EUROPEAN CHEMICALS AGENCY

Helsinki, 14 October 2016

Addressee: [redacted]

Decision number: CCH-D-2114340407-54-01/F
Substance name: propyl acetate
EC number: 203-686-1
CAS number: 109-60-4
Registration number: [redacted]
Submission number: [redacted]
Submission date: 08.09.2010
Registered tonnage band: 1000 tonnes or more per year

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. **In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2, test method: EU B.10/OECD TG 473) or in vitro micronucleus study (Annex VIII, Section 8.4.2, test method: OECD TG 487) with the registered substance;**

2. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3; test method: OECD TG 476 or TG 490), provided that the study requested under 1. has negative results, with the registered substance;**

3. **Sub-chronic toxicity study (90-day), inhalation route (Annex IX, Section 8.6.2; test method: OECD TG 413) in rats with the registered substance;**

4. **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.**

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

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

"You are required to submit the requested information in an updated registration dossier by **21 April 2020** except for the information requested under point [3] for a sub-chronic toxicity study (90-day) which shall be submitted in an updated registration dossier by **23 October 2017**. You may only commence the extended one-generation reproductive toxicity study as requested under point [4] after **22 January 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 Ofelia Bercaru, Head of Unit, Evaluation E3

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

Appendix 1: Reasons

In the registration, you have adapted the standard information requirements for the following studies:

- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.);
- *In vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study (Annex VIII, Section 8.4.2.);
- *In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.);
- Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3);
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species; and
- Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species

by applying a read-across adaptation following REACH Annex XI, Section 1.5. The read-across approach is described in the following section.

0. 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, 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 read-across hypothesis, together with ECHA's analysis concerning the justification in both a generic and property-specific context.

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

You have provided justifications for read-across to two analogue substances, propan-1-ol and n-butyl acetate. For propan-1-ol, you stated: "*As indicated by toxicokinetic studies (see chapter on toxicokinetics, metabolism and distribution), n-propyl acetate is rapidly hydrolyzed to propan-1-ol and acetate (acetic acid). Available data on propan-1-ol is therefore suitable for filling data gaps of n-propyl acetate.*"

For n-butyl acetate, you stated: "*N-propyl acetate and n-butyl acetate differ structurally by only one –CH2 group and both substances have a similar toxicological profile. The available data for n-butyl acetate is therefore suitable for filling the data gaps of n-propyl acetate due to structural similarities.*"

ECHA therefore understands that your hypothesis has two strands. The first strand is that the registered substance undergoes rapid hydrolysis to propan-1-ol and acetic acid, and that therefore the properties of these two hydrolysis products can be used to predict the properties of the registered substance. The second strand is that n-butyl acetate is structurally similar and has comparable physicochemical properties to the registered substance, and that it can therefore be used to predict the properties of the registered substance. ECHA understands that your hypothesis is the basis on which the human health effects may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach).

0.2 Support of the grouping and read-across approach

Propan-1-ol

In the documentation provided in your comments you state that "*propyl acetate is hydrolysed by several carboxylesterases to propan-1-ol and acetic acid. This hydrolysis step is dependent on the affinity of the carboxylesterases towards the respective ester and on the amount of carboxylesterase present.*" You further argue that the reported toxicokinetic data (supporting the read across hypothesis to propan-1-ol) and summarised as "*Respiratory bioavailability experiments in rats with n-propyl acetate demonstrated the rapid hydrolysis of this acetate ester to its corresponding alcohol. Blood levels of propyl alcohol were between 2.5 and 5-fold greater than propyl acetate within the 90-minute exposure interval*", are referring to an acute toxicokinetics study during which there was "*not enough time for induction of carboxylesterase activity. After repeated exposure, propyl acetate will be rapidly hydrolysed due to the then increased carboxylesterase activity as the result of the induction after repeated exposure.*"

You also conclude that "*the presence of propyl alcohol following propyl acetate inhalation exposure clearly demonstrates that propyl alcohol was the major metabolite of propyl acetate metabolism. Blood levels of propyl alcohol (88 µM) exceeded those of propyl acetate (17 µM) at the first time point measured (5 minutes into the exposure). At the next time point (10 minutes into exposure), the levels of propyl alcohol in the blood were approximately 3-fold higher (102 µM) than the blood levels of propyl acetate (29 µM). Propyl acetate levels peaked at 15 minutes (36 µM) and remained fairly level over the next 15 minutes. Chamber concentrations decreased from time zero, both due to loss to chamber equipment surfaces as well as uptake by the rat (data not shown). Blood propyl alcohol levels were up to 2.5 to 8-fold higher than blood propyl acetate levels from 10 to 90 minutes after the start of the exposure.*"

In your comments, you further conclude that "*a read-across to propan-1-ol may not be justified for acute toxicity endpoint [...] but definitely for endpoints for which repeated exposure is required.*"

n-Butyl acetate

No further information is present in the registration dossier to support the justification for read across to n-butyl acetate as presented in the registration dossier which is as follows: "*N-propyl acetate and n-butyl acetate differ structurally by only one –CH2 group and both substances have a similar toxicological profile. The available data for n-butyl acetate is therefore suitable for filling the data gaps of n-propyl acetate due to structural similarities.*" In your comments you state that "*if comparing the metabolism of propyl acetate and butyl acetate, both substances are hydrolysed by carboxylesterases",* and that the subsequent metabolisation steps involve conversion to the respective aldehyde and the respective acid, and eventually to carbon dioxide and water.

Hence you rely on the fact that both the target and source substances are biotransformed to common compounds. "*As hydrolysis is rapid, the hydrolysis products predominate with regard to potential systemic toxic effects.*" ECHA notes that you have not substantiated the rate of hydrolysis for n-butyl acetate.

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

Propan-1-ol

ECHA notes that, in accordance with Annex XI, section 1.5 of the REACH regulation, "*similarities may be based upon common precursors and/or the likelihood of common breakdown products via physical and biological processes, which result in structurally similar chemicals*". ECHA understands that the hypothesis is that the registered substance undergoes rapid hydrolysis to propan-1-ol and acetic acid, and that therefore the properties of these latter two substances can be used to predict the properties of the registered substance. ECHA accepts that propan-1-ol is indeed a relevant hydrolysis product of the registered substance, and that data on propan-1-ol is informative on the effects due to the registered substance after hydrolysis.

In your comments, you indicate that "*as the reaction is rapid, the most considerable part of the n-propyl acetate will be hydrolysed and metabolised shortly after entering the body.*" And you reported a study that "*demonstrate that hydrolysis is rapid as 5 minutes after exposure to propyl acetate vapour the concentration of propyl alcohol exceed the concentration of the ester by far, and that level of propyl alcohol started to decrease 15 minutes, indicating that further metabolisation steps follow immediately.*" However, under this hypothesis, ECHA considers that there is no basis set out in relation to the properties of the registered substance prior to its hydrolysis to propan-1-ol and acetic acid from the properties of propan-1-ol.

Following inhalation exposure to propyl acetate, the toxicokinetic information presented shows that there is significant exposure to propyl acetate at all time points within the 90-minute period of the study provided. Accordingly propyl acetate is present, and ECHA notes that you have not provided any basis for predicting the properties of the (parent) registered substance from propan-1-ol, other than through its hydrolysis. Therefore, ECHA considers that the hypothesis provided in respect of propan-1-ol does not provide a reliable basis whereby human health effects may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach).

n-Butyl acetate

ECHA understands that you have attempted to demonstrate similarity in the toxicological properties of the registered substance (n-propyl acetate) and the analogue (n-butyl acetate) based on structural similarities of the source and the target substances, which "*differ structurally by only one $-CH_2$ group*" in the chain.

In your comments, you have provided additional information to substantiate your claim of similarity. Structural similarity is a prerequisite for applying the grouping and read-across approach, but ECHA does not accept in general or this specific case that structural similarity *per se* is sufficient to enable the prediction of human health properties of a substance, since structural similarity does not always lead to predictable or similar human health properties.

Likewise, although you propose that "*both substances have a similar toxicological profile*", you have not provided sufficient data to substantiate this proposal, and ECHA does not accept that similarity of toxicological properties by itself necessarily provides a basis for a reliable prediction of properties. You have provided a well-founded hypothesis of (bio)transformation to a common compound(s), to allow a prediction of human health properties that does not underestimate risks.

However ECHA considers that, as described above, and acknowledging that the read-across justification may be plausible, the requirement of Annex XI, 1.5, that human health effects may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach), has not been met.

0.4 Conclusion on the read-across approach

ECHA considers that structural similarity alone is not sufficient for predicting toxicological properties. It has to be justified why such prediction is possible in view of the identified structural differences and the provided evidence has to support such explanation. With the additional information provided, which still have to be further substantiated, ECHA considers that, even though there appears to be some likelihood for acceptance of the read-across approach, for the following endpoints the conditions required to predict the properties of the registered substance are not met at this stage and therefore your adaptation cannot be accepted:

- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.);
- *In vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study (Annex VIII, Section 8.4.2.);
- *In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.);
- Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3);
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species; and
- Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species.

Thus, currently the adaptation does not comply with the general rules of adaptation as set out in Annex XI, 1.5.

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

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

An "*In vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study" is a standard information requirement as laid down in Annex VIII, Section 8.4.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a key study record for a Chromosomal aberration test in Chinese hamster lung fibroblast cell line (as described by Ishidate *et al.*, 1984), (not an OECD Test guideline) with the analogue substance n-butyl acetate (EC number 204-658-1).

However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement cannot be accepted. In the comments to the draft decision you agreed with the information requirement in the draft decision, as "*the read-across for these specific endpoint(s) may not be sufficiently justifiable*".

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

ECHA considers that the *in vitro* mammalian chromosome aberration test (test method EU B.10./OECD TG 473) and the *in vitro* micronucleus test (OECD TG 487) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.2. of the REACH Regulation.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* cytogenicity study in mammalian cells (test method: EU B.10./OECD TG 473) or *in vitro* mammalian cell micronucleus study (test method: OECD TG 487).

2. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

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

An "*In vitro* gene mutation study in mammalian cells" is an information requirement as laid down in Annex VIII, Section 8.4.3. of the REACH Regulation, "if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2." is obtained. ECHA notes that the registration dossier does not contain an appropriate study record for the information requirement of Annex VIII, section 8.4.2 (as per section 1 above), while a negative result was obtained in the OECD 471 study provided to meet the information requirement of Annex VII, section 8.4.1.

Therefore, adequate information *on in vitro* gene mutation in mammalian cells needs to be present in the technical dossier for the registered substance to meet this information requirement provided that the study required under section 1 above returns a negative result.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a key study record for an *in vitro* gene mutation test in CHO cells (HPRT Locus Assay) (OECD TG 476) with the analogue substance propan-1-ol (EC number 200-746-9).
However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement cannot be accepted. In the comments to the draft decision you agreed with the information requirement in the draft decision, as *"the read-across for these specific endpoint(s) may not be sufficiently justifiable"*.
The information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

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

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, provided that the study requested under section 1 displays negative results, you are requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* mammalian cell gene mutation test (test method: OECD TG 476 *or* OECD TG 490).

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

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

A "sub-chronic toxicity study (90-day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

In the technical dossier, you have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records for two 90-day inhalation studies: EPA OTS 798.2450 (90-Day Inhalation Toxicity) and EPA 540/09-91-123, with the analogue substance n-butyl acetate (EC number 204-658-1).

However, as explained above in section 0.4 of this decision, ECHA considers that, even though there appears to be some likelihood for acceptance of the read-across approach, the conditions are not met at this stage and therefore your adaptation of the information requirement cannot be accepted.

Therefore the information provided on this endpoint in the technical dossier for the registered substance 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. The information provided in the technical dossier and the chemical safety report on properties of the registered substance (liquid with vapour pressure of 47.9 hPa at 25 °C), its uses (exposure of professional workers by inhalation because of transfer of the registered substance is described, as per PROC 8a, 8b and 9) and the reported exposure concentrations (up to [redacted] mg/m^3 /workers, long-term local effects) indicate that human exposure to the registered substance by the inhalation route is likely. Furthermore, there is potential concern for local respiratory tract effects following inhalation exposure because the substance is classified for eye irritation (cat. 2) and the classification as STOT SE 3 (H336) i.e. due to narcotic effects and/or respiratory tract irritation.

Therefore, ECHA considers that the inhalation route is the most appropriate route of administration. Hence, the test shall be performed by the inhalation route using the test method OECD TG 413.

According to the test method OECD TG 413 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: Sub-chronic inhalation toxicity: 90-day study (test method: OECD TG 413) in rats.

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

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

The basic test design of an extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X. If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

a) The information requirement

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records for a two-generation study (OECD TG 416) with the analogue substances propan-1-ol and n-butyl acetate (EC numbers 200-746-9 and 204-658-1 respectively).

However, as explained above in section 0.4 of this decision, ECHA considers that, even though there appears to be some likelihood for acceptance of the read-across approach, the conditions are not met at this stage and therefore your adaptation of the information requirement cannot be accepted.

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

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).

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 an organic liquid, with a vapour pressure of 47.9 hPa at 25°C and boiling point of 101°C, 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, no triggers for the extension of Cohort 1B and the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity)] have been identified based on the available information. However, the sub-chronic toxicity study (90-day) requested in this decision (request [3]) and/ or any other relevant available information, including information which has become available since the point in time when the sub-chronic toxicity study (90-day) was requested, may provide information that could trigger such 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 [exact date – 12 months from the date of the decision].

In such update you may also include your considerations whether in light of these results and/ or other available information if changes in the study design are needed. If, on the basis of this update, a need for changes to the study design is identified, ECHA will inform you by [exact date - 15 months from the date of the decision] (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 [exact date - 15 months from the date of the decision], 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 which results will need to be submitted by [exact date covering all requests.

Notes for your consideration

When submitting the study results of the sub-chronic toxicity study (90-day) you may also include in the registration update your considerations whether changes in the study design are needed because new information shows that the triggers for expanding the study as described in column 2 of Section 8.7.3. are met (see also ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.6 (version 4.1, October 2015)). Furthermore, in cases where you have already commenced the study in accordance with this decision, you may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study 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.

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

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

A "pre-natal developmental toxicity study" (test method EU B.31./OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing two study records for a pre-natal developmental toxicity study (OECD TG 414), in rats with the analogue substances propan-1-ol and n-butyl acetate (EC numbers 200-746-9 and 204-658-1, respectively).

However, as explained above in section 0.4 of this decision, ECHA considers that, even though there appears to be some likelihood for acceptance of the read-across approach, the conditions are not met at this stage and therefore your adaptation of the information requirement cannot be accepted.

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

According to the test method EU B.31/OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default 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.

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 (rats or rabbits) by the oral route.

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

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

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

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing one study record for a pre-natal developmental toxicity study (no test guideline reported), in rabbits with the analogue substance n-butyl acetate (EC number 204-658-1).

However, as explained above in section 0.4 of this decision, your adaptation of the information requirement cannot be accepted.

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

According to 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 (rabbits or rats) 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.

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 4 November 2015.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation

ECHA notified you of the draft decision and invited you to provide comments. ECHA took into account your comments, which were sent within the commenting period, and they are reflected in the Reasons (Appendix 1).

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) for amendment.

ECHA received proposal(s) for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendment(s).

ECHA referred the draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

In addition, you provided comments on the draft decision. These comments were not taken into account by the Member State Committee as they were considered to be outside of the scope of Article 51(5).

The Member State Committee reached a unanimous agreement on the draft decision during its MSC-48 meeting and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. The substance subject to the present decision is provisionally listed in the Community rolling action plan (CoRAP) for start of substance evaluation in 2017.

2. This compliance check decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage.

3. 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.

4. 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.