EUROPEAN CHEMICALS AGENCY

Helsinki, 16 July 2018

Addressee [redacted]

Decision number: CCH-D-2114412040-75-01/F
Substance name: Ethyl 4-hydroxybenzoate
EC number: 204-399-4
CAS number: 120-47-8
Registration number: [redacted]
Submission number: [redacted]
Submission date: 05.04.2013
Registered tonnage band: 10-100T
Joint submission tonnage band: 100-1000T

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

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

3. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) with the registered substance if the test listed in section 2 gives a negative result;**

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

5. **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 **25 January 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], 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.

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Appendix 1: Reasons

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 the endpoints Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2), In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2.), In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.), Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.) and Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) adaptation arguments in 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, 3, 4 and 5).

0. Grouping of substances and read-across approach

You have sought to adapt the information requirements for Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2), In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2.), In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.), Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.) and Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) by applying a read-across approach in accordance with Annex XI, Section 1.5. According to Annex XI, Section 1.5., there needs to be structural similarity among the substances within a group or category and furthermore, 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). Furthermore, Annex XI, Section 1.5. lists several additional requirements, including that adequate and reliable documentation of the applied method have to be provided.

You consider to achieve compliance with the REACH information requirements for the registered substance ethyl 4-hydroxybenzoate (ethyl paraben) (hereafter 'target substance' or registered substance) using data of structurally similar substances: methyl 4-hydroxybenzoate (EC No 202-785-7) (hereafter 'source substance' or methyl paraben) and propyl 4-hydroxybenzoate (EC No 202-307-7) (hereafter 'source substance' or propyl paraben).

You have provided read-across documentation as a separate attachment in the dossier ([redacted].pdf). In the above-mentioned document, you also provided a data matrix with several relevant physico-chemical properties of the target and source substances and with mammalian toxicity data. In addition, in the Section 7.1. of IUCLID dossier you provided several toxicokinetics studies with the registered substance, on the basis of which you concluded that "*Ethylparaben is rapidly absorbed, metabolised and eliminated predominantly via urine.*"

You use the following arguments to support your read-across: similarity in structure, physico-chemical and toxicological properties, and similarity in profiles with the OECD toolbox. In respect of similar metabolic pathways, you state: "*In summary, ethylparaben, methylparaben and propylparaben were rapidly absorbed, metabolized to p-hydroxybenzoic acid, p-hydroxyhippuric acid and conjugates with glucuronic acid and excreted mainly via urine. No species differences were observed.*" ECHA understands that the justification of your read-across is that the source and target substances are rapidly (bio)transformed to identical/similar substances and that therefore the toxicological properties with respect to repeated dose toxicity, genetic toxicity and reproductive toxicity are similar and can be therefore predicted. You propose that the source and target substances have "*structural similarity and correlated properties*" (physico-chemical, toxicological properties) for the above-mentioned information requirements.

ECHA considers that this information is your read-across hypothesis.

ECHA's evaluation and conclusion

Similarity in structure, physico-chemical, ecotoxicological and toxicological properties

Your proposed adaptation argument is that the similarity in structure/ physico-chemical/ ecotoxicological/ toxicological properties between the source and target substance is a sufficient basis for predicting the properties of the substance. Similarity in structure/ physico-chemical/ ecotoxicological/ toxicological properties is a prerequisite for applying the grouping and read-across approach, but per se is not sufficient to enable the prediction of human health properties of a substance. This is because similarity in structure/ physico-chemical/ ecotoxicological/ toxicological properties does not always lead to predictable or similar human health properties. Further elements are needed[2], such as a well-founded hypothesis of (bio)transformation to a common compound(s), or that different compounds have the same type of effect(s), to allow a prediction of human health properties that does not underestimate risks.

Similar profiling with OECD toolbox

You have provided 'profiles' in section 2.4.1 of the "Rationale & justification for the Analogue read across approach used in the registration dossier of ethyl 4-hydroxybenzoate CAS No. 120-47-8". The methodology used to provide these profiles is not stated, and consequently ECHA is unable to evaluate what this information is. ECHA therefore considers that this information does not show that the read-across is able to predict the properties of the registered substance.

[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 and 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).

(Bio)transformation to common product

The registered and source substances are all esters of p-hydroxybenzoic acid; ECHA understands that your argument is that there is rapid hydrolysis of the esters to the p-hydroxybenzoic acid (and subsequent metabolites), and that the corresponding methyl/ethyl/propyl alcohols have known toxicological properties. Thus, ECHA understands that the basis for your read-across is the hypothesis that the systemic availability of the p-hydroxybenzoic acid is solely responsible for the toxicity.

Firstly, ECHA notes that the toxicokinetic properties of the substances is unclear because the rate of uptake and (bio)transformation is not provided. ECHA notes that while for the registered substance the existing evidence in the dossier (in the Toxicokinetics endpoint) shows that ethyl paraben metabolizes to p-hydroxybenzoic acid, p-hydroxyhippuric acid and conjugates with glucuronic acid, for the source substances, there are no toxicokinetics data provided in the dossier. In the read-across justification in Section 13 of IUCLID, only references to relevant studies are given but no study summaries are provided. Thus ECHA concludes that you have not provided sufficient information to characterise the formation of the common p-hydroxybenzoic acid metabolite from the source and registered substances, and on this basis, it is not possible to conclude that there is only systemic exposure to the common hydrolysis product (p-hydroxybenzoic acid), and not to the parent esters.

Secondly, from the data provided in the Toxicokinetics section of the IUCLID dossier, there is systemic exposure to the parent registered substance, as hours after administration of the test substance, the unmetabolised test substance was found in animals' serum (Heim 1957, after 2 h) and urine (Derache and Gourdon 1963, after 1.5h, Kiwada 1979, after 5h). Given that there is systemic exposure to parent compound, the above hypothesis that underlies your read-across is incomplete: not only the formed p-hydroxybenzoic acid may be responsible for the toxicity, but also the unchanged parent substance. Without a correct and complete basis to justify the application of read-across, this read-across cannot be accepted. Formally, you have not provided an adequate basis for predicting the properties of the systemically available parent substance per se, and consequently you have not provided a reliable basis for predicting the properties of the registered substance from the source substances.

Additionally, ECHA notes that different effects at different dose levels are observed in the provided repeated dose and reproductive toxicity studies. For example, for the repeated dose toxicity, the data matrix in Table 4 from the read-across justification provided a NOAEL (28 d, rat) of 250 mg/kg bw/d for methylparaben which is about 5 folds lower than for the target substance (NOAEL (175 d, rat): 1200 mg/kg bw/d) and propylparaben (NOAEL (OECD 422, rat): 980-1076 mg/kg bw/d). The study with methylparaben is not provided in the dossier and the effect basis on which this value was derived cannot be assessed. Significant reproductive effects were observed in the study performed with ethyl paraben (Moriyama, et al. 1975), which were not seen with other parabens. This is evidence which contradicts your hypothesis of similar toxicology and which indicates that either the rate of formation of p-hydroxybenzoic acid is different between the source and target substances, or that p-hydroxybenzoic acid is not the only responsible agent for the toxicity.

Additionally, ECHA has taken into account all of your arguments together. ECHA firstly notes that you have not provided a reasoning as to why these arguments add to one another to provide sufficient basis for read-across. Secondly, ECHA considers that the arguments and submitted data, when taken all together do not provide a proper basis for predicting the

properties of the registered substance. ECHA considers that this grouping and read-across approach does not provide a robust basis whereby the human health effects may be predicted from data for reference substance(s) within the group, and hence does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation.
ECHA notes that there are specific considerations for the individual endpoints, which also result in a failure to meet the requirement of Annex XI, 1.5, and these are set out under the endpoint concerned.

Consideration of your comments on the draft decision

Following the notification of the draft decision, you have provided comments to the draft decision. You disagreed with the rejection of the read-across and submitted further arguments to support your hypothesis. In respect of biotransformation to a common product, you questioned in the comments what ECHA means by "*the methodology used to provide these profiles is not stated*".

ECHA notes that adequate and reliable documentation of the applied method is required by Annex XI, 1.5. and it is also a condition specified by ECHA Guidance Chapter R.6-QSARS and Grouping of Chemicals. You have not provided adequate documentation of the methodology, as specified above. You assert that OECD Toolbox v 2.3 and METEOR NEXUS v2.02 are "globally scientifically accepted", but this is not sufficient to show that a scientific method is robust. ECHA understands that these programmes estimate quantitative structure activity relationships for metabolism, and so you must meet the criteria of Annex XI, 1.3 governing QSARs. You have not provided adequate and reliable documentation of the applied method.

In support to biotransformation leading to the same main metabolite "*p-hydroxy benzoic acid*", you state this is supported by the Meteor Nexus Prediction Report and the OECD Toolbox prediction. ECHA notes that the OECD toolbox prediction "(please refer to the attached read across justification; Annex I, p.8)", the "Profiling with the OECD Toolbox" in the read-across justification, contains no direct information about metabolism. ECHA evaluated the Meteor Nexus Prediction Report submitted by you. ECHA notes that Meteor Nexus does not provide quantitative predictions for Structure Activity Relationship, and that the Meteor Nexus output does not provide kinetic information on the hydrolysis of parabens to the principal metabolite para-hydroxybenzoic acid (PHBA). Thus this method is not a scientifically valid method for the purpose for which it is being used (quantitative prediction of metabolism), as required by Annex XI, 1.3.

You stressed in your comments that "*considering the comparable chemical structure of the alkyl 4-hydroxybenzoates and the knowledge of general widespread metabolic pathways of mammalian species, "p-hydroxy benzoic acid" has to be regarded as the most likely metabolite resulting from the enzymatic hydrolysis.*" Indeed, based on the chemical similarity of the target and source substances it is plausible to assume that "*p-hydroxy benzoic acid*" may be regarded as a likely metabolite for all these substances. However, this does not provide information on the rate of uptake and (bio)transformation for the registered substance (or the source substances).

Also, for the source substances, there were no toxicokinetics data provided in the dossier. In the read-across justification in Section 13 of IUCLID, only references to relevant studies were given but no study summaries were provided. In your comments, you provided in Table 1 a summary of the results for the available metabolism studies for the target and

source substances showing similar peak concentration times for all the compounds, similar excretion times and similar metabolites. You also stated that in the metabolism studies the amount of unmetabolized substance in urine did not exceed 0.6% of the applied amount and argued that the exposure to unmetabolized substance would only be relevant at doses of 500 mg/kg bw ethyl 4-hydroxybenzoate or higher (Heim et. al.) but even such high doses would result in only negligible serum concentrations (5 µg/mL). However, no robust study summaries for the source substances are provided either in your comment or in the dossier of the registered substance, and so ECHA cannot independently evaluate this information. Information about the rate of uptake and (bio)transformation of registered or source substances were not provided in your comment, so as to enable the characterisation of the formation of the common p-hydroxybenzoic acid metabolite from the source and registered substances. Consequently the information provided is still not sufficient to conclude that there is only systemic exposure to the common hydrolysis product (p-hydroxybenzoic acid), and not to the parent esters. In your comments on the draft decision you acknowledged that unmetabolized substance was found in serum at high doses of 500 mg/kg bw or above (Heim et al). ECHA considers this as evidence that systemic exposure to the parent compound has occurred, and disagrees with your characterisation of this as negligible serum concentration, in view of (a) lack of information about the rate of uptake and (bio)transformation of the registered substance (b) lack of an acceptable basis for predicting the properties of the parent (unmetabolised) substance.

You argue that as no significant toxicity of ethyl 4-hydroxybenzoate has been observed in all relevant endpoint studies, it is unclear whether any potential systemic exposure to the parent compound is of relevance.

ECHA notes that for the five endpoints in question there is not adequate information available and thus it is not possible to conclude that the registered substance has no significant toxicity. An absence of adequate toxicity information cannot be used to justify the read-across through concluding that the substance has no significant toxicity.

Addressing the provided toxicity data on the registered substance and on the source substances, you disagreed with ECHA's opinion that there are "*different effects at different dose levels*" in the provided repeated dose and reproductive toxicity studies, for the following reasons:

You explained the apparent differences in the NOAELs derived for methyl 4-hydroxybenzoate (250 mg/kg bw/d based on "clinical signs" at the next dose in an OECD 407 study, Annex IV to your comment) and propyl 4-hydroxybenzoate (980.9 mg/kg bw/d for males and 1076.4 mg/kg bw/d for females in an OECD 422 study, Annex III to your comment) by the dose spacing of the studies, as well as by the difference in application route (bolus application via gavage; no bolus application via diet). ECHA notes that the "clinical signs" in the highest group of 1000 mg/kg bw/d methyl 4-hydroxybenzoate included two deaths and "piloerection and/or hunched posture were noted among the surviving animals..." (Annex IV) while at a comparable dose level, albeit via diet, no effects were observed with propyl 4-hydroxybenzoate. While your explanation for the difference in toxicity is plausible, it is not adequately supported by direct information that shows that these differences are due to the use of gavage versus dietary dosing, and so it is speculative. It is an equally valid hypothesis that the two parabens differ in their toxicological potency; accordingly, you have not established that the two parabens have similar toxicological properties, and that there is therefore a basis for prediction of the properties of the registered substance from the data on the source substance(s).

For the pre-natal developmental toxicity, you established for Moriyama et al. (1975) study that a NOAEL of 517-658 mg/kg bw/d ethyl 4-hydroxybenzoate should be considered for developmental toxicity as well as for maternal toxicity, a dose range which is comparable to the results obtained with methyl 4-hydroxybenzoate. This would be due to the fact that "*The maternal food consumption in the referring treatment groups was significantly decreased and in the high dose group, the females were malnourished during the treatment period, indicating that developmental effects are most likely to be triggered by bad maternal condition especially of the high dose animals.*" However, ECHA notes that this conclusion has not been unequivocally demonstrated by the data provided. In Moriyama et al.(1975) study, the food intake between days 8-15 of gestation was 155.2 g in the control group, 124.7 g in the low dose group, 113.8 g in the mid dose group and 58.8 g in the high dose group. Nevertheless, in this strain (Wistar), food restriction of up to 6 g/rat/d from day 6-17 of gestation was not associated with any fetal external, visceral, or skeletal malformations (http://journals.sagepub.com/doi/pdf/10.1177/0960327116660750)

Furthermore, you established a NOAEL for developmental toxicity as for maternal toxicity of 517-658 mg/kg bw/d ethyl 4-hydroxybenzoate which is the mid dose. However, you also stated in the dossier that:
"*The bleeding in the parietal brain area of the fetuses of the mid and high dose groups was considered to be related to test substance treatment and therefore judged as adverse effect.*" Based on this conclusion a NOAEL of 54-63 mg/kg bw/d (the low dose) would have been more appropriate since treatment related effects were seen at the mid dose. Therefore, also the available reproductive toxicity data give indication of possible different toxicological potencies between different parabens.

Based on the above considerations of further arguments presented in your comments, ECHA considers that your hypothesis of "biotransformation to a common product" does not fully take into account the presence of parent substance in the body, and its possible effects, and so there is not an adequate basis for predicting the properties of the registered substance. Additionally, there is toxicological evidence of differences in the relevant properties compared between different parabens, and as you have not provided an adequate explanation for this, so your hypothesis of similar properties is contradicted; on this basis also, the proposed read-across does not provide an adequate basis for predicting the properties of the registered substance.

Finally, you have proposed a testing strategy, to increase the robustness of the read-across and to address any remaining uncertainties. Specifically, you propose to await the results of toxicological tests on the analogue substance, propyl 4-hydroxybenzoate (which are required under a separate ECHA decision) and only upon the completion of these tests would you perform studies on the registered substance. ECHA has rejected your proposed read-across, and the proposed tests do not address the problems of rate of uptake and (bio)transformation of the registered substance identified in your read-across hypothesis. Moreover, the results of such proposed studies are not currently known, and it is not currently possible to judge how the results of such proposed studies could change the information requests which would ensure compliance for the registered dossier. In these circumstances the proposed strategy does not remedy the incompliance relating to this endpoint.

Consideration of proposals for amendment and your comments on them

Following a proposal for amendment (PfA) made by one of the Member State Competent Authorities (MSCAs) on the read-across, you expressed your agreement to this PfA.

However, following assessment of the PfA along with your comments, ECHA notes the following:

Firstly, the basis proposed by you for read-across is that the substance is rapidly absorbed, metabolised to common products with the other read-across substances. ECHA considers that this argument is not sufficient: systemic exposure to the parent substance (ethylparaben) cannot be ruled out, and indeed that there is evidence that there is systemic exposure to the parent substance. ECHA understands from the PfA that the MSCA agrees with the scientific underpinning of this argument, and that it agrees that biotransformation data for the three substances should be provided to substantiate the read-across.

The MSCA suggests that it may be expected that all three parent substances show a rapid hydrolysis of the esters to the p-hydroxybenzoic acid and corresponding methyl/ethyl/propyl alcohol and consequently a similar amount of exposure to the parent substance can be expected. Therefore, the read-across via interpolation using methylparaben and propylparaben as source substances should be possible. ECHA notes the hypothesis that a rapid hydrolysis may be expected, but considers this has not been demonstrated (i.e. the rate of biotransformation was not provided). Moreover, there is not currently an adequate basis for considering that the parent substances have similar or predictable human health properties (see above in this decision), and the argument that methyl paraben is a worst case is not adequately justified. ECHA is unable to speculate about the results of future studies. ECHA therefore, considers that there is not an adequate basis for accepting the read-across.

Secondly, ECHA considers that addressing the presence and contribution of the parent compound to the observed toxicity is an important argument in your read-across justification.

ECHA notes that a difference in toxicity between the three substances cannot be excluded. The MSCA disagrees with this argument which was understood as based on the observation that methyl paraben gave a factor 5 lower NOAEL than ethyl paraben and propyl paraben. However, ECHA cited the developmental toxicity study of Moriyama et al. (1975) as an additional reason for considering there is a difference in toxicity. You established a NOAEL for developmental toxicity as well as for maternal toxicity of 517-658 mg/kg bw/d ethyl 4-hydroxybenzoate (the mid dose). This would have been a dose range which is comparable to the results obtained with methyl 4-hydroxybenzoate. However, ECHA notes that "*The bleeding in the parietal brain area of the fetuses of the mid and high dose groups was considered to be related to test substance treatment and therefore judged as adverse effect.*" Based on this conclusion a NOAEL of 54-63 mg/kg bw/d (the low dose) would have been more appropriate since treatment related effects were seen at the mid dose. This would make a difference by a factor of 10 between the target and source substance. It also questions whether the methyl paraben would be a "worst case" scenario.

Thirdly, you proposed that the source and target substances have similar ("*correlated*") properties. The observed differences in toxicity cannot be ignored, and indeed need to be explained in order to be able to predict the properties of the registered substance.

ECHA notes that in your comment to the PfA you made arguments that have previously been addressed, and you indicated your disagreement with ECHA's viewpoint; ECHA will not further address these comments. You also provided new information, not previously referenced in your dossier or your comments to the draft decision, and these are addressed below.

Firstly, in the context of biotransformation, you provided new data on hydrolysis rate constants measured with human liver microsomes. Depending on the alkyl chain length, the half-life varied from 22 min for methylparaben to 69 min for propylparaben. Insufficient information is provided for ECHA to be able to evaluate if this information is reliable, as for example the experimental methodology is not described. Nonetheless, the half-lives described suggest that the parent compound would be present in the body as parent compound for significant amounts of time, and so the concern of exposure to the parent compound still remains, as set out in the decision above. You made reference to several other new sources ([redacted] 2007; [redacted] 2010; [redacted] 2013; [redacted] .2013) to support the contention that alkyl 4-hydroxybenzoates are uniformly metabolized leading to 4-hydroxybenzoic acid as common (main) metabolite and the respective alcohols. However, you have not provided the full reference information to identify these sources, nor provided sufficient information so that ECHA can evaluate what these sources contain. ECHA cannot accept your contention based on information that you have not provided.

Secondly, you referred to the Substance Evaluation Conclusion Document EC No 202-804-9, by the evaluating Member State Czech Republic, dated 26th May, 2016 which concluded that 4-hydroxybenzoic acid is considered safe for human health and that concerns regarding estrogenic activity of 4-hydroxybenzoic acid the concerns are unjustified. ECHA notes that the Substance Evaluation Conclusion Document EC No 202-804-9 does not state that 4-hydroxybenzoic acid is considered safe for human health, but does conclude that "for the evaluated substance concerns about the endocrine activity are unjustified". However, an absence of concern for endocrine activity of 4-hydroxybenzoic acid is not relevant for establishing whether there is compliant information present for the relevant endpoints for the registered substance, nor is it relevant for your justification that the conditions of Annex XI, 1.5 are met for the registered substance.

Thirdly, in your comments on the PfA you also informed about the test program on propyl 4-hydroxybenzoate which has started already and comprises a sub chronic 90-day oral toxicity study (OECD TG 408), a developmental toxicity study (OECD TG 414) and an EOGRTS (OECD TG 443). You are also willing to perform the required tests for methyl 4-hydroxybenzoate and you proposed to run comparative metabolism studies also for methyl- and ethyl 4-hydroxybenzoate in addition to the one for propyl paraben. ECHA understand that this is a proposed strategy to substantiate the read-across to these substances in order to cover the information requirements for the registered substance. However, the results of these experiments are not yet known, and consequently it is a matter of speculation as to whether the results would support or disprove your read-across justification for the registered substance. At this step of the decision making process the information still to be provided cannot be taken into account.

Finally, in your comments to the PfA you proposed that a decision on testing ethyl 4-hydroxybenzoate be delayed until the results of tests for methyl- and propyl- 4-hydroxybenzoate are known. ECHA points out that it is not possible to delay the ECHA decision on this compliance check, since the timelines for decision making are set out in Article 51.

It would also be possible to interpret your request as a request for an extended deadline, in order for you to start testing on the registered substance once the results for tests on methyl- and propyl- 4-hydroxybenzoate become available. ECHA considers that your proposed read-across is dependent upon a number of tests which are not yet available, and so it is a matter of speculation as to whether it could be acceptable. Moreover, ECHA must

also balance the need to generate information on properties in a timely fashion. Accordingly, ECHA considers that it would not be appropriate to extend the deadline for this decision.

Conclusion

For all the reasons explained above in this section, your proposed read-across approach is rejected on the basis of the information available.

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

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.

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 1.2., weight of evidence. Hence, ECHA has evaluated your adaptation with respect to this adaptation.

a) Information provided

You have provided in the endpoint summary the following justification for the weight of evidence adaptation:

"*The available information comprises studies which each alone are regarded insufficient for assessment (Klimisch score 2). However, the information from these independent sources is consistent and provides sufficient weight of evidence for hazard assessment leading to an endpoint conclusion in accordance with Annex XI, 1.2, of Regulation (EC) No 1907/2006. Therefore, the available information as a whole is sufficient to fulfil the standard information requirements set out in Annex VII, 8.5, of Regulation (EC) No 1907/2006.*"

To support your weight of evidence adaptation, you have provided provided three studies of Klimisch reliability 2: Sado (1973), a 25-week study with the registered substance, Matthews (1956), a 12-week study with the registered substance and [redacted] (2012), an OECD 422 study with the read-across substance propyl 4-hydroxybenzoate. You also provided two studies of Klimisch reliability 4 with the registered substance in dogs and rabbits.

b) ECHA's evaluation and conclusion of the information provided

Evaluation approach/criteria

An adaptation pursuant to Annex XI, Section 1.2. requires sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property with respect to the information requirement in question including an adequate and reliable documentation.

Your weight of evidence adaptation needs to address the specific dangerous (hazardous) properties of the registered substance with respect to a sub-chronic toxicity study (EU B.26/OECD TG 408). Relevant elements are in particular exposure route, duration and levels, two genders, sensitivity and depth of investigations to detect specific organ toxicity. Furthermore, the relative values/weights of different pieces of the provided information need to be assessed as indicated in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.4.4. In particular relevance, reliability and adequacy for the purpose as well as consistency of results/data need to be considered.

Evaluation of the provided information

You provided two studies (Schübel & Manger (1929)) of Klimisch reliability 4 with the registered substance in dogs and rabbits. ECHA notes that insufficient reporting on the design and on the outcome of the examinations performed in each of these studies is provided in the endpoint study records. The very limited level of information reported prevents ECHA from assessing the reliability of this data. This is in agreement with your assessment of the reliability of the information obtained from some of these studies to which you assigned a Klimisch score of 4.

ECHA notes that you disregarded the Schübel & Manger (1929) studies in dog and rabbit due to major methodological deficiencies and availability of an abstract only. ECHA agrees with your conclusion. Therefore, this information cannot be used as reliable source of information within a weight of evidence adaptation.

You have also provided a Klimisch reliability 2 OECD 422 study ([redacted] 2012) with the read-across substance propyl 4-hydroxybenzoate. However, since the read-across approach for this study is rejected (see Appendix 1, section 0 above) this information can (currently) not be used as reliable source of information within a weight of evidence adaptation.

You provided two studies rated as Klimisch reliability 2 with the registered substance. In the assessment of each individual source of information you have provided, ECHA has found that in regard of quality and relevance, the studies have severe deficiencies.

Sado (1973) has insufficient statistical power (5 animals per group, vs 10 in the test guideline), no ophthalmological examination, no functional observational battery, missing haematology parameters (total and differential leukocyte count, platelet count and a measure of blood clotting time/potential), insufficient clinical chemistry parameters (sodium, potassium, glucose, urea, blood urea nitrogen, creatinine, albumin, and more than two enzymes indicative of hepatocellular effects (such as alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma glutamyl transpeptidase, and sorbitol dehydrogenase), and ECHA considers that the organ weights, gross histology and histopathology of the organs as specified in OECD TG 408 has not been performed. Accordingly, this study does not have adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3). No information is provided on the test material, nor the analytical verification of doses, and so ECHA cannot conclude that this is representative of the registered substance.

Matthews (1956) does not have exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) (12 weeks, vs 13 weeks in the OECD TG), sufficient dose groups (two, vs three in the OECD TG), it measure food intake and bodyweight less frequently than required in the OECD TG (at least once per week), did not

examine haematology, clinical chemistry, ophthalmology, functional observational battery, organ weights, and examined only 6 organs at necropsy/histopathology (as opposed to 33 listed in the OECD TG). Accordingly, this study does not have adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3). No information is provided on the test material, nor the analytical verification of doses, and so ECHA cannot conclude that this is representative of the registered substance.

Therefore the studies specified above provide only limited evidence in regard of the information requirement.

ECHA notes that all three of the individual sources of information rated as reliable are individually insufficient to cover the information requirement.

You argue that there is consistency, and assert that there is sufficient weight of evidence. However, you did not set out detailed reasoning explaining for what reasons the individual studies are insufficient to fulfil the information requirement or explaining how the three studies together provide sufficient weight, other than by arguing for consistency. ECHA has rejected the read-across to propyl paraben, and so the Harlan (2012) study provides no support for consistency of the properties of the registered substance.

In view of the severity of the deficiencies in Sado (1973) and Matthews (1956), ECHA considers the assertion of consistency to be based on insufficient measured parameters, and the three studies together do not provide sufficient weight of evidence to overcome the deficiencies of the individual studies. ECHA therefore considers there is not sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property, in this case for sub-chronic (90-day) repeated dose toxicity.

Therefore, your adaptation of the information requirement is rejected.

Following the notification of the draft decision, you commented on the relevance of submitted studies in the context of the read-across adaptation provided for this endpoint. You argued that the two reliable studies with the registered substance (Sado, 1973 and Matthews, 1956), together with the two studies of reliability 4 provided with the registered substance, are sufficient as supporting evidence, when considered in the context of a read across approach which includes an OECD 422 study on the analogue propyl 4-hydroxybenzoate.

You considered that the study of Sado, 1973 has a study design equivalent to an OECD 408 study. However, as ECHA specified above, this study does not have adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3), and you have not provided in your comments information to remedy the identified defects in the study design. The statement that the study follows scientific principles does not address ECHA's stated concern. Similarly, the study of Matthews 1956 does not have adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3), you have not provided in your comments information to remedy the identified defects in the study design, and so the same arguments apply.

The other two reliability 4 studies with the registered substance (Schübel & Manger (1929) studies in dog and rabbit), were performed with increasing doses for several days in two and one animal respectively. Therefore, there is not adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3) as required by Annex XI, 1.1.2 for non-GLP non-guideline studies, specifically as related to dose-level setting, number of dose groups and number of animals per dose group.

The OECD 422 (diet) study performed with the structural analogue propyl 4-hydroxybenzoate does not have exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) (maximal "approximately 7 weeks" for females, males "minimum 4 weeks", versus 13 weeks in the OECD TG). In addition, the read-across was rejected.

The individual studies have severe shortcomings, and you have provided no argument as to why the shortcomings of one particular study could be complemented by the other studies. ECHA concludes that all of the individual sources of information are neither individually or together sufficient to cover the information requirement.

For the reasons 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 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 6.0, July 2017) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration. More specifically,

- the properties of the registered substance support the oral route (solid with a water solubility of 885 mg/L at 25 °C, a vapor pressure of 0.0127 Pa at 25 °C and its octanol/water partition coefficient (log Pow) was determined to be 2.3.)
- even though the information indicates that human exposure to the registered substance by the dermal route is likely, there are differences in the metabolism of parabens between rats and human via dermal route, and the conditions set in Annex IX, Column 2, 8.6.2. (3) are currently not fulfilled on the basis of the provided data.

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.

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.

Notes for your consideration

ECHA notes that a revised version of OECD TG 408 was adopted this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. You should test in accordance with the revised version of the guideline as published on the OECD website for adopted test guidelines *(https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788)*.

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

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.

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.

In the technical dossier you have provided a study record for an in vitro chromosome aberration test (Ishidate, 1978), Klimish reliability 4 with the registered substance and two in vivo studies (an OECD Guideline 478 (Genetic Toxicology: Rodent Dominant Lethal Test) and an OECD Guideline 475 (Mammalian Bone Marrow Chromosome Aberration Test)), both from 1974, performed with methyl 4-hydroxybenzoate. However, these studies do not provide the information required by Annex VIII, Section 8.4.2., because of several reasons. The in vitro chromosome aberration tests with the registered substance is an old non-guideline, non-GLP test with important limitations such as no reporting on metabolic activation, cytotoxicity or how the test was performed and interpreted except the statement:"*After 48 h, in 11% of the cells chromosome aberration was noticed. The aberration types observed were gaps, breaks, exchanges and rings. The dose, at which 20% aberrations were observed (D20) was 0.19 mg/mL*". In view of the failure to describe the methodology for this study, ECHA considers that there is not adequate and reliable documentation of the study (Annex XI, 1.1.2). Noting also your evaluation of this study as Klimisch 4, ECHA considers that this study is not reliable information.

The in vivo data provided in the dossier for cytogenicity are performed with methyl 4-hydroxybenzoate. However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

For the reasons 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.

In your comments, you reaffirm that you consider the read-across valid for genotoxicity. However, ECHA has assessed your additional arguments and considered that they do not allow changing the initial conclusion of rejecting your adaptation of the information

requirement, as set out in Appendix 1, Section 0. Grouping of substances and read-across approach.

ECHA considers that the *in vitro* mammalian chromosome aberration test (test method OECD TG 473) and the *in vitro* mammalian cell 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* mammalian chromosome aberration test (test method: OECD TG 473) or *in vitro* mammalian cell micronucleus study (test method: OECD TG 487).

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

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.

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.

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 OECD Guideline 476 (In Vitro Mammalian Cell Gene Mutation Test) with the analogue substance propyl 4-hydroxybenzoate EC No 202-307-7. However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

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.

In your comments, you reaffirm that you consider the read-across valid for genotoxicity. However, ECHA has assessed your additional arguments and considered that they do not allow changing the initial conclusion of rejecting your adaptation of the information requirement, as set out in Appendix 1, Section 0. Grouping of substances and read-across approach.

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, 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).

4. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

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.

"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 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 Screening for reproductive/developmental toxicity (OECD TG 422) with the analogue substance propyl 4-hydroxybenzoate EC 202-307-7 . However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

You have also provided in the dossier a supporting non-guideline test (Oishi, 2004), in which male rats were treated with the registered substance in diet for 8 weeks and in which no fertility effects were observed up to the highest dose of 1043 mg/kg bw/d. However, this study lacks key parameters (Annex XI, 1.1.2) of an OECD 422/421 study on: female reproductive performance (such as gonadal function, mating behaviour, conception, development of the conceptus and parturition), functional evaluation of male reproductive capacity, and offspring parameters. Therefore, this study cannot fulfill the requirement for a screening study.

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.

In your comments, you reaffirm that you consider the read-across valid for this endpoint. However, ECHA has assessed your additional arguments and considered that they do not allow changing the initial conclusion of rejecting your adaptation of the information requirement, as set out in Appendix 1, Section 0. Grouping of substances and read-across approach.

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) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a solid, 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 6.0, July 2017).

The registrant 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) Section R.7.6.2.3.2., pages 484 to 485 of version 6.0 – July 2017.

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

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.

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.

a) Information provided

You have sought to adapt this information requirement. You have explicitly claimed an adaptation according to Annex XI, Section 1.2., weight of evidence. Hence, ECHA has evaluated your adaptation with respect to this adaptation.

ECHA understands that you conclude that the registered substance does not have a dangerous (hazardous) property with respect to prenatal and developmental toxicity endpoint because the observed effects on fetal development seen in one study with the registered substance (Moriyama, 1975) were secondary to maternal toxicity, and the read-across studies showed no developmental toxicity. However, you have not provided an explanation or justification on how the sources of information, which you have provided, enable an assumption or conclusion that the registered substance does or does not have a dangerous property with respect to prenatal and developmental toxicity endpoint.

To support your weight of evidence adaptation you have provided the following sources of information:

- A developmental study (Moriyama, 1975) with the registered substance
- Four old studies (claimed equivalent or similar to OCED 414, all with various deviations) with methyl paraben.

b) ECHA's evaluation and conclusion of the information provided

An adaptation pursuant to Annex XI, Section 1.2. requires sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property with respect to the information requirement in question including an adequate and reliable documentation.

You used a weight of evidence approach consisting in one study with the registered substance and four old studies with methyl paraben. In the endpoint study summary, with regard to the developmental toxicity you state: "*There are no further animal data available on the developmental toxicity of ethylparaben. However, there are reliable data for methylparaben and propylparaben which are structurally related to ethylparaben.* " . The four studies provided in the dossier for this endpoint and claimed equivalent or similar to OECD 414 are performed with methyl paraben. However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected. Therefore, the only other information for this endpoint stems from the study of Moriyama (1975) on the registered substance. In this study, however, several important deficiencies are present:

- exposure of pregnant dams during gestation, did not include even all the organogenesis period (GD) 5-15 for rats but only Day 8 to 15 of gestation. According to OECD 414, "*the test substance is administered to pregnant animals at least from implantation to one day prior to the day of scheduled kill, which should be as close as possible to the normal day of delivery without risking loss of data resulting from early delivery*."
- the provided study used 5 pregnant rats for control, 8 pregnant rats for 0.1% test substance in diet, 8 pregnant rats for 1% test substance in diet, and 12 pregnant rats for 10% test substance in diet. According to OECD 414 "*Each test and control group should contain a sufficient number of females to result in approximately 20 female animals with implantation sites at necropsy. Groups with fewer than 16 animals with implantation sites may be inappropriate.*"
- the highest dose level is not adequately set. OECD 414 requires that "*Unless limited by the physical/chemical nature or biological properties of the test substance, the highest dose should be chosen with the aim to induce some developmental and/or maternal toxicity (clinical signs or a decrease in body weight) but not death or severe suffering.*" At the the top dose, of ~700 mg/kg/day, only a "decreased maternal food intake" was observed and therefore, this concentration is under the limit dose.
- There are no data on statistics, no report on clinical signs.

Furthermore, in this study developmental effects were observed as opposed to the studies performed with methylparaben.

Your weight of evidence adaptation needs to address the specific dangerous (hazardous) properties of the registered substance at equivalent level as investigated in a pre-natal developmental toxicity study (EU B.31/OECD TG 414). Relevant elements are in particular information about exposure route, duration and levels, sensitivity and depth of investigations to detect pre-natal developmental toxicity (including growth, survival, external, skeletal and visceral malformations) and maternal toxicity. The only study available with the registered substance does not provide the information needed for this endpoint. You have not provided a justification for how the individual studies add together to form a sufficient weight of evidence, and ECHA considers that there is not a sufficient weight of evidence.

Following the notification of the draft decision, you commented the relevance of submitted studies in the context of the weight of evidence and read-across adaptation provided for this endpoint.

For this endpoint you provided data from studies performed with propyl 4-hydroxybenzoate and methyl 4-hydroxybenzoate.
However, ECHA has assessed your additional arguments and considered that they do not allow changing the initial conclusion of rejecting your adaptation of the information requirement, as set out in Appendix 1, Section 0. Grouping of substances and read-across approach.

You also commented on the non-GLP and non-guideline developmental toxicity study of Moriyama et al. 1975 on the registered substance, but this study fails to meet the criteria of Annex XI, 1.1.2 and does not cover the information requirements of this endpoint. ECHA has assessed your additional arguments and considered that they do not allow changing the initial conclusion of rejecting your adaptation of the information requirement according to Annex XI, 1.2, as set out above.

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) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a solid, 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 (rat or rabbit) by the oral route.

Notes for your consideration

ECHA notes that a revised version of OECD TG 414 was adopted this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. You should test in accordance with the revised version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788).

Appendix 2: Procedural history

ECHA notes that the tonnage band for several members of the joint submission is 100 to 1 000 tonnes per year per year.

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 7 December 2016.

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

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

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

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

ECHA received a proposal for amendment and did not modify 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.

The Member State Committee reached a unanimous agreement on the draft decision during its MSC-59 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 the start of substance evaluation in 2020.

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 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.

4. 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.