ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 7 March 2017

Addressee: [redacted]

Decision number: CCH-D-2114355711-52-01/F
Substance name: Neodecanoic acid
EC number: 248-093-9
CAS number: 26896-20-8
Registration number: [redacted]
Submission number: [redacted]
Submission date: 09.09.2014
Registered tonnage band: 1000+T

DECISION ON A COMPLIANCE CHECK

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

1. **Name(s) in the IUPAC nomenclature or other international chemical name(s) (Annex VI, Section 2.1.1.) of the registered substance;**
   - **Manufacturing process**

2. **Composition (Annex VI, Section 2.3.) of the registered substance;**
   - **Identity of the constituents**

3. **Spectral data (Annex VI, Section 2.3.5) of the registered substance;**
   - **Infra-red spectrum**

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

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. In case renal toxicity in male rats is observed, the study will need to be modified to include urinalysis and a full histopathological examination which is to include immunohistochemical investigation of renal pathology to determine if the pathology is mediated by alpha-2u globulin nephropathy.**

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.; 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. Identification of degradation products (Annex IX, 9.2.3.).

You are required to submit the requested information in an updated registration dossier by **14 September 2020** 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 **14 March 2018**. You may only commence the extended one-generation reproductive toxicity study as requested under point 8 after **14 June 2018**, unless an indication to the contrary is communicated to you by ECHA before that date. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective Annex, and an adequate and reliable documentation.

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

Appeal

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

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

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

Appendix 1: Reasons

IDENTIFICATION OF THE SUBSTANCE

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

1. Name(s) in the IUPAC nomenclature or other international chemical name(s) (Annex VI, Section 2.1.1.)

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

You included in Section 1.2 in the Remarks field of the main constituent the following remark "[redacted]." Also the analytical information included in IUCLID Section 1.4 in the attachment "[redacted]" indicates that the substance is composed of a multitude of constituents showing variable alkyl chain lengths. A substance including such a large number of constituents is regarded as a substance of Unknown or Variable composition, Complex reaction products or Biological materials (UVCB).

Information required to be provided according to Annex VI, Section 2.1. of the REACH Regulation on the naming of UVCB substances shall consist of two parts: (a) the chemical name and (b) a more detailed description of the manufacturing process, as indicated in section 4.3 of the Guidance for identification and naming of substances under REACH and CLP (Version: 1.4, June 2016) – referred to as "the SID Guidance" hereinafter.

According to the SID Guidance, the description of the manufacturing process shall include information on the chemical identity of the starting materials and information on the most relevant steps of the process.

In IUCLID 5 section 3.1 you provided the following description of the manufacturing process for the registered substance: "[redacted]." No further information has been included on the identity or composition of the "[redacted]" used as the starting material, on the ratios of the reactants, or on the manufacturing process parameters (i.e. pressure, temperature, etc.) which determine the composition of the registered substance and therefore its identity. Without such information, the identity of the substance remains unclear.

Therefore, ECHA considers that you did not provide sufficient information about the identity of the registered substance.

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you agreed with the information request in the draft decision. In addition, you indicated your intention to address the information requirement in an update of the registration.

Furthermore, in your comments you accepted the UVCB designation of the substance due to the complexity of the numerous isomers of neodecanoic acid which are present in the substance. You also indicated that the chemical name "neodecanoic acid" is retained.

In response to your comment regarding the chemical name of the substance ECHA notes that the chemical name reported in the IUPAC name field in section 1.1 of the latest registration dossier [redacted] "[redacted]" refers to a specific isomer of neodecanoic acid, whereas the structural formula that was provided in section 1.1 was for [redacted]. Therefore, the name is considered as not representative of the UVCB substance neodecanoic acid and needs to be changed.

You are accordingly required to provide the missing details of the manufacturing processing steps that are applied to the starting materials. The information submitted shall at least include the following:

- the identity and the composition of the "[redacted]" starting material
- ratio of starting materials used and other reactants used (e.g. the catalyst used);
- description of relevant steps of the manufacturing process;
- for each step of the manufacturing process, all relevant process parameters, such as temperature and pressure, that affect the composition and therefore the identity of the substance;
- isolation steps and related parameters.

As for the reporting of the information in IUCLID, the manufacturing process description shall be specified in the "Description of composition" field in IUCLID 6 section 1.2.

You shall ensure that the chemical name reported in the IUPAC name field and the other identifiers including the structural formula reported in section 1.1 of the IUCLID dossier are representative of the UVCB substance as described by the manufacturing process.

Further technical details on how to report the identifiers of UVCB substances in IUCLID are available in the Manual "How to prepare registration and PPORD dossiers" on the ECHA website.

2. Composition of the substance (Annex VI, Section 2.3.)

Annex VI, section 2.3 of the REACH Regulation requires that each registration dossier contains sufficient information for establishing the composition of the registered substance and therefore its identity.

In that respect, according to chapter 4.3 of the SID Guidance you should note that for UVCB substances presenting a large number of constituents, such as the registered substance, the following applies:

- All constituents present in the substance with a concentration of ≥ 10 % shall be identified and reported individually,

- All constituents relevant for the classification and/or PBT assessment of the registered substance shall be identified and reported individually; and
- Other constituents shall be identified by a generic description of their chemical nature.

Furthermore for each constituent required to be reported individually, the IUPAC name, CAS name and CAS number (if available), molecular and structural formula, as well as the minimum, maximum and typical concentration, should be reported in the appropriate fields in IUCLID.

For the other constituents to be reported under a generic description, a generic chemical name describing the group of constituents, generic molecular and structural information (if applicable), as well as the minimum, maximum and typical concentration, should be reported in the appropriate fields in IUCLID.

You reported in IUCLID Section 1.2 the presence of [redacted]% of the registered substance "[redacted]" and included the remark that "[redacted]. *The shown structure represents one isomer and is provided as an example."* Such information indicates that the registered substance includes a number of constituents having branched alkyl chains. However, no further information is provided in relation to the structural formulae representing this group of constituents, more specifically no information on the degree of branching is reported in the registration dossier. In addition, the structure that you provided as an example does not refer to a neodecanoic acid isomer (showing branched alkyl chains), but to a different substance [redacted] (showing a linear alkyl chain).

Furthermore, the analytical information included in IUCLID Section 1.4 in attachment "[redacted] indicates that the substance contains groups of constituents based on other carbon number than [redacted]. The chemical nature of these groups of constituents, such as "[redacted]" is indicated in the analytical report. However these constituents have not been reported in Section 1.2.

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you indicated that neodecanoic acid consists of isomers with different branching patterns, (for) which structural formula cannot be individually determined. You proposed to provide average structural properties determined by new analyses (C- and H-NMR were specifically indicated), and to include data supporting the proposed structure characteristics.

In response to your comments ECHA agrees that the substance is complex. Irrespective of whether the newly provided information may be sufficient to meet the information requirement addressed in this decision, ECHA can already point out the following: It is not necessary to provide information about individual isomers. In addition to the analyses proposed in the comments, you can also provide information on the composition on the basis of the starting material alkene and the manufacturing process (if useful).

ECHA therefore considers that the registration does not contain sufficient and appropriate information for establishing unambiguously the composition of the registered substance and therefore its identity, as you have not provided sufficient and consistent information on the degree of branching and the structural formula. Furthermore, constituents identified in the analytical data in section 1.4 have not consistently been reported in section 1.2.

You are accordingly requested to revise the composition of the registered substance by providing appropriate information on the degree of branching of the alkyl chains of the constituents present in the registered substance. You are also requested to provide information on the identity of the constituents and groups of constituents required to be reported in section 1.2 of the dossier, including known group of constituents such as "[redacted]" as identified in the analytical report provided.

Regarding how to report the composition in IUCLID, the following applies: you shall indicate the composition of the registered substance in IUCLID section 1.2. For each constituent required to be reported individually, the IUPAC name, CAS name and CAS number (if available), molecular and structural formula, as well as the minimum, maximum and typical concentration, shall be reported in the appropriate fields in IUCLID. For the other constituents to be reported under a generic description, a generic chemical name describing the group of constituents, generic molecular and structural information (if applicable), as well as the minimum, maximum and typical concentration, shall be reported in the appropriate fields in IUCLID.

You shall ensure that the information on the composition of the substance is verifiable and therefore supported by a description of the analytical methods and corresponding results used for its identification, as required under Annex VI section 2.3.7. of the REACH Regulation.

Further technical details on how to report the composition of UVCB substances in IUCLID are available in the Manual "How to prepare registration and PPORD dossiers" on the ECHA website.

3. Spectral data (Annex VI, Section 2.3.5.)

"Spectral data" are necessary to confirm the identy of the registered substance and therefore an information requirement as laid down in Annex VI, Section 2.3.5 of the REACH Regulation. Adequate information needs to be present in the technical dossier for the registered substance to meet this information requirement.

ECHA notes that the registration dossier does not contain a comlete set of analytical data for the registered substance as infra-red (IR) spectral data, as required under Annex VI Section 2.3.5 of the REACH Regulation have not been submitted. Neither a scientifically based justification why this information would not be necessary to identify the substance has been included.

ECHA regards IR data as scientifically relevant for the identification of the registered substance, as the IR spectrum displays characteristic vibration bands of covalent bonds in molecules present in the substance, including characteristic vibration bands from the chemical functionalities expected to be present in the composition.
In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you agreed with the information requirement in the draft decision. In addition, you indicated your intention to address the information requirement in an update of the registration.

You are accordingly requested to submit the following information derived from the registered substance subject to the present decision: IR spectrum. You shall ensure that the information is consistent throughout the dossier.

Regarding how to report the spectral data, the information shall be attached in IUCLID section 1.4. You shall ensure that the description of the analytical methods used for recording the spectra is specified in the dossier in such detail to allow the methods to be reproduced, in line with the requirements under Annex VI Section 2.3.7 of the REACH Regulation.

PROPERTIES OF THE SUBSTANCE

You have adapted the information requirements according Annex XI, Section 1.5. in a "read-across" approach for certain toxicological standard information requirements which are addressed in the current decision. The applied read-across is discussed in section A of this decision. The corresponding sections 5 (sub-chronic toxicity study, 90-day) and 6 (pre-natal developmental toxicity) refer back to this section.

A. Grouping of substances and read-across approach

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

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

A.1. Information provided for the read-across approach

You have provided the following study summaries in IUCLID:

- Repeated dose toxicity; all studies flagged as supporting studies, read-across and reliability 4 (not assignable); secondary references from [redacted]:
  - Sub-acute oral toxicity study (28 days) in rats with the analogue substance pivalic acid (CAS No 68938-07-8; [redacted], NOAEL 300 mg/kg bw/d (increased salvation at 300 mg//kg bw/d, in males increased kidney weights and changes in kidney at 300 mg/kg bw/d, hyaline droplets at all treatment groups ≥10 mg/kg bw/d);
  - Sub-acute oral toxicity study (28 days) in rats with the analogue substance 2,2-dimethyl-propanoic acid (CAS No 75-98-9; [redacted]), NOAEL 300 mg/kg bw/d (clinical signs due to mild irritative effects and changes in clinical chemistry at 100 and 300 mg/kg bw/d, increase in kidney and liver weights at 300 mg/kg bw/d);
  - Sub-acute dermal toxicity study (10 applications) in rabbits with the analogue substance 2,2-dimethyl-propanoic acid acid (CAS No 75-98-9; [redacted]), $NOAEL_{systemic}$ 300 mg/kg bw/d (local irritation effects already at the low dose of 30 mg/kg bw/d);

- Sub-acute dermal toxicity study (10 applications) in rabbits with the analogue substance 2-ethyl-2,5-dimethylhexanoic acid (CA No 95823-36-2; [redacted]), $NOAEL_{systemic}$ 554 mg/kg bw/d (with marked local irritation).

- Pre-natal developmental toxicity (flagged as key study)
  - Oral teratology study in rats of PMN 93-1033 (OECD TG 414), [redacted] (study report), Rel. 1 ("*acceptable, well-documented study performed according to GLP*") with the analogue substance neoheptanoic acid (CAS No 95823-36-2), $NOAEL_{maternal}$ 250 mg/kg bw/d, $LOAEL_{maternal}$ 600 mg/kg bw/d (mortality, decreased body weights); $NOAEL_{development}$ 250 mg/kg bw/d (statistically non-significant increase in resorptions), LOAEL 600 mg/kg bw/d embryotoxicity, fetal malformations)

You did not provided a document to justify your read-across approach.

A.2. ECHA analysis of the grouping and read-across approach

ECHA notes that the provided study summaries for repeated dose toxicity are exclusively secondary references to sub-acute oral (28 day) or dermal (ten administrations) toxicity studies with analogue substances. You indicated that the provided information is non-reliable and robust study summaries were not provided. None of the studies (alone or in combination) provides reliable information for the property in question. Concerning pre-natal developmental toxicity you provided one study record of a teratology study in rats (equivalent or similar to OECD TG 414) with an analogue substance.

However, you have not explained how this information can be used to predict the properties for the substance subject to this decision. Consequently, ECHA considers that you have failed to meet the requirements of Annex XI, Section 1.5 of the REACH Regulation. More specifically, you failed to provide adequate and reliable information that would cover the key parameters and exposure duration of the corresponding test methods referred to in Article 13(3), which are the sub-chronic toxicity study (90 days) according to OECD TG 408 and a pre-natal developmental toxicity study according to OECD TG 414.

ECHA concludes that there is no hypothesis and justification establishing a basis whereby toxicological properties for the sub-chronic toxicity and developmental toxicity endpoints of the registered substance may be predicted from data for the analogue substances described as [redacted] and referred to with identifiers CAS 68938-07-8, CAS 75-98-9 and CAS 95823-36-2, respectively. In the absence of any justification supporting the proposed grouping/read-across approach, ECHA considers that you have failed to provide an adequate and reliable documentation of the applied method as required by Annex XI, Section 1.5 of the REACH Regulation.

Therefore, ECHA is not in a position to conclude that the current read-across approach allows for predicting relevant properties of the registered substance from information provided for the analogue substances. The read-across is therefore rejected.

A.3. Conclusion on the read-across approach

The adaptation of the standard information requirements for the endpoints sub-chronic toxicity and pre-natal developmental toxicity in the technical dossier is based on the proposed read-across approach examined above. ECHA does not consider the read-across adaptation to be a reliable basis to predict the properties of the registered substance for the reasons set out above.The adaptation does not comply with the general rules of adaptation as set out in Annex XI, 1.5., Therefore, ECHA does not accept the read-across for adapting the above-identified information requirements.

4. Water solubility (Annex VII, Section 7.7.)

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

"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 a study according to ASTM E1064 which is a method to determine water content in organic liquids by a coulometric Karl Fischer titration. Thus, you have determined that the water content in the registered substance is 0.2 wt% at 25 C.

However, the water solubility endpoint in Annex VII, Sectin 7.7. requires the determination of the solubility of the registered substance in water rather than the content of water in the registered substance.

Furthermore, you have only provided information on the standard used and a numeric result. The information is not sufficient to be considerd a study summary as defined by Article 3(29) and required by Article 10(a)(vi) of REACH.

In your comments to the draft decision you agreed with the information request in the draft decision.

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).

Guidance for determining appropriate test methods for the water solubility is available in the ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.1.7 (July 2015).

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

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation. The 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 (90 day) in the dossier that would meet the information requirement of Annex IX, Section 8.6.2.

Furthermore, you have sought to adapt this information requirement according to Annex IX, Section 8.6.2., column 2. You provided the following justification for the adaptation:

"The 90-subchronic test for neodecanoic acid is not scientifically justified based on several findings. This approach is consistent with Annex IX (column 2 – end point 8.6.2 in Reach):

"The sub-chronic toxicity study (90 days) does not need to be conducted if a reliable chronic toxicity study is available, provided that an appropriate species and route of administration."

Details of the scientific justification are provided below:

- *First, as indicated in acute toxicity studies, neodecanoic acid has a low potential for acute toxicity.*
- *Second, in a repeated dose dermal study, neodecanoic acid was applied once daily for 10 applications to the skin of rabbits at doses of 0.5 or 2.5 ml/kg. All animals survived the exposure. Other than local irritation effects, there were no indications that exposure resulted in systemic toxicity.*
- *Third, repeated dose testing has occurred with structurally related materials via the oral and dermal routes of exposure: [...].*
- *Finally, a modified three generation reproductive and developmental study has been conducted to evaluate the effects of long-term ingestion of neodecanoic acid on reproduction in albino rats in which animals were exposed to neodecanoic acid for greater than 90 days. Neodecanoic acid was administered in the diet at levels of 100, 500, and 1500 ppm (approximately 5, 25 and 75 mg/kg/day, respectively) to rats through two parental and to two-litter filial generations. There was no evidence at any test level of an adverse effect on the survival, appearance, behavior, body weight gain, and food consumption of the parental generations; on the reproductive performance of the parents reflected by the various indices; or on the growth, appearance, and behavior of the offspring. Additionally, there were no gross and/or macroscopic pathological findings indicative of a compound-related effect at any of the dietary levels.*

Based on these data, it can be concluded that a 90-day repeated dose toxicity study is not justified."

ECHA notes the following:

Firstly, ECHA notes that acute toxicity profile in general is not relevant for the purpose of adapting a standard information requirement for a sub-chronic toxicity study based on Annex IX, Section 8.6.2., column 2.

Secondly, ECHA notes that, the information provided on a sub-acute toxicity study with the registered substance by the dermal route does not allow the adaptation of a sub-chronic toxicity study according to Annex IX, Section 8.6.2., column 2, for the following reasons:

- A reliable short-term toxicity study (28-day) can be used for purposes of adapting the information requirement of a sub-chronic toxicity study in case of severe toxic effects according to criteria for classifying the substance as R48 and allowing the extrapolation towards the NOEL-90 days for the same route of exposure. ECHA considers that no such toxic effects have been reported in the provided dermal sub-acute toxicity study performed with the registered substance that would lead to a classification corresponding to R48 and the NOAEL of a dermal study could not be used to extrapolate to an oral and inhalation NOAEL-90 day. Hence, this rule for adaptation does not apply.
- An available reliable chronic toxicity study can also be used to adapt the requirement of a sub-chronic toxicity study. However, ECHA notes that such a study has not been provided. ECHA notes further that in the multi-generation study the exposure duration of any of the generations is not chronic (i.e. < 100 weeks). Hence, this rule for adaptation does not apply.
- The sub-chronic toxicity study can be adapted if the substance undergoes immediate disintegration and there is sufficient data on the cleavage products (both for systemic effects and effects at the site of uptake). However, ECHA notes that you indicated that [redacted] are relatively resistant to biotransformation. Hence, this rule for adaptation does not apply.
- The sub-chronic toxicity study can also be adapted if 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. However, ECHA notes that the registered substance is neither unreactive nor insoluble or not inhalable and the provided 28-day dermal study toxicity showed local toxicity. Hence, this rule for adaptation does not apply.

Thirdly, ECHA notes that you have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing information on repeated dose toxicity with analogue substances. However, as explained above in Appendix 1, section A "*Grouping of substances and read-across*", your adaptation of the information requirement cannot be accepted.

Finally, ECHA notes that the modified "*three generation reproductive and developmental study*" ("*performed equivalent or similar to OECD TG 416*") does not provide the information on the key parameters a sub-chronic toxicity study (e.g., OECD TG 408) would provide as indicated in REACH Annex XI, Section 1.1.2. More specifically, even if the duration of dosing of adult animals might be comparable to that of a sub-chronic toxicity study, the doses used (up to 75 mg/kg bw/d) were not sufficiently high to lead to toxicity and hence, are not appropriate for hazard identification.

Furthermore, a study performed according to OECD TG 416 does not investigate all organs and tissues required for a sub-chronic toxicity study. ECHA notes further that reporting of this study is not sufficient to verify which organs have been examined histopathologically. Hence, the provided "*three generation reproductive and developmental study*" study does not provide sufficient information to adapt the sub-chronic toxicity study based on Annex XI, Section 1.1.2.

Considering the above, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 8.6.2., column 2, nor the general rules for adaptation of Annex XI, section 1.1.2. or 1.5.

Therefore, your adaptation of the information requirement is rejected.

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you express your intention to adapt the information requirement by invoking either Section 8.6.2. Column 2 of Annex IX or Section 1.2., 1.5., or 3.2.(a) of Annex XI and develop appropriate documentation to justify this. ECHA notes that no justification specifically claiming the intended adaptation has been provided and that an adaptation justification specifically claiming the intended adaptation needs to be included in the registration dossier.

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

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration. More specifically, the substance is a liquid of very low vapour pressure. Hence, at ambient temperature, human inhalation exposure by vapours of the substance is unlikely.

However, ECHA notes that uses with industrial and professional spray application are reported in the chemical safety report. Consequently, inhalation exposure to aerosols of inhalable size is possible. However, in an acute inhalation study no mortality or signs of toxicity were recorded. Hence, ECHA considers that there is no specific concern with regard to the inhalation route. In the absence of concern for exposure by inhalation and the necessity for having an appropriate repeated dose toxicity study by the oral route with the registered substance that could provide relevant information for the design of an extended one-generation reproductive toxicity study (see below) ECHA considers that the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

In addition, ECHA notes that some information you provided with proposed analogue substances showed effects on the kidneys. More specifically, increased kidney weights and histopathological changes in kidneys of male rats at 300 mg/kg bw/day were reported in the sub-acute oral toxicity study (28 days) with the analogue substance pivalic acid (CAS No 68938-07-8) while no adverse effects were observed in the kidneys of female rats.

Furthermore, increased kidney weights at 300 mg/kg bw/day were reported in the sub-acute oral toxicity study (28 days) in rats (sex not reported) with the analogue substance 2,2-dimethyl-propanoic acid (CAS No 75-98-9) and were not considered as a treatment-related adverse effect by you. The fact that some of these effects were only observed in male rats may indicate that the analogue substances tested may induce alpha-2u-globulin-mediated nephropathy. Even if ECHA has rejected your proposed read-across approach, ECHA considers that due to the structure of the registered substance (hydrocarbon) there is a concern that the registered substance may also lead to alpha-2u-globulin-mediated nephropathy in male rats. Since humans do not excrete alpha-2u-globulin and this mode of action is considered not relevant to humans, the involvement of alpha-2u-globulin in the kidney effects is a key parameter for establishing the relevance of the kidney effects for risk assessment. In circumstances that renal toxicity in male rats is observed, ECHA considers that urinalysis is required to investigate kidney function (which is optional in paragraphs 3, 30 and 32 of OECD TG 408, and the relevant part of Section 1.5.2.2. of EU Method B.26.). Additionally, a full histopathological examination (paragraphs 3, 35 and 36 of OECD TG 408, Section 1.5.2.4. of EU Method B.26.) is required, which is to include immunohistochemical investigation of renal pathology to determine if the pathology is indeed mediated by alpha-2u globulin.

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. In case renal toxicity in male rats is observed, the study will need to be modified to include urinalysis and a full histopathological examination which is to include immunohistochemical investigation of renal pathology to determine if the pathology is mediated by alpha-2u globulin nephropathy.

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

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation. The 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 sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for an oral teratology study in rats (equivalent or similar to OECD TG 414) with the analogue substance neoheptanoic acid (CAS no 95823-36-2). However, as explained above in Appendix 1, section A "*Grouping of substances and read-across approach*" of this decision, your adaptation of the information requirement is rejected.

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

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

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

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you express your intention to adapt the information requirement by invoking either Section 8.7.2. Column 2 of Annex IX or Section 1.2. or 1.5. of Annex XI and develop appropriate documentation to justify this. ECHA notes that no justification specifically claiming the intended adaptation have been provided and that an adaptation justification specifically claiming the intended adaptation indeed needs to be included in the registration dossier.

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

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

Pre-natal developmental toxicity studies (test method EU B.31./OECD TG 414) on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

The technical dossier does not contain information on a pre-natal developmental toxicity study with the registered substance.

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you express your intention to adapt the information requirement by invoking either Section 1.2. or 1.5. of Annex XI and develop appropriate documentation to justify this. ECHA notes that no justification specifically claiming the intended adaptation have been provided and that an adaptation justification specifically claiming the intended adaptation indeed needs to be included in the registration dossier.

According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed with rabbits or rats as a second species, depending on the species tested in the first pre-natal developmental toxicity study.

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

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a second species (rabbit or rat) by the oral route.

Notes for your consideration

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

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

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation. The 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 the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015). Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

a) The information requirement

In the technical dossier you have provided a study record for a modified "three generation reproductive and developmental study". However, this study does not provide the information required by Annex X, Section 8.7.3., because it does not cover key elements.

More specifically, the main missing key elements are an extensive postnatal evaluation of the F1 generation and appropriate dose selection. ECHA notes that, poorly described post-mortem examinations (parental animals and offspring) suggest that histopathological examinations and organ weights were omitted. Furthermore, ECHA considers the high-dose group of 75 mg/kg bw/day as not sufficient high in the absence of toxic effects observed throughout the study. ECHA notes that, in the absence of relevant toxicokinetic data, the dose levels should be based on toxic effects and that the highest dose should be chosen with the aim to induce some systemic toxicity, but not death or severe suffering of the animals.

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you express your intention to adapt the information requirement by invoking Section 1.2., 1.5., or 3.2.(a) of Annex XI and develop appropriate documentation to justify this. ECHA notes that no justification specifically claiming the intended adaptation have been provided and that an adaptation justification specifically claiming the intended adaptation indeed needs to be included in the registration dossier.

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

Premating exposure duration and dose-level setting

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

Ten weeks premating exposure duration is required 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 4.1, October 2015). Ten weeks exposure duration is supported also by the lipophilicity of the substance to ensure that the steady state in parental animals has been reached before mating.

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

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

Species and route selection

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

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

c) Outcome

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443), in rats, oral route, according to the following study-design specifications:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce some toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) 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 **14 March 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 **14 June 2018** (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 **14 June 2018**, 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 **14 September 2020**.

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 5.0, December 2016)*).

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

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

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

ECHA observes that in the registration dossier you have concluded that the substance is not readily biodegradable. Thus, condition for adaptation given in Annex IX, Section 9.2.3. column 2 is not met.

ECHA notes that you have not provided information on the identity of degradation products in the registration dossier.

ECHA notes that information on degradation products is required for the PBT/vPvB assessment as Annex XIII of the REACH Regulation explicitly requires that PBT/vPvB properties of degradation products need to be taken into account. Information on degradation products shall also be taken into account for the exposure assessment (Annex I 5.2.4. of the REACH Regulation) and for the hazard assessment (e.g. column 2 of Annex X 9.4 and Annex X 9.5.1 of the REACH Regulation). Finally, ECHA further points out that information on degradation products is required for the preparation of Section 12 of the safety datasheet (Annex II of the REACH Regulation).

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

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you indicated your intention to adapt the information requirement by invoking Section 1.1.2. of Annex XI. In Annex 2 to your comments you have provided a justification for this adaptation. You have assumed the following biodegradation mechanism:

1) terminal hydroxylation of the alkyl chains,
2) successive dehydrogenations of the subsequent alkanols to the corresponding aldehydes and carboxylic acids,
3) sequential β-oxidations of the carboxylic acids forming at each step new carboxylic acids with two fewer carbon atoms and two CO_2 molecules.

You further indicated that the enzymatic β-oxidation was in practice likely to be inhibited by the steric hindrance created by the highly branched structure of the different constituents of the substance and because they contain a quaternary carbon.

ECHA agrees that the biodegradation can be expected to be slow because of the structures of the constituents of the substance, i.e. highly branched alkyl chains and quaternary carbon. This is confirmed by the available results for ready biodegradability reported in the dossier.

ECHA considers that the explanations you provided are generally plausible but notes that the biodegradation pathway may in practice be less straightforward that the one you have proposed[2]:

- the hydroxylation of the alkyl chains may not necessarily happen on the terminal methyl carbon,
- β-oxidation may be blocked by the chain branching but a carboxylation pathway may take place instead.
- For quaternary substituted structures, more complex mechanisms may occur, which potentially involve various rearrangements in the molecules.

However, ECHA agrees that neither the registered substance itself nor its potential degradation products are expected to be PBT/vPvB.

Since you intend to adapt the information requirement, the justification for this adaptation needs to be included in the registration dossier itself. The adaptation also entails that the request for using a test method EU C.25./OECD TG 309 at the temperature of 20 °C in the current decision is not warranted.

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

[2] See for example Organic Chemicals in the Environment, Mechanisms of Degradation and Transformation, Second Edition – Alasdair H. Neilson, Ann-Sofie Allard, CRC Press, 2013.

Other remarks

In your comments to the draft decision, you suggest that "*Neodecanoic acid is a relatively low volume product which is used no less than 80% as a chemical intermediate.*"

ECHA points out that information requirements of Article 10 can only be exempted in accordance with Articles 17 and 18 of the REACH Regulation in circumstances where strictly controlled conditions (SCC) have been claimed in context of on-site isolated intermediate or transported isolated intermediate uses. ECHA further notes that your full registration is currently reported as more than 1000 tonnes per year. No intermediate tonnages or SCC have been claimed in the registration dossier. Therefore, ECHA considers that no exemption from the Article 10 obligations can be currently made on basis of intermediate uses.

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 16 June 2016.

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

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

ECHA took into account your comments and amended the request for the identification of degradation products.

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

3. In relation to the information required by the present decision, the sample of the substance used for the new test(s) 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 test(s) 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 test(s) must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.