ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 26 February 2018

Addressee: [redacted]

Decision number: CCH-D-2114394588-28-01/F
Substance name: Pentyl propionate
EC number: 210-852-7
CAS number: 624-54-4
Registration number: [redacted]
Submission number: [redacted]
Submission date: 18/05/2017
Registered tonnage band: 100-1000

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

2. **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;**

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 have to submit the requested information in an updated registration dossier by **2 September 2019**. You also have to 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 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.

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Appendix 1: Reasons

TOXICOLOGICAL INFORMATION

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Your registration dossier contains for multiple endpoints adaptation arguments in the form of a grouping and read-across approach under Annex XI, Section 1.5. of the REACH Regulation. ECHA has considered first the scientific and regulatory validity of your read-across approach in general before assessing the individual endpoints (sections 1 and 2).

Grouping of substances and read-across approach

You have sought to adapt information requirements by applying a read-across approach in accordance with Annex XI, Section 1.5, for the endpoints:

- screening study for reproductive/developmental toxicity (Annex VIII, Section 8.7.1)
- pre-natal developmental toxicity study (Annex IX, Section 8.7.2.).

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological or ecotoxicological property is reliable and should be based on recognition of the structural similarities and differences between the source and registered substances[2]. This hypothesis explains why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration. Key physicochemical properties may determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests.

[2] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals.

Similarly, biotic and abiotic degradation may alter the fate and bioavailability of compounds as well as be themselves hazardous, bioaccumulative and/or persistent. Thus, physicochemical and degradation properties influence the human health and environmental properties of a substance and should be considered in read-across assessments. However, the information on physicochemical and degradation properties is only a part of the read-across hypothesis, and it is necessary to provide additional justification which is specific to the endpoint or property under consideration.

The ECHA Read-across assessment framework foresees that there are two options which may form the basis of the read-across hypothesis[3]- (1) (Bio)transformation to common compound(s)- the read-across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed and (2) Different compounds have the same type of effect(s)- the read-across hypothesis is that the organism is exposed to different compounds which have similar (eco)toxicological and fate properties as a result of structural similarity (and not as a result of exposure to common compounds).

Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the quality of the studies which are to be read-across.

You consider to achieve compliance with the REACH information requirements for the registered substance n-pentyl propionate using data of structurally similar substances n-butyl propionate (EC No 209-669-5) and n-propyl propionate (EC No 203-389-7) (hereafter the 'source substances').

Read-across hypothesis

You have provided a read-across documentation as a separate attachment in section 13 of IUCLID.

In your read-across documentation, you have concluded that "*based on the common functional groups (prior to and subsequent to metabolism), their common routes of metabolism and similar physical chemical properties it is considered scientifically robust to use data from propyl and butyl propionate to support the hazard characterization of pentyl propionate*".

As an integral part of this prediction, you propose that the sources and registered substance(s) have similar properties for the above-mentioned information requirements. ECHA considers that this information is your read-across hypothesis.

ECHA's evaluation and conclusion

Based on the information provided, ECHA understands that the read-across hypothesis is based on:

A) Structural similarity (due to common functional groups)
B) Similar toxicological properties of source and target substance with respect to reproductive toxicity
C) Similar metabolism profile
D) Similar toxicological profile of the metabolites
E) Similar physic-chemical properties

[3] Please see ECHA's Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across).

With regard to structural similarity, the source substances and the target substance are alcohols linked via an ester bond to the acid (propionic acid). The structural difference lies in the number of carbons attached to the alcohol groups (i.e., three (propyl) and four (butyl) carbons for the source substances and five (pentyl) carbons for the target substance).

ECHA acknowledges the structural similarity of the substances. However, you have not discussed the impact of the structural differences on the prediction of the toxicological properties with respect to reproductive toxicity for the target substance from the source substances.

With regard to the metabolism profile, it is likely that both the source and target substances are metabolised to the respective alcohols and the acid (propionic acid). ECHA notes that in your read-across justification document you have stated that the metabolism will be rapid and complete. However, you have not provided factual information to support the rate of metabolism.

With regard to toxicological properties of the metabolites you indicate that *"the toxicity of the compound will be driven primarily by the alcohol released rather than the propionic acid"*. You further state that *"The toxicity of the three alcohols, propanol, butanol and pentanol is of a low order. None of the alcohols are reproductive or developmental toxicants, genotoxic or carcinogenic."* However, you have not provided data to support your claim that the alcohols do not have reproductive and developmental toxicity.

With regard to physico-chemical properties, your read-across documentation contains information only on the molecular weight for the source and target substances. Hence, you have not provided sufficient data that the physico-chemical properties of the source substances and the target substance would not influence the human health properties of the substances.

As described above, further elements are needed to establish a reliable prediction for a toxicological property, based on recognition of the structural similarities and differences between the source and registered substances. This could be achieved (if it is possible) by a well-founded hypothesis of (bio)transformation to a common compound(s), or that the registered and source substance(s) have the same type of effect(s), together with sufficient supporting information to allow a prediction of human health properties.

In your comments on the draft decision according to Article 50(1) of the REACH Regulation you have agreed that the read-across justification lacked the necessary detail to support the read-across hypothesis and indicated to strengthen the read-across approach with the missing information.

In conclusion, on the basis of the information available, ECHA does not consider the read-across approach to be a reliable basis to predict the properties of the registered substance for the reasons set out above. Thus, the adaptation does not comply with the general rules of adaptation as set out in Annex XI, section 1.5 of the REACH Regulation. Therefore, your adaptation of the information requirement is rejected.

1. Screening study for reproductive/developmental toxicity (Annex VIII,

Section 8.7.1.)

"Screening for reproductive/developmental toxicity" (test method OECD TG 421 or 422) is a standard information requirement as laid down in Annex VIII, Section 8.7.1. of the REACH Regulation if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from *in vitro* methods that the substance may be a developmental toxicant. No such evidence is presented in the dossier. Therefore, adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have not provided any study record of a screening for reproductive/developmental toxicity in the dossier that would meet the information requirement of Annex VIII, Section 8.7.1.

Instead, 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 screening for reproductive / developmental toxicity (OECD TG 422) with the analogue substance n-propyl propionate (EC No 203-389-7).

However, as explained above in Appendix 1, section "*Grouping of substances and read-across approach* " of this decision, your adaptation of the information requirement is currently rejected.

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

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

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 5.0, December 2016) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

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

Notes for your considerations

For the selection of the appropriate test, please consult ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.5 and 7.6 (version 5.0, December 2016).

You should also carefully consider the order of testing especially the requested screening (OECD TG 421/422) and the developmental toxicity studies (OECD TG 414) to ensure unnecessary animal testing is avoided, paying particular attention to the end point specific guidance (https://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf) p 461/2."

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

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 a pre-natal developmental toxicity (OECD TG 414) with the analogue substance n-butyl propionate (EC No 209-669-5).

However, as explained above in Appendix 1 under "*Grouping of substances and read-across approach*", your adaptation of the information requirement according to Annex XI, Section 1.5., is currently rejected.

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

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

In your comments on the draft decision according to Article 50(1) of the REACH Regulation you have indicated to perform the study 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 5.0, December 2016) Chapter R.7a, Section 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 comments on the draft decision according to Article 50(1) of the REACH Regulation you indicated to perform the study via inhalation route. However, you have not provided any justification to deviate from the oral route. In addition, the substance is irritating to the respiratory tract. More specifically, in the sub-acute toxicity study by inhalation performed with the registered substance, the LOAEC for irritating effects was 350 ppm and the NOAEC 116 ppm.

Hence, the irritating property will also limit the concentrations that could be applied in a pre-natal developmental toxicity study performed by the inhalation route, whereas oral administration usually allows higher dosing.

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.

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 29 June 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.

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend 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 carrying out the tests required by the present decision, it is important to ensure that the particular sample of substance tested is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported. If the registration of the substance covers different grades, the sample used for the new tests must be suitable to assess these.

   Furthermore, 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.