EUROPEAN CHEMICALS AGENCY

~~Confidential~~

Helsinki, 14 January 2021

Addressee: [redacted]

Decision number: CCH-D-2114538554-45-01/F
Substance name: 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)cyclohexan-1-ol
EC number: 222-294-1
CAS number: 3407-42-9
Registration number: [redacted]
Submission number subject to follow-up evaluation: [redacted]
Submission date subject to follow-up evaluation: 28 January 2019

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

By decision CCH-D-2114336558-41-01/F of 19 July 2016 ("the original decision") ECHA requested you to submit information by 28 January 2019 in an update of your registration dossier.

Based on Article 42(1) of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA examined the information you submitted with the registration update specified in the header above, and concludes that

Your registration still does not comply with the following information requirement(s):

Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats

You are therefore still required to provide this information requested in the original decision.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. Advice and further observations are provided in Appendix 3.

The respective Member State competent authority (MSCA) and National enforcement authority (NEA) will be informed of this decision. They may consider enforcement actions to secure the implementation of the original decision and exercise the powers reserved to them under Article 126 of Regulation No 1907/2006 (penalties for non-compliance)[1].

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, shall be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under http://echa.europa.eu/regulations/appeals.

Approved[2] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

[1] See paragraphs 61 and 114 of the judgment of 8 May of the General Court of the European Court of Justice in Case T-283/15 Esso Raffinage v. ECHA
[2] 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 1: Reasons

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

You were requested to submit information derived with the registered substance ('the Substance') for sub-chronic toxicity study (90-day) endpoint.

In the updated registration subject to follow-up evaluation, you have provided the results of a key GLP-compliant sub-acute toxicity (28-day) study, conducted with the Substance on rat via oral route (gavage), according to the test method OECD TG 407 (2015), instead of the requested sub-chronic toxicity study. You have also included an adaptation according to Column 2 of Annex IX, Section 8.6.2.

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

To be considered compliant and enable concluding whether the Substance has dangerous properties and supports the determination of the No-Observed Adverse Effect Level (NOAEL), a study has to meet the requirements of OECD TG 408. The following key parameter(s) of this test guideline include, among others:

- at least 10 female and 10 male animals should be used at each dose level (including control group);
- dosing of the Substance daily for a period of 90 days until the scheduled termination of the study.

The study you have provided was conducted with less than 10 animals per sex per test dose group (7 animals per sex per group). The statistical power of the information provided is not sufficient because it does not fulfil the criterion of 20 animals (10 males + 10 females) for each test group set in OECD TG 408.

The study you have provided does not have the required exposure duration of 90 days as required in OECD TG 408, because you indicated an exposure duration of 28 days.

As provided in Annex IX, Section 8.6.2, Column 2, you may adapt the information requirement, provided you fulfil one of the identified criteriaincluding:

- the Substance is unreactive, insoluble and not inhalable and there is no evidence of absorption/ of toxicity in a 28-day 'limit test', particularly if it is coupled with limited human exposure.

You stated that "the substance is unreactive, insoluble and not inhalable and there is no evidence of absorption and no evidence of toxicity in a 28-day 'limit test' and human exposure is limited". While you have not provided a justification, ECHA has evaluated the provided information according to Annex IX, Section 8.6.2, Column 2.

As reported by you in the IUCLID dossier, the solubility of test chemical in water was determined to be 5.906 mg/L at 25°C (OECD TG 105) and the Substance was considered to be slightly soluble in water. Therefore, the Sbstance is not considered insoluble. ECHA further notes that you self-classified the Substance as Eye Irrit Cat 2 and Aquatic Chronic 2. In the provided 28-day study, you reported significant changes in the percentage of monocytes and basophils, white blood cells count, mean corpuscular volume and mean corpuscular haemoglobin levels in hematology, total protein and total cholesterol, sodium, potassium, total proteins, blood urea nitrogen levels in clinical biochemistry in treated rats (absolute and relative liver and heart

weight were also changed as compared to control). Therefore, there is an evidence of both acute and systemic toxicity of the Substance. ECHA finally notes that human exposure is unlikely to be limited as the Substance is used in industrial, professional settings and by consumers in air care products, biocides, polishes/waxes and cosmetics.

Consequently, you have not demonstrated that the Substance is unreactive, insoluble, not inhalable, that there is no evidence of absorption of toxicity in a 28-day 'limit test' and that there is limited human exposure. On the contrary, the submitted results of the OECD 407 study indicates systemic toxicity and that human exposure is likely. Therefore, your adaptation is rejected.

In your comments to the draft decision, you have provided information seeking to adapt the standard information requirement for sub-chronic toxicity (Annex IX, Section 8.6.2) by applying a weight of evidence approach. To support your weight of evidence approach, you have provided two new sources of information performed with analogue substances:

(i) sub-chronic (13 weeks) toxicity study in rats, oral-gavage (no guideline or GLP reported, [redacted] 1971) conducted with the analogue substance isobornyl acetate (EC No: 204-727-6, CAS RN: 125-12-2);
(ii) chronic (103 weeks) dietary toxicity study in rats (no guideline or GLP reported, [redacted], 1979) conducted with the analogue substance menthol (EC No: 201-939-0, CAS RN: 89-78-1).

You further claimed that these studies have been included in the updated registration dossier. ECHA notes that by 29 October 2020, no update of the registration dossier has been submitted and consequently, the abovementioned studies have not been provided.

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 approach.

As indicated above, in your comments to the draft decision you have provided two new sources of information (i) and (ii) for the sub-chronic toxicity endpoint. You have concluded that the studies are suitable for regulatory purposes, provide adequate and reliable information on the critical parameters, and cover the information requirement of a repeated dose 90-day oral toxicity study.

ECHA assessed the validity of your weight of evidence adaptation and identified the following deficiencies:

Relevance of the supporting 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. This information is covered by information similar to OECD TG 408.

1.Key element/key investigations
In-life observations
Description of information required in more detail (relevance and coverage)
In-life observations must include information on survival, body weight development, clinical signs, functional observations, food/water consumption and other potential aspects of in life observations on the relevant physiological systems (circulatory, digestive/excretory, integumentary, musculoskeletal, nervous, renal/urinary, and respiratory).

Only the source of information (i) provides relevant information on survival, body weight development, clinical signs, food/water consumption and renal/urinary system. However, both sources of information (i-ii) do not inform on functional observations other potential aspects of in life observations on the relevant physiological systems (circulatory, digestive/excretory, integumentary, musculoskeletal, nervous, and respiratory). Therefore, these sources of information, i.e. source of information (i), provide limited information on this key element.

However, the reliability of source of information (i) is significantly affected by the reliability issues adressed further below (see under "Reliability of the provided information with analogue substances").

2.Key element/key investigations
Blood chemistry
Description of information required in more detail (relevance and coverage)
Information on blood chemistry must include haematological (full-scale) and clinical chemistry analysis (full-scale), and other potential aspects related to blood chemistry to address relevant physiological systems (circulatory digestive/excretory, endocrine, immune, musculoskeletal, and renal/urinary).

Only source of information (i) provides relevant information on some haematological and clinical-chemistry parameters; however, not a full-scale. Therefore, this source of information provides limited information on this key element.

However, the reliability of source of information (i) is significantly affected by the reliability issues adressed further below (see under "Reliability of the provided information with analogue substances").

3.Key element/key investigations
Organ and tissue toxicity
Description of information required in more detail (relevance and coverage)
Organ and tissue toxicity must include information on terminal observations on organ weights, gross pathology and histopathology (full-scale and other potential aspects related to organ and tissue toxicity to address relevant physiological systems (circulatory, digestive/excretory, endocrine, immune, integumentary, musculoskeletal, nervous, renal/urinary system, reproductive, and respiratory).

Source of information (i) provides some relevant information on histopathology, but not full scale and the source of information (ii) only provides some information on incidence of tumors. Therefore, these sources of information, (i) and (ii) provide limited information on this key element.

However, the reliability of sources of information (i) and (ii) are significantly affected by the reliability issues adressed further below (see under "Reliability of the provided information with analogue substances").

Reliability of the provided information with analogue substances

ECHA understands that you intend to predict the toxicological properties of the Substance for a sub-chronic oral toxicity from data obtained with analogue substances in a read-across approach as part of your weight of evidence adaptation.

Grouping of substances and read-across approach

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. 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 (read-across approach).

A read-across hypothesis needs to be provided, establishing why a prediction for a toxicological property is reliable. This hypothesis should be based on recognition of the structural similarities and differences between the source substance(s) and your Substance[3]. It should explain why the differences in the chemical structures should not influence the toxicological properties or should do so in a regular pattern.

Predictions for toxicological properties

As indicated above, for sub-chronic oral toxicity endpoint, you propose to read-across between the two following substances, reported in your comments to the draft decision, as source substances and the Substance as target substance:
(i) sub-chronic (13 weeks) toxicity study in rats, oral-gavage (no guideline or GLP reported, [redacted] 1971) conducted with the analogue substance isobornyl acetate (EC No: 204-727-6, CAS RN: 125-12-2;
(ii) chronic (103 weeks) dietary toxicity study in rats (no guideline or GLP reported, [redacted], 1979) conducted with the analogue substance menthol (EC No: 201-939-0, CAS RN: 89-78-1).

As also noted above, the abovementioned studies conducted with analogue substances are not present in the registration dossier of the Substance.

In your comments to the draft decision you proposed to adapt this information requirement by applying a read-across as a part of your weight of evidence aproach and included a read-across justification document entitled [redacted]
In your justification document you have indicated that 'Scenario 2' was selected to for the analogue approach. You provided the following reasoning for the prediction of (eco)toxicological properties:

[3] ECHA Guidance R.6

- Identifying the analogue substances based on common functional groups, *further* subcategorized based on mechanistic approach, and finally fine-tuned with structural similarity using the QSAR Toolbox Version 3.4;
- Common physico-chemical properties;
- Cycloalkane as the most common basic moiety.

You conclude that "*overall, the descriptors, various alerts, and scenario (for analogue approach), which were taken into consideration for toxicological assessment as reported in this RA justification document obtained by using OECD QSAR toolbox v.3.4 of the target substance and read-across analogues were evaluated to be similar and therefore justified and appropriate.*".

Based on the above, ECHA understands that you used the QSAR Toolbox for the identification of analogues in order to predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects. The properties of your Substance are predicted to be quantitatively equal to those of the source substances.

ECHA notes the following deficiencies with regards to predictions for toxicological properties.

I. Read-across hypothesis

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. 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 (read-across approach).

A read-across hypothesis needs to be provided, establishing why a prediction for a toxicological or ecotoxicological property is reliable. This hypothesis should be based on recognition of the structural similarities and differences between the source substance(s) and your Substance[4]. It should explain why the differences in the chemical structures should not influence the toxicological properties or should do so in a regular pattern.

Your read-across hypothesis is that the similarity in chemical structure and physico-chemical properties between the Substance and the analogue substances is a sufficient basis for predicting the properties of the Substance for other endpoints.

While structural and physico-chemical similarity is a prerequisite for applying the grouping and read-across approach, it does not necessarily lead to predictable or similar toxicological properties. ECHA notes that target substance is UVCB, whereas the proposed read-across analogues are mono-and multi-constituents. You only identified cycloalkane and terpene as a common basic moieties in the structure of target and both source substances but did not explain what would be the impact of any other constituents on the toxicity.

Therefore, you have not provided a well-founded hypothesis to establish a reliable prediction for a toxicological or ecotoxicological property, based on recognition of the structural similarities and differences between the target and source substances.

II. *Characterisation of the source substances*

[4] ECHA Guidance R.6

Annex XI, Section 1.5 of the REACH Regulation provides that "*substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as group.*"

According to the ECHA Guidance, "*the purity and impurity profiles of the substance and the structural analogue need to be assessed*", and "*the extent to which differences in the purity and impurities are likely to influence the overall toxicity needs to be addressed, and where technically possible, excluded*". The purity profile and composition can influence the overall toxicity/properties of the Substance and of the source substance(s).[5] Therefore, qualitative and quantitative information on the compositions of the Substance and of the source substance(s) should be provided to allow assessment whether the attempted predictions are compromised by the composition and/or impurities.

Furthermore, whenever the Substance and/or the source substance(s) are UVCB (Unknown or Variable composition, Complex reaction products or of Biological materials) substances qualitative compositional information of the individual constituents of the substances needs to be provided; as well as quantitative characterisation in the form of information on the concentration of the individual constituents of these substances; to the extent that this is measurable.[6]

You have not provided any information on the composition of the selected analogue substances, including their purity profile and the presence of impurities.

Therefore, no qualitative or quantitative comparative assessment of the compositions of the Substance and of the analogue substances can be completed. Therefore, ECHA considers that it is not possible to assess whether the attempted predictions are compromised by the composition of the source substances.

III. *Supporting information for toxicological properties*

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*"[7].

Supporting information must include information to confirm the read-across hypothesis, to confirm that the Substance and the source substances have similar toxicological properties and establish that the properties of the Substance can be predicted from the data on the source substance(s).

You have provided the following information to support your hypothesis:

- Information on the identity details of the Substance and the analogues;
- Information on structural alerts;
- Information on physicochemical properties;
- Results of sub-acute toxicity, oral 28-day study, conducted with the Substance; Narrative summaries of results of two (sub-chronic and chronic) studies conducted with analogue substances.

[5] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.3.1
[6] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.5.5
[7] ECHA Guidance R.6: Section R.6.2.2.1.f

ECHA has assessed the provided supporting information below and identified the following issues:

Adequacy of supporting information

According to Annex XI, Section 1.5 there needs to be structural similarity between substances resulting in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties.

You have identified target and source substances as structurally similar and indicate that *"The target substance,3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)cyclohexanol [CAS: 3407-42-9; EC Number: 222-294-1] is also known as Isobornyl cyclohexanol. This substance is from the group of alicyclic terpenes. The read-across analogues that are used also belong to the same group of alicyclic terpenes. The target and the read-across analogues have cycloalkane and terpene as a common basic moieties in their structure".*

You have assessed the impact of structural differences using a set of physico-chemical properties and common structural alerts obtained from the QSAR Toolbox v. 3.4 for the Substance and for each of the source substances.

You indicate that *"as the target and read-across analogues show the presence of similar functional groups, different structural activity amongst the various read-across substances is notexpected.As per the analysis conducted with the OECD (Q)SAR Toolbox v.3.4, it was indicated that the target and the read-across analogues share similar structural alerts. <...>. The target substance and all read-across analogues share common alerts in general mechanistic, which include Protein and DNA binding alerts. As per the endpoint specific alert of Repeated Dose (HESS), the target substance and the read-across analogues have similar activity."*

While the similarity in presence or absence of structural alerts may indicate that the differences do not influence the reactivity of the substance, e.g. on protein or DNA binding, this information does not confirm that the Substance and the source substances have similar toxicological properties such as repeated dose toxicity. The complexity of systemic interactions and the large number of mechanisms associated with this are of toxicity is not covered by computational tools.

Reliability of the supporting information

As indicated above, your read-across hypothesis is based on the assumption that the structurally similar substances cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the Substance and the source substance(s) is necessary to confirm that both substances cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and of the source substances.

As indicated above, to support the hypothesis that the sub-chronic toxicity of the Substance can be predicted from the source substances, in your comments to the draft decision you have provided narrative summaries of the results of the two studies conducted on analogue substances.

These studies may allow to compare the properties of the Substance of or the source substances. The studies (i) and (ii) were conducted using sufficient number of animals and appropriate time of exposure. However, in the 28-days study conducted the Substance administered up to 1125 mg/kg bw/day did not induce any adverse effect during 28 days of exposure. ECHA notes that for your proposed source substances, you established the following no adverse effects levels (NOAELs): 15 mg/kg bw/day for (i) isobornyl acetate (EC: 204-727-6, CAS: 125-12-2), based

on renal toxicity, and 375 mg/kg bw/day for (ii) dl-menthol (EC: 201-939-0, CAS: 89-78-1). Based on 75 (i) and 3 (ii) fold differences in NOAELs between the Substance and source substances, you have not established that the Substance and of the source substance(s) are likely to have similar toxicological potency. Based on this, the properties for 90-day repeated toxicity of the Substance are expected to be different from that reported for analogue substances, and the information provided with analogue substances cannot contribute to the formation of reliable conclusions on the properties of the Substance in the context of this weight of evidence.

Taken together, even though, the sources of information (i) and (ii) as indicated above may provide (partially) relevant information, their reliability is affected significantly, therefore, they cannot contribute to the conclusion on the information requirement of Section 8.6.2 at Annex IX.

Conclusion
It is therefore not possible to conclude, based on any of the sources of information (i) and (ii) alone or considered together, whether your Substance has or has not the particular dangerous property foreseen to be investigated in OECD TG 408. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

As detailed above, ECHA therefore considers that the information requirement addressed by the original decision has not been met and you still have to provide the results of a sub-chronic toxicity study in rats, oral route using the Substance, and according to the test guideline EU Test Method B.26/OECD TG 408, as requested in the original decision.

Appendix 2: Procedural history

In accordance with Article 42(1) of the REACH Regulation, the Agency examined the information submitted by you in consequence of decision CCH-D-2114336558-41-01/F. The Agency considered that this information did not meet one or more of the requests contained in that decision. Therefore, a new decision-making process was initiated under Article 41 of the REACH Regulation.

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft of this decision was notified to the Member States Competent Authorities according to Article 51(1) of the REACH Regulation.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

ECHA notified you of the draft decision and invited you to provide comments

ECHA took into account your comments and did not amend the requests.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix 3: Further information, observations and technical guidance

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

2. The Article 42(2) notification for the original decision is on hold until all information requested in the original decision has been received.