EUROPEAN CHEMICALS AGENCY

Helsinki, 17 September 2019

Addressee: [redacted]

Decision number: CCH-D-2114482148-43-01/F
Substance name: Dibutyl phosphonate
EC number: 217-316-1
CAS number: 1809-19-4
Registration number: [redacted]
Submission number: [redacted]
Submission date: 11/10/2017
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. **Skin sensitisation (Annex VII, Section 8.3.) with the registered substance:**
   - i. ***in vitro/in chemico* skin sensitisation information on molecular interactions with skin proteins, inflammatory response in keratinocytes and activation of dendritic cells (Annex VII, Section 8.3.1.); and**
   - ii. **in case the *in vitro/in chemico* test methods specified under point i) are not applicable for the substance or the results obtained are not adequate for classification and risk assessment:**

     ***in vivo* skin sensitisation information (Annex VII, Section 8.3.2.; test method: OECD TG 429) with the registered substance;**
2. **Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD 421 or 422) in rats, oral route with the registered substance;**
3. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) in rats with the registered substance;**
4. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**

You have to submit the requested information in an updated registration dossier by **24 September 2021**. 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 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

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 1.2, 2.3, 2.4).

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.)
- Sub-chronic toxicity (90-day) study (Annex IX, Section 8.6.2.)
- 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. Similarly, biotic and abiotic degradation may alter the fate and bioavailability

[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.

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 Dibutyl phosphonate (DBHP, hereafter the 'target substance')using data of structurally similar substances Dimethyl phosphonate, Fosetyl-Aluminium, and butanol (hereafter the 'source substances', respectively DMHP, Fosetyl-Al, and BuOH).

You have provided a read-across documentation in the CSR, toxicokinetics section.

You use the following main arguments to support the prediction of properties of the registered substance from data for source substances within the group:

1. *"...it can be assumed that DBHP is transformed in vivo into monobutyl phosphonate and further degraded into phosphorous acid and butanol. [...]*
2. *Dimethyl, Diethyl and dibutyl phosphonates are all spontaneously hydrolysed in water to the correspondent monoalkyl phosphorous acid and afterwards to the alcohols and to phosphorous acid [...]*
3. *The fact that the first degradation step leads to the alcohol and phosphorous acid may justify also that ADME is very similar between rats and mice (DMHP) and rats and dogs (Fosetyl-Al). [...]*
4. *The alcohols produced by DMHP and Fosetyl-Al are further oxidised in vivo to the aldehyde, the acids and eventually to CO2. Exactly the same pathway is followed by butanol, ..."*

As an integral part of this prediction, you propose that the source 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

Your proposed main adaptation argument is that the similarity in chemical structure between the registered and source substances is a sufficient basis for predicting the properties of the registered substance for other endpoints. Structural similarity is a prerequisite for applying the grouping and read-across approach. However similarity in

[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).

chemical structure does not necessarily lead to predictable or similar human health properties in other endpoints. Your justification based on structural similarity has not established why the prediction is reliable for the human health end-points for which the read across is claimed. More specifically, with regards to your main arguments 1-4 above:

1) Due to the absence of results from studies with repeated exposure or toxicokinetics conducted with the target substance, there is no evidence available to support your argument of similarity of toxicokinetics and toxicodynamics between the target substance and the source substances, particularly DMHP. Instead, lower tier studies indicate differences, e.g. in *in vivo* mammalian genotoxicity.
2) For the target substance, the hydrolysis and biodegradation results as reported in the technical dossier demonstrate degradation halftimes from several hours to several days, depending on pH. Although hydrolysis may occur eventually, systemic uptake and exposure to the parent compound seems likely. There is no comparison between the hydrolysis rates of the target and source substances, *e.g.* under gastric conditions.
3) The argumentation regarding likely degradation is not substantiated for the target substance with experimental toxicological data. Apart from those data mentioned under 2), there is no data available on the target substance to compare the quantitative and qualitative aspects of metabolism between the target and source substances.
4) While this argument relates to the source substances, there is no experimental evidence with the target substance available. Thus, the prediction for higher-tier endpoints is not sufficiently demonstrated.

ECHA has taken into account all of your arguments together. ECHA firstly notes that you have not provided reliable supporting evidence to prove your assumptions. Therefore these arguments do not add to one another to provide sufficient basis for read-across. Secondly, the defects of each individual argument are not mitigated by the other arguments you have provided, and so ECHA considers that the arguments when taken all together do not provide a reliable basis for predicting the properties of the registered substance.

Therefore, ECHA considers that this grouping and read-across approach does not provide a reliable basis whereby the human health effects of the target substance may be predicted from data for source substances within the group. Hence, this approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation.

As described above, further elements are needed to establish a reliable prediction for a toxicological or ecotoxicological property. This should be based on recognition of the structural similarities and differences between the source and registered substances. Furthermore, this could be achieved *e.g.* by demonstrating that the registered and source substances have the same type of effects for the respective endpoint in question with adequate supporting information to allow a judgment on the validity of the prediction of the respective human health properties listed below.

1. Skin sensitisation (Annex VII, Section 8.3.) with the registered substance

"Skin sensitisation" is a standard information requirement as laid down in Annex VII, Section 8.3. of the REACH Regulation: "*Information allowing: - a conclusion whether the substance is a skin sensitiser and whether it can be presumed to have the potential to*

produce significant sensitisation in humans (Cat. 1A) and -risk assessment, where required". According to subsection 8.3.1 this includes information from *in vitro/in chemico* test addressing each of the following key events of skin sensitisation: (a) molecular interactions with skin proteins, (b) inflammatory response in keratinocytes, (c) activation of dendritic cells. Provided that the *in vitro/in chemico* test methods are not applicable, or the results obtained from those studies are not adequate for classification and risk assessment according to point 8.3, also information from an *in vivo* study is required according to subsection 8.3.2.

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 provided a study record for *in vitro* skin sensitisation: human Cell Line Activation Test (h-CLAT) (comparable to OECD TG 442E). However, this study does not provide the information required by Annex VII, Section 8.3., because the method used has not been validated and is not properly described. More specifically, the OECD TG 442 (h-CLAT) has been validated to assess gene expression on cell surface markers which is then measured by with flow cytometry (FACS). The use of quantitative PCR (qPCR) to measure gene expression has not been validated and hence the results of this assay cannot be accepted as the in-vitro method cannot be considered as a"suitable" pursuant to Annex XI, Section 1.4 of the REACH Regulation.

Furthermore, you have provided a study record for a QSAR Toolbox prediction (2017), which identified an analogue substance "diethyl phosponate, CAS 762-04-9". ECHA notes that you have not provided adequate documentation for the QSAR prediction, as requested in Annex XI, Section 1.3 of the REACH Regulation, i.e. QMRF and QPRF are missing from the dossier. However, ECHA also notes that diethyl phosphonate has been classified as moderate skin sensitiser (CLP Cat. 1B) by the registrant of that substance. ECHA observes that you did not classify the registered substance as skin sensitiser (CLP Cat 1B), based on a prediction using the information from the analogue substance diethyl phosphonate. Apparently, you did not consider the result from the prediction as adequate for the classification and labelling and thus the third condition of Annex XI Section 1.3 is not met.

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.

To address the skin sensitisation endpoint *in vitro/in chemico* methods have been developed. The ECHA Guidance on information requirements and chemical safety assessment (version 5.0, December 2016), Chapter R.7.3 describes the applicability and the limitations of the currently adopted test methods. ECHA Guidance also lists the *in vitro/in chemico* methods that have either already been validated or are under validation assessment at the time of the publication. It is your responsibility to select the test methods which are most appropriate for the registered substance.

Provided that an *in vivo* study is required, the murine local lymph node assay (LLNA; EU B.42./OECD TG 429) is the first-choice method for *in vivo* testing.

In your comments to the draft decision, you have indicated that additional information will be provided on the validity of the non-guideline h-CLAT assay and *in vitro* methods addressing molecular interactions with skin proteins (OECD TG 442C, DPRA) and

inflammatory responses in keratinocytes (OECD TG 442D, LuSens) will be performed. In addition to the *in vitro* methods, you have indicated that the experimental data will be supported with updated QSAR systems.

ECHA notes the additional information with *in vitro* assays is not available in the registration dossier. In case conflicting results are obtained from the *in vitro* assays, limitations of each assay should be considered, e.g., lack of or limited metabolic capacities that may result in false predictions.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information on skin sensitisation derived with the registered substance subject to the present decision:

i. *in vitro/in chemico* information on molecular interactions with skin proteins, inflammatory response in keratinocytes and activation of dendritic cells (Annex VII, Section 8.3.1.) and
ii. in case the *in vitro/in chemico* test methods specified under point i) are not applicable for the substance or the results obtained are not adequate for classification and risk assessment:
local lymph node assay (Annex VII, Section 8.3.2.; test method: EU B.42./OECD TG 429) with the registered substance.

Notes for your consideration

In case positive prediction is obtained from the *in chemico/in vitro* test methods, ECHA notes that the findings from the test using an analogous substance (OECD TG 406) may be used to conclude on the potency (Cat 1A or not) of sensitising properties of the registered substance, as specified in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.3.6.3.

2. Screening 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. As apparently no such evidence exists, 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.

You have also sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing the study records for analogue substances as listed below:

- Screening study for reproductive/developmental toxicity (OECD TG 421) (OECD 2004; secondary reference) with the analogous substance DMHP in rats;
- Two-generation reproductive toxicity study (equivalent to OECD TG 416) (EPA

1990b) with the analogous substance fosetyl-Al in rats;
- Unspecified reproductive toxicity study (non-guideline) (OECD 2001c) with the analogous substance butanol in rats;
- Unspecified reproductive toxicity study (non-guideline) (Sitarek et al, 1994) with the analogous substance n-butanol in female rats.

These studies are referred to as weight of evidence studies. However, as they were performed with analogous substances ECHA has evaluated them against the requirements of Annex XI, Section 1.5 (Grouping of substances and read-across approach). As explained above in Appendix 1, section "Grouping of substances and read-across approach" of this decision, your adaptation of the information requirement according to Annex XI, Section 1.5. is rejected.

Because the source substances used in such studies are considered inadequate as source substances for the read-across, ECHA considers that the studies do not contribute to an overall weight of evidence to cover this information requirement. ECHA further observes that a weight of evidence adaptation would require additionally adequate and reliable documentation, as stipulated by REACH Annex XI, 1.2, last sentence. ECHA considers that, if an improved read-across adaptation is acceptable, these existing studies may be adequate to fulfil the information requirement for this endpoint.

Therefore, 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 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 6.0, July 2017) 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 to the draft decision, you explain that "The necessity of this test is included in a tiered approach, as previously explained". ECHA observes that you refer to a combined repeated dose toxicity and screening for reproductive/developmental toxicity test OECD TG 422 with the analogous substance dioctylphosphonate (see comment to request 3, below). ECHA notes that any read-across adaptation must comply with the general rules for adaptation according to Annex XI, Section 1.5 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: 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 consideration

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 6.0, July 2017).

ECHA observes that you attempted to adapt the information requirement for several endpoints according to REACH Annex XI, section 1.5 (grouping and read-across). To this end, the test method OECD TG 422 is usually preferable over OECD TG 421 when used as a bridging study, because it includes additional parameters and possibly longer exposure duration of male animals, which would allow comparison with findings from the higher-tier studies conducted with the source substance.

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 486.)

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

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 sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records for

- sub-chronic and chronic toxicity studies with rats and mice with the analogous substance DMHP (NTP 1985b)
- sub-chronic toxicity studies in rats and chronic toxicity studies in dogs with the analogous substance fosetyl-Al (EPA 1990a; EFSA 2005a)
- sub-chronic toxicity in rats by the oral and inhalation route with the analogous substance n-butanol (OECD 2001a; Korsak et al 1994).

These two studies are referred to as weight of evidence studies. However, as they were performed with analogous substances ECHA has evaluated them under Annex XI, Section 1.5 (Grouping of substances and read-across approach). As explained above in Appendix 1, section "Grouping of substances and read-across approach" of this decision, your adaptation of the information requirement according to Annex XI, Section 1.5. is rejected.

Because the source substances used in such studies are considered inadequate as source substances for the read-across, ECHA considers that the studies do not contribute to an overall weight of evidence to cover this information requirement. ECHA further observes that a weight of evidence adaptation would require additionally adequate and reliable documentation, as stipulated by REACH Annex XI, 1.2, last sentence. ECHA considers that, in case an improved read-across adaptation was acceptable, these existing studies may be adequate to fulfil the information requirement for this endpoint.

Therefore, your adaptation of the information requirement is currently rejected.

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

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 5.0, December 2016) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. More specifically, the substance is a liquid of very low vapour pressure and no uses with spray application are reported that could potentially lead to aerosols of inhalable size. Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

According to the test method EU B.26./OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

In your comments to the draft decision, you outline a testing strategy with tiered testing comprised of 1) a pre-natal developmental toxicity study (OECD TG 414) and 2) an *in vitro* metabolism study, both with the registered substance. Also, 3) a combined screening study (OECD TG 422) with the analogous substance, dioctylphosphonate is ongoing. You further state 4) that you will consider testing of the registered substance in a sub-chronic toxicity study (OECD TG 408) or a combined repeated dose toxicity and screening for reproductive/ developmental toxicity study (OECD TG 422), in case further investigations are necessary. Furthermore, 5) you mention limited exposure of workers to the substance.

ECHA notes that in the above testing strategy, the concern for specific target organ toxicity to the lung, liver and testes/sperm raised by studies with the analogous source substance Dimethylphosphonate and Fosetyl-Al, might not be covered. More specifically, the findings from 14-day acute dose range finding studies do not correspond with the findings from the sub-chronic and chronic studies with these source substances, as presented in the technical dossier. Therefore, *(ad 1)* the shorter exposure duration in a PNDT study (OECD TG 414) and the differences in organ investigations and sex of the exposed animals do not allow conclusions on the effects in lung, liver and testes after (sub-)chronic exposure durations. Should *(ad 2)* an *in vitro* metabolism study with the registered substance demonstrate rapid and quantitative hydrolysis of the registered substance, that is before any uptake of parent compound is likely, the resulting metabolites should be covered by an updated read-across adaptation. ECHA notes that more sensitive studies with a metabolite (di-/sodium phosphonate) exist, than currently provided in the technical dossier.

A successful read-across adaptation predicts properties of the target substance from the source substance(s). An absence of effects for the target substance cannot be predicted from adverse effects with one or more source substance(s). In the absence of repeated dose toxicity studies (OECD TGs 407, 408, 422) with the registered substance, it will be challenging to justify *(ad 3)* whether the properties of Dibutylphosphonate are more likely to be similar to those of Dimethylphosphonate or to those of Dioctylphosphonate. ECHA notes that any read-across adaptation must comply with the general rules for adaptation according to Annex XI, Section 1.5 of the REACH Regulation. In this context, ECHA wishes to remind you that *(ad 4)*, if the results from further testing do not support the read-across hypothesis, the information requirements may need to be fulfilled by testing with the

registered substance. Any adaptation based on negligible exposure *(ad 5)* must comply with the general rules of Annex XI, Section 3 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: Repeated dose 90-day oral toxicity study (test method: EU B.26./OECD TG 408) in rats.

4. 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.

In your dossier, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Sections 1.2 and 1.5, by providing study records for a

- Screening study for reproductive/developmental toxicity (OECD TG 421) (OECD 2004; secondary reference) with the analogous substance DMHP in rats;
- Unspecified developmental toxicity study (non-guideline) (EFSA 2005d) with the analogous substance fosetyl-Al in rats;
- Unspecified developmental toxicity study (non-guideline) (EFSA 2005a) with the analogous substance fosetyl-Al in rabbits;
- Unspecified developmental toxicity study (non-guideline) (Nelson et al, 1988) with the analogous substance n-butanol in rats;
- Unspecified developmental toxicity study (non-guideline) (Sitarek et al, 1994) with the analogous substance n-butanol in rats.

However, ECHA notes that your adaptation does not meet the general rule for adaptation of Annex XI; Section 1.2. (weight of evidence) because the study record for a "reproduction/ developmental toxicity screening test" (test method: OECD TG 421) does not provide the information required by Annex IX, Section 8.7.2., because it does not cover key parameters of a pre-natal developmental toxicity study, such as examinations of foetuses for skeletal and visceral alterations.

Furthermore, ECHA notes that a robust study summary is required under Article 10(a)(vii), and ECHA considers that the information provided in the endpoint study records do not meet the requirements of a robust study summary, as defined in Article 3(28). Specifically, none of the endpoint study records for the developmental toxicity studies listed above does provide coverage of the key parameters of a pre-natal developmental toxicity study. More specifically, the reporting does not detail the major investigations, any deviations from a guideline-conforming pre-natal developmental toxicity study, nor considerations of how these deviations would have impacted the reliability. For more detailed information, please refer to the practical guide "How to report robust study summaries", available at: http://echa.europa.eu/documents/10162/13643/pg_report_robust_study_summaries_en.pdf. ECHA considers there is not sufficient information to make an independent assessment of the studies, minimising the need to consult the full study report.

For these studies,you have additionally failed to meet the requirement of Annex XI, Section 1.5. that adequate and reliable documentation of the applied method shall be provided.

Furthermore, as explained above in Appendix 1, section "grouping and read-across" of this decision, your adaptation of the information requirement according to Annex XI, Section 1.5 (grouping and read-across), is rejected.

Therefore, 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 6.0, July 2017) 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 according to the draft decision, you agree to perform this test.

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 24 July 2017.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:
ECHA notified you of the draft decision and invited you to provide comments.

ECHA took into account your comments and 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 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.