At 500 mg/kg bw/day, the weights of kidneys (absolute and relative) were increased in males (approximately 25% on Day 28) and this was associated with hyaline deposition in tubular cells".)* but not in male control rats or in exposed/control female rats.

This indicates that the kidney is a target organ of the Substance which may induce alpha-2u-globulin-mediated nephropathy. Since this mode of action is considered not relevant to humans, the involvement of alpha-2u-globulin in the kidney effects is a key parameter for establishing the relevance of the kidney effects for risk assessment.

Therefore, although optional (as per paragraph 37 of OECD TG 408), a urinalysis is required to investigate further the kidney function after administration of the Substance. Additionally, a full histopathological examination (paragraphs 45 and 47 of OECD TG 408), including immune-histochemical investigation of renal pathology is required to determine if the pathology is mediated by alpha-2u globulin.

In your comments on the initial draft decision, you agree that "the α2u-globulin mediated toxicity is a species and gender specific finding which occurs only in the male rat and has no relevance to human risk assessment". To get confirmation on this mode of action, urinalysis is therefore requested.

2. Long-term toxicity testing on aquatic invertebrates

Long-term toxicity testing on aquatic invertebrates is an information requirement under Annex IX to REACH (Section 9.1.5.).

You have provided the following information:

- a justification to omit the study which you consider to be based on Annex IX, Section 9.1., Column 2. In support of your adaptation, you provided the following justification:

  "Waiving according to "column 2" in Annex IX of REGULATION (EC) No 1907/2006: according to CSA no long term tests needed (No toxicity in acute tests observed; substance readily biodegradable)."

We have assessed this information and identified the following issue:

Annex IX, Section 9.1., Column 2 does not allow omitting the need to submit information on

long-term toxicity to aquatic invertebrates under Column 1. It must be understood as a trigger for providing further information on aquatic invertebrates if the chemical safety assessment according to Annex I indicates the need (Decision of the Board of Appeal in case A-011-2018)

Your adaptation is therefore rejected.

3. Long-term toxicity testing on fish

Long-term toxicity testing on fish is an information requirement under Annex IX to REACH (Section 9.1.6.).

You have provided the following information:

- a justification to omit the study which you consider to be based on Annex IX, Section 9.1., Column 2. In support of your adaptation, you provided the following justification:

  "Waiving according to "column 2" in Annex IX of REGULATION (EC) No 1907/2006: according to CSA no long term tests needed (No toxicity in acute tests observed; substance readily biodegradable)."

We have assessed this information and identified the following issue:

Annex IX, Section 9.1., Column 2 does not allow omitting the need to submit information on long-term toxicity to fish under Column 1. It must be understood as a trigger for providing further information on long-term toxicity to fish if the chemical safety assessment according to Annex I indicates the need (Decision of the Board of Appeal in case A-011-2018).

Study design

To fulfil the information requirement for the Substance, the Fish, Early-life Stage Toxicity Test (test method OECD TG 210) is the most appropriate (ECHA Guidance R.7.8.2.).

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[4].

B. Test material

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 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.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[5].

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

Appendix C: Procedure

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.

The compliance check was initiated on 14 August 2020.

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.

Appendix D: List of references - ECHA Guidance[6] 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)[7]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[8]

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[9]

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

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.