ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 28 April 2017

Addressee: [redacted]

Decision number: CCH-D-2114359360-53-01/F
Substance name: Ionone, methyl-
EC number: 215-635-0
CAS number: 1335-46-2
Registration number: [redacted]
Submission number: [redacted]
Submission date: 23.10.2015
Registered tonnage band: 1000+T

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 of the substance (Annex VI, Section 2.1.) of the registered substance;**

2. **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;**

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

4. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a second species (rabbit or rat), oral route with the registered substance;**

5. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce some toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation.**

6. **Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: Fish, acute toxicity test, OECD TG 203) with the registered substance;**

7. **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;**

8. 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);

You are required to submit the requested information in an updated registration dossier by **5 May 2021** except for the information requested under point 2 for a sub-chronic toxicity study (90-day) which shall be submitted in an updated registration dossier by **6 May 2019**. You may only commence the extended one-generation reproductive toxicity study as requested under point 5 after **5 August 2019**, unless an indication to the contrary is communicated to you by ECHA before that date. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

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. 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/regulations/appeals.

Authorised[1] by Kevin Pollard, Head of Unit, Evaluation E1

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix 1: Reasons

IDENTIFICATION OF THE SUBSTANCE

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.

The name and other identifiers are used to identify the substance in an unambiguous manner and are therefore essential parts of substance identification and the corner stone of all the REACH obligations.

ECHA notes that you identified the registered substance as a multi-constituent substance. A multi-constituent substance should be named as a reaction mass of the main constituents of the substance, as indicated in chapter 4.2. of the 'Guidance for identification and naming of substances under REACH and CLP', referred thereafter as "the Guidance".

ECHA observes that you did not provide appropriate information on the naming of the substance as required under Annex VI Section 2.1 of the REACH Regulation.

ECHA notes that you identified the registered substance as a multi constituent substance with the chemical name 'Ionone, methyl', EC number 215-635-0, and CAS number 1335-46-2. These chemical identifiers are generic and refer to different isomers of '[redacted]'. Furthermore, for the Reference Substance in section 1.1, you indicated a structural formula, a SMILES notation, and a InChI code that refer to one specific isomer.

According to section 1.2 and 1.4 of your IUCLID dossier, the registered substance is a specific multi-constituent substance consisting of two main constituents: [redacted] % of [redacted], EC [redacted], CAS [redacted] and [redacted] %.

According to the Guidance, the generic format to name a multi-constituent substance should be: "Reaction mass of [names of the main constituents]". It is recommended that the names of the constituents are presented in alphabetical order and they are separated by the conjunction "and". Only main constituents typically ≥ 10% contribute to the name. In principle, the names should be given in English language according to the IUPAC nomenclature rules. Other internationally accepted designations can be given in addition.

ECHA therefore concludes that the chemical name and the other identifiers in section 1.1 are not consistent with the information provided in section 1.2 and 1.4.

In line with the observation above you are accordingly requested to revise the chemical name assigned to the registered substance. You shall ensure that the chemical name is representative of the specific substance which is the subject of this registration. Based on the information currently contained in the dossier (section 1.2 and 1.4), ECHA invites you to consider if a chemical name such as "[redacted]" would be appropriate for the identification of the registered substance.

You shall also delete the CAS information currently assigned to the substance and provide instead any available CAS information specifically corresponding to the substance.

As for the reporting of the information in IUCLID, you shall include the revised information in the reference substance assigned in IUCLID section 1.1.

Further technical details on how to report the identifiers of multi-constituent substances in IUCLID are available in paragraphs 2.1 of the Data Submission Manual 18 on the ECHA website.

You shall note that the registration is currently linked to the EC number 215-635-0 which refers to the chemical name "Ionone, methyl-". You can however not remove or modify at this stage the EC number for technical reasons, because the registration is linked to that number in REACH-IT. To ensure unambiguous identification of the registered substance and in case the name provided in the registration dossier is not appropriate, you shall indicate, in the "Remarks" field of the reference substance in IUCLID section 1.1, the following: "The EC number 215-635-0 currently assigned does not specifically correspond to the registered substance. This identifier cannot be modified or deleted at this stage in the present registration update for technical reasons". You shall also specify, in the same "Remarks" field, any available and appropriate EC or List number for the substance.

You should note that ECHA has established a process, subject to certain conditions, enabling registrants to adapt the EC identifier of an existing registration, while maintaining the regulatory rights already conferred to the substance concerned.

Should the information submitted by the Registrant as a result of the present decision enable ECHA to identify the substance unambiguously, the process of adapting the identifier will be considered relevant. In that case, ECHA will inform you in due time as to when the identifier adaptation process shall be initiated.

In any case, you should note that the application of the process of adapting the identifier does not affect his obligation to fulfil the requirements specified in this decision.

PROPERTIES OF THE SUBSTANCE

0. Grouping of substances and read-across and weight of evidence approach

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally related substances (grouping of substances and read-across), "provided that the conditions set out in Annex XI are met".

In the registration, you have adapted the standard information requirements for

- Sub-chronic toxicity study (90-day)(Annex IX, Section 8.6.2.);
- Pre-natal developmental toxicity study (Annex IX and X, Section 8.7.2.);
- Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

by applying a read-across adaptation following REACH Annex XI, Section 1.5.

Annex XI, Section 1.5. requires a structural similarity among the substances within a group or category such that relevant properties of a substance within the group can be predicted from the data on reference substance(s) within the group by interpolation. The following analysis presents your justification for the proposed grouping approach and read-across hypothesis, together with ECHA's analysis concerning the justification in both a generic and an property-specific context.

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you state that you "*intended to use weight of evidence (WoE) approach to provide additional support to the submitted earlier 'The read-across assessment for ionone category'*".

An adaptation pursuant to Annex XI, Section 1.2. requires 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 with respect to the information requirement in question including an adequate and reliable documentation. You apply this approach for Annex IX, Section 8.6.2. (sub-chronic toxicity study), Annexes IX and X, Section 8.7.2. (pre-natal developmental toxicity study in a first and second species), and Annex X, Section 8.7.3. (extended one-generation reproductive toxicity study).

To appropriately address the information requirement in question, your weight of evidence adaptation needs to address the properties of the registered substance by covering the relevant elements investigated in a sub-chronic toxicity study (EU B.26/OECD TG 408), pre-natal developmental toxicity studies in two species (EU B.31/OECD TG 414) and an extended one-generation reproductive toxicity study (EU B.56./OECD TG 443) as requested in this decision. ECHA considers that the extended one-generation reproductive toxicity study provides relevant information on two aspects, namely on sexual function and fertility in P1 and F1 generations (further referred to as "sexual function and fertility") and on developmental toxicity observable peri- and postnatally in F1 generation (further referred to as "post-natal developmental toxicity").

Furthermore, the relative values/weights of different pieces of the provided information needs to be assessed as indicated in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.4.4. In particular relevance, reliability and adequacy for the purpose as well as consistency of results/data need to be considered.

0.1 Description of the grouping and read-across and weight of evidence approach proposed by the Registrant

Read-across

You have provided the following arguments to justify the read-across approach:

"*Ionones are chemically related substances consisting of a cyclohexene ring and butanone side chains. Thereby, the position of the hexene ring double bond as well as methyl side chains at the butanone or hexene ring determine the identity of the molecule. Many ionones exist as positional or stereo-isomers, such as α- and β-ionone or β-ionone and trans-β-ionone, respectively.*

The registered substance methyl ionone consists of ca. [redacted]

[redacted]

About 0.5% are impurities (reaction mass of 3,6,10-trimethylundeca-3,5,9-trien-2-one (methylpseudoionone) and 7,11-dimethyldodeca-4,6,10-trien-3-one (pseudo-methylionone)). Since these impurities themselves are ionones and therefore can be placed into the same category of substances as the main component, their toxicological impact can be neglected.

In order to obtain a valid read-across for methyl ionone, data from the four mentioned principal components of methyl ionone were used as well as data from related ionones"

ECHA considers this as the hypothesis under which you make predictions for the properties listed above.

Weight of Evidence

You have not provided an explanation or justification on how the sources of information/studies, which you have provided enable an assumption or conclusion that the registered substance does or does not have a dangerous property with respect to to sub-chronic toxicity, pre-natal developmental toxicity in two species and sexual function and fertility as well as peri- natal post natal developmental toxicity. ECHA understands that you conclude that the registered substance does not have a dangerous (hazardous) property with respect to those endpoints.

0.2 Support of the grouping and read-across and weight of evidence approach

Read-across

You have provided a read-across justification as a separate attachment Section 13 of IUCLID in the registration. In summary you provide the following arguments to support the read-across approach:

- In support for the grouping you state that ionones are chemically related substances consisting of a cyclohexene ring and butanone side chains. The position of the hexene ring double bond as well as the methyl side chains at the butanone or hexene ring determine the identity of the molecule. You also state that ionones share, with some exceptions, the same classification, and that physico-chemical data further support the grouping of the substances into a category.

- In support for the RA approach you state that the ionones most likely behave similarily with regard to absorption, distribution and metabolization. It has furthermore been suggested that the alfa-ionones share a common metabolic pathway and that beta-ionones share one common metabolic pathway.

- The data matrix you provide over toxicological properties for ionones contain information primarily on acute toxicity, genetic toxicity and skin irritation/sensitisation for your registered substance. Furthermore it contains information on acute, sub-acute and sub-chronic toxicity, toxicity to reproduction and skin and eye irritation and skin sensitisation for [redacted] **[1]** (CAS no [redacted]). For [redacted] **[2]** (CAS no [redacted]) only information on genetic toxicity is given. For [redacted] **[3]** (CAS no [redacted] information on acute toxicity, skin irritation and skin sensitization is given. For [redacted] **[4]** (CAS no [redacted] no toxicological information is given.

- For ionones that are not constituents of the registered substance data on acute and subchronic toxicity are given for pseudoionone, ionone, beta-ionone and trans-beta-ionone. There is one chronic toxicity study reported for ionone and one carcinogenicity study for trans-beta-ionone. Furthermore data on genetic toxicity is given for these four substances. There are also studies reported for skin-and eye irritation as well as for skin sensitization.

  With the exception of for four studies on reproductive toxicity (two pre-natal development toxicity studies with trans-beta-ionone ([redacted] 2004 and 2014), a one-generation study with pseudoionone ([redacted] /Beekhuizen 2003, and a two-generation study with ionone (Sporn et al 1963)) these studies are not part of the technical dossier but only included in the read-across justification to support the read-across hypothesis.

You conclude, based on the toxicological studies reported in the data matrix, that the toxicological potential in acute, subchronic, genetic and developmental toxicity is highly similar.

Weight of evidence

In your comment(s) to the draft decision according to Article 50(1) of the REACH Regulation you indicate that "*Several lines of evidence are used to support the case for the sufficient similarity of ionones*":

1. (Q)SAR predictions considering a number of models:
   1. OSIRIS DataWarrior (version 4.2.2) to identify structural similarity of molecules;
   2. Meteor Nexus: 2.1.0, Nexus: 2.0.0 to identify common metabolic pathways;
   3. Derek Nexus: 5.0.1, Nexus: 2.1.0 to identify similar structural alerts;
   4. OECD QSAR Toolbox (version 3.3.5.17) to identify structural alerts using profilers relevant to human health hazards;

2. Published opinions of regulatory and authoritative bodies including the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1999), EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (EFSA, 2014), and RIFM (Research Institute for Fragrance Materials) Expert Panel (2007).

You provided information related to structural similarity of ionones using the OSIRIS DataWarrior 4.2.2. Based on their chemical structures, ionones were divided into two groups:

- [redacted] (CAS No. [redacted]; constituent A), [redacted] (CAS No. [redacted]; constituent B) and [redacted] (CAS No. [redacted]).
- [redacted] (CAS No. [redacted]; constituent C), [redacted]).

The [redacted] and [redacted] were compared pairwise with each other, respectively. The similarity analysis resulted in over 0.95 similarity scores (1 is the maximum possible score) with each pair of [redacted], indicating high structural similarity between them. The same was true for [redacted]: their similarity scores were over 0.97. You concluded that [redacted] chemical structures are very similar to each other, and that [redacted] structures are very similar to each other.

As a second line of support for the grouping of ionones you refer to two international risk assessment organisations, JECFA and EFSA, who both grouped ionones as alpha- and beta ionones for risk assessment purposes.

You also provided information showing that constituents of methyl ionone (your registered substance) triggered the same alerts when evaluated for structural alerts using two different programs (Derek and OECD QSAR Toolbox). Moreover, the same structural alerts were noted for [redacted] and [redacted].

Based on this information you conclude that ionones can be divided into two [redacted] - with high structural similarity within groups. You also conclude that [redacted] (CAS.-No. [redacted]; constituent A) can support a read-across for [redacted] CAS-No. [redacted]; constituent B), and that [redacted] (CAS No. [redacted]) can support the two minor constituents of [redacted], [redacted] (CAS-No. [redacted]; constituent C) and [redacted] (CAS-No. [redacted]; constituent D).

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

With regard to the proposed predictions ECHA has the following observations:

(i) Support of a similar or regular pattern as a result of structural similarity

Read-across

Annex XI, Section 1.5. provides that "*substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances.*" One prerequisite for a prediction based on read-across therefore is that the substances involved are structural similar and are likely to have similar properties. One important aspect in this regard is the analysis of the data matrix to compare the properties of source and target substances and to establish whether indeed they are similar or follow a regular pattern.

ECHA notes the following observations:

a. Information on toxicological properties of your registered substance is provided for acute toxicity, genetic toxicity and skin irritation/sensitisation. As there is no information available for repeated dose toxicity or reproductive toxicity for the registered substance the submitted information does not provide sufficient evidence to conclude that information on repeated dose toxicity or reproductive toxicity derived from studies with other ionone substances could be used to predict repeated dose toxicity or reproductive toxicity of the registered substance.

b. Information on toxicological properties of the main constituent (ca [redacted]%) of your registered substance, [redacted] (CAS-No. [redacted]) [1], is provided for sub-chronic toxicity, pre-natal developmental toxicity, skin and eye irritation and skin sensitisation.

c. For the remaining constituents [2-4] (ca [redacted]% of the registered substance) the toxicological database provided is limited to information on genetic toxicity, acute toxicity, skin irritation and skin sensitization. No studies are available for these constituents on repeated dose toxicity or reproductive toxicity. Thus, it is not possible to compare their toxicological profile for these endpoints with those of other ionones. Consequently it has not been demonstrated how studies with [redacted] or with the ionones not present in your registered substance ([redacted]) could be used to predict repeated dose toxicity or reproductive toxicity of constituents [2-4].

d. The substances [redacted] seems to be less toxic in rat (NOAEL 250 mg/kg bw/d for fetal toxicity in the one/generation study by [redacted] /Beekhuizen 2003) than [redacted] (NOAEL 30 mg/kg bw/d for fetal toxicity in the pre-natal developmental study by [redacted], 2007.) As [redacted] is the major constituent of the registered substance, [redacted] does not seem to be suitable for read-across to the registered substance containing 60-70% of a higher toxic substance.

e. The substances [redacted] seems to be less toxic in rat (NOAEL 400 mg/kg bw/d for fetal toxicity in the pre-natal developmental toxicity study by [redacted] 200) than [redacted] (NOAEL 30 mg/kg bw/d for fetal toxicity in the pre-natal developmental study by [redacted], 2007.) As [redacted] is the major constituent of the registered substance [redacted] does not seem to be suitable for read-across to the registered substance containing 60-70% of a higher toxic substance.

Weight of evidence
ECHA acknowledges that the information provided with the comments on the draft decision may add further support to the structural similarity and similarity of metabolic pathways for the [redacted], respectively, for sub-chronic toxicity and pre-natal developmental toxicity in a first species. However, structural similarity or structural alerts per se and similar metabolic pathway are not enough to justify the read-across and weight of evidence adaptation for the other endpoints.

Taken the read-across and weight of evidence information together the submitted information does not provide sufficient evidence to conclude that information on repeated (sub-chronic) dose toxicity or reproductive toxicity derived from studies with other ionone substances could be used to predict repeated toxicity or reproductive toxicity of the registered substance or of constituents [2-4].

ECHA concludes that the presented evidence in the data matrix does not support a similar or regular pattern of toxicity as a result of structural similarity. Therefore it cannot be verified that the proposed group/analogue substance(s) can be used to predict properties of the registered substance.

(ii) Reliability and adequacy of the source studies

Annex XI, Section 1.5 provides, with regard to the reliability and adequacy of the source studies, that in all cases the results of the read-across should:

- *be adequate for the purpose of classification and labelling and/or risk assessment,*
- *have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3),*
- *cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter, and*
- *adequate and reliable documentation of the applied method shall be provided.*

ECHA has the following observations:

a. In the one-generation study using pseudo ionone ([redacted] /Beekhuizen 2003), the F1 generation was terminated on post-natal day 21 and not on post-natal day 90 as would be required in an extended one-generation reproductive toxicity study. Hence, extensive investigations in the F1 generation, e.g sexual maturation and histopathology of reproductive organs were not conducted.

b. The two-generation study performed by Sporn (1963) with the analogue substance ionone (mixed isomers) (CAS number 8013-90-9) is an old non-guideline study and is not reported in sufficient detail. Furthermore, the study seems to have relevant shortcomings; e.g., obviously only one dose not reaching the maximum tolerated dose was given, and no histopathological evaluation of reproductive organs of adult animals seems to have been performed.

ECHA concludes that the source studies by [redacted] /Beekhuizen (2003) and Sporn (1963) do not provide the information required by Annex X, Section 8.7.3. Hence, these studies do not provide reliable information for read across for that endpoint.

(iii) Toxicokinetics

One important aspect in establishing that substances have similar effects or follow a regular pattern is the comparison of absorption, distribution, metabolism and elimination of source and target substances. This allows assessing the qualitative and quantitative internal systemic exposure of the test organism when exposed to source and target, respectively.

ECHA observes that in the read-across justification you have provided a toxicokinetic assessment covering the registered substance and a number of related ionones. ECHA notes however that this assessment is rather general and not a systematic comparison between the substances. Consequently, it is not possible to conclude whether there are similarities in the toxicokinetic behaviour, in particular in metabolic fate / (bio)transformation of the substances and how these differences may influence the toxicity profile of the target and source substances.

In your comments to the draft decision according to Article 50(1) of the REACH Regulation you provide information for methyl ionone (your registered substance) and two related ionones when evaluated using Meteor Nexus: 2.1.0, Nexus: 2.0.0. Analysis of types of suggested biotransformation confirmed that most of the predicted pathways were identical for all four constituents of methyl ionone, as well as for [redacted] You conclude that constituents of methyl ionone show a high degree of metabolic homology. Moreover, the same biotransformation pathways predicted for both [redacted] as for the constituents of methyl ionone.

ECHA has taken note of the provided *in silico* information on the metabolism of the registered substance and two related ionones. However, while such information may contribute to conclusions on metabolism it is generally not on its own sufficient to replace experimental data in substantiating a read-across hypothesis.

ECHA concludes that based on the toxicokinetic information available, there is not an adequate basis for predicting the properties of the registered substance from the data of the source substances.

0.4 Conclusion on the read-across approach

ECHA considers that, for the reasons presented above, you have failed to explain as to how and why, in qualitative and quantitative terms, the toxicological properties of the registered substance can be accurately predicted by using the available infromation from the proposed source substances.

Pursuant to Article 41(1) of the REACH Regulation, ECHA concludes that the adaptation of the standard information requirements for the endpoints Sub-chronic toxicity study (90-day; Annex IX, Section 8.6.2.), Pre-natal developmental toxicity studies (Annex IX and X, Section 8.7.2.), Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.) in the technical dossier based on the proposed read-across approach does not comply with the general rules of adaptation as set out in Annex XI, 1.5. Therefore, ECHA rejects all adaptations in the technical dossier that are based on Annex XI, 1.5.

Furthermore, ECHA considers that the individual sources of information you provided, taken together with your justification for the adaptation, do not allow to assume/conclude that the substance does not have a particular dangerous property with respect to the information requirement for Annex IX, Section 8.7.2., Annex IX and X, Sections 8.7.2, and Annex X, Section 8.7.3. Therefore, the general rules for adaptation laid down in Annex XI, Section 1.2. of the REACH Regulation are not met and your adaptation of the information requirement is rejected.

2. 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)(e) and 13(4) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X 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 1.5. of the REACH Regulation by providing two study records for repeated dose 90-day oral toxicity study in rat (OECD TG 408) with the analogue substance [redacted] (CAS no [redacted]). You have also submitted two 90 day dermal toxicity studies (no guideline given) with the analogue substance [redacted] (CAS no [redacted]). However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is currently rejected.

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.

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, the substance is a liquid of very low vapour pressure and no uses with spray application are reported that could potentially lead to aerosols of inhalable size. 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 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.

3. 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)(e) and 13(4) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation.

A "pre-natal developmental toxicity study" (test method EU B.31./OECD TG 414) 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 1.5. of the REACH Regulation by providing study records a prenatal developmental toxicity study (OECD TG 414) in rats with the analogue substance [redacted] (CAS no [redacted]).

You have also submitted a pre-natal developmental toxicity study in rats according to the U. S. Food and Drug Administration (1994), International Conference on Harmonisation, Guideline on detection of toxicity to reproduction for medicinal products, with the analogue substance [redacted] (CAS no [redacted]), and a one-generation reproduction toxicity study in rats according to OECD guideline 415 with the analogue substance [redacted] (CAS number [redacted]). However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does currently not meet the information requirement. 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 consideration, ECHA considers testing should be performed with rabbits or rats as a second species, depending on the species tested in the first pre-natal developmental toxicity study.

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 (rabbit or rat) by the oral route.

4. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species

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

Pre-natal developmental toxicity studies (test method EU B.31./OECD TG 414) on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation). You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a prenatal developmental toxicity study (OECD TG 414) in a second species (rabbit) with the analogue substance [redacted] (CAS no [redacted]). However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

Therefore, 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 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 consideration, ECHA considers testing should be performed with rabbits or rats as a second species, depending on the species tested in the first pre-natal developmental toxicity study.

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 second species (rabbit or rat) by the oral route.

Notes for your consideration

You are reminded that before performing a pre-natal developmental toxicity study in a second species you must consider the specific adaptation possibilities of Annex X, Section 8.7.2., column 2 and general adaptation possibilities of Annex XI. If the results of the test in the first species enable such adaptation, testing in the second species should be omitted and the registration dossier should be updated containing the corresponding adaptation statement.

5. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

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

The basic test design of an extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X.

If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015).

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

a) The information requirement

You have not provided any study record of an extended one-generation reproductive toxicity study in the dossier that would meet the information requirement of Annex X, Section 8.7.3.

You have sought to adapt this information requirement according to Annex XI, Section 1.5 of the REACH Regulation by providing a study record for a one-generation study according to OECD guideline 415 with the analogue substance [redacted] (CAS number [redacted]) and a non-guideline, two-generation reproduction toxicity study with the analogue substance [redacted] (mixed isomers) (CAS number [redacted]). However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

Hence, 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. Thus, an extended one-generation reproductive toxicity study according Annex X, Section 8.7.3. is required. The following refers to the specifications of this required study.

b) The specifications for the study design

Information from studies to be conducted before the extended one-generation reproductive toxicity study

The sub-chronic toxicity study shall be conducted before the extended one-generation reproductive toxicity study and the results from that study shall be used, among other relevant information, to decide on the study design of the extended one-generation reproductive toxicity study following ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015). The sub-chronic toxicity study may provide information on effects that is relevant for triggers (e.g. weight changes and histopathological observations of organs as indication(s) of one or more modes of action related to endocrine disruption which may meet the toxicity-trigger for extension of Cohort 1B or as evidence of specific mechanism/modes of action and/or neurotoxicity and/or immunotoxicity which may meet the particular concern criteria for developmental neurotoxicity and/or developmental immunotoxicity cohorts).

Premating exposure duration and dose-level setting

To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to ECHA Guidance, the starting point for deciding on the length of premating exposure period should be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required if there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015). In this specific case ten weeks exposure duration is supported by the lipophilicity of the substance (with log Kow values of the registered substance of 4.5 to 5) to ensure that the steady state in parental animals has been reached before mating.

The highest dose level shall aim to induce some toxicity to allow comparison of effect levels and effects of reproductive toxicity with those of systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

If there is no existing relevant data to be used for dose level setting, it is recommended that results from a conducted range-finding study (or range finding studies) are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

Extension of Cohort 1B

If the column 2 conditions of 8.7.3., Annex X are met, Cohort 1B must be extended, which means that the F2 generation is produced by mating the Cohort 1B animals. This extension provides information also on the sexual function and fertility of the F1 animals.
The use of the registered substance is leading to significant exposure of professionals because the registered substance is used by professionals and consumers as odour agent (PROCs 3, 4, 5 8a, 8b, 9, 15).

In addition, there are indications that the internal dose for the registered substance will reach a steady state in the test animals only after an extended exposure as log Kow values of the substance are between 4.5 and 5, which indicates a bioaccumulative potential. Therefore, ECHA concludes that Cohort 1B must be extended to include mating of the animals and production of the F2 generation because the uses of the registered substance are leading to significant exposure of professionals and consumers and there are indications that the internal dose for the registered substance will reach a steady state in the test animals only after an extended exposure.

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Species and route selection

According to the test method EU B.56./ OECD TG 443, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in 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.

c) Outcome

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: Extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443), in rats, oral route, according to the following study-design specifications:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce some toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation

Currently, the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) are not requested. However, the sub-chronic toxicity study (90-day) requested in this decision (request 2) and/or any other relevant information may trigger changes in the study design. Therefore, the sub-chronic toxicity study (90-day) is to be conducted first and the study results submitted to ECHA in a dossier update by **6 May 2019**. If, on the basis of this update and/or other relevant information, a need for changes to the study design is identified, ECHA will inform you by **5 August 2019** (i.e. within three months after expiry of the 12-month deadline to provide the sub-chronic toxicity study (90-day)) of its intention to initiate a new decision making procedure under Articles 41, 50 and 51 of the REACH Regulation to address the design of the extended one-generation reproductive toxicity study. If you do not receive a communication from ECHA by **5 August 2019**, the request of the present decision for the extended one-generation reproductive toxicity study remains effective and you may commence the conduct of the study and the results will need to be submitted by the deadline given in this decision [exact date covering all requests].

Notes for your consideration

When submitting the study results of the sub-chronic toxicity study (90-day) you are invited to also include in the registration update your considerations whether changes in the study design are needed (see also *ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.6 (version 4.1, October 2015)*).

Furthermore, after having commenced the extended one-generation reproduction toxicity study in accordance with the ECHA decision, you may also expand this study to address a concern identified during the conduct of it and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the changes in the study design must be documented. The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/ triggers must be documented.

6. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)

"Short-term toxicity testing on fish" is a standard information requirement as laid down in Annex VIII, Section 9.1.3. 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.

Column 2 of Annex VIII, Section 9.1.3 specifies that long-term aquatic toxicity study on fish (Annex IX, Section 9.1.6) shall be considered if the substance is poorly water soluble.

In the technical dossier you have provided a study record for an OECD 203 study. However, this study does not provide the information required by Annex VIII, Section 9.1.3., because of the following.

Solvents should generally be avoided for testing of multi constituent substances such as Ionone, methyl-. Guidance OECD 23 (Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, OECD Publishing, Paris) and Guidance R.7b (2014) state both "*that solvents are not appropriate for mixtures where the use of the solvent can give preferential dissolution of one or more components*". Furthermore, OECD 203 (1992, Test No. 203: Fish, Acute Toxicity Test, OECD Publishing, Paris) and OECD 23 state that the concentration of the solvents should be in any case below 100 mg/L. However, in the short-term toxicity test to fish with Ionone, methyl- the acetone concentration exceeded 100 mg/L/0.01 ml/L (up to 10 times) in treatments crucial for the determination of effect concentrations. Such high solvent concentration can affect the toxicity significantly (OECD 23). Therefore, the short-term toxicity test to fish is regarded as invalid and cannot be used for the risk assessment. ECHA notes that the EC50 from the OECD 203 fish study has been used for PNEC derivation.

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.7b (version 3.0, February 2016) fish acute toxicity test (test method EU C.1. / OECD TG 203) is the preferred test to cover the standard information requirement of Annex VIII, Section 9.1.3.

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, acute toxicity test (test method: EU C.1./OECD TG 203).

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

"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 according to Annex IX, Section 9.1.5., column 2. You provided the following justification for the adaptation: "*Methyl-Ionone has been identified as a class 3 type compound (Vinyl/Allyl Ketone) according to Verhaar (1992). Thus the mode of action is assumed as unspecific reactive. For these MoA class an a/c-ratio (90-percentile) of 31.7 is reported by ECETOC (Technical report No. 91). Taking this into account it can be concluded, that - considering an a/c-ratio <100 - it is unlikely that a chronic daphnia study would decrease the PNEC (relative to the PNEC from acute studies with an AF of 1000) and thus not significantly change the risk assessment. Furthermore the substance is readily biodegradable. In conclusion, a chronic daphnia study therefore is deemed not to be necessary.*"

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.1.5., because as fully discussed in the section on short-term toxicity testing on fish, the OECD 23 study currently in the technical dossier used for PNEC derivation is not valid. Consequently, also the environmental risk assessment is not valid and it is not possible to determine whether the chronic daphnia study would be needed for the purpose of risk assessment.

Furthermore, stating that substance is readily biodegradable is not a valid adaptation possibility according to Annex IX section 9.1.5.

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.

According to ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 3.0, February 2016) 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).

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

"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 [according to Annex IX, Section 9.1.6., column 2. You provided the following justification for the adaptation: "*Methyl-Ionone has been identified as a class 3 type compound (Vinyl/Allyl Ketone) according to Verhaar (1992). Thus the mode of action is assumed as unspecific reactive. For these MoA class an a/c-ratio (90-percentile) of 31.7 is reported by ECETOC (Technical report No. 91). Taking this into account it can be concluded, that - considering an a/c-ratio <100 - it is unlikely that a long-term fish study would decrease the PNEC (relative to the PNEC from acute studies with an AF of 1000) and thus not significantly change the risk assessment. Furthermore the substance is readily biodegradable. In conclusion, a long-term fish study therefore is deemed not to be necessary.*"

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.1.6., column 2 because as fully discussed in the section on short-term toxicity testing on fish, the OECD 23 study currently in the technical dossier used for PNEC derivation is not valid. Consequently, also the environmental risk assessment is not valid and it is not possible to determine whether the long-term study on fish study would be needed for the purpose of risk assessment. In addition, there is currently no information on toxicity to fish. Furthermore, stating that substance is readily biodegradable is not a valid adaptation possibility according to Annex IX section 9.1.5.

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.

According to ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 3.0, February 2016) fish early-life stage (FELS) toxicity test (test method OECD TG 210), fish short-term toxicity test on embryo and sac-fry stages (test method EU C.15. / OECD TG 212) and fish juvenile growth test (test method EU C.14. / OECD TG 215) are the preferred tests to cover the standard information requirement of Annex IX, Section 9.1.6.

However, the FELS toxicity test according to OECD TG 210 is more sensitive than the fish, short-term toxicity test on embryo and sac-fry stages (test method EU C.15 / OECD TG 212), or the fish, juvenile growth test (test method EU C.14. / OECD TG 215), as it covers several life stages of the fish from the newly fertilized egg, through hatch to early stages of growth (see ECHA Guidance on information requirements and chemical safety assessment (version 3.0, February 2016), Chapter R7b, Figure R.7.8-4).

Moreover, the FELS toxicity test is preferable for examining the potential toxic effects of substances which are expected to cause effects over a longer exposure period, or which require a longer exposure period of time to reach steady state (ECHA Guidance Chapter R7b, version 3.0, February 2016).

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).

Note for consideration concerning the aquatic toxicity tests (sections 6 to 8) requested above

Once results of the aquatic toxicity test(s) are available, you shall revise the chemical safety assessment as necessary according to Annex I of the REACH Regulation.

Due to your substance being a multiconstituent you should consult the 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 3.0, February 2016), 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). If you decide to conduct the study(ies) using the water accommodated fraction approach analytical monitoring would be required to fulfil the standard requirements and to provide adequate testing data.

Concerning the order of the aquatic studies to be conducted and the necessity to conduct all of the aquatic studies requested you shall also consult the aquatic ITS given in ECHA Guidance on information requirements and chemical safety assessment (version 3.0, February 2016), Chapter R7b (Section R.7.8.5., including Figure R.7.8-4). ECHA also notes that since your substance may be difficult to test (due to range of solubilities of 21-44 mg/L and high range of Log Kow, 4.5 to 5) you may consider it relevant to carry out the long-term toxicity test on fish directly instead of the short-term toxicity test on fish.

Deadline to submit the requested information in this decision

In the draft decision communicated to you, the time indicated to provide the requested sub-chronic toxicity study (90-day) and submit the study results to ECHA in a dossier update by information was 12 months from the date of adoption of the decision. In your comments on the draft decision, you requested an extension of this timeline to 24 months. You justified this request by providing a justification from your laboratory explaining that, as this substance has so far not been subject to repeated dose toxicity testing, and as you foresee testing of the substance to be difficult due to its properties, you will need additional time to conduct formulation which most likely will be encapsulation. Furthermore you explained that you will need to conduct a 14-day repeated dose study adressing palatability and first information on potential toxicity after repeated administration. You further explained the need to perform a 28-day oral toxicity study (OECD 407) to address the maximum tolerated dose level and potential target organs. All in all you concluded that the preparations for the sub-chronic toxicity study (90-day) and performing the test sums up to 24 months for this case.

Based on the provided information, ECHA has granted the request and set the deadline for providing the sub-chronic toxicity study (90-day) to 24 months. To accommodate the fact that you are required to only commence the extended one-generation reproductive toxicity study as requested under point 5 after **5 August 2019**, unless an indication to the contrary is communicated to you by ECHA before that date, the overall draft decision deadline to submit the requested information in an updated registration dossier has been extended from 42 months to 48 months.

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 12 April 2016.

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

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

ECHA took into account your comments and amended the deadline.

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.

You did not provide any comments on the proposed amendment(s).

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-52 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 or imported. 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.

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