Decision number: CCH-D-2114310747-50-01/F Helsinki, 18 November 2015

DECISION ON A COMPLIANCE CHECK OF A REGISTRATION PURSUANT TO ARTICLE 41(3) OF REGULATION (EC) NO 1907/2006

For 2,2',2''-(hexahydro-1,3,5-triazine-1,3,5-triyl)triethanol, CAS No 4719-04-4 (EC No 225-208-0), 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 41(1) of the REACH Regulation ECHA has performed a compliance check of the registration for 2,2',2''-(hexahydro-1,3,5-triazine-1,3,5-triyl)triethanol, CAS No 4719-04-4 (EC No 225-208-0), submitted by [redacted] (Registrant). In the registration dossier the Registrant refers to the substance as "HHT".

The scope of this compliance check decision is limited to the standard information requirements of Annex I, Annex VI, Sections 2 and 4, and Annex X, Section 8.7.2. of the REACH Regulation. The information requirements of Annex X, Section 8.7.3. are not addressed in this decision.

This decision is based on the registration as submitted with submission number [redacted], for the tonnage band 1000 tonnes or more per year. This decision does not take into account any updates after the deadline for updating (15 March 2015) communicated to the Registrant by ECHA on 06 February 2015.

The substance subject to the present decision is provisionally listed in the Community rolling action plan (CoRAP) for start of substance evaluation in 2016.

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

The compliance check was initiated on 2 June 2014.

On 13 November 2014 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision. That draft decision was based on submission number [redacted].

On 19 December 2014 ECHA received comments from the Registrant agreeing to ECHA's draft decision regarding the request for information in the technical dossier related to the identity and classification and labelling of the substance and commenting on the information requests for the Pre-natal developmental toxicity study and the environmental exposure assessment and risk characterisation.

On 12 February 2015 the Registrant updated his registration dossier with the submission number [redacted].

The ECHA Secretariat considered the Registrant's comments and update.
On basis of this information, Section II was amended. The Statement of Reasons (Section III) was changed accordingly.

On 3 September 2015 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.

As no proposal for amendment was submitted, ECHA took the decision pursuant to Article 51(3) of the REACH Regulation.

II. Information required

A. Information in the technical dossier derived from the application of Annexes VII to XI

Pursuant to Articles 41(1), 41(3), 10(a)(vi) and/or (vii), 12(1)(e), 13 and Annex X of the REACH Regulation the Registrant shall submit the following information using the indicated test methods and the registered substance subject to the present decision:

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

B. Information related to chemical safety assessment and chemical safety report

Pursuant to Articles 41(1), 41(3), 10(b), 14 and Annex I of the REACH Regulation the Registrant shall submit in the chemical safety report:

Environmental exposure assessment and risk characterisation (Annex I, Sections 5.2.4. and 6.3.).

C. Deadline for submitting the required information

Pursuant to Articles 41(4) and 22(2) of the REACH Regulation the Registrant shall submit to ECHA by **25 November 2016** an update of the registration dossier containing the information required by this decision including, where relevant, an update of the Chemical Safety Report.

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 sound 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 Authorities of the Member States for enforcement.

The Registrants agreed in his comments after re-evaluation of all available information to

classify the registered substance for eye effects category 2 according to CLP.
The revised classification is already included in the updated dossier, submitted with submission number [redacted] on the 12th February 2015, in the technical IUCLID file, but not in the Chemical Safety Report. The Chemical Safety Report should be revised accordingly.

III. Statement of reasons

Pursuant to Article 41(3) of the REACH Regulation, ECHA may require the Registrant to submit any information needed to bring the registration into compliance with the relevant information requirements.

A. Information in the technical dossier derived from the application of Annexes VII to XI

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(e) of the REACH Regulation, a technical dossier for a substance manufactured or imported by the Registrant in quantities of 1000 tonnes or more per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation.

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

Pre-natal developmental toxicity studies on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

The technical dossier contains information on a pre-natal developmental toxicity study in rats by the oral route using the registered substance as test material.

However, there is no information available for a pre-natal developmental toxicity study in a second species. The technical dossier does not contain an adaptation in accordance with column 2 of Annex X, Section 8.7. or with the general rules of Annex XI for this standard information requirement.

As explained above, the information available on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

The test in the first species was carried out by testing a rodent species and ECHA therefore considers that the test in a second species should be carried out in a non-rodent species. According to the test method EU B.31/OECD 414, the rabbit is 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 rabbit as a second species to be used.

The Registrant in his comments to the draft decision, has proposed to cover the human health information requirements for Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method EU B.31./OECD 414) in rabbits, oral route by using the general rules for adaptation of Annex XI, Section 1.5 (read-across, RA) and Section 1.2. (weight of evidence, WoE) approach using the data of the hydrolysis products of the registered substance, formaldehyde and monoethanolamine (MEA).

The Registrant supports his arguments with an updated registration dossier in which he provides a read-across justification and study summaries for a hydrolysis study under gastric conditions and for developmental studies performed with formaldehyde in rats, mice and dogs, and with MEA in rats and rabbits.

Article 13(1) of REACH provides that information on intrinsic properties of substances may be generated by means other than tests through the use of alternative methods. Such other means include e.g. the use of information from structurally related substances (grouping of substances and read-across) and weight of evidence, "provided that the conditions set out in Annex XI are met".
In a weight of evidence approach as defined in Annex XI, 1.2, there has to be "sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property, while the information from each single source alone is regarded insufficient to support this notion" and adequate and reliable documentation shall be provided. When using a read-across approach as part of the weight of evidence justification, the Registrant should demonstrate that the read-across complies with the general rules for adaptation in Annex XI, 1.5.

The grouping and read-across approach outlined in Annex XI, 1.5. requires a structural similarity among the substances within a group or category such that relevant properties of a substance within the group can be predicted from the data on reference substance(s) within the group by interpolation. In all cases results should be adequate for the purpose of classification and labelling and/or risk assessment, have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), cover an exposure duration comparable to or longer than the corresponding test method, and adequate and reliable documentation of the applied method shall be provided.

The following analysis presents the Registrant's justification for the weight of evidence approach and read-across hypothesis, together with ECHA's analysis concerning the justification.

ECHA analysis of the weight of evidence approach and read-across hypothesis in light of the requirements of Annex XI, 1.2 and 1.5.

Based on the information provided, ECHA understands that the Registrant proposes a read-across and weight of evidence approach that is based on the hypothesis that the registered substance rapidly hydrolyses to formaldehyde and monoethanolamine (MEA) in aqueous solutions at pH values 4 and 7, and therefore the data from the hydrolysis products can be used to predict the developmental toxicity properties of the registered substance.

Hydrolysis

According to the study summary of the study described in the Registrant's comments ([redacted]) hydrolysis was assessed immediately and after 1, 2 and 6 hours at pH 4, 5, 7 and 9. The Registrant states that there was "rapid hydrolysis" at pH of 4 and 7 but does not report the results at pH 5. At pH 9 he reports "*signals for a mixture of undecomposed HHT, monoethanol amine and formaldehyde*", again without quantification and precise information about the time. In another hydrolysis study ([redacted]) reported in the IUCLID technical file under 5.1.2 but not mentioned in the Registrant's comments or RA/WoE argument "*The test item was completely hydrolysed after 2h, 50° +/-0.5°C at pH4, pH7 and pH9.*"

ECHA acknowledges that hydrolysis of HHT in aqueous solution and decomposition into formaldehyde and MEA may be feasible. However, ECHA considers that the Registrant has not demonstrated that the hydrolysis reaction is rapid and complete, and that the parent substance and possible intermediates are not expected to impact the toxicity.

Firstly, ECHA notes that the Registrant has not provided

- detailed data on the hydrolysis reaction, i.e. quantitative data on the formation of the hydrolysis products and disappearance of the parent compound in relation to time, and
- data on the (possible) formation of other hydrolysis products (intermediates), e.g.for the hydrolysis study under gastric conditions the corresponding NMR spectra that would allow to see whether there are hydrolysis interim products which are not included in the IUCLID file.
- An explanation for the inconsistencies between the two hydrolysis studies reported in the registration dossier under section 5.1.2 ([redacted]) and 7.1.1 ([redacted])

Secondly, during the time till complete hydrolysis (not specified in the [redacted]) study and 2 hours according to the OECD111 study ([redacted])) one can expect exposure to the decomposed registered substance, formaldehyde, MEA and potentially unidentified interim hydrolysis products in unknown quantities. However, the relative impact of the different hydrolysis products on the overall toxicity has not been addressed by the Registrant.
Without better knowledge about the timeline for all hydrolysis products at the relevant pH ranges typical for the GI tract, the precise composition of the "mixture" of parent compound, and hydrolysis products, to which the mammalian organism will be exposed after oral exposure cannot be determined with sufficient certainty.
For the above reasons, ECHA considers consequently that the developmental toxicity of the registered substance cannot be predicted from the properties of formaldehyde and monoethanolamine.

Source studies

Further the studies available for the hydrolysis products formaldehyde and MEA, suggested as source substances, do not correspond to the information request, which is for a PNDT via the oral route in rabbits, as the 2nd, i.e. non-rodent species.

The Registrant refers to developmental studies conducted with formaldehyde in rats, mice and dogs, and to developmental studies in rats and rabbits preformed with MEA.

As the information request is for a non-rodent study ECHA will only reflect on the two non-rodent studies and not reflect in detail on the information provided on developmental toxicity studies conducted with the formaldehyde or MEA in rodents (rats and mice). ECHA notes however that no teratogenic effects are reported from these rodent studies for formaldehyde, MEA or the registered substance (the study summary for the registered substance only reports a dose-related not statistically significant increase of skeletal variations that was not considered treatment related).

The Registrant argues in his comments that the dermal and inhalation routes are not appropriate for developmental toxicity testing of HHT in rabbits; ECHA agrees with this view.

The available non-rodent PNDT study for MEA is conducted in rabbits via the dermal route. The maternal NOAEL is reported to be 10mg/kg bw/d, based on local effects, while the developmental NOAEL is given as 75 mg/kg bw/d (highest dose tested). While this study may indeed be regarded as "reliable with restrictions" (Klimisch score 2) as classified by the Registrant it has not been conducted via the exposure route that is most appropriate for the registered substance. The Registrant has not addressed the quantitative and qualitative consequences of this deviation, e.g. comparability of internal dose levels, organ distribution and potential metabolites.

The available non-rodent PNDT study for formaldehyde is conducted in Beagle dogs via diet at two very low doses of 3.1 and 9.4 mg/kg bw/d, which did not lead to maternal or developmental toxicity and only a limited number of parameters was examined (e.g. data on visceral or skeletal alterations only in stillborn pups or pups, which died later in post-natal observation period). The study does not follow any recognised test guideline, the GLP status is unknown, there are no data about the purity of the test substance, no historical control data and no statistical analysis.
Consequently, due to the above described deficiencies, neither the information from each single source alone nor all together is sufficient to conclude whether the substance has or has not the dangerous property relevant to fulfil the information needs. In particular, all of the studies with the source substances are lacking adequate and reliable coverage of the key parameters (only two low doses in the dog study with formaldehyde, only a limited number of parameters examined, no historical control data and no statistical analysis) or have not been conducted via the most relevant route of exposure that corresponds to the information request (dermal study with MEA in rabbits instead of the oral route; no explanation how to extrapolate). Additionally, the Registrant has not provided other relevant information on the endpoint to support their adaptation.

Combined exposure to multiple hydrolysis products

Further the Registrant fails to explain how he intends to account for the combined exposure to MEA and formaldehyde. In his read-across justification the Registrant provided information on the physico-chemical and toxicological properties of MEA and formaldehyde. ECHA notes that MEA, formaldehyde and the registered substance differ in their physico-chemical properties (physical state, melting/boiling point and vapour pressure), toxicological profile (in the endpoints corrosion/irritation, skin sensitisation, genotoxicity and carcinogenicity) and consequently classification and labelling. This alone raises questions on whether an assessment based on tests conducted with MEA and formaldehyde separately is an adequate basis for the assumption that the registered substance is or is not a developmental toxicant or whether it might rather lead to an underestimation of the hazard.

Outcome

ECHA concludes that the read-across and weight of evidence approach cannot be accepted in its current form for the reasons set out above. In conclusion, the developmental toxicity effects cannot be predicted from data for source substances as required by Annex XI, 1.2 and 1.5.

Consequently, ECHA considers that in the absence of relevant information related to the presence of developmental toxicity properties of the registered substance, further testing is required.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the following information derived with the registered substance subject

to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD 414) in rabbits by the oral route.

B. Information related to the chemical safety assessment and chemical safety report

Pursuant to Articles 10(b) and 14(1) of the REACH Regulation the registration shall contain a chemical safety report which shall document the chemical safety assessment conducted in accordance with Article 14(2) to (7) and with Annex I of the REACH Regulation.

Environmental exposure assessment and risk characterisation (Annex I, Sections 5.2.4. and 6.3.)

According to Article 14(1) and (4) and Annex I, section 0.6., the Registrant is required to perform a chemical safety assessment (CSA) for the registered substance. The CSA shall cover 1) Human health hazard assessment, 2) Human health hazard assessment of physicochemical properties, 3) Environmental hazard assessment and 4) persistent, bioaccumulative and toxic (PBT) and very persistent and very bioaccumulative (vPvB) assessment.

If, as a result from these steps, the substance meets the criteria for any hazard classes or categories[1] set out in Annex I to the CLP Regulation, or it is assessed to be a PBT or vPvB, the CSA shall also include in accordance with Article 14(4) of the REACH Regulation the additional steps:

a) exposure assessment, including generation of exposure scenario(s) and exposure estimation, and
b) risk characterisation.

The additional steps of the CSA shall be carried out in accordance with Sections 5 (for Exposure assessment) and 6 (for Risk characterisation) of Annex I of the REACH Regulation.

Further, according to Annex I, section 5.0., the objective of the exposure assessment is to make quantitative or qualitative estimate of the dose/concentration of the substance to which humans and the environment are or may be exposed. The assessment shall consider all stages of the life-cycle of the substance and shall cover any exposures that may relate to the hazards identified in Sections 1 to 4 of chapter 0.6 of Annex I.

The Registrant has omitted the exposure assessment and risk characterisation for the environment in the CSA with the following justification: *"In the chemical safety assessment performed according to Article 14(3) in connection with Annex I section 3 (Environmental Hazard Assessment) and section 4 (PBT/vPvB Assessment) no hazard was identified. Therefore according to REACH Annex I (5.0) an exposure estimation and risk characterization is not necessary. Consequently all identified uses of the substance are assessed as safe for the environment."*

However, the registered substance has a harmonized classification for human health as

---

[1]
- hazard classes 2.1 to 2.4, 2.6 and 2.7, 2.8 types A and B, 2.9, 2.10, 2.12, 2.13 categories 1 and 2, 2.14 categories 1 and 2, 2.15 types A to F.
- hazard classes 3.1 to 3.6, 3.7 adverse effects on sexual function and fertility or on development, 3.8 effects other than narcotic effects, 3.9 and 3.10.
- hazard class 4.1:
- hazard class 5.1;

Acute Tox. 4; H302 and Skin Sens.1; H317 according to the CLP Regulation. Therefore, according to Article 14(4) and Annex I, section 0.6, as the substance meets the criteria for classification, the CSA shall include two additional steps, meaning that exposure assessment and risk characterisation are required.

With regard to the scope of the required exposure assessment, as stated above and in accordance with Annex I, section 5.0., it has to cover all hazards that have been identified according to sections 1 to 4 of Annex I of REACH Regulation.

It is clear from the data submitted in the technical registration dossier that hazards to the environment have been identified. Effects are for example seen in algae growth inhibition test (*Desmodesmus subspicatus* EC50=6.6 mg/L).

Therefore, the Registrant is required to carry out the exposure assessment and subsequent risk characterisation also for the environment in order to address all hazards identified for the environment.

As further outlined in Guidance on information requirements and chemical assessment, chapter B.8 Scope of Exposure Assessment (Version 2.1, December 2011), such identified hazards (among others) necessitating exposure assessment are the *"hazards for which there are classification criteria and there is information on these properties of the substance showing that it does have these properties, but the severity of the effects is lower than the criteria for classification and so the substance is not classified"*. Moreover, the above mentioned Guidance specifies further (in Section 8.4.2.2) that *"If there are ecotoxicity data showing effects in aquatic organisms, but the substance is not classified as dangerous for the aquatic environment, an aquatic PNEC can nevertheless be derived thus indicating a hazard to the aquatic environment. (...) Hence, quantitative exposure assessment, i.e. derivation of PECs, is mandatory for the water, sediment and soil environmental compartments."*

With regard to the comments provided by the Registrant challenging the request for exposure assessment for not being consistent in the understanding of the term 'hazard' in the provisions of the REACH and CLP Regulation, and to neglect general principles of EU law, ECHA points out the following:

Generally, two of the main purposes of both the REACH and CLP Regulation are to ensure a high level of protection of human health and the environment (Article 1(1) of the REACH and CLP Regulation respectively). The additional steps in a chemical safety assessment of exposure assessment and risk characterisation serve this objective as they allow estimating and characterising any risk to mankind or the environment. The formal arguments of the Registrant that this shall be done only for CLP-classified hazards ignore this overall context.

Both the REACH and CLP Regulation distinguish between the terms 'hazard', 'hazardous' and 'hazard classes'. The legislator would have used the term 'hazard classes' only if that was his intention for Annex I, Section 5 to the REACH Regulation. This becomes clear from the distinct references used in Article 3 of the CLP Regulation, Article 14(4) and Annex I, Sections 0.6.3. and 5. to the REACH Regulation. Under REACH, a hazard is identified by the results generated from the tests used to fulfil the information requirements set out in Annexes VII to XI. Pursuant to Article 13(3) of the REACH Regulation tests define endpoints/effects to be observed and reported for identification of (no)effect levels/concentrations as well as a limit dose and therefore, if a hazard is identified it is when an adverse effect is observed below that limit dose.

The REACH and CLP Regulations can be interpreted in a coherent and consistent way without reducing unnecessarily their respective scopes. The chemical safety assessment/report is regulated by law in order to assess and document that any risks arising from a substance are adequately controlled during manufacture and use. The burden of safe use lies with operators. ECHA therefore considers the additional steps of exposure assessment and risk characterisation for any identified hazard irrespective of classification as a measure in line with the precautionary principle that is underpinning the REACH Regulation (Article 1(3)) and which the Registrant seems to ignore.

Pursuant to Annex I, Section 3.0.2. of the REACH Regulation five environmental spheres shall be assessed for hazards. Annex I, Sections 5 and 6 require an exposure assessment and risk characterisation for the "environmental spheres for which exposure to the substance is known or reasonably foreseeable". Following the Registrant's argumentation, the environmental exposure assessment and risk characterisation would only be possible for the aquatic environmental sphere since the results for a number of standard data requirements for the other environmental spheres (e.g. information on soil/sediment toxicity,) do not lead to the classification of substances as hazardous, as no hazard classes or classification criteria exist. It cannot be correct that a large part of standard data requirements set out in the REACH Annexes would become irrelevant. Instead, the legislator has a clear intention to use the standard information required in Annexes VII to X of the REACH Regulation for the hazard assessment without prejudice of classification needs.

For reasons of proportionality, the requirement of a chemical safety assessment is limited to those substances meeting the criteria for classification of any hazard class/category set out in Article 14(4) of the REACH Regulation/Annex I CLP Regulation. In that regard the request by ECHA to understand exposure and risk of the substance subject to the present decision is not exceeding of what is appropriate and necessary to attain the objectives of the legislation. The identified hazard in this case has been demonstrated by mortality of algae as outlined in above. In addition and contrary to the Registrant's claim that "*The results of any such data would not even be scientifically meaningful*" ECHA considers that they are meaningful and notes that effects were observed in all three taxa (Short term fish LC50 16.07 mg/L, Short term Daphnia EC50 11.9mg/L, and, most sensitive as already described above, in aquatic algae Desmodesmus subspicatus EC50 6.66 mg/L (growth rate)) and comparing PNECs with exposure is needed to assess whether it poses any risk to the environment.
At the same time, as ECHA is not requiring exposure assessment and risk characterisation on all environmental endpoints, it does not exceed what is necessary to address the concern.

ECHA respects the principle of equal treatment as it requires for any substance meeting the criteria for classification in any of the hazard classes/categories an exposure assessment and risk characterisation.

Finally, the Registrant cannot claim that ECHA's action would jeopardise legal certainty as ECHA has issued guidance on when exposure assessment and risk characterisation are expected (Guidance on information requirements and chemical safety assessment Part B: Hazard assessment; Version: 2.1; December 2011).

In conclusion, the arguments by the Registrant cannot lead to omit the required data that is needed in order to comply with the REACH Regulation.

Therefore, the Registrant is requested to perform an environmental exposure assessment covering all life-cycle stages of the registered substance originating from manufacture and

identified uses, and subsequently perform risk characterisation for each exposure scenario to demonstrate the safe use of the substance, and update the dossier accordingly.

IV. Adequate identification of the composition of the tested material

In relation to the information required by the present decision, the sample of substance used for the new studies must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is within the specifications of the substance composition that are given 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 substance tested in the new studies 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 by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new studies 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 studies to be assessed.

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 an appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on 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 Claudio Carlon, Head of Unit, Evaluation, E2.

[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.