Helsinki, 23 September 2019

Addressee: [redacted]

Decision number: TPE-D-2114483614-43-01/F
Substance name: branched-nonyl 3,5,5 trimethylhexanoate
EC number: 701-133-3
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 08/03/2019
Registered tonnage band: 100-1000

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation ((EC) No 1907/2006) (the REACH Regulation), ECHA examined your testing proposal(s) and decided as follows.

While your originally proposed test for Sub-chronic toxicity study (90-day), oral route (EU B.26./OECD TG 408) using the analogue substance [redacted] is rejected, you are requested to perform:

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

You have to submit the requested information in an updated registration dossier by **30 March 2021**. You shall also update the chemical safety report, where relevant.

The reasons for 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 Wim De Coen, Head of Unit, Hazard Assessment

[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

The decision of ECHA is based on the examination of the testing proposal submitted by you for the registered substance branched-nonyl 3,5,5 trimethylhexanoate (EC no 701-133-3; hereafter referred to as "target substance"), proposed to be performed with an analogue substance [redacted] hereafter referred to as "source substance") on the submitted read-across justification. ECHA has considered first the scientific validity of the read-across hypothesis before assessing the testing proposed.

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

Pursuant to Article 40(3)(c) of the REACH Regulation, ECHA may require the Registrant to carry out one or more additional tests in case of non-compliance of the testing proposal with Annexes IX, X or XI of the REACH Regulation.

A sub-chronic toxicity study (90 day) is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. ECHA additionally notes that there are consumer and professional uses in the joint submission. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

a) Evaluation of the testing proposal

You have submitted a testing proposal for a sub-chronic toxicity study (90 day) in rats by the oral route according to EU B.26./OECD TG 408 with the analogue substance [redacted].

Read across

ECHA requested your considerations for alternative methods to fulfil the information requirement for Sub-chronic toxicity (90-day): oral. ECHA notes that you provided your considerations and you applied read-across to fulfil the respective information requirement, and no other alternative methods were available. ECHA has taken these considerations into account.

ECHA has evaluated your proposal to perform the test with the analogue substance [redacted].

As explained in more detail below your read-across is rejected.

(i) Grouping of substances and read-across approach

Article 13(1) of the REACH Regulation requires information on intrinsic properties of substances on human toxicity to be generated whenever possible by means other than vertebrate animal tests, including from information from structurally related substances (grouping or read-across), "*provided that the conditions set out in Annex XI are met*".

According to Annex XI, 1.5 there needs to be structural similarity among the substances within a group or a category and furthermore, it is required that the relevant properties of a substance within the group can be predicted from the data for reference substance(s) by

interpolation, and the data should be adequate for the purpose of classification and labelling and/or risk assessment.

(ii) Description of the grouping and read-across approach proposed by you

You have proposed to cover the standard information requirement for a sub-chronic toxicity study (90-days; Annex IX, Section 8.6.2.) by performing the test with a source substance.

You have provided the following hypothesis/justification:

"The present analogue approach contemplates isononyl isononanoate (IUPAC name branched-nonyl 3,5,5 trimethylhexanoate, previously CAS 42131-25-9) as target substance for read-across from the source substances listed in Table 1. Isononyl isononanoate is a [redacted] substance derived from [redacted] (see report in section 1.2)."

"Based on structural features and anticipated metabolism, suitable source substances for read-across are [redacted] with an analogue structure regarding [redacted], respectively. The common metabolic fate of [redacted] involves a stepwise hydrolysis of the [redacted] by gastrointestinal enzymes by which the breakdown results in structurally similar chemicals, [redacted] ([redacted] 1993; [redacted] 1972)."

"The toxicological properties show that the target and source substances have similar toxicokinetic behaviour due to the common metabolic fate, which is independent of the [redacted], respectively."

"Due to the structural similarities and consistent trend in physico-chemical, toxicological and toxicokinetic behaviour, the selected source substances are considered suitable and human health effects can be directly read-across to isononyl isononanoate in accordance with Regulation (EC) No 1907/2006, Annex XI, 1.5."

In summary you provide the following justification for your read-across approach:

"The key points that the target and source substances share are:

- *Common functional groups: Target and source substances are [redacted] Most of the substances are [redacted] one substance shows [redacted]. An additional substance is [redacted] in both [redacted];*

- *Similar physico-chemical properties: For the purpose of read-across of (eco)toxicity data, the most relevant physico-chemical parameter are physical state (appearance), vapour pressure, octanol/water partition coefficient and water solubility. All substances have in common, a low water solubility, high log Pow (>5.7), and a low vapour pressure (<0.1 Pa at 20 °C).*

- *Similar metabolic pathways: [redacted] are anticipated to be initially metabolised via enzymatic hydrolysis in the corresponding [redacted]. The hydrolysis products are absorbed via the lymphatic system and subsequently enter the bloodstream. [redacted] can be oxidised or [redacted] and stored, depending on the need*

for metabolic energy. The [redacted] is, in general, enzymatically oxidized to the corresponding [redacted], which can then be degraded via β-oxidation ([redacted] 1993). The [redacted] is unlikely to be used for energy generation and storage, since [redacted] are described to be subjected to alpha- and/or omega-oxidation due to [redacted], which results in the formation of various [redacted]. In contrast to the products of beta-oxidation, these metabolites may be conjugated to glucuronides or sulphates, which subsequently can be excreted via urine or bile or cleaved in the gut with the possibility of reabsorption (entero-hepatic circulation) ([redacted] 1998);

• Common levels and mode of human health related effects: The available data indicate that the target and source substances have similar toxicokinetic behaviour (hydrolysis of the [redacted] before absorption followed by absorption and metabolism or excretion of the breakdown products) and that the constant pattern consists in a lack of potency change of properties. Thus, based on the available data, the target and the source substances of the analogue approach show a low acute oral and inhalative toxicity, no skin or eye irritation properties and no skin sensitisation. Furthermore, all category members are not mutagenic or clastogenic and have no effect on intrauterine development."

(iii) Information/documentation submitted to support the grouping and read-across hypothesis

You have provided a read-across justification as a separate attachment in the registration, [redacted] Furthermore you have provided information on the choice of test substance in the document [redacted]

You have also provided a data matrix covering physico-chemical properties and mammalian toxicity.

In the technical dossier you have provided for repeated dose toxicity the following studies conducted with the target substance:

- Key study, [redacted] 2013 (rel 2), 10 day dermal dose range-finding study for a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD 422) in rats. Non GLP. Study report.
- Key study, [redacted] 2013 (rel 1), dermal study in rats. Protocol designed in general accordance with the OECD Guidelines for the Testing of Chemicals, Guideline 422, Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test. [redacted] GLP compliant. Study report.

and studies conducted with the source substance:

- Key study, [redacted] 2001 (rel 2), OECD guideline 407, repeated dose 28-day oral toxicity study in rodents (rat). GLP compliant. Study report.
- Supporting study, [redacted] 2001 (rel 2), OECD guideline 410, repeated dose dermal toxicity: 21/28 day study (rat). [redacted] GLP compliant. Study report.

In your dossier update 8 March 2019 [redacted] you have included additional information on the composition of the source and target substances, and information from a QSAR test - [redacted] in January 2019.

(iv) ECHA analysis of the grouping approach and read-across hypothesis in light of the requirements of Annex XI, 1.5.

Based on the information provided, ECHA understands that the proposed read-across hypothesis is based on structural similarity, similar physico-chemical and toxicokinetic properties, and similar toxicological properties of the target and source substances.

Structural similarity and dissimilarity

You have provided substance identity data, including composition of the target and source substances. You explain that both substances are [redacted] with the [redacted] group being the common functional group.

ECHA observes that you have provided some information to demonstrate the structural similarities and differences between the target and source substances. ECHA notes that the target substance is a [redacted] while the source substance is a [redacted].

With the additional information on composition of the substances given in your updated dossier [redacted] ECHA finds that the composition of the substances has been made sufficiently clear.

However, you have not in sufficient detail compared the [redacted] target substance to the source substance, and you have not demonstrated that the [redacted] of the target substance with [redacted] different from those of the source substance do not influence the toxicity profile of the target substance as compared to the source substance. In particular, possible differences in toxicological profiles due to [redacted] have not been addressed.

ECHA concludes that you have not addressed sufficiently the structural differences between the target and the source substance, such as differences [redacted], and you have not explained why those differences would not lead to differences in the toxicity profile of registered and source substances. Given the structural differences between the target and source substances, ECHA considers that there is not an adequate/sufficient basis for predicting the properties of the target substance from source substances.

Physico-chemical properties

You have provided data on the physico-chemical properties of the target and source substances. ECHA observes that based on the data provided it can be concluded that the substances have similar physico-chemical properties.

ECHA notes that the fact that physico-chemical parameters are in the same range may support the similar toxicokinetic and toxicity profile, but cannot be used alone to justify a prediction of properties related to human health.

Toxicokinetic properties

You have only provided general information on the hydrolysis, absorption, distribution and metabolism of [redacted] which is not specific to your target or source

substances. As there are no substance-specific experimental data on the target or source substances, it is not possible to make a detailed comparison of the toxicokinetic properties of the substances. Hence, ECHA concludes that you did not in sufficient detail address important aspects such as the toxicokinetics of the parent substances and their metabolic fate / (bio)transformation and the resulting possible difference in the metabolite profiles. Therefore, it is not possible to verify the substances which are likely to govern the toxicity profiles of the source and target substances. In the absence of such information there is not an adequate basis for predicting the properties of the registered substance from the data obtained with the source substance.

In your updated dossier you report results from simulations made with the OASIS TIMES platform for simulating metabolism with TIMES metabolic simulators.

To further explore the validity of your QSAR simulations ECHA assessed the metabolites from branched-nonyl 3,5,5 trimethylhexanoate and [redacted] by using the metabolic liver simulators in TIMES and METEOR. ECHA also screened the generated metabolites with DEREK to determine potential differences in toxicity.
The results show that the metabolisation pathways are similar for both substances. However, uncertainty remains as to the adequacy for read-across given that:

- Many more different potential metabolites are generated for the target (the UVCB) than for the source, both with TIMES and METEOR.
- The metabolisation rates are not known, so even if similar metabolites are formed it cannot be foreseen that they will appear equally fast.
- Some of the metabolites generated for the target substance trigger alerts for hepatotoxicity, which are not triggered for the source.
- Several metabolites of the target substance show an alert for nephrotoxicity. Some of them are phase II metabolites, which will be quickly excreted and hence of less concern, but some are not.

Due to these discrepancies, ECHA finds that read-across is not supported by the analysis of predicted metabolites.

Toxicological data
You have proposed that the source substance has similar toxicity regarding sub-chronic toxicity and therefore the properties of the target substance can be predicted from data obtained from the source substance.

However, there is only one oral repeated dose toxicity study available on the source substance and there is no respective/similar information on the target substance. For that reason no comparison of the toxicological profiles following oral exposure can be made.

Furthermore data on repeated dose toxicity following dermal administration do not provide sufficient evidence to conclude that the target substance does not give rise to a different toxicological profile than that of the source substance. For the source substance there is information available from an OECD guideline 410, repeated dose dermal toxicity: 21/28 day study. For the target substance there is data available from:

- a 10 day dose-range finding study with limited investigations of 5 animals per dose group (for example, no histopathological investigations). Due to its limitations, this study is however not regarded as of sufficient quality to provide information on the toxicological profile as regard systemic toxicity of the target substance;

- a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test where dosing of the animals were interrupted after 8 days due to the clinical condition of the animals, including moribundity and adverse clinical findings. Due to the interruption of the study, this study is however not regarded as of sufficient quality to provide information on the toxicological profile regarding systemic toxicity of the target substance.

Hence, none of the repeated dose toxicity studies on the target substance are of an acceptable quality to be used to justify your read-across.

ECHA concludes that comparison of the toxicological profiles of the substances regarding repeated dose toxicity cannot be done due to lack of suitable and comparable studies on the source and target substances. Therefore there is not an adequate basis for predicting the properties of the registered substance from the data obtained with the source substance.

(v) Conclusion on the read-across approach

Based on the data submitted by you, ECHA concludes that you have not provided adequate and reliable information to demonstrate that the read-across approach is plausible for the endpoint in consideration.

ECHA therefore concludes that the criteria of Annex XI, 1.5. are not met, and the read-across approach, as presented by you, cannot be considered plausible to meet the information requirements.

Route for testing

You proposed testing by the oral route. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA agrees 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, even though the information indicates that human exposure to the registered substance by the inhalation route is likely, the exposure concentrations are likely to be low due to the low vapour pressure of the substance.

Species

You proposed testing in rats. 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.

Other parameters

You proposed to extend the sub-chronic toxicity study (90 day) by including additional examinations/parameters (additional sperm motility parameters and careful examination of reproductive organs/tissues). ECHA notes, that it is at your discretion to perform the intended additional examinations during the testing program, as long as those additional examination do not interfere with the examinations according to test method OECD TG 408 and you use the results to ensure the safe use of the substance. You are reminded that the proposed extension of this study does not fulfil the standard information requirement in the registration dossier for reproductive toxicity set out in Annex X, Section 8.7.3.

c) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

Third party information:
The third party has indicated that the findings in the previously performed sub-acute studies performed with the registered substance and with the analogous substance [redacted] have not resulted in classification for human health endpoints and therefore, according to the commenter, the registered substance meets the definition of a low (sub)acute toxicity profile as defined by [redacted] (2014), [redacted] (2017) (full reference given in the comment). The commenter therefore finds it unlikely that the proposed 90-day study will demonstrate a lower NOAEL for human-relevant effects, and the value of the proposed 90-day study is therefore questioned.

ECHA notes, however, that the sub-acute/screening studies submitted for this dossier do not provide the information required by Annex IX, Section 8.6.2., because the exposure duration is less than 90 days and the number of animals examined per dose group for histopathology and clinical chemistry is significantly lower than in the 90 day sub-chronic toxicity study (OECD TG 408). Therefore, the sensitivity of a 28-day study or a screening study is much lower than that of a 90-day study, and classification of the registered substance cannot be concluded until data from a sub-chronic study are available.

d) Cosmetics uses

In your comments to the draft decision, you indicate that you face difficulties testing the substance because the end use of the substance is cosmetics only and there is a ban for testing cosmetic ingredients under the Cosmetics Regulation (Regulation (EC) N° 1223/2009). However, you acknowledge that other uses than cosmetic uses appear on ECHA's website. You indicate that the Lead Dossier only contains cosmetics uses, and that you have advised your co-registrants that only cosmetics uses will be supported.

ECHA has the following observations.

First, ECHA refers to the news alert jointly developed with the European Commission entitled Clarity on interface between REACH and the Cosmetics Regulation (https://echa.europa.eu/view-article/-/journal_content/title/clarity-on-interface-between-reach-and-the-cosmetics-regulation) and the related fact sheet (https://echa.europa.eu/documents/10162/13628/reach_cosmetics_factsheet_en.pdf/2fbcf6bf-cc78-4a2c-83fa-43ca87cfb314). ECHA also refers to a recent answer from the European Commission to the European Parliament on this issue http://www.europarl.europa.eu/doceo/document/E-8-2019-000044-ASW_EN.html.

As explained in these documents the testing and marketing bans in the Cosmetics Regulation do not apply to testing required under REACH for environmental endpoints, exposure of workers and non-cosmetic uses of substances under REACH.

Second, ECHA notes that registrants within your joint registration still cover many other uses than those in cosmetics. Accordingly, the animal testing and marketing bans set out in

the Cosmetics Regulation do not apply to testing performed for the purposes of covering these non-cosmetic uses.

Third, and in any event, ECHA notes that the registration dossier does not indicate that the substance is handled under strictly controlled conditions and that therefore worker exposure cannot be excluded. Indeed, according to the news alert, the fact sheet and the Commission's response to the European parliament's question referred to above, even if the substance is registered exclusively for cosmetics uses, the animal testing and marketing bans in the Cosmetics Regulation do not apply where animal testing is needed to assess the risks from exposure to workers in the Chemical Safety Assessment.

e) Outcome

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the additional study with the registered substance: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26./OECD TG 408) while the originally proposed test for Sub-chronic toxicity study (90-day), oral route (EU B.26./OECD TG 408) using the analogue substance [redacted] is rejected according to Article 40(3)(d) of the REACH Regulation.

f) Deadline to submit the requested Information

In your comments on the draft decision, you requested for a deadline extension for the "sub-chronic toxicity study" from 18 months to 24 months. Your main argument for the extension is that you foresee a complex and careful development of analytical methods, in particular if the test will be performed on your registered substance and not on the proposed [redacted] analogue.

In your dossier update 8 March 2019 [redacted] you have included additional information about the development of analytical methods from your laboratory. This information originates from your preparations of a different test, a skin penetration assay. The laboratory states that:

"the possibility of evaluating the in-vitro skin penetration profile of branched-nonyl 3,5,5 trimethylhexanoate was considered. However, branched-nonyl 3,5,5 trimethylhexanoate is [redacted] *, making it technically extremely challenging to accurately quantify in biological matrices issued from a skin penetration assay."*

You conclude that for toxicity studies where analytics (in biological matrices) is required, the [redacted] form is preferred.

ECHA has considered your comments and concludes that for performing an OECD TG 408 assay, it is not required to quantify the test material in biological matrices. For such study it is sufficient to characterize as far as possible the chemical identity of the test materials used to expose the animals. ECHA considers that this characterization can be done based on the current information. Therefore your request to prolong the deadline is rejected.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 11 June 2018.

ECHA held a third party consultation for the testing proposal from 21 May 2018 until 5 July 2018. ECHA received information from third parties (see Appendix 1).

This decision does not take into account any updates after **11 March 2019**, 30 calendar days after the end of the commenting period.

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

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

ECHA took into account your comments and did not amend the request(s) or the deadline.

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 decision does not imply that the information provided in your registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the 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 the Member States.

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.