EUROPEAN CHEMICALS AGENCY

Helsinki, 19 July 2016

Addressee: [redacted]

Decision number: CCH-D-2114336558-41-01/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: [redacted]
Submission date: 12.05.2015
Tonnage band: 100-1000T

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA requests you to submit information on

1. **Name or other identifier (Annex VI, Section 2.1.) of the registered substance;**

2. **Description of the analytical methods (Annex VI, Section 2.3.7.) on the registered substance;**

3. **Hydrolysis as a function of pH (Annex VIII, Section 9.2.2.1; test method: EU C.7/OECD TG 111) with the registered substance;**

4. **In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13./14 /OECD TG 471) with the registered substance;**

5. **In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method: EU B.10./OECD TG 473) or in vitro micronucleus study (Annex VIII, Section 8.4.2, test method: OECD TG 487) with the registered substance;**

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

7. **Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD 421 or 422) with the registered substance;**

8. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2; test method: EU B.31./OECD TG 414) in a first species (rats or rabbits), oral route with the registered substance;**

9. **Simulation testing on ultimate degradation in surface water (Annex IX, Section 9.2.1.2; test method: Aerobic mineralisation in surface water – simulation biodegradation test, EU C.25/OECD TG 309) at a temperature of 12 °C with the registered substance;**

10. **Sediment simulation testing (Annex IX, Section 9.2.1.4; test method:**

Aerobic and anaerobic transformation in aquatic sediment systems, EU C.24 / OECD TG 308) at a temperature of 12 °C with the registered substance;

11. **Soil simulation testing (Annex IX, Section 9.2.1.3; test method: Aerobic and anaerobic transformation in soil, EU C.23/OECD TG 307) at a temperature of 12 °C with the registered substance;**

12. **Identification of the degradation products (Annex IX, Section 9.2.3.) by means of one of the above test methods under points 9-11;**

13. **Bioaccumulation in aquatic species (Annex IX, Section 9.3.2; test method: Bioaccumulation in fish: aqueous and dietary exposure, OECD TG 305-I, aqueous exposure) with the registered substance or alternatively, if the study is deemed to be relevant and reliable, provide in the dossier robust study summary for the study reported in the dossier for experimental study on bioaccumulation: aquatic/sediment;**

14. **Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1; test method: Fish, early-life stage (FELS) toxicity test, OECD TG 210) with the registered substance;**

15. **Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5; test method: Daphnia magna reproduction test, EU C.20/OECD TG 211) with the registered substance;**

16. **Growth inhibition study aquatic plants (Annex VII, Section 9.1.2; test method: Alga, growth inhibition test, EU C.3/OECD TG 201) with the registered substance.**

You 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 and conforming to the appropriate rules in the respective Annex, and an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by:
- **26 July 2017** for 1-5 and 13-16; and
- **28 January 2019** for 6-12.

You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

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.

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/web/guest/regulations/appeals.

Authorised[2] by Ofelia Bercaru, Head of Unit, Evaluation E3

[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.

EUROPEAN CHEMICALS AGENCY

Appendix 1: Reasons

IDENTIFICATION OF THE SUBSTANCE

In order to ensure that potential hazardous properties of the substance are not underestimated, the substance identification deficiencies must be resolved before identifying the test sample to be used for the testing requested in the present decision.

1. Name or other identifier of the substance (Annex VI, Section 2.1.);

Pursuant to Article 10(a)(ii) of the REACH Regulation, the technical dossier shall contain information on the identity of the substance as specified in Annex VI, Section 2 of the REACH Regulation. In accordance with Annex VI, Section 2 the information provided shall be sufficient to enable the identification of the registered substance.

"Name or other identifier of the substance" is an information requirement as laid down in Annex VI, Section 2.1. of the REACH Regulation. The name and other identifiers are used to identify the substance in an unambiguous manner and are therefore fundamental for substance identification. Adequate information needs to be present in the technical dossier for the registered substance to meet this information requirement.

According to the ECHA Guidance for identification and naming of substances under REACH (Version 1.2, March 2012):

A mono-constituent substance is a substance, defined by its quantitative composition, in which one main constituent is present to at least 80% (w/w).

Multi-constituent substances are those where more than one well-defined constituent is present in a concentration ≥10% (w/w) and <80% (w/w).

Variability of composition for well-defined substances is specified by upper and lower limit of the concentration range(s) of the main constituent(s).

As opposite, UVCB substances (substances of Unknown or Variable composition, Complex reaction products or Biological materials) cannot be sufficiently identified by their chemical composition, because:

- The number of constituents is relatively large and/or
- The composition is, to a significant part, unknown and/or
- The variability of composition is relatively large or poorly predictable.

ECHA notes that the registered substance has been identified in the registration dossier as a well-defined mono-constituent substance with the following identifiers: EC number 222-294-1, CAS number 3407-42-9 and chemical name "3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)cyclohexan-1-ol".

You have reported only one reference substance corresponding to "3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)cyclohexan-1-ol" in the composition information of the IUCLID dossier.
ECHA notes the following:

- The registered substance, identified as described above, refers to a substance containing six different stereocenters that give rise to multiple stereoisomers. The above-mentioned name and identifiers are generic and therefore refer to a substance consisting of all possible stereoisomers of "[redacted]

[redacted]". Considering the large number of possible stereoisomers, a substance described by these identifiers would not be regarded as a mono-constituent substance but rather as a UVCB substance.

- The chromatographic analysis included in the registration dossier shows several undefined peaks. This indicates that a multitude of constituents are present in the composition of the registered substance. No further information on how you derived the composition of the registered substance is provided in the IUCLID dossier. No information is given on the stereoisomeric composition of the registered substance.

- You did not provide any information on the manufacturing process of the registered substance. Therefore no conclusion can be made on the stereoisomerism.

On the basis of the information included in the registration dossier ECHA is not in the position to conclude whether the registered substance consists of all possible stereoisomers of "[redacted]" or whether the substance consists of a subset of these stereoisomers.

Consequently, further information is required to appropriately identify and name the registered substance, in line with Annex VI, Section 2.1 of the REACH Regulation. In that respect ECHA foresees two possibilities:

A. <u>If the substance subject to this registration is considered as a UVCB substance</u>
As indicated in ECHA Guidance for identification and naming of substances under REACH (Version 1.2, March 2012), chapter 4.3, the naming of UVCB substances, shall consist of two parts: (i) the chemical name and (ii) a more detailed description of the manufacturing process. You are therefore required to provide a detailed description of the manufacturing process, including the chemical identity of the starting materials, ratio of reactants, and information on the most relevant steps and parameters of the manufacturing process.

ECHA observes that the type of substance described in the dossier may be produced following different manufacturing processes. Depending on the manufacturing process used, different regioisomers of [redacted] could also be formed. Therefore, the manufacturing process description shall include sufficient information for determining the specific regioisomers and stereoisomers produced.

B. <u>If the registered substance is regarded as a well-defined substance</u>
In case the composition of the substance is known (i.e. the isomers can be identified and quantified by appropriate analytical methods), and includes a limited number of the possible stereoisomers of [redacted] as main constituents, the substance would be identified as a well-defined multi-constituent substance. In this case, the chemical name of the substance shall be modified according to ECHA Guidance for identification and naming of substances under REACH (Version 1.2, March 2012), following the rules for naming of multi-constituent substances. In addition, the identified isomers shall be reported in the composition in section 1.2, and their identification should be supported by appropriate analytical data in section 1.4.

Note for your consideration

If the registered substance does not consist of all possible stereoisomers of [redacted] you are furthermore requested to delete from the dossier the CAS information currently assigned to the substance and provide instead any available CAS information specifically corresponding to the substance. In addition, if the current EC number does not correctly identify the registered substance, it will need to be revised. However, for technical reasons, at this stage you are requested not to remove or revise the EC entry in the updated dossier. As this registration is linked to this EC entry in REACH-IT, the IT system will not accept the updated dossier as an update when the EC entry has changed. You are requested to include in the "Remarks field" of the reference substance the following: "*The EC entry currently assigned does not specifically correspond to the registered substance. This identifier cannot be modified in the present registration at this stage for technical reasons*". You shall also specify, in the same "Remarks" field, any available and appropriate EC number for the substance. You shall note that ECHA has established a process, subject to certain conditions, enabling registrants to adapt an existing registration, while maintaining the regulatory rights already conferred to the substance concerned.

Regarding how to report the requested information in IUCLID the following applies:

- if the substance manufactured is best identified as a UVCB substance, the description of the manufacturing process of the UVCB substance shall be included in the Description field in section 1.1 of IUCLID.

- if the substance manufactured is best identified as a multi-constituent substance, the chemical name shall be revised, as described in ECHA Guidance for identification and naming of substances under REACH (Version 1.2, March 2012), using the general format "Reaction mass of [names of the main constituents]", where only main constituents typically ≥10% (w/w) contribute to the name. The revised name shall be reported in the IUPAC name field in section 1.1 of IUCLID.

You shall ensure that representative identifiers are used throughout the dossier, and are consistent with the information on the composition in section 1.2 and the analytical data in section 1.4 of the IUCLID dossier.
Further information on how to report the chemical name, the molecular and structural formulae, other identifiers and the description of the manufacturing process is available in "Data submission manual Part 18 – How to report the substance identity in IUCLID 5 for registration under REACH" (version 2.0, July 2012), available on the ECHA website.

2. Description of the analytical methods (Annex VI, Section 2.3.7.)

Pursuant to Article 10(a)(ii) of the REACH Regulation, the technical dossier shall contain information on the identity of the substance as specified in Annex VI, Section 2 of the REACH Regulation. In accordance with Annex VI, Section 2 the information provided shall be sufficient to enable the identification of the registered substance.

"Description of the analytical methods" is an information requirement as laid down in Annex VI, Section 2.3.7. of the REACH Regulation. Adequate information needs to be present in the technical dossier for the registered substance to meet this information requirement.

ECHA observes that you did not provide sufficient description of the analytical methods used for the identification and quantification of the constituents/groups of constituents required

to be reported in the composition of the registered substance, as requested according to Annex VI, Section 2.3.7. of the REACH Regulation.

You provided in IUCLID section 1.4 a copy of a gas chromatogram, as well as a peak table with associated retention time and peak areas. However ECHA notes that the description of the methods used for the quantification of the substance was not provided and therefore it is not possible to unambiguously verify the composition of the substance.

More specifically, ECHA observes that:

- The chromatogram shows several peaks, which reveal the presence of numerous constituents. The peaks shown in the chromatogram have not been identified and no information is given on how the results of the provided chromatogram were translated into the composition reported in section 1.2, and how, based on these results, the substance could be identified as a well-defined mono-constituent substance.

- The description of the analytical protocol used to obtain the chromatogram is not provided (i.e. column, experimental conditions, etc.).

In line with Annex VI, Section 2.3.7. of the REACH Regulation, you are requested to submit a suitable description of the analytical methods (chromatography or any other suitable analytical method) used for the quantification of the constituents/groups of constituents required to be reported in the composition of the registered substance, including stereoisomers. You shall note that if the presence of a multitude of stereoisomers leads to such a complex composition that does not enable the identification and quantification of each constituent/isomer present in the substance, considerations on the starting materials and the manufacturing process specificity can be carried out in order to derive the stereoisomeric composition.
The description shall be sufficient for the methods to be reproduced and shall therefore include details of the experimental protocol followed, any calculation made and the results obtained.

You shall ensure that the analytical information is supporting the composition in section 1.2 of the IUCLID dossier.
As for the reporting of the above data in the registration dossier, the information shall be attached in IUCLID section 1.4.

PROPERTIES OF THE SUBSTANCE

A. Preliminary considerations

Article 13(1) of the REACH Regulation stipulates that information on intrinsic properties of substances may be generated by means other than tests, provided that the conditions set out in Annex XI are met.

In that respect, ECHA notes that you have adapted many of the information requirements addressed in the present decision with weight of evidence approaches. Section 1.2 of the Annex XI of the REACH Regulation sets out the prerequisites of weight of evidence approaches as follows:

> *"There may 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".

Therefore, an evidence based approach involves an assessment of the relative values/weights of different pieces of the available information that have been retrieved and gathered in previous steps. To this end, a value needs to be assigned to each piece of information. These weights/values can be assigned either in an objective way by using a formalised procedure or by using expert judgement. The weight given to the available evidence depends on factors such as the quality of the data, consistency of results, nature and severity of effects, relevance of the information for the given regulatory endpoint.

In the present case, the weight of evidence approaches you propose are themselves based on sources of information such as QSAR, grouping and read-across or existing studies. These sources of information are themselves adaptations described in respective sections of Annex XI and subject to specific conditions. The fulfillment of all or parts of these conditions determines the quality and reliability of these sources of information for assuming or concluding that a substance has or has not a particular dangerous property.

However, ECHA notes systematic deficiencies regarding the conformity of these sources of information with the conditions set out in Annex XI of the REACH Regulation. These deficiencies are such that they call into question the quality and reliabity of these sources of information as valid pieces of a weight of evidence argumentation.

The following development addresses the invalidity of these sources of information for the purpose of justifyng a weight of evidence approach.

a. Use of Qualitative or Quantitative structure-activity relationship ((Q)SAR) models

ECHA notes that you have provided sources of information based on Qualitative or Quantitative structure-activity relationship ((Q)SAR) models as part of weight of evidence approaches to fulfil several information requirements. (Q)SARs, are theoretical models that can be used to predict in a qualitative or quantitative manner the physico-chemical, biological (e.g. toxicological) and environmental fate properties of compounds from a knowledge of their chemical structure.

The quality and reliability of the (Q)SAR models can be assessed in the light the criteria established in Section 1.3. of Annex XI to the REACH Regulation:

- results are derived from a (Q)SAR model whose scientific validity has been established,
- the substance falls within the applicability domain of the (Q)SAR model,
- results are adequate for the purpose of classification and labelling and/or risk assessment, and
- adequate and reliable documentation of the applied method is provided.

Adequate and reliable documentation should provide information on the scientific validity of the approach. The justification for using the (Q)SAR information should be based on the use of the QSAR Reporting Formats described in ECHA Guidance on information requirements and chemical safety assessment (May 2008), Chapter R.6 (Section R.6.1.6.):

- the description of a particular (Q)SAR model (i.e. description of the algorithm, its

development and validation based on the OECD principles) will be stored in the (Q)SAR Model Reporting Format (QMRF).

- the (Q)SAR Prediction Reporting Format (QPRF) will explain how an estimate has been derived by applying a specific model or method to a specific substance. This should include information on the model prediction(s), including the endpoint, a precise identification of the substance modelled and the relationship between the modelled substance and the defined applicability domain.

These required reporting formats are essential to provide a comprehensive description of the reliability and use of the (Q)SAR during the chemical safety assessment, including the classification of a given substance for a specific endpoint. They are also necessary for justifying any further testing considered necessary to obtain adequate and complete information.

However, ECHA notes that you have not provided any documentation of the applied methods in order to support the predictions. More concretely, because you have not provided any documentation to support your (Q)SAR model predictions, there is no basis on which the presence or absence of a certain dangerous property of the registered substance can be predicted. The absence of a reliable and justified basis disqualifies such QSAR models as sources of information for the respective weight of evidence approach intended to assume or conclude on the presence or absence of a certain dangerous property of the registered substance.
All the more, the non-fulfilment of the primary condition described above invalidates this adaptation for endpoints where QSAR models were invoked as adaptations as such and not as a mere source of information of a weight of evidence argumentation.

b. Use of OECD QSAR Toolbox - grouping of substances

ECHA notes that, for some information requirements, you have provided information on analogue substances identified from the OECD QSAR toolbox. More specifically, you have used these analogues as sources of information as part of a weight of evidence argumentation. Even though you have reported this information as "QSAR" in the field study result type in IUCLID, on the basis of the indications included in the corresponding prediction report, ECHA understands that these arguments do not refer to QSAR models but rather to read-across approaches. Therefore, the quality and reliability of such sources of information shall be assessed against the conditions applying to read-across approaches.

c. Category approach

For several endpoints, ECHA notes that you also invoked a category approach as a source of information of your weight of evidence argumentation.

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 a group, or 'category' of substances. These similarities may be due, like in the present case, to a chemical similarity within the group (i.e. common functional group).

If a structural similarity is established, it may be possible to make predictions within the group for the target substance(s) on the basis of a demonstrable regular pattern. Alternatively, whenever there is more than one source substance in the category and no regular pattern is demonstrated for the property under consideration, the prediction may be based on a read-across from a category member with relevant information in a conservative manner (worst case).

The supporting evidence is considered as an essential part of the category justification. Due to the diversity of cases, the (eco)toxicological property under consideration and the range of possible explanations, it is not possible to provide rules for the type of supporting evidence which would be required to support a particular read-across hypothesis.

In the present case, you have included a category justification document in IUCLID section 13 of your dossier. This justification document presents the methodology applied to select the category members, based on the presence of structural features and on the absence of alerts for specific mechanisms of toxicity. This led to the formation of a category composed of the registered substance and 3 analogue substances for human health endpoints and 1 analogue substance for environmental endpoints. In total you are referring to 4 different analogue substances. As a result of this category approach, you have used experimental data obtained from several category members as sources of information in the context of weight of evidence approaches to fulfil multiple information requirements applying to the registered substance.
In the summary of the category approach, you justify the proposed category on the basis that all the category members share some structural elements and that "*it is observed that the physicochemical and toxicological properties of all the category members are similar and comparable as a result of that structural similarity*". Furthermore, you conclude that "*All category members are non-persistent in nature and are have a bio-accumulative potential based on the BCF as well toxico-kinetics values*" and that "*all members are in ecotox group have similar aquatic classification of aquatic chronic 3 category*". You also consider that "*Based on the human health data it is observed that all the chemicals are not toxic in nature and safe for the human health. Therefore the chemical category is likely justified with similar category members*".

Furthermore, you support the approach described above with several arguments. ECHA has assessed these arguments and consider for the following reasons that they cannot legitimately support a weight of evidence approach.

1. Argument relating to the structural similarity of the substances in the category

You have detailed in the category justification document the list of profilers applied in the selection of the analogues. These elements can be regarded as elements of structural similarity among the category members. Despite compliance with the structural similarity profilers, the category members exhibit structural differences such as presence of an additional functional group, different position of the functional group, different type of ring structures and number of ring structures. The category justification document does not contain information on the allowed structural differences within the category, thereby creating uncertainty on the boundaries of this category. Should the structural differences observed among the category members be allowed within the category, you did not provide information on how these structural differences may or may not affect the prediction of properties within the category. Further, according to the information included in the category justification document, absence or presence of mechanistic alert has been used to refine the selection of category members. ECHA is of the opinion that these selection criteria do not constitute a basis on which the properties of the registered substance can be established from the data on other category members. The presence of one mechanistic alert (strong estrogen receptor binding) does not preclude qualitative and quantitative differences in toxicity. Furthermore, the absence of predicted activity on mechanisms like protein and DNA binding does not preclude that other pathways and mechanisms of toxicity may be activated. This is particularly relevant in the context of the prediction of properties for particularly complex higher tier endpoints for which the mechanisms of toxicity are many and largely unknown. The selection of members of the category on the basis of the selected

mechanistic alerts appears to suggest a bias in the prediction of the properties of the registered substance. Therefore, ECHA is of the opinion that the limits of the category have not been unambiguously defined; that a structure-activity relationship is missing from the category as currently documented; and that the impact of the structural differences among the category members on the prediction of properties within the category has not been assessed and reported.

2. Argument relating to the similarity of the physicochemical properties of the substances in the category

Your category justification document includes a data matrix presenting physicochemical properties of the category members. On that basis, you compare the physicochemical properties among the category members. However, ECHA notes that there is no information either in the justification document or in the IUCLID technical dossier on the nature of the investigations leading to these physico-chemical values. Therefore, the reliability and relevance of the results cannot be verified.

Furthermore, you outlined in the category justification document "*it is likely that all the chemicals belong to same category with few exceptions in the phys-chem data*". Based on that, the claimed similarity in some physicochemical parameters does not apply to all the category members, but only to one substance (CAS 66068-84-6). As you acknowledged it, there appear to be "a few exceptions". These exceptions appear to be particularly relevant as they affect parameters such as molecular weight, melting point, boiling point, water solubility and log Kow for the category members with the CAS numbers 77-59-8 and 126-19-2 which are used to predict human health effects and log Kow vapour pressure and biodegradability for the category member with the CAS number 80-04-6 which is used to predict aquatic toxicity properties. Even though you acknowledged these exceptions, you did not further explain how these differences may impact the prediction of properties of the target substance. Overall, in the absence of further justification, the differences in physico-chemical properties of the category members do not support a likely similarity in the toxicological and ecotoxicological properties of the substances.

3. Argument relating to the similarity of the environmental exposure and fate properties of the substances in the category

Your category justification document includes a data matrix presenting environmental exposure and fate properties for the category members.

On that basis, you claim that "*based on the half-life values all the category members are non-persistent in both the mediums*", that "*all category members have the tendency as the bio accumulative substances*" and that "the rate of *hydrolysis is estimated to be very low and comparable for all the chemicals*". ECHA notes that there is no information where these data originate and which degradation and/or partition processes have been considered in calculating the half-life values. Similarly, there is no information presented in justification document to indicate where the logKoc, BCF and hydrolysis values originate. Therefore, the reliability and relevance of the results cannot be verified.
In addition, the absence of further explanation and without prejudice to the adequacy and relevance of the source of information, the data matrix provided neither demonstrates a similarity in fate properties for these endpoints among the identified category members, nor supports a possibility to predict properties of the registered substance from data on other members of the category.

4. Argument relating to the similarity of aquatic toxicity of the substances in the category

Your category justification document includes a data matrix presenting aquatic toxicity properties, i.e., toxicity to fish, daphnia, algae and micro-organisms, for the registered substance (the "target substance") and aquatic toxicity values (apart toxicity to micro-organisms) for only one analogue (CAS 80-04-6).

On that basis, you claim that *"the aquatic toxicity related values it is observed that the values for both target as well as analogues are comparable"* and that *"the aquatic classification of the substance remains similar based on the values for both target as well as analogue substance"*. ECHA notes that in addition to the values provided for the registered substance (target) you have provided toxicity value for only one analogue. There is no sufficient information on the tests where the values originate (most of information on the study design/test conditions are missing). Thus the reliability, adequacy and relevance of the source of information cannot be evaluated. As a consequence, the ecotoxicity values provided cannot be used to demonstrate a similarity in ecotoxicological properties among the identified category members and nor support a possibility to predict properties of the registered substance from data on other members of the category.

5. Argument relating to the difference in NOEL/NOAELs of the substances in the category

Your category justification document includes an argumentation that due to the absence of toxicokinetic data for the target substance, physico-chemical properties and bio-accumulation are considered. It also includes a data matrix presenting dose descriptors for the category members for the following toxicological endpoints: acute toxicity, sensitisation, repeated dose toxicity, reproductive toxicity developmental toxicity.

However, ECHA notes that for the category member with the CAS number 66068-84-6, only information on acute toxicity is provided but no information on higher tier toxicity studies. Furthermore, for the category member with the CAS number 126-19-2, the provided information is a study with 14 day oral administration of Sarsasapogenin to groups of 10 male mice with examination of neurobehaviour and measurement of metabolites and enzymes. Hence, this study does not address key parameters of a sub-chronic toxicity study like 90-day exposure duration of groups of 10 male and female rodents followed by an appropriate histopathological evaluation of organs as described in the test methods EU B. 26/OECD TG 408.
For the category member with the CAS number 126-19-2, the provided information is a study with 14 day oral administration of tomatidine to pregnant and non-pregnant female mice with examination of the body and liver weights of the dams and weight and mortality of foetuses. Hence this study does neither address relevant key parameters of a sub-chronic toxicity study like 90-day exposure duration of groups of 10 male and female rodents followed by an appropriate histopathological evaluation of organs as described in the test methods EU B. 26/OECD TG 408 nor does this information address relevant key parameter for a pre-natal developmental toxicity study like skeletal and visceral examinations of the foetuses as described in test methods EU B.31/OECD TG 414. Furthermore, this information does not address key parameters for a screening study for reproductive/ developmental screening like exposure of male and female rodents 2 weeks before mating, during mating, during delivery and until post-natal day 13 with examination of functional fertility, histopathological examination of reproductive organs of male and females parental animals as well as examination of the offspring for post-natal developmental toxicity as described in the test methods OECD TG 421 and 422.

Furthermore, ECHA notes that significant differences in the NOEL/NOAELs and LOEL/LOAELs for different category members for the endpoints repeated dose toxicity, reproductive and developmental toxicity are reported in the data matrix included in the category justification document. This observation appears to conflict with your conclusion that "*all the category member has comparable toxicological data although they may not have all toxicological data available*". These differences neither demonstrate a similarity in toxicological properties for these endpoints among the identified category members and nor support a possibility to predict properties of the registered substance from data on other members of the category.

For the reasons above, ECHA considers that you have not established a basis according to which the properties of the registered substance can be predicted from other members of this category. In the absence of a reliable and justified basis for reading across information from members of the category, these sources of information cannot be used as part of weight of evidence approaches intended to determine the properties of the registered substance.

Based on the above, the absence of a reliable and justified basis disqualifies the category approach as source of information for the respective weight of evidence approach intended to assume or conclude on the presence or absence of a certain dangerous property of the registered substance.

All the more, the non-fulfilment of the primary condition described above invalidates this adaptation for endpoints where a category approach was invoked as an adaptation as such and not as a mere source of information of a weight of evidence argumentation.

B. Endpoints specific considerations

3. Hydrolysis as a function of pH (Annex VIII, Section 9.2.2.1.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

"Hydrolysis as a function of pH" is a standard information requirement as laid down in Annex VIII, Section 9.2.2.1 of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You did not provide data generated by the corresponding test method referred to in Article 13(3) of the REACH Regulation (i.e. the EU C.7). Instead, you estimated hydrolysis half-life by calculation using "*AOP Program (v1.92) from EPI Suite estimation database*" and thus sought to adapt this information requirement by means of Annex XI Section 1.3. (Q)SAR models. You reported that "*The Hydrolysis rate constant of 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)cyclohexan-1-ol is estimated to be 0.0000000000288 cm3/molecule-sec. at half life of 4.456 hrs.The estimated half life of the substance indicates that the substance is moderately hydrolysable.*"

ECHA notes that you have not provided documentation of the applied method. Therefore, for the reasons described above in section A "Preliminary Considerations", the technical dossier does not contain evidence that the provided estimations by the model are scientifically valid and the substance would fall within the applicability domain of the model. ECHA further notes that according to the AOPWIN v1.92 user guide: "*The Atmospheric Oxidation Program for Microsoft Windows (AOPWIN) estimates the rate constant for the*

atmospheric, gas-phase reaction between photochemically produced hydroxyl radicals and organic chemicals. It also estimates the rate constant for the gas-phase reaction between ozone and olefinic/acetylenic compounds. The rate constants estimated by the program are then used to calculate atmospheric half-lives for organic compounds based upon average atmospheric concentrations of hydroxyl radicals and ozone." The method applied cannot be used to predict hydrolysis.

As a consequence, ECHA considers that you have not used reliable methods according to which the presence or absence of a certain property of the registered substance can be predicted. As a consequence, the adaptation of the information requirement of hydrolysis does not fulfil the general adaptation rules of Annex XI.

As explained above, the information provided 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.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Hydrolysis as a function of pH (test method: EU C.7/OECD TG 111).

4. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

An "*In vitro* gene mutation study in bacteria" is a standard information requirement as laid down in Annex VII, Section 8.4.1. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.3. "Qualitative or quantitative structure-activity relationship ((Q)SAR))". However, you did not provide a comprehensive description of the use of the (Q)SAR in form of a (Q)SAR Model Reporting Format (QMRF). You have provided information on analogue substances obtained from the OECD QSAR toolbox. More specifically, you attached a "*QSAR Toolbox prediction based on read-across: Prediction of Gene mutation for cyclohexanol, 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)-*" to the endpoint study record with the conclusion "*Toxicity of the target chemical (Negative) is predicted from category members using read-across based on 4 values (Negative x4) from 4 nearest neighbours compared by prediction descriptors.*"

For the reasons presented above in section A "Preliminary Considerations", ECHA considers that the dossier does not contain evidence that the provided information is scientifically valid. Nevertheless, ECHA has assessed your adaptation as a read-across approach in accordance with REACH Annex XI, Section 1.5. The conclusions of this assessment are reported below.
You provided the following category justification in the prediction report: "*The analogs are identified in a two stage approach, first stage where in the generic categorisation (broad screening of analogs) is done based upon the functional group and mechanistic approach. In second stage these set of substances are further screened based upon endpoint specific criteria. The final result is based upon at least 4 levels of screening. Further the closest five to seven analogs that are used for the purpose of prediction are based upon the Active*

Descriptor (Kow) having narrow interval (values range) of the domain – thus further justifies the selection of these analogs as valid for the purpose of read across."

You listed in the prediction report a series of required structural elements for the category members. However, ECHA observes that you did not clearly establish why structural similarity among the category members could constitute an element according to which properties of the registered substance could be predicted from the category members. Further, ECHA notes that no information on the allowed structural differences among the category members is included in the prediction report. According to information provided in the appendix 1 of the report, significant structural differences are observed among the analogue substances. The impact of these considerable differences in the chemical structures of the category members on the possibility to predict properties of the registered substance has not been accounted for.

The prediction report refers to data obtained from "*bacterial reverse mutation assay performed in Salmonella typhimurium*". Whilst information from such tests may constitute relevant information in the context of your QSAR prediction, in the absence of robust study summaries presenting the details of the study protocols, the type of strains used and demonstrating the validity of these assays, the validity of the read-across cannot be determined. In the absence of further information, your following conclusions cannot be verified: "*Thus the uncertainty in the prediction is minimal based upon available results. The results are further supported by other predictions and studies*" and "*The prediction is adequate for regulatory purpose as the prediction is in domain and is for requisite duration, species, and the information available is adequate for classification of the substance."*

For the reasons listed above, ECHA considers that the general rules for adaptation of Annex XI, Section 1.5. are not met and therefore your adaptation of the information requirement cannot be accepted. Consequently there is an information gap and it is necessary to provide information for this endpoint.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Bacterial reverse mutation test (test method: EU B.13/14. / OECD TG 471).

5. In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

An "*In vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study" is a standard information requirement as laid down in Annex VIII, Section 8.4.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.3. "Qualitative or quantitative structure-activity relationship ((Q)SAR))". However, you did not provide a comprehensive description of the use of the (Q)SAR in form of a (Q)SAR Model Reporting Format (QMRF). You have provided information on analogue substances obtained from the OECD QSAR toolbox. More specifically, you attached a "*QSAR Toolbox prediction based on read-across: Prediction of Chromosome aberration for cyclohexanol, 3-(5,5,6-*

trimethylbicyclo[2.2.1]hept-2-yl)-" to the endpoint study record with the following conclusion: "*Toxicity of the target chemical (Negative) is predicted from category members using read-across based on 5 values (Negative x5) from 5 nearest neighbours compared by prediction descriptors.*"

For the reasons presented above in the section A "Preliminary Considerations", ECHA considers that the dossier does not contain evidence that the provided information is scientifically valid. Nevertheless, ECHA has assessed your adaptation as a read-across approach in accordance with REACH Annex XI, Section 1.5. The conclusions of this assessment are reported below.

You provided a similar category justification as for the endpoint "gene mutation in bacteria". You listed in the prediction report a series of required structural elements for the category members. However, ECHA observes that you did not clearly establish why structural similarity among the category members could constitute an element according to which properties of the registered substance could be predicted from the category members. Further, ECHA notes that no information on the allowed structural differences among the category members is included in the prediction report. According to information provided in the appendix 1 of the report, significant structural differences are observed among the analogue substances. The impact of these considerable differences in the chemical structures of the category members on the possibility to predict properties of the registered substance has not been accounted for.

The prediction report refers to data obtained from "chromosomal aberration". Whilst information from such tests may constitute relevant information in the context of your QSAR prediction, in the absence of robust study summaries presenting the details of the study protocols, the type of strains used and demonstrating the validity of these assays, the validity of the prediction cannot be determined. In the absence of further information, your following conclusions cannot be verified: "*Thus the uncertainty in the prediction is minimal based upon available results. The results are further supported by other predictions and studies*" and "*The prediction is adequate for regulatory purpose as the prediction is in domain and is for requisite duration, species, and the information available is adequate for classification of the substance.*"
For the reasons listed above and in the section A "Preliminary Considerations", ECHA considers that the general rules for adaptation of Annex XI, Section 1.5. are not met and therefore your adaptation of the information requirement cannot be accepted. Consequently there is an information gap and it is necessary to provide information for this endpoint. Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* cytogenicity study in mammalian cells (test method: EU B.10./OECD TG 473) or *in vitro* mammalian cell micronucleus study (test method: OECD TG 487).

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

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

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. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.2.

In the endpoint summary for repeated dose toxicity in IUCLID you provided the following justification for the adaptation: "*The oral administration of 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)cyclohexan-1-ol to male Sprague-Dawley rat by gavage, at a dose level of 267 mg/kg bw/day, resulted in decreased body weight, decreased relative organ weight as well as decreased food consumption. Thus the LOEL for repeated dose toxicity study was considered to be 267 mg/kg bw/day, it is regarded that there is no repeated dose toxicity at concentrations lower than 267 mg/kg bw/day when administered orally.*"

The weight of evidence approach is based on:

1) A QSAR Toolbox prediction based on read-across;
2) A Category approach including
   - Category justification based upon the OECD QSAR toolbox 3.1 for the registered substance (CAS: 3407-42-9) and 3 analogue substances (CAS: 66068-84-6, 77-59-8, 126-19-2)
   - information on a 14 day subacute toxicity study in mice "*Antidepressant-Like Effects of Sarsasapogenin from Anemarrhena asphodeloides BUNGE (Liliaceae)*" (CAS: 126-19-2);
   - information on a 14 day subacute toxicity study in mice "*Effect of feeding solanidine, solasodine and tomatidine to non-pregnant and pregnant mice*" (CAS: 77-59-8).

ECHA has assessed the weight of each of these lines of evidence and the conclusions of this assessment are reported below.

1) QSAR Toolbox prediction based on read-across

You attached a "*QSAR Toolbox prediction based on read-across: Prediction of LOEL, NOEL, study NOEL for cyclohexanol, 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl*" to the endpoint study record with the following summary: "*Toxicity of the target chemical (267 mg/kg/day) is predicted from category members using read-across based on 5 values within the range 32.0 - 7.36E+03 mg/kg/day from 5 nearest neighbours compared by prediction descriptors.*"

As explained above in the section A "Preliminary Considerations", ECHA understands that this line of evidence is a read-across approach where analogue substances have been identified within the QSAR toolbox and a property of the registered substance is predicted from experimental data included in the QSAR toolbox training set. Therefore, ECHA has assessed this line of evidence as a read-across approach.
In the prediction report, you listed a series of required structural elements for the category members. However, ECHA observes that you did not clearly establish why structural similarity among the category members could constitute an element according to which properties of the registered substance could be predicted from the category members. Further, ECHA notes that no information on the allowed structural differences among the category members is included in the prediction report. According to information provided in the appendix 1 of the report, significant structural differences are observed among the analogue substances. The impact of these considerable differences in the chemical structures of the category members on the possibility to predict properties of the registered substance has not been accounted for.

The prediction report indicates that the prediction has been established for "*LOEL, NOEL, study NOEL*" on the basis of one experimental value (CAS number 5333-42-6) and 4 "*recalculated endpoint values*" (CAS numbers: 111-03-5, 511-09-1, 116355-83-0, 8001-79-4). No information on the scope of the investigations and the duration of the source study is provided from which the experimental value is derived. Hence, the relevance of this information to fulfil the information requirement for a 90-day repeated dose toxicity study cannot be determined. Furthermore, no details on the nature of the recalculated endpoint values mentioned in the prediction report have been provided.

Furthermore, the prediction report refers to data obtained from "study NOEL". However, it is not specified for which type of study the NOAEL is derived and for which exposure duration. Information from such tests might potentially constitute relevant information in the context of your QSAR prediction in case it would cover the correct study with the correct study duration (sub-chronic toxicity study according to test method EU B.26./OECD 408). However, in the absence of robust study summaries presenting the details of the study protocols and demonstrating the validity of these assays, the validity of the prediction cannot be determined.

For the reasons listed above and in the section A "Preliminary Considerations", ECHA is of the opinion that the NOEL predicted for the registered substance of 267 mg/kg bw/d is not reliable and that this information, as currently provided, does not constitute relevant information in the context of a weight of evidence approach intended to determine whether the registered substance has or has not a dangerous property for the endpoint under consideration.

2) Category approach

For the reasons described above in section A "Preliminary Considerations", ECHA considers that you have not established how data generated with substances included in this category can be used to predict the properties of the registered substance. Therefore, ECHA is of the opinion that this information, as currently provided, does not constitute relevant information in the context of a weight of evidence approach intended to determine whether the registered substance has or has not a dangerous property for the endpoint under consideration.

Thus, ECHA considers that this read-across approach does not allow a reliable prediction of the properties of the registered substance for the endpoint under consideration. As a consequence, ECHA is of the opinion that this information, as currently provided, cannot be regarded as relevant and reliable information in the context of this weight of evidence approach.

Taking into consideration the weight of each of the lines of evidence provided, ECHA considers that the overall weight of the evidence is not sufficient to assume that the registered substance has or has not a particular dangerous property in relation to the endpoint under consideration. Therefore, the general rule for adaptation of Annex XI, Section 1.2. is not met and your adaptation of the information requirement cannot be accepted. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015)

Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration. More specifically, even though the information indicates that human exposure to the registered substance by the inhalation route is likely, there is no concern for severe local effects following inhalation exposure. Furthermore, ECHA points out that no repeated dose toxicity study by the oral route is available. Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

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

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Repeated dose 90-day oral toxicity study (test method: EU B.26./OECD TG 408) in rats.

7. Screening study for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

"Screening for reproductive/developmental toxicity" (test method OECD TG 421 or 422) is a standard information requirement as laid down in Annex VIII, Section 8.7.1. of the REACH Regulation if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from *in vitro* methods that the substance may be a developmental toxicant. No such evidence is presented in the dossier. Therefore, adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.
You have not provided any study record of a screening for reproductive/developmental toxicity in the dossier that would meet the information requirement of Annex VIII, Section 8.7.1.

You have sought to adapt this information requirement according to Annex XI, Section 1.2. In the endpoint summary for toxicity to reproduction in IUCLID you have provided the following justification for the adaptation: "*The oral administration of 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)cyclohexan-1-ol to male/female wistar rat, at a dose level of 255 mg/kg bw/day. No effects observed on body weight and clinical signs at this dose concentration. Thus the NOAEL for reproductive toxicity study was considered to be 255 mg/kg bw/day.*"

The weight of evidence approach is based on:

1) A QSAR Toolbox prediction based on read-across

2) A Category approach including
   - Category justification based upon the OECD QSAR toolbox 3.1 for the registered substance (CAS: 3407-42-9) and 3 analogue substances (CAS: 66068-84-6, 77-59-8, 126-19-2)
   - Information on a 14 day subacute toxicity study in mice "*Effect of feeding solanidine, solasodine and tomatidine to non-pregnant and pregnant mice*" (CAS: 77-59-8)

ECHA has assessed the weight of each of these lines of evidence and the conclusions of this assessment are reported below.

1) *QSAR Toolbox prediction based on read-across*

You attached a "*QSAR Toolbox prediction based on read-across: Prediction of NOEL for cyclohexanol, 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)-*" to the endpoint study record with the following conclusion: "*Toxicity of the target chemical (254 mg/kg bw/day (actual dose received)) is predicted from category members using read-across based on 2 values within the range 209 - 300 mg/kg bw/day (actual dose received) from 2 nearest neighbours compared by prediction descriptors.*"
As explained above in the section A "Preliminary Considerations", ECHA understands that this line of evidence is a read-across approach where analogue substances have been identified within the QSAR toolbox and a property of the registered substance is predicted from experimental data included in the QSAR toolbox training set. Therefore, ECHA has assessed this line of evidence as a read-across approach.

You listed in the prediction report a series of required structural elements for the category members. However, ECHA observes that you did not clearly establish why structural similarity among the category members could constitute an element according to which properties of the registered substance could be predicted from the category members. Further, ECHA notes that no information on the allowed structural differences among the category members is included in the prediction report. According to information provided in the appendix 1 of the report, significant structural differences are observed among the analogue substances. The impact of these considerable differences in the chemical structures of the category members on the possibility to predict properties of the registered substance has not been accounted for.

The prediction report indicates that the prediction has been established for "*NOAEL, NOAEL Growth and Development, NOAEL Reproduction, NOAEL Toxicity,*" on the basis of two experimental values. However, no information on the scope of the investigations and the duration of the source studies is provided from which the experimental values are derived. Hence, the relevance of this information to fulfil the information requirement for a screening for reproductive/developmental toxicity cannot be determined.

The prediction report refers to data obtained from "*study NOEL*". However, it is not specified for which type of study the NOAEL is derived and for which exposure duration. Information from such tests might potentially constitute relevant information in the context of your QSAR prediction in case it would cover the correct study with the correct study duration (e.g., screening for reproductive/developmental toxicity: OECD TG 421/422). However, in the absence of robust study summaries presenting the details of the study protocols the validity of the prediction cannot be determined. Furthermore, you did not provide information on the uncertainty of your prediction.

For the reasons listed above and in the section A "Preliminary Considerations", ECHA is of the opinion that the NOEL predicted for the registered substance of 254 mg/kg bw/d is not reliable and that this information, as currently provided, does not constitute relevant information in the context of a weight of evidence approach intended to determine whether the registered substance has or has not a dangerous property for the endpoint under consideration.

2) *Category approach*

For the reasons described in section A "Preliminary Considerations" above, ECHA considers that you have not established how data generated with substances included in this category can be used to predict the properties of the registered substance. Therefore, ECHA is of the opinion that this information, as currently provided, does not constitute relevant information in the context of a weight of evidence approach intended to determine whether the registered substance has or has not a dangerous property for the endpoint under consideration.
Thus, ECHA considers that this read-across approach does not allow a reliable prediction of the properties of the registered substance for the endpoint under consideration. As a consequence, ECHA is of the opinion that this information, as currently provided, cannot be regarded as relevant and reliable information in the context of this weight of evidence approach.
Taking into consideration the weight of each of the lines of evidence provided, ECHA considers that the overall weight of the evidence is not sufficient to assume that the registered substance has or has not a particular dangerous property in relation to the endpoint under consideration. Therefore, the general rule for adaptation of Annex XI, Section 1.2 is not met and your adaptation of the information requirement cannot be accepted. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test methods OECD TG 421/422, the test is designed for use with rats. On the basis of this default assumption ECHA considers testing should be performed with rats.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Reproductive/developmental toxicity screening test (test method: OECD TG 421) *or* Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD TG 422) in rats by the oral route.

Notes for your considerations

For the selection of the appropriate test, please consult ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, section R.7.5 and 7.6 (version 4.1, October 2015).

8. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

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. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.2. In the endpoint summary for toxicity to reproduction in IUCLID you have provided the following justification for the adaptation: "*A teratogenicity study for 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)cyclohexan-1-ol in female Sprague Dawley rats by oral administration was carried out. The NOEL value for the 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)cyclohexan-1-ol was estimated to be 119.45 mg/kg bw/day.*"

The weight of evidence approach is based on:

1) A QSAR Toolbox prediction based on read-across

2) A Category approach including
   - Category justification based upon the OECD QSAR toolbox 3.1 for the registered substance (CAS: 3407-42-9) and 3 analogue substances (CAS: 66068-84-6, 77-59-8, 126-19-2)
   - Information on a 14 day subacute toxicity study in mice "*Effect of feeding solanidine, solasodine and tomatidine to non-pregnant and pregnant mice*" (CAS: 77-59-8)

ECHA has assessed the weight of each of these lines of evidence and the conclusions of this assessment are reported below.

1) QSAR Toolbox prediction based on read-across

You attached a "*QSAR Toolbox prediction based on read-across: Prediction of NOEL for cyclohexanol, 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)-*" to the endpoint study record with the following conclusion: "Toxicity of the target chemical (119 mg/kg/day) is predicted from category members using read-across based on 5 values within the range 25.0 - 1.20E+03 mg/kg/day from 5 nearest neighbours compared by prediction descriptors."

As explained above in the section A "Preliminary Considerations", ECHA understands that this line of evidence is a read-across approach where analogue substances have been identified within the QSAR toolbox and a property of the registered substance is predicted from experimental data included in the QSAR toolbox training set. Therefore, ECHA has assessed this line of evidence as a read-across approach.

In your prediction report, you listed a series of required structural elements for the category members. However, ECHA observes that you did not clearly establish why structural similarity among the category members could constitute an element according to which properties of the registered substance could be predicted from the category members. Further, ECHA notes that no information on the allowed structural differences among the category members is included in the prediction report. According to information provided in the appendix 1 of the report, significant structural differences are observed among the analogue substances. The impact of these considerable differences in the chemical structures of the category members on the possibility to predict properties of the registered substance has not been accounted for.

The prediction report indicates that the prediction has been established for "*NOEL,*" on the basis of three experimental values and two "*recalculated endpoint values*". No information on the scope of the investigations and the duration of the source studies conducted with the analogue substances is provided so their relevance for the information expected to be provided to fulfil the information requirement for pre-natal developmental toxicity study

cannot be determined. No details on the nature of the recalculations mentioned in the prediction report for the different source substances have been provided. Further, the information included in the report suggests that the data used to establish the prediction has been collected from studies conducted in different species, i.e. mouse, rabbits and rats. No information describing how the potential interspecies differences between the different species have been accounted for has been reported. Altogether, these observations do not support your conclusions that the "*uncertainty in the prediction is minimal based upon available results*" and that "*the prediction is adequate for regulatory purpose as the prediction is in domain and is for requisite duration, species, and the information available is adequate for classification of the substance*".

Furthermore, the prediction report refers to data obtained from "study NOEL". However, it is not specified for which type of study the NOAEL is derived and for which exposure duration. However, in the absence of robust study summaries presenting the details of the study protocols, the type of species used and demonstrating the validity of these assays, the validity of the prediction cannot be determined. Furthermore, you did not provide information on the uncertainty of your prediction.

For the reasons listed above and in the section A "Preliminary Considerations", ECHA is of the opinion that the NOEL predicted for the registered substance of 119 mg/kg bw/d is not reliable and that this information, as currently provided, does not constitute relevant information in the context of a weight of evidence approach intended to determine whether the registered substance has or has not a dangerous property for the endpoint under consideration

2) Category approach

For the reasons described above in section A "Preliminary Considerations", ECHA considers that you have not established how data generated with substances included in this category can be used to predict the properties of the registered substance. Therefore, ECHA is of the opinion that this information, as currently provided, does not constitute relevant information in the context of a weight of evidence approach intended to determine whether the registered substance has or has not a dangerous property for the endpoint under consideration.

Thus, ECHA considers that this read-across approach does not allow a reliable prediction of the properties of the registered substance for the endpoint under consideration. As a consequence, ECHA is of the opinion that this information, as currently provided, cannot be regarded as relevant and reliable information in the context of this weight of evidence approach.

Taking into consideration the weight of each of the lines of evidence provided, ECHA considers that the overall weight of the evidence is not sufficient to assume that the registered substance has or has not a particular dangerous property in relation to the endpoint under consideration. Therefore, the general rule for adaptation of Annex XI, Section 1.2 is not met and your adaptation of the information requirement cannot be accepted. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first species.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are 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 TG 414) in a first species (rats or rabbits) by the oral route.

9. Simulation testing on ultimate degradation in surface water (Annex IX, Section 9.2.1.2.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

"Simulation testing on ultimate degradation in water" is a standard information requirement as laid down in Annex IX, section 9.2.1.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

ECHA observes that in the respective section of the registration dossier you have concluded that the substance is not readily biodegradable.

You have not provided any study record of simulation testing on ultimate degradation in water in the dossier that would meet the information requirement of Annex IX, Section 9.2.1.2. Instead, you estimated biodegradation and degradation half-lifes in water and sediment by calculation using Level III Fugacity Model (within EPI Suite and PBT Profiler) and thus sought to adapt this information requirement by means of Annex XI Section 1.3. Qualitative or Quantitative structure-activity relationship ((Q)SAR) models. You describe the adaptation by: "*Based on the Level III Fugacity Model, the half life period of the 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)cyclohexan-1-ol was estimated. The half life period of 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)cyclohexan-1-ol in water is 38 days (912 hrs) therefore it is considered that the substance will qualify as not persistent as the half life does not exceed the threshold of 60 days. In sediment medium the half life is estimated to be 340 days (8160 hrs). Based on this value, it can be inferred that the substance is persistent in sediment medium. However, it can be observed that there is only 3 percent diffusion of the substance in the sediment medium and hence persistence in the sediment compartment is not likely to be critical.*"

ECHA notes that you have not provided documentation of the applied method. Therefore, for the reasons described above in section A "Preliminary Considerations", the technical dossier does not contain evidence that the provided estimations by the models are scientifically valid and the substance would fall within the applicability domain of the models.

Furthermore, ECHA observes that according to the Fugacity model guide in EPI Suite: "*fugacity models predict the partitioning of an organic compound in an evaluative environment. A Level III model assumes steady-state but not equilibrium conditions. The Level III model in EPI Suite predicts partitioning between air, soil, sediment and water using a combination of default parameters and various input parameters that may be user defined*

or estimated by other programs within EPI Suite." Thus, ECHA notes that standard fugacity models predict background steady state concentration that might arise from a particular emission or load to an environmental compartment. They require inputs of the transport characteristics between environmental compartments and the degradation rates for each compartment. Data from environmental simulation testing can be used as an input to the models, not as an output.
ECHA considers that you have not established a basis according to which the presence or absence of a certain dangerous property of the registered substance can be predicted using the provided methods. As a consequence, the adaptation of the information requirement of simulation testing on ultimate degradation in surface water does not fulfil the general adaptation rules of Annex XI.

As explained above and in the section A "Preliminary Considerations", the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 2.0, November 2014) Aerobic mineralisation in surface water – simulation biodegradation (test method EU C.25. / OECD TG 309) is the preferred test to cover the standard information requirement of Annex IX, Section 9.2.1.2.

One of the purposes of the simulation test is to provide the information that must be considered for assessing the P/vP properties of the registered substance in accordance with Annex XIII of REACH regulation to decide whether it is persistent in the environment. Annex XIII also indicates that "*the information used for the purposes of assessment of the PBT/vPvB properties shall be based on data obtained under relevant conditions*". The Guidance on information requirements and chemical safety assessment R.7b (version 2.0, November 2014) specifies that simulation tests "attempt to simulate degradation in a specific environment by use of indigenous biomass, media, relevant solids [...], and a typical temperature that represents the particular environment". The Guidance on information requirements and chemical safety assessment Chapter R.16 on Environmental Exposure Estimation, Table R.16-9 (version 2.1 October 2012) indicates 12°C (285K) as the average environmental temperature for the EU to be used in the chemical safety assessment. Performing the test at the temperature of 12°C is within the applicable test conditions of the Test Guideline OECD TG 309. Therefore, the test should be performed at the temperature of 12°C.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Aerobic mineralisation in surface water – simulation biodegradation test (test method: EU C.25./OECD TG 309).

10. Sediment simulation testing (Annex IX, Section 9.2.1.4.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

"Sediment simulation testing" is a standard information requirement as laid down in Annex IX, section 9.2.1.4. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

ECHA observes that in the respective sections of the registration dossier you have concluded that the substance is not readily biodegradable and has a logarithmic value of octanol-water partitioning coefficient of app. 5.5 which indicates potential for high adsorption of the substance to sediment.

You have not provided any study record of sediment simulation testing in the dossier that would meet the information requirement of Annex IX, Section 9.2.1.4. Instead, you estimated biodegradation and degradation half-lifes in water and sediment by calculation using Level III Fugacity Model (within EPI Suite and PBT Profiler) and thus sought to adapt this information requirement by means of Annex XI Section 1.3. Qualitative or Quantitative structure-activity relationship ((Q)SAR) models. You describe the adaptation by: "*Based on the Level III Fugacity Model, the half life period of the 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)cyclohexan-1-ol was estimated. The half life period of 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)cyclohexan-1-ol in water is 38 days (912 hrs) therefore it is considered that the substance will qualify as not persistent as the half life does not exceed the threshold of 60 days. In sediment medium the half life is estimated to be 340 days (8160 hrs). Based on this value, it can be inferred that the substance is persistent in sediment medium. However, it can be observed that there is only 3 percent diffusion of the substance in the sediment medium and hence persistence in the sediment compartment is not likely to be critical.*"

ECHA notes that you have not provided documentation of the applied method. Therefore, for the reasons described above in section A "Preliminary Considerations", the technical dossier does not contain evidence that the provided estimations by the models are scientifically valid and the substance would fall within the applicability domain of the models.

Furthermore, ECHA observes that according to the Fugacity model guide in EPI Suite: "*fugacity models predict the partitioning of an organic compound in an evaluative environment. A Level III model assumes steady-state but not equilibrium conditions. The Level III model in EPI Suite predicts partitioning between air, soil, sediment and water using a combination of default parameters and various input parameters that may be user defined or estimated by other programs within EPI Suite.*" Thus, ECHA notes that standard fugacity models predict background steady state concentration that might arise from a particular emission or load to an environmental compartment. They require inputs of the transport characteristics between environmental compartments and the degradation rates for each compartment. Data from environmental simulation testing can be used as an input to the models, not as an output.

ECHA considers that you have not established a basis according to which the presence or absence of a certain dangerous property of the registered substance can be predicted using the provided methods. As a consequence, the adaptation of the information requirement of simulation testing in sediment does not fulfil the general adaptation rules of Annex XI.

As explained above and in the section A "Preliminary Considerations", the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.
According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 2.0, November 2014) Aerobic and anaerobic transformation in aquatic sediment systems (test method EU C.24. / OECD TG 308) is the preferred test to cover the standard information requirement of Annex IX, Section 9.2.1.4.

One of the purposes of the simulation test is to provide the information that must be considered for assessing the P/vP properties of the registered substance in accordance with Annex XIII of REACH regulation to decide whether it is persistent in the environment. Annex XIII also indicates that "*the information used for the purposes of assessment of the PBT/vPvB properties shall be based on data obtained under relevant conditions*". The Guidance on information requirements and chemical safety assessment R.7b (version 2.0, November 2014) specifies that simulation tests "attempt to simulate degradation in a specific environment by use of indigenous biomass, media, relevant solids [...], and a typical temperature that represents the particular environment". The Guidance on information requirements and chemical safety assessment Chapter R.16 on Environmental Exposure Estimation, Table R.16-9 (version 2.1 October 2012) indicates 12°C (285K) as the average environmental temperature for the EU to be used in the chemical safety assessment. Performing the test at the temperature of 12°C is within the applicable test conditions of the Test Guideline OECD TG 308. Therefore, the test should be performed at the temperature of 12°C.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Aerobic and anaerobic transformation in aquatic sediment systems (test method: EU C.24./OECD TG 308).

11. Soil simulation testing (Annex IX, Section 9.2.1.3.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

"Soil simulation testing" is a standard information requirement as laid down in Annex IX, section 9.2.1.3. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

ECHA observes that in the respective sections of the registration dossier you have concluded that the substance is not readily biodegradable and has a logarithmic value of octanol-water partitioning coefficient of app. 5.5 which indicates potential for high adsorption of the substance to soil.

You have not provided any study record of soil simulation testing in the dossier that would meet the information requirement of Annex IX, Section 9.2.1.3. Instead, you estimated biodegradation and degradation half-life in soil by calculation using Level III Fugacity Model (within EPI Suite and PBT Profiler) and thus sought to adapt this information requirement by means of Annex XI Section 1.3. Qualitative or Quantitative structure-activity relationship ((Q)SAR) models. You describe the adaptation by: "*The PBT Profiler & EPI Suite has estimated that 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)cyclohexan-1-ol is expected to be found predominantly in soil and its persistence estimate is based on its availability in this medium. Its half-life in soil, 75 days (1800 hrs).,does not exceeds the threshold of 120 days as per Annex XIII of REACH.Therefore, 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)cyclohexan-1-ol is estimated to be not persistent in the soil environment.*"

ECHA notes that you have not provided documentation of the applied method. Therefore, for the reasons described above in section A "Preliminary Considerations", the technical dossier does not contain evidence that the provided estimations by the models are

scientifically valid and the substance would fall within the applicability domain of the models.
Furthermore, ECHA observes that according to the Fugacity model guide in EPI Suite: "*fugacity models predict the partitioning of an organic compound in an evaluative environment. A Level III model assumes steady-state but not equilibrium conditions. The Level III model in EPI Suite predicts partitioning between air, soil, sediment and water using a combination of default parameters and various input parameters that may be user defined or estimated by other programs within EPI Suite.*" Thus, ECHA notes that standard fugacity models predict background steady state concentration that might arise from a particular emission or load to an environmental compartment. They require inputs of the transport characteristics between environmental compartments and the degradation rates for each compartment. Data from environmental simulation testing can be used as an input to the models, not as an output.

ECHA considers that you have not established a basis according to which the presence or absence of a certain dangerous property of the registered substance can be predicted using the provided methods. As a consequence, the adaptation of the information requirement of simulation testing in sediment does not fulfil the general adaptation rules of Annex XI.

As explained above and in the section A "Preliminary Considerations", the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 2.0, November 2014) Aerobic and anaerobic transformation in soil (test method EU C.23. / OECD TG 307) is the preferred test to cover the standard information requirement of Annex IX, Section 9.2.1.3.

One of the purposes of the simulation test is to provide the information that must be considered for assessing the P/vP properties of the registered substance in accordance with Annex XIII of REACH regulation to decide whether it is persistent in the environment. Annex XIII also indicates that "*the information used for the purposes of assessment of the PBT/vPvB properties shall be based on data obtained under relevant conditions*". The Guidance on information requirements and chemical safety assessment R.7b (version 2.0, November 2014) specifies that simulation tests "attempt to simulate degradation in a specific environment by use of indigenous biomass, media, relevant solids [...], and a typical temperature that represents the particular environment". The Guidance on information requirements and chemical safety assessment Chapter R.16 on Environmental Exposure Estimation, Table R.16-9 (version 2.1 October 2012) indicates 12°C (285K) as the average environmental temperature for the EU to be used in the chemical safety assessment. Performing the test at the temperature of 12°C is within the applicable test conditions of the Test Guideline OECD TG 307. Therefore, the test should be performed at the temperature of 12°C.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Aerobic and anaerobic transformation in soil (test method: EU C.23./OECD TG 307).

Notes for your consideration

Before conducting the requested tests (under sections 9-11 above) you are advised to consult the ECHA Guidance on information requirements and chemical safety assessment, Chapter R7b, Sections R.7.9.4 and R.7.9.6 (version 2.0, November 2014) and Chapter R.11, Section R.11.4.1.1 (version 2.0, November 2014) on PBT assessment to determine the sequence in which the simulation tests are to be conducted and the necessity to conduct all of them. The order in which the simulation biodegradation tests are performed needs to take into account the intrinsic properties of the registered substance and the identified use and release patterns which could significantly influence the environmental fate of the registered substance.

In accordance with Annex I, Section 4, of the REACH Regulation you should revise the PBT assessment when results of the tests detailed above (under sections 9-11) are available. You are also advised to consult the ECHA Guidance on information requirements and chemical safety assessment (version 2.0, November 2014), Chapter R.11, Section R.11.4.1.1. and Figure R. 11-3 on PBT assessment for the integrated testing strategy for persistency assessment in particular taking into account the degradation products of the registered substance.

12. Identification of degradation products (Annex IX, Section 9.2.3.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

The identification of the degradation products is a standard information requirement according to column 1, Section 9.2.3. of Annex IX of the REACH Regulation. Column 2 of Section 9.2.3. of Annex IX further states that the information does not need to be provided if the substance is readily biodegradable.

ECHA observes that in the respective sections of the registration dossier you have concluded that the substance is not readily biodegradable. Furthermore, ECHA notes that there is no information on identity of degradation products provided in the registration dossier, as well as there is no valid adaptation provided by you.

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

Regarding appropriate and suitable test method, the methods will have to be substance specific. When analytically possible, identification, stability, behaviour, molar quantity of metabolites relative to the parent compound should be evaluated. In addition degradation half-life, log Kow and potential toxicity of the metabolite may be investigated.

Therefore, pursuant to Article 41(1)(a) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision:

Identification of the degradation products using an appropriate and suitable test method, as explained above in this section.

Notes for your consideration

Before providing the above information you are advised to consult the ECHA *Guidance on information requirements and chemical safety assessment* (version 2.0, November 2014), Chapter R.7.9., Sections R.7.9.2.3 and R.7.9.4. These guidance documents explain that the data on degradation products is only required if information on the degradation products following primary degradation is required in order to complete the chemical safety assessment. Section R.7.9.4. further states that when substance is not fully degraded or mineralised, degradation products may be determined by chemical analysis.

13. Bioaccumulation in aquatic species (Annex IX, Section 9.3.2.).

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

"Bioaccumulation in aquatic species, preferably fish" is a standard information requirement as laid down in Annex IX, Section 9.3.2.of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.2 weight of evidence. You provided the following justification for the adaptation in the endpoint summary for bioaccumulation, aquatic /sediment in IUCLID section 5.3.1: "*Based on studies evaluated for target substance 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)cyclohexan-1-ol for bioaccumulation from reliable sources having Klimisch rating 2 and 4, considering the weight of evidence approach*", and further elaborated that "*Based on the above BCF values summarized for the target substance 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)cyclohexan-1-ol, the endpoint value of bioaccumulation was found to vary between BCF =1985 to 6420 L/kg in fish based on the values for target. The values are greater than the threshold 2000. Thus it is concluded that the test substance 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)cyclohexan-1-ol is expected to bio-accumulate in the food chain because it does exceed the BCF criteria of 2000.*"

The weight of evidence approach is based on information from one experimental study and results of estimation of bioconcentration factor (BCF) with three (Q)SAR models. ECHA has assessed the weight of each of these lines of evidence and the conclusions of this assessment are reported below.

As the first line of evidence, you have provided experimental study results originating from an authoritative Japanese database J-CHECK for CAS 3407-42-9, i.e. the same as the registered substance. A number of BCF values for 3 components (called A, B and C) are reported. The following conclusion is provided for that study in the dossier: "*The test substance 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)cyclohexan-1-ol BCF value was found to be 2180 L/kg. The value is greater than threshold 2000.Hence it is concluded that the test substance is bioaccumulative in nature.*" ECHA observes that a study reliability score of 4 has been assigned by you. Furthermore, ECHA notes there is no sufficient information on the test (e.g. about relevance of tested substance with 3 components to the registered substance, about the study design and test conditions) and thus the adequacy and relevance of the information reported cannot be evaluated by ECHA, and concequently cannot be accepted.

The other three lines of evidence include BCF estimations using (Q)SAR models:

1. PBT profiler, Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency; version 1.301. The reported BCF is 2000.
2. BCFBAF Program (v3.00), Estimation Programs Interface Suite™ United States Environmental Protection Agency, Washington, DC, USA. version 4.1. The reported BCF is 1985 L/kg.
3. Calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994-2014 ACD/Labs. The reported BCF is 6420.

ECHA notes that you have not provided documentation of the applied methods. Therefore, for the reasons described above in section A "Preliminary Considerations", the technical dossier does not contain evidence that the provided estimations by the models are scientifically valid and the substance would fall within the applicability domain of the models. Accordingly, ECHA considers that you have not established a basis according to which the presence or absence of a certain dangerous property of the registered substance can be predicted using the provided methods.
As a consequence, ECHA is of the opinion that this information generated by the use of (Q)SAR models, as currently provided, cannot be regarded as relevant and reliable information in the context of the weight of evidence approach.

Taking into consideration the weight of each of the lines of evidence provided, ECHA considers that the overall weight of the evidence is not sufficient to assume that the registered substance has or has not a particular dangerous property in relation to the endpoint under consideration. Therefore, the general rule for adaptation of Annex XI, Section 1.2 is not met and your adaptation of the information requirement cannot be accepted.
As explained above, the information provided 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.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7c* (version 2.0, November 2014) bioaccumulation in fish: aqueous and dietary exposure (test method EU C.13. / OECD TG 305) is the preferred test to cover the standard information requirement of Annex IX, Section 9.3.2. It is noted in the ECHA *Guidance on information requirements and chemical safety assessment* (version 2.0, November 2014), Chapter R.11. that "*OECD TG 305-I: Aqueous Exposure Bioconcentration Fish Test (OECD, 2012) or an equivalent test protocol in fish is preferred for producing experimental bioconcentration data. Valid results from this test can be used directly for comparison with the B and vB criteria*". Based on the information provided in the registration dossier, ECHA considers that an aqueous exposure bioconcentration fish test is feasible for the registered substance.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Bioaccumulation in fish: aqueous exposure bioconcentration fish test (test method: OECD TG 305-I). Alternatively, if the study is deemed to be relevant and reliable, provide in the dossier a robust study summary for the study reported in the dossier for experimental study on bioaccumulation: aquatic/sediment.

Notes for your consideration

Due to the relatively low solubility of the substance in water and high potential for adsorption you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA *Guidance on*

information requirements and chemical safety assessment (version 2.0, November 2014), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity test(s) and for calculation and expression of the result of the test(s).

Before conducting the above test you are advised to consult the ECHA *Guidance on information requirements and chemical safety assessment* (version 2.0, November 2014), Chapter R.11.4. and Figure R.11-4 on the PBT assessment for further information on the integrated testing strategy for the bioaccumulation assessment of the registered substance. You should revise the PBT assessment when information on bioaccumulation is available.

14. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

"Long-term toxicity testing on fish" is a standard information requirement as laid down in Annex IX, Section 9.1.6. of the REACH Regulation. Adequate information on Fish, early-life stage (FELS) toxicity test (Annex IX, 9.1.6.1.), or Fish, short-term toxicity test on embryo and sac-fry stages (Annex IX, 9.1.6.2.), or Fish, juvenile growth test (Annex IX, 9.1.6.3.) needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement. The justification of the adaptation given by you is: *"According to annex IX of column I , Long-term toxicity testing on fish need not to be conducted as it is already provided as part of Annex VIII requirements.Therefore this study was considered to be waived."*

ECHA notes that you did not provide in the dossier data generated by the corresponding long-term fish toxicity test method referred to in Article 13(3) of the REACH Regulation. Instead, you referred to the results provided as a part of Annex VIII information requirements to fulfil the information requirement on long-term toxicity to fish. Therefore, ECHA considers that you sought to adapt the information requirement in accordance with Annex XI, Section 1.1.2.
In accordance with Annex XI, Section 1.1.2., data generated by another method than the corresponding test methods referred to in Article 13(3) of the REACH Regulation shall be considered equivalent if the following conditions are met:

(1) adequacy for the purpose of classification and labelling and/or risk assessment;
(2) adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
(3) exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and
(4) adequate and reliable documentation of the study is provided.

Regarding the study records for aquatic toxicity in Annex VIII, you have provided three endpoint study records for short-term toxicity to fish as a weight of evidence approach. The study records were reported to provide results on the toxicity to fish in 96-h exposure and the parameter investigated was mortality.

With regard to the exposure duration, ECHA notes that aquatic toxicity studies can only be regarded as long-term when sensitive life stages (e.g. juveniles, eggs, larvae) are exposed for a duration dependent on species and test guideline (ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 2.0, November 2014). For example, according to OECD test guideline 210, the test duration is 60-d post-hatch for rainbow trout or approximately 30 days for warm water fish. Observational endpoints include hatching success, survival and growth.

In none of the study records provided as a part of Annex VIII information requirements for fish, the exposure duration is comparable to or longer than the corresponding test methods referred to in Article 13(3). Furthermore, the life stage tested and the parameters investigated in the tests do not adequately and reliably cover the key parameters in the corresponding test methods of long-term toxicity to fish referred to in Article 13(3).

Thus, the endpoint study records provided as a part of Annex VIII requirements for fish cannot be considered as long term tests.

Therefore, your adaptation of the information requirement cannot be accepted.

As explained above, the information provided 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. Furthermore, ECHA notes that based on the data provided in the dossier solubility of the substance in water is app. 3 mg/l, which is below the limit concentration of 10 mg/l given in the respective long-term fish toxicity guidelines (e.g. OECD 210). All the short-term effect concentrations (i.e. LC50s) reported for fish in the dossier are above water solubility of the substance. Thus, ECHA considers that for such case, i.e. when the water solubility of the substance is below 10 mg/l and reported LC50s are above water solubility limit, the short-term toxicity testing with fish would not be relevant and conclusive. Therefore, ECHA considers that it is necessary to provide information on long-term toxicity with fish.

Regarding the long-term toxicity testing on fish pursuant to Annex IX, section 9.1.6.1, ECHA considers that the FELS toxicity test according to OECD TG 210 is the most sensitive of the standard fish tests available as it covers several life stages of the fish from the newly fertilised egg, through hatch to early stages of growth and should therefore be used (see ECHA Guidance on information requirements and chemical safety assessment (version 2.0, November 2014), Chapter R7b, Figure R.7.8-4). The test method OECD TG 210 is also the only suitable test currently available for examining the potential toxic effects of bioaccumulation (ECHA Guidance Chapter R7b, version 2.0, November 2014). For these reasons, ECHA considers the FELS toxicity test using the test method OECD TG 210 as most appropriate and suitable.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Fish, early-life stage (FELS) toxicity test (test method: OECD TG 210).

15. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

"Long-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex IX, Section 9.1.5. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement. The justification of the adaptation given by you is: *"According to column I of annex IX ; Long-term toxicity testing on invertebrate (species : Daphnia magna) need not to be conducted as it is already provided as a part of Annex VII requirements.Therefore this end point was considered for waiver."*

ECHA notes that you did not provide in the dossier data generated by the corresponding long-term aquatic invertebrates toxicity test method referred to in Article 13(3) of the REACH Regulation. Instead, you referred to the results provided as a part of Annex VII information requirements to fulfil the information requirement on long-term toxicity to aquatic invertebrates. Therefore, ECHA considers that you sought to adapt the information requirement in accordance with Annex XI, Section 1.1.2.

In accordance with Annex XI, Section 1.1.2., data generated by another method than the corresponding test methods referred to in Article 13(3) of the REACH Regulation shall be considered equivalent if the following conditions are met:

(1) adequacy for the purpose of classification and labelling and/or risk assessment;
(2) adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
(3) exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and
(4) adequate and reliable documentation of the study is provided.

Regarding the study records for aquatic toxicity in Annex VII, you have provided two endpoint study records for short-term toxicity to aquatic invertebrates as a Weight of evidence approach. Both of them were reported to provide results on the toxicity to *Daphnia magna* in 48-h exposure. ECHA notes that according to ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 2.0, November 2014), aquatic toxicity studies can only be regarded as long-term when the test organisms of *Daphnia sp.* are exposed to the substance for 21 day. At least 3 broods should be produced during the exposure period and for daphnids, 21 days is sufficient for maturation and the production of 3 broods.

Furthermore, the parameter investigated in the tests provided as a part of Annex VII information requirements was mortality. ECHA notes that according to ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 2.0, November 2014), observational endpoints in long-term tests include time to first brood, number of offspring produced per female (reproduction), growth, and survival (lethality).

Thus, the endpoint study records provided as a part of Annex VII requirements for aquatic invertebrates cannot be considered as long term tests. In none of the study records provided, the exposure duration is comparable to or longer than the corresponding test methods referred to in Article 13(3) and the endpoints measured do not cover adequately and reliably the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3).

Thus, the endpoint study records provided as a part of Annex VII requirements for aquatic invertebrates cannot be considered as long term tests.

Therefore, your adaptation of the information requirement cannot be accepted.

As explained above, the information provided 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.

Furthermore, ECHA notes that based on the data provided in the dossier solubility of the substance in water is app. 3 mg/l, which is below the limit concentration of 10 mg/l given in the respective long-term toxicity to aquatic invertebrates guideline (OECD 211). Irrespective of scientific validity of the information provided in the dossier in relation to short-term toxicity to aquatic invertebrates, ECHA notes that all the short-term effect concentrations (i.e. LC/EC50s) reported for aquatic invertebrates in the dossier are above water solubility of the substance. Thus, ECHA considers that for such case, i.e. when the water solubility of the substance is below 10 mg/l and reported LC/EC50s are above water solubility limit, the short-term toxicity testing with aquatic invertebrates would not be relevant and conclusive. Therefore, ECHA considers that it is necessary to provide information on long-term toxicity with aquatic invertebrates.

According to ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 2.0, November 2014) *Daphnia magna* reproduction test (test method EU C.20. / OECD TG 211) is the preferred test to cover the standard information requirement of Annex IX, Section 9.1.5.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *Daphnia magna* reproduction test (test method: EU C.20./OECD TG 211).

16. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

"Growth inhibition study aquatic plants" is a standard information requirement as laid down in Annex VII, Section 9.1.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.2 Weight of evidence. You provided the following justification for the adaptation in the endpoint summary for toxicity to aquatic algae and cyanobacteria in IUCLID section 6.1.5: *"Based on weight of evidence approach, the number of studies were reviewed for target substance 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)cyclohexan-1-ol for Short-term toxicity to aquatic algae from reliable sources having Klimisch rating 2 considering weight of evidence approach"* and further elaborated that *"Based on results summarized in above table for the target substance 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)cyclohexan-1-ol the effective concentration (EC50) ranges from* [redacted] *mg/L. Thus considering the EC50 value from CLP criteria for aquatic classification of the substance it is concluded that test substance would exhibit toxicity to aquatic algae and cyanobacteria in Aquatic chronic 3*

classification category. Also the target test substance is not readily biodegradable and BCF>500 fulfilling the criteria of aquatic classification in aquatic chronic 3 category."

The weight of evidence approach is based on information from two lines of evidence:

1) A QSAR Toolbox prediction based on read-across;
2) A Category approach including
   - Category justification based upon the OECD QSAR toolbox 3.1 for the registered substance (CAS: 3407-42-9) and 1 analogue substance (CAS: 80-04-6)
   - Information on a 72 h algae toxicity study according to OECD Guideline 201 with analogue substance (CAS: 80-04-6).

ECHA has assessed the weight of each of these lines of evidence and the conclusions of this assessment are reported below.

1) QSAR Toolbox prediction based on read-across

You attached a "*Prediction of EC50 for cyclohexanol, 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)-*" to the endpoint study record with the following conclusion: "*Toxicity of the target chemical (11.8 mg/L) is predicted from category members using read-across based on 7 values within the range* [redacted] *mg/L from 5 nearest neighbours compared by prediction descriptors.*"

As explained above in section A "Preliminary Considerations", ECHA understands that this line of evidence is a read-across approach where analogue substances have been identified within the QSAR toolbox and a property of the registered substance is predicted from experimental data included in the QSAR toolbox training set. Therefore, ECHA has assessed this line of evidence as a read-across approach.

You listed in the prediction report a series of required structural elements for the category members. However, ECHA observes that you did not clearly establish why structural similarity among the category members could constitute an element according to which properties of the registered substance could be predicted from the category members. Further, ECHA notes that no information on the allowed structural differences among the category members is included in the prediction report. According to information provided in the appendix 1 of the report, significant structural differences are observed among the analogue substances. The impact of these considerable differences in the chemical structures of the category members on the possibility to predict properties of the registered substance has not been accounted for (e.g. only target substance and one of category members are predicted to have strong estrogen receptor binding potential, the toxicities of category members differ within the range of [redacted] mg/L).

The prediction report indicates that the "*the result is based upon 5 nearest data points and all the data points are experimental value and thus the uncertainty is minimum*". However, no information on the scope of the investigations and the duration of the source studies is provided from which the experimental values are derived. Hence, the relevance of this information to fulfil the information requirement for toxicity to aquatic algae and cyanobacteria cannot be determined. In the absence of robust study summaries presenting the details of the study protocols the validity of the prediction cannot be determined.

Based on the above and on section A "Preliminary Considerations", ECHA is of the opinion that the EC50 predicted for the registered substance of 11.8 mg/l is not reliable and that this information, as currently provided, does not constitute relevant information in the

context of a weight of evidence approach intended to determine whether the registered substance has or has not a dangerous property for the endpoint under consideration.

2) Category approach

For the reasons described above in section A "Preliminary Considerations", ECHA considers that you have not established how data generated with substances included in this category can be used to predict the properties of the registered substance. Therefore, ECHA is of the opinion that this information, as currently provided, does not constitute relevant information in the context of a weight of evidence approach intended to determine whether the registered substance has or has not a dangerous property for the endpoint under consideration.

Taking into consideration the weight of each of the lines of evidence provided, ECHA considers that the overall weight of the evidence is not sufficient to assume that the registered substance has or has not a particular dangerous property in relation to the endpoint under consideration. Therefore, the general rule for adaptation of Annex XI, Section 1.2 is not met and your adaptation of the information requirement cannot be accepted.

As explained above and in section A "Preliminary Considerations", the information provided 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.

According to ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 2.0, November 2014) Algae growth inhibition test (test method EU C.3. / OECD TG 201) is the preferred test to cover the standard information requirement of Annex VII, Section 9.1.2.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Algae growth inhibition test, EU C.3./OECD TG 201).

Notes for your consideration

Due to the relatively low solubility of the substance in water and high potential for adsorption you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA Guidance on information requirements and chemical safety assessment (version 2.0, November 2014), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested (under sections 14-16 above) ecotoxicity tests and for calculation and expression of the result of the tests.

Appendix 2: Procedural history

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 decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 27 November 2015.

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

ECHA did not receive any comments by the end of the commenting period.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation:

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) for amendment.

ECHA received proposals for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendments.

ECHA referred the draft decision to the Member State Committee.

Your comments on the proposed amendments were taken into account by the Member State Committee.

In addition, you provided comments on the draft decision. These comments were not taken into account by the Member State Committee as they were considered to be outside of the scope of Article 51(5).

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-48 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

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

2. Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In carrying out the test(s) required by the present decision it is important to ensure that the particular sample of substance tested 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. If the registration of the substance covers different grades, the sample used for the new test(s) must be suitable to assess these. Furthermore, 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.