EUROPEAN CHEMICALS AGENCY

Helsinki, 9 November 2017

Addressee: [redacted]

Decision number: CCH-D-2114375450-52-01/F
Substance name: BENZOIC ACID, C12-15-ALKYL ESTERS
EC number: 270-112-4
CAS number: 68411-27-8
Registration number: [redacted]
Submission number: [redacted]
Submission date: 19/10/2012
Registered tonnage band: Over 1000

**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. **Water solubility (Annex VII, Section 7.7.; test method: EU A.6./OECD TG 105)**

2. **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;**

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

4. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) with the registered substance, provided that the studies requested under 2. and 3. have negative results;**

5. **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;**

6. **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;**

7. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2., column 2; test method: EU B.31./OECD TG 414) in a second species (rat or rabbit), oral route with the registered substance;**

8. **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) without extension to mate the Cohort 1B animals to produce the F2 generation;**

9. **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;**

10. **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;**

11. **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;**

12. **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.**

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 to the REACH Regulation. 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 adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by **17 May 2021** except for the information requested under point *5* for a sub-chronic toxicity study (90-day) which shall be submitted in an updated registration dossier by **16 November 2018**. You may only commence the extended one-generation reproductive toxicity study as requested under point *8* after **18 February 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.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and 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, has to 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 Ofelia Bercaru, Head of Unit, Evaluation E3

[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

### 0. Grouping of substances and read-across approach

ECHA based its decision on the evaluation of your registration dossier that contains adaptation arguments in the form of a grouping and read-across approach under Annex XI, 1.5. of the REACH Regulation, for certain (eco)toxicological endpoints which are addressed in the current decision. ECHA has assessed first the scientific and regulatory validity of your read-across approach in general before the individual endpoints (sections 2-11). The proposed read-across is discussed in the following section (section 0) of this decision. The corresponding sections 2 – 11 cross-refer back to this section.

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 similar substances (grouping of substances and read-across), "provided that the conditions set out in Annex XI are met". According to Annex XI, section 1.5. there needs to be structural similarity among the substances within a group or category and furthermore, it is required that the relevant properties of a substance within the group can be predicted from the data for the reference substance(s), and the data should be adequate for the purpose of classification and labelling and/or risk assessment. The REACH Regulation aims at promoting wherever possible the use of alternative means, where equivalent results to the prescribed test are provided on health and environmental hazards. In accordance with these objectives and the objectives of the Compliance Check process, ECHA shall assess whether a prediction of the relevant properties of the substance subject to this decision by using the results of the proposed read-across is acceptable based on the information currently available.

#### 0.1 Description of the grouping and read-across approach as proposed by you

In your registration dossier you intend to adapt the following standard human health and environment information requirements, subject to the current decision:

- *in vitro* mammalian chromosomal aberration test (OECD TG 473) (Annex VIII, Section 8.4.2);
- sub-chronic toxicity study (90-day) (OECD TG 408) (Annex IX, Section 8.6.2);
- pre-natal developmental toxicity study (OECD TG 414), first species (Annex IX, Section 8.7.2);
- pre-natal developmental toxicity study (OECD TG 414), second species (Annex X, Section 8.7.2);
- extended one generation reproductive toxicity study (EOGRTS; OECD TG 443) (Annex X, Section 8.7.3)
- growth inhibition study aquatic plants (EU C.3, OECD TG 201) (Annex VII, Section 9.1.2)
- short-term toxicity testing on fish (EU C.19, OECD TG 121) (Annex VIII, Section 9.1.3)

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

You have proposed a read-across between the substance subject to this decision, benzoic acid, C12-15 alkyl esters (EC 270-112-4, CAS 68411-27-8) as a target substance and nonylbenzoate, branched and linear (EC 447-010-5, CAS 670241-72-2) as a source substance.

### 0.2 Information submitted to support the grouping and read-across approach

You provided the following information to support the grouping and read-across approach:

- a read-across justification included in the chemical safety report (CSR), part B (pages 2-3);
- a hypothesis to support the prediction of properties of the registered (target) substance from data for source substance: *"Benzoic acid, C12-15-alkyl esters (CAS No 68411-27-8) is an UVCB mixture containing approx.* [redacted] *. Benzoic acid, C12-15-alkyl esters (CAS No 68411-27-8) is the reaction product of benzoic acid with a mixture of mainly linear alcohols in the C12-C15 range. Read-across from isononyl benzoate (CAS No 670241-72-2) is justified, as isononyl benzoate is of the same composition. Since the alcohol moiety is shorter than for benzoic acid, C12-15-alkyl esters (CAS No 68411-27-8), it is prudent to assume that this analogue substance has a higher bioavailability as benzoic acid, C12-15-alkyl esters (CAS No 68411-27-8). Thus this approach is unlikely to underestimate potential effects of benzoic acid, C12-15-alkyl esters (CAS No 68411-27-8) in biological systems."*

In addition your technical dossier contains toxicological and ecotoxicological studies on the target and source substances, which are further discussed under the endpoint specific sections.

You have provided the following key toxicological studies using the registered substance (you considered all studies as reliability 2 according to Klimish score):

- an acute oral toxicity study (non-GLP, following OECD TG 401, [redacted], 1978);
- an acute oral toxicity study (non-GLP, following OECD TG 401, [redacted], 1979);
- an acute inhalation toxicity study (non GLP, following OECD TG 403, [redacted], 1979);
- an acute dermal toxicity study (non GLP, following OECD TG 402, [redacted], 1979);
- an *in vitro* skin irritation study, GLP, OECD TG 439 ([redacted], 1998);
- an *in vivo* skin corrosion/irritation study, non GLP, following OECD TG 404 ([redacted], 1978);
- an *in vivo* skin corrosion/irritation study, non-GLP, no guideline ([redacted], 1988);
- an *in vivo* serious eye damage/eye irritation study, non-GLP, following OECD TG 405 ([redacted] 1978);
- an *in vitro* eye irritation study, GLP, MatTek's Corporation *in vitro* EpiOcular corneal Model ([redacted] 1998);
- a skin sensitisation study, non GLP, according to OECD TG 406 ([redacted] 1979);

- a human data on skin sensitisation, non GLP, Repeated Insult Patch Test ([redacted], 1994); and
- an *in vitro gene* mutation study in bacteria, no GLP, following OECD TG 471 ([redacted], 1994).

You have provided the following key toxicological studies using the source substance (you considered all studies as reliability 2 according to Klimish score):

- an *in vitro* chromosomal aberration study, GLP, OECD TG 473 ([redacted] 2003);
- an *in vivo* oral mammalian erythrocyte micronucleus test, GLP, OECD TG 474 ([redacted], 2005);
- a sub-acute 28-day repeated does toxicity study, GLP, OECD 407 ([redacted] 2003); and
- a reproduction/developmental toxicity screening test, GLP, OECD TG 421 ([redacted] (2004).

You have provided the following key ecotoxicological study using the registered substance:

- a study on short-term toxicity to aquatic invertebrates (*Daphnia sp.* Acute Immobilisation Test), GLP, according to OECD TG 202, [redacted] (2008).

You have provided the following key ecotoxicological studies using the source substance (you considered all studies as reliability 2 according to Klimish score):

- study on short-term toxicity to fish, GLP, according to OECD TG 203, Analytical Technical Services, [redacted] (2002a);
- an algae growth inhibition test, according to OECD TG 201, GLP, [redacted] (2002b); and
- a study on toxicity to microorganisms (Activated sludge, respiration inhibition test), according to OECD TG 209, GLP, [redacted] (2002c).

The following analysis presents your read-across hypothesis and justification together with ECHA's analysis concerning the above listed elements of your hypothesis and justification.

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

According to ECHA's understanding you suggest that based on similarity of composition of the target and source substances, both substances have similar human health and ecotoxicological properties. ECHA further understands that you propose that the source substance has a shorter alcohol moiety and therefore you assume it has a higher bioavailability than the target substance, thus potential effects of the target substance should not be underestimated.

You use the following arguments to support the prediction of properties of the registered substance from data for source substances within the group. Firstly, you propose that both substances possess similar physico-chemical properties (water solubility and octanol-water partition coefficient) and that impurities are not expected to influence the toxicological and environmental fate properties. Secondly, you claim that both substances are readily biodegradable, and therefore hydrolysis is not a relevant degradation pathway in the environment. You further propose that toxicity of both substances for aquatic organisms is negligible, as acute ecotoxicity tests did not reveal adverse effects.

Finally, you make a generic reference to mammalian toxicity data available on both substances and conclude that both substances are found not to be harmful. You propose that the source and registered substances have similar human health and ecotoxicological properties for the above-mentioned information requirements.

In the following, ECHA examines whether the substances have indeed similar properties or that they would follow a regular pattern in their properties, before assessing the scientific validity of your postulation.

(i) Substance characterisation of source and target substances

The substance characterisation of the source substance need to be sufficiently detailed in order to assess whether the attempted prediction is not compromised by the composition and/or impurities. In the Chapter 4.4 of ECHA practical guide "How to use alternatives to animal testing to fulfil your information requirements for REACH registration" it is recommended to follow the ECHA Guidance for identification and naming of substances under REACH and CLP (version 2.1, May 2017) also for the source substances. This ensures that the identity of the source substance and its impurity profile allows an assessment of the suitability of the substances for read-across purposes.

ECHA notes that the source substance has solely been characterised by its chemical name and CAS No and no information on the composition, impurity profile and structure have been provided in the technical dossier of the target substance.

ECHA considers that currently the composition and the impurity profile of the source and target substances cannot be compared using the information provided in the registration dossier. Consequently, based on the provided information, ECHA considers there is not sufficient information to establish a scientifically credible link between the substance characterisation of source and target substances and predicting the properties of the registered substance.

Structural (dis)similarities and their impact on prediction

Structural similarity is a prerequisite for applying the grouping and read-across approach, but ECHA does not accept in general or this specific case that structural similarity *per se* is sufficient to enable the prediction of human health properties of a substance, since structural similarity does not always lead to predictable or similar human health properties. It has to be justified why such prediction is possible in view of the identified structural differences and the provided evidence has to support such explanation. In particular, the structural similarities must be linked to a scientific explanation of how and why a prediction is possible.

ECHA notes that the target substance is an ester containing a benzyl ring moiety and a linear or branched C12-C15 alkyl chain moiety. Similarly, the source substance is an ester containing a benzyl ring moiety, however the benzyl ring is connected to a shorter and a linear C9 alkyl chain. ECHA observes that target and source substances display significant differences in their structure regarding the alkyl chain moiety. More specifically, the available information suggests that the target substance may contain up to [redacted] % of branched C12-C15 alkyl chains (as reported in the IUCLID dossier) which are not present in the source substance. Furthemore, there is no information present in the dossier on the place of branching, the degree of saturation and on the structure of the branched chains of the target substance.

ECHA notes that you do not describe all structural differences between the target and source substances and do not provide information on how the structural differences mentioned above may impact the toxicity of the substances and thus affect the possibility to predict properties of the target substance from the data obtained with the source substances.

The provided information is therefore not sufficient to establish a scientifically credible link between the structural similarity and the prediction.

In your comments on the draft decision (DD), you do not agree with ECHA's conclusion that the structural differences are significant to an extent that would preclude the possibility of read-across for all endpoints.
In your comments and the updated read-across justification document ([redacted]) attached therein, you acknowledge that the target and source substance have some differences in their structure "*mainly related to the chain length and the portion of branched moieties*". You clarify that while the source has more branched moieties ([redacted] %) also the target has branched constituents ranging between [redacted] %. You also clarify that both substances "*contain exclusively fully saturated alkyl chains*". Considering the placing of branching you explain, in the read-across justfiication document, that for the source "*more than [redacted] % of the moieties are branched near the alcohol oxygen ([redacted] position)*". You indicate that "*for the target substance the place of branching seems to be similar but is not exactly known due to limitations in analytical methods*". You nevertheless indicate that for the target "*branching is closer than 4 carbon atoms from the ester bonding and is placed at a carbon quite close to the oxygen*".

ECHA acknowlegdes that in your comments you have clarified the structural composition of the target and the source substances. However, ECHA notes that you are yet to describe how the observed differences may impact the toxicity of the substances and thus affect the possibility to predict properties of the target substance from the data obtained with the source substances. In your comments, you also acknowledge this short-coming and make a generic commitment, without further specifications, to provide further information on the possible impact of structural differences on the toxicity of the substances.

ECHA notes that such information, fully documented, may further support the read-across approach proposed by you and should be included in the technical dossier and reflected in the read-across justification. However, it is lacking at this moment, which does not allow to conclude that prediction between the source and target substances is possible.

(ii) Similar properties or regular pattern as a result of structural similarity

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 structurally 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.

**Physico-chemical and ecotoxicological properties**

In the following, ECHA examines to which extent similar patterns are indeed demonstrated for physico-chemical and ecotoxicological properties.

You claim that *"Partition coefficient log Pow exceeds 6 for both substances. <...> Water solubility is low (isononylbenzoate) to moderate (Benzoic acid, C12-15-alkyl esters). <...>.*

*Both substances for which tests are available are readily biodegradable and therefore hydrolysis is not a relevant degradation pathway in the environment. <...>.*

*Available acute toxicity study results show that toxicity of both substances, for aquatic organisms is negligible (no effects up to the limit of water solubility for all three trophic levels fish, dapnia and algae in short term tests)."*

ECHA notes that the physico-chemical properties of the target and source substances are expected to be different due to different molecular size. You have not provided accurate values for the water solubility ("*low*") and the Log Kow ("*exceeds 6*") for the source substance in the read-across justification. In addition, there is uncertainty on the water solubility value of the target substance, as discussed in section 1 of this decision under the water solubility request. As a consequence, ECHA considers that there is no basis to conclude that the source and target substances have similar physico-chemical properties.

ECHA further notes that you have not provided measured data on ready biodegradability of the source substance. In additon, you have not provided hydrolysis data for the target and source substances. Therefore, there is no basis to conclude that the source and target substances have similar environmental fate properties.

According to ECHA's understanding you consider that the target and the source substance have similar ecotoxicological properties based on the provided acute aquatic toxicity data and that using toxicity data from the source substance would constitute a worst-case approach for predicting the toxicity of the target substance based on higher bioavailability of the source substance. However, ECHA notes that this statement has not been substantiated by the provided information in the technical dossier or in the read across justification.

First, ECHA notes that there are indications that the registered and source substances have low water solubility, as further explained in the sections 1 and 10 of this decision under the water solubility and the short-term fish toxicity requests, respectively. As per the ECHA Guidance on information requirements and chemical safety assessment (Version 2.0, November 2014), Chapter R7b, absence of toxicity in short-term studies can not be used to conclude on the toxicity potential of low water solubility substances since the time taken for an equilibrium to be reached and toxic effects to be shown for a low water solubility substance is too long for an effect to be revealed in an acute study. Therefore, ECHA considers that, based only on acute ecotoxicity data, it is not possible to conclude whether the target and source substances possess similar ecotoxicological properties.

Second, in your read-across justification you state that the source substance nonyl benzoate has a shorter alcohol moiety. You consider this to indicate that the source substance has a higher bioavailability than the target substance. However, ECHA considers that higher bioavailability alone does not necessarily lead to higher ecotoxicity. ECHA highlights that you have not demonstrated how this difference in bioavability may impact the prediction of ecotoxicity of the target substance.

For example, you have not discussed how and why the differences in bioaccumulation potential between the target and source substances may influence their ecotoxicity. Furthermore, as indicated above, in absence of chronic ecotoxicological data it is not possible to compare the ecotoxic potential of these two substances.

Concerning your claim of both substances having similar pattern in ecotoxicological properties, ECHA concludes that based on the presented information it is not possible to confirm that the target substance and the source substance would have similar properties.

ECHA notes that in your comments on the draft decision and in the updated read-across document you indicate that "*No read-across to a designated species or a special test with fish, daphnia or algae will be done in the updated dossier*". You consider that "*Overall it is questionable, that a water concentration that can be reached sufficient to initiate chronic effects*". You nevertheless propose "*to test the chronic (long-term) effects for the most sensitive species*" and indicate that "*It is also expected that also the ecotoxicological tests to be done will further support the read-across hypothesis and thus one chronic (long-term) ecotoxicological test can be avoided*".

ECHA understands that you no longer wish to pursue a read-across adaptation according to Annex XI section 1.5 for the endpoints of Growth inhibition study aquatic plants (Annex VII, section 9.1.2.) and Short-term toxicity testing on fish (Annex VIII, section 9.1.3.). You agree to conduct an algae study on the registered substance, whereas for the endpoint of Short-term toxicity testing on fish (Annex VIII, section 9.1.3.), you intent to provide an adaptation according to Annex VIII, section 9.1.3. column 2 and agree to carry out a long-term fish study, also requested in this decision, on the registered substance instead of the short-term. ECHA notes that your comments on the specific endpoints are addressed in the endpoint specific sections below.

You continue that "*However, read-across will be done to the sequence (rank) of sensitivity of aquatic species (for the purpose of waiving the test on long-term toxicity to invertebrates)", and* indicate that based on "*Information available from MSDS for the source substance (being in accordance to the source registration dossier): algae NOEC>1mg/l; daphnia: NOEC>78µg/l; fish: NOEC>42.8µg/l. As a read-across, the same sequence of species sensitivity is anticipated for the target substance*". As proof of your proposed approach you indicate that the target and the source "*have an identical chemical structure with only small differences in the alcohol C-chain (source C9, target C12-15)*", "*very similar phys.-chem. Properties*", "*almost identical behavior in the test on readily biodegradability*". You maintain that the source substance has "*higher bioavailability based on molecular size*" and that there is "*no conflicting data from the existing ecotox test*". You conclude that "*properties (phys.-chem. and biological effects) are sufficiently similar for source and target substance and no contradicting facts are known to dispel the read-across approach to the target substance which has the same sequence of species sensitivity as the source substance*".

ECHA notes that according to your comments you now wish to adapt the standard information requirement of the registered target substance for the endpoint of Long-term toxicity testing on aquatic invertebrates (Annex IX, section 9.1.5.) using the aquatic data on the read-across substance nonylbenzoate, branched and linear (EC No 447-010-5, CAS No 670241-72-2) to prove that as daphnia is the least sensitive species for the source, data on algae and fish is adequate to conclude on the aquatic toxicity of the target.

ECHA notes that while this read-across differs from that addressed in the initial DD and no read-across approach for the endpoint of Long-term toxicity testing on aquatic invertebrates (Annex IX, section 9.1.5.) was initially proposed by you, the elements of the initial read-across assessment are applicable as the source substance is the same and read-across in aquatic endpoints was addressed in the initial assessment. In the following ECHA addresses the updated read-across justification provided in your comments in relation to physico-chemical and ecotoxicological properties, and specifically in relation to your claim that also for the target substance aquatic invertebrates would be the least sensitive species.

Firstly, with respect to the physicochemical properties of the target and the source substances ECHA notes that you have submitted information concerning water solubility. More specifically, you have submitted a document titled "[redacted]", containing a Robust Study Summary (RSS) for an OECD 105 water solubility study on the source substance ("[redacted]*Water solubility 001*").
According to this study the water solubility of the source is < 1 mg/L. You indicate that based on the EPI Suite QSAR predictions the water solubilities of the constituents of the target and the source ranges from 0.2 to 10 µg/L for the target and from 0.5 to 1 µ/L for the source. ECHA notes that according to the provided robust study summaries on the EPI QSAR calculations, the actual results are 0.3-9 µg/L (target) and 340-390 µg/L (source). ECHA considers that based on the information provided both the target and the source appear to have a poor water solubilities. ECHA stresses that data from an experimental water solubility study, which you are requested in the current decision under point 1, may provide more definitive confirmation.

You have also clarified the Log Kow of the source, and initially indicated that it "*exceeds 6*". In your comments you have submitted a RSS for an OECD 117 (HPLC method) study ("[redacted] *Partition coefficient 001*") on the source substance and indicate that "*a logKow of 6.1 – 6.4 was measured*". In this document you have also included RSSs of the EPI Suite QSAR predictions of Log Kow for the constituents with log Kow values 5.6-5.7 (source) and Log Kow 7.2-8.7 (target). ECHA notes that based on the information provided both the target and the source have log Kow values of above 6.

Based on the above, ECHA considers that there are minor differences with Log Kow and possibly also with water solubility. However it appears evident that water solubility of both substances is low and Log Kow high and that these properties may support the read-across approach proposed. Differences with water solubility will be further examined after performing the water solubility study with the target substance.

Secondly, concerning the environmental fate properties of the two substances, ECHA notes that in your comments you have also provided a RSS for an OECD 301 B (Ready bidoegradability: CO2 Evolution test) on the source substance ("[redacted] *Biodegradation in water: screening tests.001"*). In your read-across document you conclude that the ready biodegradation data "*supports the read-across approach as both substances are easily metabolized and the kinetic of metabolizing is quite similar (no lag-phase, high early degradation rate)".* In your comments you indicate that providing hydrolysis data for the substances would be difficult however you indicate that you may look for further information. ECHA considers that such information may further support your read-across, however, ECHA acknowledges that based on the ready biodegradation data provided both substances appear to have similar environmental fates.

Thirdly, with regards to the substances' ecotoxicity, you claim that the source is more toxic than the target and maintain that short-term data at least demonstrate absence of acute effects. ECHA notes that as indicated in the initial DD, absence of effects in short-term studies for substances with low water solubility cannot be used to conclude on their toxic potential, similarly they cannot be used to confirm similar toxicities. Only long-term aquatic data could be used to assess whether the ecotoxicities of the target and the source are similar or follow a similar pattern.

Such comparison cannot be made at this moment for the following reasons: (i) no long-term aquatic data is yet available on the registered target substance; (ii) the reliability of the algae study on the source substance, submitted in the technical dossier of the target, is questionable, as discussed in section 9 below, however ECHA notes your commitment to provide further information; and (iii) you have not provided the RSSs for the long-term data on invertebrates and fish, that you claim are available on the source substance making it not possible for ECHA to assess the validity of these studies on the source. For all the above mentioned reasons, ECHA considers that your claim of aquatic invertebrates being the least sensitive species is not supported by data.

In conclusion, ECHA notes thatpending confirmation on water solubility, and most importantly, due to lack of information on the chronic ecotoxicology endpoints it is not possible to conclude that the toxicities of the two substances would be the same or would follow a similar pattern as per the requirements of Annex XI section 1.5. As ecotoxicological data requested here becomes available, it may provide further proof of how the (dis)similarities of the substances affect the possibility to predict.

With the information currently available, ECHA hence considers it not justified to state that for the target substance daphnids would be the least sensitive out of the three trophic levels needed for testing and that data on fish and algae alone would be sufficient to conclude on the aquatic toxicity potential of the registered target substance. ECHA notes also that in general the aquatic ITS cannot be applied for substances with low water solubility as further elaborated in section 11. below. However, ECHA acknowledges that as aquatic chronic data on the target substance becomes available, you may consider whether it can be used to *"support the read-across hypothesis and thus one chronic (long-term) ecotoxicological test can be avoided"*. The timeline given in this decision does allow for sequential testing of the aquatic endpoints if you wish to follow that approach. ECHA notes that all data supporting your read-across approach, including RSSs of the data on the source substance, should be included in the technical dossier of the registered substance and reflected in the read-across justification. ECHA notes that dossier updates and any adaptations therein will be evaluated by ECHA at the follow up stage.

**Toxicological properties**

In the following, ECHA examines to which extent similar patterns are indeed demonstrated for toxicological properties.

ECHA notes that there is no toxicokinetics data and information on whether metabolic pathways of the parent substances and/or its (bio)transformation products would occur and thus play a role in the systemic toxicity of the substances, provided in the dossier.

You further propose that "*based on the available data, benzoic acid, C12-15-alkyl-esters (CAS No 68411-27-8) and isononyl benzoate (CAS No 670241-72-2) were not found to be harmful to the mammalian organism in any aspect including acute toxicity, irritation, sensitisation, repeated dose toxicity, genetic toxicity and reproduction toxicity*".

ECHA notes that, as outlined in Section 0.2 of the current draft decision, the registration dossier contains acute toxicity, skin and eye corrosion/irritation, skin sensitisation studies and an *in vitro* gene mutation study in bacteria study (non GLP, OECD TG 471, Rel. 2, [redacted] (1994), conducted with the target substance. The dossier also contains the results of key studies, all considered as reliability score 2 and GLP compliant, on the source substance, of an *in vitro* chromosomal aberration study (OECD TG 473, [redacted], 2003); an *in vivo oral* mammalian erythrocyte micronucleus test (OECD TG 474, [redacted], 2005); an sub-acute 28-day repeated dose toxicity study (OECD TG 407, [redacted], 2003); and a combined reproductive and repeated dose toxicity screening study (OECD TG 422, [redacted],2004).

ECHA notes that acute toxicity, skin and eye corrosion/irritation and sensitisation studies and *in vitro* gene mutation study in bacteria provided for the target substance are not sufficient to establish the toxicological profile of a substance with regard to mutagenicity, reproductive toxicity and repeated dose toxicity.

In addition, ECHA notes that *in vitro* gene mutation study in bacteria, provided for the target substance, is i) not considered adequate to fulfil information requirements for mutagenicity (see section 2 below) and ii) itself is not sufficient to conclude whether the target substance has or has not genotoxic potential, as no other mutagenicity studies are provided for the target substance. Therefore, ECHA is not in a position to conclude whether genotoxic potential of the target and source substance is similar.

Furthermore, as no e.g. combined reproductive and repeated dose toxicity screening study (OECD TG 422), or other relevant supportive evidence (bridging data for repeated dose toxicity and reproductive toxicity), is available for the target substance, comparison of toxicological profiles of the substances is not possible.
ECHA notes that in your comments to the draft decision and in the updated read-across justification document ([redacted] submitted therein you indicate that "*No experimental data on toxicokinetics is available for either source or target substances. However, there is substantial public information available on other benzoic acid esters, which will be discussed below in addition to the comparative consideration on the source and target substances*".` You further indicate that "*A revised expert statement on toxicokinetics taking into account possible metabolic pathways of the parent substances and examination on whether differences in their biotransformation products might play a role in the systemic toxicity of the substances is already given in the revised* "[redacted]". ECHA notes that in the updated read-across justification document you provided an extensive literature overview on the metabolism of various esters of benzoic acid and linear and branched aliphatic alcohols (JECFA, 1997, 2001, 2002; SCF, 1994; SCCP, 2005; EFSA, 2016; OECD SIDS, 2006). ECHA considers that, based on the information provided, it appears that both source and target substances are likley to metabolise into benzoic acid and corresponding alcohols which demonstrate relatively low order of systemic toxicity.

ECHA notes that as part of your coment you have submitted a document titled "[redacted]". Within this document you have submitted Robust Study Summaries (RSSs) for the source substance:

- OECD 408 sub-chronic toxicity study ("[redacted] *90 day Repeated dose toxicity oral 001;* [redacted]*, 2005);*
- OECD 414 pre-natal developmental study in rats *(*[redacted] *OECD 414 rat Developmental toxicity / teratogenicity001; Benzoic acid isononylester oral prenatal developmental toxicity study in rats,* [redacted]*, 2005);*
- OECD 414 pre-natal developmental study in rabbits *(*[redacted] *OECD 414 rabbit Developtoxicity / teratogenicity 003; Benzoic acid isononylester oral prenatal developmental toxicity study in rabbits,* [redacted]*, 2006).*

You have also indicated that you intend to apply a read-across approach to fulfil standard information requirement for extended one-generation reproductive toxicity study (OECD TG 443, Annex X, 8.7.3) for the target substance, as such a study is currently being conducted on a source substance nonylbenzoate, branched and linear.

To strenghten your read-across hypothesis and to demonstrate that the source and target substances possess similar toxicological properties, in your comments you proposed two options: a) to use available supporting evidence to avoid unnecessary testing:*"The preferred strategy would be to use a supporting evidence that both structurally similar parent substances will be hydrolysed by enzymatic cleavage of the ester bond and then further metabolized. <...> If evidence can be produced to show that both esters are readily hydrolysed by mammalian enzymes to constituents whose metabolic fate and biological interactions are fully understood, further toxicological studies may not be necessary. <...>"*; and b) to conduct additional study – *"to perform a combined reproductive and repeated dose toxicity screening study (OECD 422) with the target substance to allow comparison of toxicological profiles of the source and target substances and to justify read-across for the 90-day study and the pre-natal developmental toxicity study already available for the source substance.<...>".*

ECHA acknowledges that, based on the provided literature overview data (as indicated above), it appears that both the target and the source substance are likley to initially metabolise into benzoic acid and corresponding alcohols which demonstrate a relatively low order of systemic toxicity. ECHA further acknowledges that, based on the information provided as robust study summaries, it appears as the source substance is not mutagenic and has a low toxicological profile for repeated dose and developmental toxicity.

ECHA notes that the available supporting evidence, proposed by you as option a) above may indeed strenghten your read-across hypothesis but may not be sufficient to allow prediction of the toxicological properties for the endpoints requested in sections 5-8 of the present decision.

In your comments, you further propose an option b) to conduct additionally a combined reproductive and repeated dose toxicity screening study (OECD 422) on the target substance, as such a study already is available for the source substance. Conducting of OECD 422 study would allow a better comparison of the toxicological properties a better comparison of the toxicological properties of the substances and may provide supporting information which demonstrates whether the substances have similar toxicity profiles in respect of repeated dose toxicity and reproductive toxicity.

ECHA also notes your commitment to conduct *in vitro* mutagenicity studies requested under sections 2 and 4 of the present decision. ECHA acknowledges that, once all these data become available they may, depending on the results, further support the read-across strategy for the endpoints of mutagenicity, repeated dose and reproductive toxicity.

In conclusion, ECHA notes that although the substances may be structurally similar, currently due to lack of information allowing the comparison of the toxicological properties of the mutagenicity, sub-chronic and reproductive toxicity and fertility endpoints it is not possible to conclude that the toxicities of the two substances would be similar. Therefore, it is not possible to predict, based on the currently provided information, the relevant properties of the target substance based on the results of the source substance.

### 0.4 Conclusion on the read-across approach for ecotoxicological and human health endpoints

The adaptation of the standard information requirements (*in vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2), sub-chronic toxicity (90-day) study (Annex IX, Section 8.6.2.), pre-natal developmental toxicity study in two species (Annex IX and X, Section 8.7.2), extended one-generation reproductive toxicity study (Annex X, Section 8.7.3), in the technical dossier is based on the proposed read-across approach examined above. ECHA does not consider the revised, based on your comments, read-across justification to be a reliable basis to predict the properties of the registered substance for the reasons set out above and taking into account data available in the registration dossier. Thus, the adaptations of the above mentioned endpoints do not comply with the general rules of adaptation as set out in Annex XI, 1.5. and therefore, ECHA rejects them. For ECHA's conclusion on the read-across based adaptation for ecotoxicological endpoints submitted in your comments, please refer above to section Physico-chemical and ecotoxicological properties.

1. **Water solubility (Annex VII, Section 7.7).**

Water solubility" is a standard information requirement as laid down in Annex VII, Section 7.7 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 provided test results from an experimental test, key study "Physical/Chemical Testing on Finsolv TN, Final Report (2009), [redacted]", performed according to EC 440/2008 (A.6 - flask method). You have performed the test following the guideline with 3 individual samples. The water solubility of the test item was determined to be 0.174 g/L at 30°C. Your interpretation of the results is that the substance is moderately soluble (100-1000 mg/L).
ECHA notes that according to EC 440/2008 (A.6 - flask method), closed vessels are pre-incubated at 30°C. However, after one day, they should be re-equilibrated and analysed at the test temperature preferably 20 ± 0,5°C for one, two and three days. Therefore in the reported study the test temperature was higher than the preferred temperature.

Furthermore, you have not reported the individual analytical determinations for the three samples and the average where more than one value was determined for each flask, as required in EC 440/2008 (A.6 - flask method) test guideline.

Based on the submitted information regarding the preparation of the concentration(s), ECHA notes that the result of 0.174 g/L cannot be obtained based on your claim that "*About 0.1 g of sample is weighed into each of 3 glass vessels containing 100 ml of water.*"

In addition, ECHA notes that for the OECD TG 202 (Daphnia sp. Acute Immobilisation Test), you have reported that the nominal concentrations of the registered substance was >320 mg/L and that the measured total concentration was 76.8 µg/L. This is much lower than the reported water solubility test result of 0.174 g/L at 30°C. This indicates that the water solubility of the registered substance may be considered as "low", which is in contradiction to the reported data under water solubility endpoint.

ECHA considers that the water solubility value submitted cannot be evaluated due to the reasons given above.

In the initial draft decision ECHA requested further information in a form of an updated robust study summary (RSS) on the water solubility study included in the technical dossier to be able to assess its validity. In your comments on the draft decision you indicate that you consider the water solubility value of 174 mg/L of the target as "*questionable*" since "*the test method used, shake flask, is not appropriate for this micelle forming substance; the absence of micelles was not proved during the test*". You indicate that instead of providing the additional information requested by ECHA in a form of an updated RSS, you will carry out a new water solubility study according to OECD 105 (column elution method). ECHA agrees with you and have accordingly reformulated the request in the current decision, with respect to the water solubility endpoint.

ECHA also notes that you have provided QSAR predicted water solubility values for the registered substance and state that the range of solubilities of the constituents range from 0.5 to 10 µg/L. ECHA considers that the QSAR predicted water solubility values can be used to support any experimentally derived water solubility value. The QSAR predictions and their acceptability to support the proposed read-across approaches are also addressed by ECHA in section 0 above.

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: Water solubility (test method: EU A.6./OECD TG 105).

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same 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.

According to Article 13(3) of the REACH Regulation, tests required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods recognised by the Commission or ECHA.

Other tests may be used if the conditions of Annex XI are met. More specifically, Section 1.1.2 of Annex XI provides that existing data on human health properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3) may be used 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.

You have provided a test from the year 1994 according to OECD TG 471 but non GLP with an assigned reliability score of 2.

ECHA notes that the provided Ames test when compared to the updated OECD TG 471 (1997) has several shortcomings.

More specifically, you used dexon (paradimethylaminobenzene diazosulfonic acid sodium salt), sodium azide, 2-nitrofluorene, and 2-aminofluorene as positive controls with and without metabolic activation. These substances are appropriate for positive controls only without metabolic activation.

You also used only one dose concentration of the test substance, while the guideline requires five different analyzable concentrations.

The guideline requires to provide the following elements of results which are missing in the provided study:

- signs of toxicity;
- signs of precipitation;
- individual plate counts;
- dose-response relationship, where possible;
- statistical analyses, if any;
- historical negative (solvent/vehicle) and positive control data, with e.g. ranges, means and standard deviations.

You also provided only mean numbers (no ranges and standard deviations) of revertant colonies and concurrent negative (solvent/vehicle) and positive control data.

Furthermore, for the provided test, four different strains of *S. typhimurium* TA 98, TA 100, TA1535, TA 1537 and TA 1538 were used. According to paragraph 13 of the current OECD TG 471 test guideline (updated 1997) at least five strains of bacteria should be used, including *S. typhimurium TA102* or *E. coli WP2 uvrA* or *E. coli WP2 uvrA* (pKM101), and this is missing from your study.

Therefore, due to the all deficiencies mentioned above the provided study does not meet the current guidelines, nor can it be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. of the REACH Regulation. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA considers that the bacterial reverse mutation test (test method EU B.13/14. / OECD TG 471) is appropriate to address the standard information requirement of Annex VII, Section 8.4.1. of the REACH Regulation.

ECHA notes that in your comments on the draft decision you agree to conduct the study requested.

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).

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same 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 1.5. of the REACH Regulation by providing a study record for an i*n vitro* mammalian chromosome aberration study (OECD TG 473) conducted with the analogue substance nonylbenzoate, branched and linear (EC 447-010-5, CAS 670241-72-2).However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

In your comments you have provided further information. However, for the reasons explained in section 0 above, there are still deficiencies in your read-across approach which do not allow change of the conclusion i.e. your adaptation is 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 considers that the *in vitro* mammalian chromosome aberration test (test method OECD TG 473) and the *in vitro* mammalian cell micronucleus test (OECD TG 487) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.2. of the REACH Regulation.

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* mammalian chromosome aberration test (test method: OECD TG 473) or *in vitro* mammalian cell micronucleus study (test method: OECD TG 487).

**4. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.) provided that both studies requested under 2 and 3 (above) have negative results**

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

An "*In vitro* gene mutation study in mammalian cells" is an information requirement as laid down in Annex VIII, Section 8.4.3. of the REACH Regulation, "if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2." is obtained.

ECHA notes that the registration dossier does not contain appropriate study records for these information requirements. Therefore, adequate information *on in vitro* gene mutation in mammalian cells needs to be present in the technical dossier for the registered substance to meet this information requirement provided that both studies requested under **2** and **3** have negative results.

You have not provided any study record of an *in vitro* gene mutation study in mammalian cells in the dossier that would meet the information requirement of Annex VIII, Section 8.4.3.

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 considers that the *in vitro* mammalian cell gene mutation tests using the – *hHprt* and *xprt* test genes (OECD TG 476) and the *in vitro* mammalian cell gene mutation tests using the thymidine kinase gene – Mouse lymphoma assay (OECD TG 490) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.3.

ECHA notes that in your comments on the draft decision you agree to conduct the study requested.

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* mammalian cell gene mutation test (test method: OECD TG 476 *or* OECD TG 490) provided that both studies requested under 2. and 3. have negative results.

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same 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 not provided any study record of a sub-chronic toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.6.2.

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 "repeated dose 28-day oral toxicity study" (test method: OECD TG 407) conducted on the analogue substance nonylbenzoate, branched and linear (EC 447-010-5, CAS 670241-72-2). However, as explained above in Appendix 1, section 0 of this decision, your read-across adaptation of the information requirement is rejected. Furthermore, the study according to OECD TG 407 does not provide the information required by Annex IX, Section 8.6.2., because exposure duration is less than 90 days and the number of animals per dose group is significantly lower.

Therefore, the sensitivity of a 28-day study is much lower than that of a 90-day study. Thus, the provided information does not address the information requirement of a sub-chronic toxicity study.

In addition, while you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex IX, Section 8.6.2., column 2. You provided the following justification:

"*The test item benzoic acid, C12-15 alkyl esters showed no toxicity in acute toxicity testing (oral, dermal and inhalative exposure) and only minor unspecific effects in a sub-acute study, thus further sub-chronic or chronic testing is not considered necessary*."

According to Column 2 of Annex X, 8.6.2, a sub-chronic toxicity study does not need to be conducted if:

- a reliable short-term toxicity study (28 days) is available showing severe toxicity effects according to criteria for classifying the substance as R48, for which the observed NOAEL-28 days, with the application of an appropriate uncertainty factor, allows the extrapolation towards the NOAEL-90 days for the same route of exposure, or

- a reliable chronic toxicity study is available, provided that an appropriate species and route of administration were used, or

- a substance undergoes immediate disintegration and there are sufficient data on the cleavage products (both for systemic effects and effects at the site of uptake), or

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

In relation to your adaptation ECHA notes that it does not meet the specific rules as noted above, for the following reasons:

- a reliable short-term toxicity study (28 days) conducted with the registered substance or accepted source substance is not available and the substance is not classified as R48,
- a reliable chronic toxicity study with the registered substance or accepted source substance is not available,
- you did not provide measured toxicokinetics data proving the substance undergoes immediate disintegration and there is no sufficient data on the cleavage products (both for systemic effects and effects at the site of uptake);
- based on data submitted, ECHA cannot conclude on the solubility of the substance (see section 1 above), it is not possible to assess whether there is no evidence of toxicity in a 28-day 'limit test', as you did not provide a limit test conducted with the registered substance. Furthermore, as the registered substance is used by consumers and professionals with personal care products as well as ink products in toners, human exposure cannot be considered as limited.

Therefore, your adaptation of the information requirement according to Column 2 of Annex X, 8.6.2 is rejected.

In your comments you have provided further information, including robust study summary on the available sub-chronic 90-days toxicity study conducted with rat on the analogue substance nonylbenzoate, branched and linear (EC 447-010-5, CAS 670241-72-2). However, for the reasons explained in section 0 above, there are still deficiencies in your read-across approach which do not allow change of the conclusion i.e. your adaptation is 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 6.0, July 2017) 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 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.

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same 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 not provided any study record of a pre-natal developmental toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.7.2.

Firstly, 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 reproduction/developmental toxicity screening test (OECD TG 421) with the analogue substance nonylbenzoate, branched and linear (EC 447-010-5, CAS 670241-72-2). However, as explained above in Appendix 1, section 0 of this decision, your read-across adaptation of the information requirement is rejected.

Furthermore, the submitted source study does not provide the information required by Annex IX, Section 8.7.2., because it does not cover key parameters of a pre-natal developmental toxicity study, such as examinations of foetuses for skeletal and visceral alterations. Thus, the provided information does not adequately address prenatal developmental toxicity.

Secondly, while you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to column 2 of Annex IX, Section 8.7 You have provided the following justification for the adaptation:

"*The test item proved to be non toxic in acute toxicity studies (oral, dermal and inhalative exposure) and induced only minor unspecific effects in a subacute study. Thus further chronic studies on reproduction are not considered necessary*". "*On the basis of the results from the OECD 421 study, the dosage of 1000 mg/kg day could be considered as the NOAEL of reproduction and development.*"

More specifically, according to Column 2 of Annex X, 8.7, reproductive toxicity studies do not need to be conducted if

- the substance is of a low toxicological activity (no evidence of toxicity seen in any of the test available), it can be proven from toxicokinetics data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure.

Regarding the condition of low toxicological activity, ECHA agrees that, based on acute oral, inhalation and dermal toxicity studies, as well as skin and eye irritation and skin sensitization studies, conducted with the registered substance, the substance could be considered as of a low toxicological activity for these properties. However, as already explained in section 0 above, ECHA notes that the studies provided for the target substance are not sufficient to establish the toxicological profile of a substance with regard to mutagenicity, reproductive toxicity and repeated dose toxicity. Furthermore, the *in vivo* mutagenicity study, 28-day repeated dose toxicity study, and screening test provided in your dossier, in which minor systemic effects have been noted, have not been conducted on the target substance, but on the source substance, and as explained in Section 0 above, the read-across adaptation is rejected. Thus, low toxicological activity cannot be estimated due to the lack of any information on toxicity after repeated dosing of the registered substance or accepted read across source substance.

ECHA further notes that you did not provide measured data on toxicokinetics to support the absence of systemic absorption. Furthermore, you claimed that "*After oral take up and intestinal absorption, the test item will be hydrolysed by cleavage of the ester bond and then further metabolized. Slightly elevated liver weights after high dose exposure are indicative of an increased liver metabolism. High dose effects further demonstrate that some systemic distribution takes place*". ECHA therefore considers that systemic absorption of the registered substance occurs following administration via the oral route.

In addition, the registered substance has wide dispersive use and is used by consumers and professionals with personal care products as well as ink products in toners, hence it cannot be considered as no or no significant human exposure.

Therefore, your adaptation of the information requirement according to Annex XI, Section 1.5 of Annex IX, or column 2, Section 8.7 of Annex IX is 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.

In your comments you have provided further information, including robust study summaries on two available pre-natal developmental studies conducted with rat and rabbit on the analogue substance nonylbenzoate, branched and linear (EC 447-010-5, CAS 670241-72-2).. However, for the reasons explained in section 0 above, there are still deficiencies in your read-across approach which do not allow change of the conclusion i.e. your adaptation is rejected.

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 6.0, July 2017) 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 (rat or rabbit) by the oral route.

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

A "pre-natal developmental toxicity study" (test method EU B.31./OECD TG 414) for a second species is a standard information requirement as laid down in Annex X, 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 not provided any study record of a pre-natal developmental toxicity study in the dossier that would meet the information requirement of Annex X, Section 8.7.2.

You have sought to adapt this information requirement as the information requirement for the pre-natal developmental toxicity for a second species. More specifically, firstly 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 reproduction/developmental toxicity screening test (OECD TG 421) with the analogue substance nonylbenzoate, branched and linear (EC 447-010-5, CAS 670241-72-2).

Secondly, while you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to column 2 of Annex X, Section 8.7.

However, both your attempts of adaptation of the information requirement are rejected, for the reasons already as explained in section 6 above, with the addition that you have not addressed the species differences for prenatal developmental toxicity.

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.In your comments you have provided further information, including robust study summaries on two available pre-natal developmental studies conducted with rat and rabbit on the analogue substance nonylbenzoate, branched and linear (EC 447-010-5, CAS 670241-72-2).. However, for the reasons explained in section 0 above, there are still deficiencies in your read-across approach which do not allow change of the conclusion i.e. your adaptation is rejected.

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 second (i.e. different) species, depending on the selected 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 6.0, July 2017) 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 (rat or rabbit) 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., column 2 and general adaptation possibilities of Annex XI. If the results of the test in the first species with other available information enable such adaptation, testing in the second species should be omitted and the registration dossier should be updated containing the corresponding adaptation statement.

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same 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 in the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 6.0, July 2017).
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 provided*

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study records for a reproduction/developmental toxicity screening test (test method: OECD TG 421) conducted on analogue substance nonylbenzoate, branched and linear (EC 447-010-5, CAS 670241-72-2). However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement by read-across is rejected.

Furthermore, the study does not provide the information required by Annex X, Section 8.7.3. because it does not cover key elements, such as exposure duration, life stages and statistical power of an extended one-generation reproductive toxicity study. More specifically, the main missing key elements are: 10 weeks pre-mating exposure duration, at least 20 pregnant females per group, and an extensive postnatal evaluation of the F1 generation. Thus, the provided information does not adequately address the information requirement for an extended one-generation reproductive toxicity study.

You have also sought to adapt this information requirement referring to the low toxicity profile of the registered substance. While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to column 2 of Annex X, Section 8.7.

You have provided the following justification: "*The test item proved to be non toxic in acute toxicity studies (oral, dermal and inhalative exposure) and induced only minor unspecific effects in a subacute study. Thus further chronic studies on reproduction are not considered necessary*".

You have provided several acute toxicity studies (oral, inhalation and dermal) conducted with the target substance, and a sub-acute 28-day repeated dose toxicity study and combined reproductive and repeated dose toxicity screening study with the source substance to justify this adaptation. However, as explained in section 6 above, ECHA considers that these studies do not sufficiently support your claim regarding a low toxicity of the substance, an absence of systemic absorption and no or no significant human exposure. Therefore, for the reasons already as explained in section 6 above, your adaptation is rejected.

In your comments you have provided further information to support your read-across approach. You also refer to a study, which is allegedly being conducted but not yet available, on the source substance. However, for the reasons explained in section 0 above, there are still deficiencies in your read-across approach which do not allow change of the conclusion i.e. your adaptation is 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. 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 6.0, July 2017).

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 because 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 6.0, July 2017). In this specific case ten weeks exposure duration is supported also by the lipophilicity of the substance (log Kow >6) 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) for the extended one-generation reproductive toxicity study are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

*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 6.0, July 2017) 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); and
- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.

Currently, the extension of Cohort 1B and 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 5) 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 **16 November 2018**. 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 **18 February 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 **18 February 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 **17 May 2021**.

*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 6.0, July 2017)*).

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.

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same 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.

Column 2 of Annex VII, Section 9.1.2 specifies that the study does not need to be conducted if there are mitigating factors indicating that aquatic toxicity is unlikely to occur for instance if the substance is highly insoluble in water or the substance is unlikely to cross biological membranes.

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 an Alga, Growth Inhibition Test (key, reliability 2, 2002, GLP, static, freshwater, Desmodesmus subspicatus, (OECD TG 201 and EU Method C.3) with the analogue substance nonylbenzoate, branched and linear (EC 447-010-5, CAS 670241-72-2).

However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement cannot be accepted.

Furthermore, ECHA considers that the source study itself is not appropriate to cover the standard information requirement. ECHA notes that in the endpoint study record you have not reported the coefficient of variation of average specific growth rates during the whole test period in replicate control cultures. Therefore, it is not possible for ECHA to verify whether the validity criteria relating to growth of control cultures, as defined in paragraph 11 of the OECD TG 201, were fulfilled in the study submitted. The study submitted thus cannot be used to fulfil the standard information requirement for the present endpoint nor does it meet the requirements of Annex XI, Section 1.5 of REACH (adequate for the purpose of classification and labelling and/or risk assessment).

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.

ECHA notes that in your comments on the draft decision you agree to conduct the study requested on the registered substance. You furthermore indicate that you will update the IUCLID of the algae study on the proposed source substance to show that the validity criteria are fulfilled. ECHA notes that dossier updates and any adaptations therein will be evaluated by ECHA at the follow up stage. Furthermore, ECHA notes that your comments on the read-across approach have been addressed above in section 0. Grouping of substances and read-across approach.

According to ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017) 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).

## 10. 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.

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 short-term toxicity to fish study, GLP, according to OECD TG 203, Analytical Technical Services, [redacted] (2002a), with the analogue substance nonylbenzoate, branched and linear (EC 447-010-5, CAS 670241-72-2). However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement cannot be accepted.

Furthermore, ECHA considers that the study on the source substance, is not appropriate to cover the standard information requirement. ECHA notes that the mean measured concentration of the source substance in this study is 1.23 mg/L. You indicate that "*effect concentrations exceeding solubility of substance in test medium: 1.23 mg/l constitutes the solubility limit of test substance under test conditions*". Although the solubility in water of the source substance is not provided in the technical dossier and it is indicated as "low" in the read-across justification, ECHA acknowledges that the observed solubility limit in the Daphnia medium can be considered as "low". Since poorly soluble substances may require longer time to be significantly taken up by test organisms and to reach steady state conditions, effects may not be observed in short-term exposures. For this reason, due to the indication of the water solubility of the source substance as being "low", ECHA considers that absence of effects in short-term tests may not give a true measure of toxicity.

Hence, ECHA considers that, although certain aspects of the study have been performed adequately (e.g. with analytical monitoring and using the number of fish and test conditions recommended in OECD TG 203), due to the "low" water solubility, this acute aquatic study is not considered as valid. The study submitted thus cannot be used to fulfil the standard information requirement for the present endpoint nor does it meet the requirements of Annex XI, Section 1.5 of REACH (be adequate for the purpose of classification and labelling and/or risk assessment).

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

ECHA notes that in your comments on the draft decision you indicate the following: "*As a study on chronic fish will be provided, the short-term toxicity testing on fish will be waived*". ECHA acknowledges that you intend to adapt the present standard information requirement by using the adaptation possibility given in Annex VIII, section 9.1.3. Column 2 specific rules of adaptation of this study may not need to be conducted if a long-term aquatic fish study is available. ECHA notes that you have the possibility to pursue this approach as a long-term fish study is also requested in this decision (request 12. below). ECHA notes that dossier updates and any adaptations therein will be evaluated by ECHA at the follow up stage. Furthermore, ECHA notes that as there are indications that the registered substance has a low water solubility (please see request 1. above), long-term testing may be more relevant than short-term as also already indicated in the request on long-term toxicity testing on fish.

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 4.0, June 2017) 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).

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same 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. You provided the following justification for the adaptation *"The test item is readily biodegradable and showed no toxicity to daphnia in an acute test up to the limit of solubility. Thus, long term toxicity testing with daphnia is not needed for environmental risk assessment of Benzoic acid, C12-15-alkyl esters"*.

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex IX, Section 9.1.5., column 2. However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.1.5., column 2. because of the following.

Firstly, ECHA notes that stating that substance is readily biodegradable is not an acceptable adaptation according to Column 2 of Annex IX, Section 9.1.5. Column 2 of REACH. Furthermore, ECHA notes that the water solubility value of the registered substance is not clear but there are indications that it is low, as explained in the section 1 of this decision. Since poorly soluble substances may require longer time to be significantly taken up by test organisms and to reach steady state conditions, effects may not be observed in short-term exposures. For this reason, ECHA considers that if the substance is poorly water soluble, absence of effects in short-term tests may not give a true measure of toxicity and thus it cannot be used as an acceptable adaptation of long term testing.

Therefore, ECHA considers that long-term testing may be more appropriate for the registered substance.

In your comments on the draft decision you indicate that you disagree "*on the necessity to conduct a long-term toxicity test on aquatic invertebrates*". You have provided further information on the read-across approach with the analogue substance nonylbenzoate, branched and linear (EC 447-010-5, CAS 670241-72-2). ECHA has fully addressed your updated read-across approach in section 0 of this decision and concluded that with the current information your proposed adaptation for this information requirement cannot be accepted.

Furthermore, as discussed earlier in this decision there are indications that the water solubility of the registered substance is low, to which you agree in your comments. You also agree to conduct a new water solubility study to confirm it. ECHA hence notes that generally the aquatic ITS cannot be applied for substances with low water solubility and chronic aquatic studies on invertebrates, fish and algae needs to be generated due to the following. For the derivation of the $PNEC_{aquatic}$ data on three trophic levels is required (ECHA Guidance on information requirements and chemical safety assessment, v.4.0, June 2017, Chapter R7b, Section R.7.8.5.3). As already discussed earlier in this section, ECHA notes that poorly soluble substances require longer time to be significantly taken up by the test organisms and consequently steady state conditions are likely not to be reached within the duration of a short-term toxicity test. For this reason, short-term tests may not give a true measure of toxicity for poorly soluble substances and toxicity may not even occur at the water solubility limit of the substance if the test duration is too short. Furthermore, Annex VIII 9.1.3. and Annex VII 9.1.1. of the REACH Regulation explicitly recommend that long-term aquatic toxicity tests be considered if the substance is poorly water soluble.

Therefore long-term data on all three trophic levels is needed for the derivation of $PNEC_{aquatic}$ and to perform the chemical safety assessment.

For the reasons stated above, ECHA considers that the integrated testing strategy (*ECHA Guidance on information requirements and chemical safety assessment*, Chapter R.7b (version 4.0, June 2017), Section R.7.8.5.3.) is not applicable and it is necessary to provide long-term data on both aquatic invertebrates and on fish.

However, in this specific case ECHA acknowledges that as aquatic chronic data on the target substance becomes available, you may consider whether it can be used to "*support the read-across hypothesis and thus one chronic (long-term) ecotoxicological test can be avoided*". The timeline given in this decision does allow for sequential testing of the aquatic endpoints if you wish to follow that approach. ECHA notes that at the follow up stage ECHA will assess the updated technical dossier including any adaptations therein.

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 4.0, June 2017) *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).

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same 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. You provided the following justification for the adaptation: "*The test item is readily biodegradable and showed no toxicity to fish in an acute test up to the limit of solubility. The acute toxicity test was done with a structurally similar isononyl benzoate, which is expected to be better bioavailable to organisms due to its shorter chain length. Thus, long-term toxicity testing with fish is not needed for environmental risk assessment of Benzoic acid, C12-15-alkyl esters.*"

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex IX, Section 9.1.6., column 2.

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.1.6., column 2 because of the following:

Firstly, ECHA notes that stating that substance is readily biodegradable is not an acceptable adaptation according to Column 2 of Annex IX, Section 9.1.6. Column 2 of REACH. Furthermore, ECHA considers that the short-term toxicity fish study performed with the source substance is not relevant due to its low water solubility, as explained in request 10. In addition, the read-across is not acceptable, as explained in section 0.

As a consequence, absence of effects in the short-term test with the source substance cannot be used as an acceptable adaptation of long term testing of the registered substance. ECHA notes that the water solubility value of the registered substance is not clear but there are indications that it is low, as explained in the section 1 of this decision. Therefore ECHA considers that long-term testing may be more appropriate for the registered substance.

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

ECHA notes that in your comments on the draft decision you agree to conduct the study requested on the registered substance.

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 4.0, June 2017) fish early-life stage 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.

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 4.0, June 2017), 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 4.0, June 2017). 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).

*Notes for your consideration for aquatic toxicity testing (requests 9 to 12 above)*

ECHA points out that according to Article 14(4) of the REACH Regulation, if a substance fulfils the criteria for any of the hazard classes of Annex I to Regulation (EC) No 1272/2008 listed in Article 14(4) of the REACH Regulation or is assessed to be a PBT or vPvB, the chemical safety assessment shall include an exposure assessment (EA) and risk characterisation (RC). Therefore if any of the criteria referred to above would be fulfilled as a result of the testing requested here you shall also consider the need to udpate the Chemical Safety Assessment and to conduct the EA and RC for environment.

As further explained in Appendix 3 of this decision, it is important to ensure that the particular sample of substance selected to be tested in the study is appropriate to assess the properties of the registered substance. Hence, it is critical that those constituents which are most relevant should be present at appropriate concentrations in any sample tested. According to the specific rule for adaptation of the information requirements short-term toxicity testing on fish (Annex VIII, Section 9.1.3, column 2), a long-term aquatic toxicity study on fish (Annex IX, Section 9.1.6) shall be considered if the substance is poorly water soluble. Once the water solubility of the registered substance is clarified, as requested in section 1 of this decision, no short-term toxicity testing on fish may need to be conducted.

ECHA notes that due to the substance having a low water solubility, as fully discussed in the sections above, the Integrated testing strategy (ITS) outlined in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b (Section R.7.8.5 including Figure R.7.8-4), is not applicable in this case and the long-term studies on both invertebrates and fish are requested to be conducted. However, ECHA refers you to the sections above where your proposed read-across based adaptation is addressed.

Due to the expected low solubility of the registered substance in water 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 4.0, June 2017), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity test and for calculation and expression of the result of the test.

ECHA observed that you have undertaken a short-term study on aquatic invertebrates with the registered substance using a Water Accommodated Fraction (WAF) approach. Consequently, if you decide to use a WAF approach in your aquatic testing required in this decision, please note the following. The WAF approach is problematic when used with a test substance containing several constituents, as in the case of the registered substance. In such cases the toxicity cannot be allocated to specific constituents directly and interpretation of the results in the risk assessment requires careful consideration taking into account differences in fate of the constituents in the environment. When constituents of varying solubility are present there can be partitioning effects which limit dissolution in the water. These effects should be minimised and appropriate loadings selected accordingly to allow an appropriate determination of the toxicity of the different constituents. In that respect, it is critical that a robust chemical analysis is carried out to identify those constituents present in the water to which the test organisms are exposed. Additionally, chemical analysis to demonstrate attainment of equilibrium in WAF preparation and stability during the conduct of the test is required. Methods capable of identifying gross changes in the composition of WAFs with time are required such as ultra-violet spectroscopy or total peak area have been used successfully for this purpose.

## 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 20 February 2017.

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 request(s).

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

As no amendments were proposed, ECHA took the decision according to Article 51(3) 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 requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests 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 by each registrant.

If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.