EUROPEAN CHEMICALS AGENCY

Helsinki, 14 December 2016

Addressee: [redacted]

Decision number: CCH-D-2114350488-42-01/F
Substance name: Propyl 4-hydroxybenzoate
EC number: 202-307-7
CAS number: 94-13-3
Registration number: [redacted]
Submission number: [redacted]
Submission date: 15 April 2013
Registered tonnage band: 100-1000 tonnes/year

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA requests you to submit information on

1. **In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14. / OECD TG 471) 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. **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;**

4. **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 of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective Annex, and an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by **21 December 2018**. You shall also update the chemical safety report, where relevant.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. Advice and further observations are provided in Appendix 3.

The scope of this compliance check decision is limited to the standard information requirement of Annexes VII to IX, Sections 8.4., 8.6. and 8.7. of the REACH Regulation.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, shall be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under http://echa.europa.eu/regulations/appeals.

Authorised[1] by Leena Ylä-Mononen, Director of Evaluation

[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

0. Grouping of substances and read-across approach

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally related substances (grouping of substances and read-across), "provided that the conditions set out in Annex XI are met".

In the registration, you have adapted the standard information requirements for

- *In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.);
- *In vitro* cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.); and
- Pre-natal developmental toxicity study, oral route, (Annex IX, Section 8.7.2.)

by applying a read-across adaptation following REACH Annex XI, Section 1.5.

Annex XI, Section 1.5. requires a structural similarity among the substances within a group or category such that relevant properties of a substance within the group can be predicted from the data on reference substance(s) within the group by interpolation. The following analysis presents your justification for the proposed grouping approach and read-across hypothesis, together with ECHA's analysis concerning the justification in both a generic and an property-specific context.

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

You have provided a read-across justification document "*Analogue approach justification*", under IUCLID section 13, in the registration.

You provided the following read-across justification: "*Propyl 4-hydroxybenzoate, here on referred to as propylparaben (CAS No. 94-13-3) occurs as a natural substance found in plants and insects. Propylparaben is a member of the chemical class of parabens (alkyl 4-hydroxybenzoates). Parabens and their salts are widely used as preservatives in cosmetic and pharmaceutical industry, primarily because of their bactericidal and fungicidal properties, and also as food additives. Apart from propylparaben, common parabens include methylparaben (CAS No. 99-76-3), ethylparaben (CAS No. 120-47-8) and butylparaben (CAS No. 94-26-8). Due to availability of data for methylparaben and ethylparaben, as well as structural similarity and correlated properties, they are suitable candidates for analogue approach.*"

In summary, ECHA considers you provide the following arguments to support the read-across approach:

(i) Structural similarity - "*Propylparaben is the propyl ester of p-hydroxybenzoic acid. As a phenol derivative, it is a weak acid. Analogically, methylparaben is the methyl ester and ethylparaben the ethyl ester of p-hydroxybenzoic acid, demonstrating similar acidic properties. The substances form a homologue series: methylparaben-ethylparaben-propylparaben.*"

(ii) Physicochemical properties – "*The comparison of physico-chemical properties of the target and source substances reveals both similarities and trends. They are solid at ambient conditions and the melting temperature decreases with the chain length of the alcohol moiety.*

The substances are non-volatile (high boiling temperatures, decomposition before boiling reported). They are soluble in water, where they dissociate as weak acids (phenol derivatives)."

(iii) Metabolic pathways - *"Propylparaben, methylparaben and ethylparaben 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. Thus, the toxicokinetic behaviour of the source substances methylparaben and ethylparaben is comparable to that of propylparaben."*

(iv) Toxicological data - *"All available experimental data indicate that methylparaben, ethylparaben and propylparaben are not acutely toxic and do not have sensitizing properties. In addition, no hazard was identified regarding repeated dose, genetic and reproductive/developmental toxicity. So target and supporting substances share similar toxicological properties. Therefore the supporting substances are used within the read across."*

ECHA considers this as the hypothesis under which you make predictions for the properties listed above.

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

ECHA has evaluated the information and documentation provided in the registration dossier in light of the requirements of Annex XI, Section 1.5. of the REACH Regulation and concludes that the requirements of Annex XI, Section 1.5. are not met for the following reasons.

With regards to the proposed justification, as per section 0.1 (i) to (iv) of this decision, ECHA has the following main observations:

(i) The justification states that these substances show "*structural similarity*". ECHA considers that structural similarity, is not in itself a sufficient basis to predict human health properties of a substance. Structural similarity is a prerequisite for applying the grouping and read-across approach, but ECHA does not accept in general or in this specific case that structural similarity *per se* is sufficient to enable the prediction of human health properties of a substance, since structural similarity does not always lead to predictable or similar human health properties.

Hence, further elements are needed, 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. ECHA considers that the requirement of Annex XI, 1.5., that human health effects may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach), has not been met.

(ii) According to the justification "*The comparison of physico-chemical properties of the target and source substances reveals both similarities and trends.*" Similarity of physicochemical properties is a prerequisite for applying the grouping and read-across approach, but ECHA does not accept in general or in this specific case that physicochemical similarity *per se* is sufficient to enable the prediction of human health properties of a substance, since physicochemical similarity does not always lead to predictable or similar human health properties.

(iii) You mention that the target and source substances show "*comparable*" toxicokinetic behaviour, are "*rapidly absorbed*", and are "*metabolized to p-hydroxybenzoic acid, p-hydroxyhippuric acid and conjugates with glucuronic acid and excreted mainly via urine*". However, comparable toxicokinetic behaviour *per se* does not show that the structural differences between the substances do not cause different toxicological effects, since there are substances with similar toxicokinetic parameters (e.g. half-life) with different toxicodynamic, and hence toxicological, properties. Moreover, you have not established that the substances are entirely hydrolysed outside the body, so that there is exposure only to the common hydrolysis product plus small chain alcohols; this would be necessary to show that the similar toxicokinetic behaviour causes similar toxicological behaviour. Therefore, ECHA considers that your observations about toxicokinetic behaviour do not provide a basis which would allow predicting toxicological properties of the registered substance as a result of structural similarity in accordance with Annex XI, Section 1.5.

(iv) In the justification document reference is also being made to "*similar toxicological properties*" of the source substances justifying the assessment of the human health endpoints of the target substance, based on the analogue approach. Comparable toxicological data is not in itself a robust basis for predicting the properties of a substance, since there are many substances which share a number of toxicological properties, but then differ in other toxicological properties. ECHA also notes that in this case the amount of information which is in common and is comparable is limited, and this further undermines the use of similar toxicological profile as a basis for predicting the properties of the registered substance. ECHA considers that the requirement of Annex XI, 1.5., that human health effects may be predicted from data for reference substances within the group by interpolation to other substances in the group (read-across approach), has not been met. Additionally, according to the data matrix provided in the justification document "*Analogue approach justification*" (Table 4 Mammalian toxicity - data matrix 2) there are differences and insufficient data in the toxicological profile that have not been accounted for. These issues further undermine the contention that there are similar toxicological properties for these substances.

a) Different toxicological data:

The different NOAEL values for repeated dose toxicity (oral) (target = 980-1076 mg/kg bw/d; source substances: methylparaben = 250 mg/kg bw/d and ethylparaben = 1200 mg/kg bw/d) may be explained with the increase of the chain length of the alkyl group. However, no information was presented to justify these differences. According to the justification document the rate of absorption and excretion is similar for the two source substances and the target substance, hence this difference might also be related to the presence of non-common metabolites.

There is also a different outcome reported for the *in vitro* chromosome aberration test (negative for the target substance while positive for the source substances). According to the justification document the results of the positive tests have limited reliability, however, there is no further explanation on why these studies should not be taken into consideration.

According to the OECD toolbox profiling presented in the justification document, the oestrogen binding receptor is alerted as moderate for the target/registered substance while weak for the source substances. According to you this difference is due to "*the slightly higher molecular weight*". The oestrogenic potency might increase with increasing length and branching of the alkyl side chains (methyl < ethyl < propyl < butyl < isobutyl), however, no information is given on the possible implications of this finding. ECHA notes further that no data on longer alkyl chain parabens has been included.

You mention butylparaben (EC no. 202-318-7) in the hypothesis, however, no data concerning this source substance has been provided within the justification document.

b) Insufficient data:

For the carcinogenicity and the *in vivo* genetic toxicity endpoints there is only data from one source hence there is insufficient data to compare and to be able to predict the properties of the registered substance.

Furthermore, there is a concern on the reliability of the source studies provided for some endpoints, namely for the genotoxicity and the developmental toxicity endpoints.

As already mentioned above, according to the justification document the "*two in vitro chromosome aberration tests of restricted reliability*" of the two source substances "*were found positive*" while for the target substance a negative result was obtained from yet another test with limited reliability (Ishidate, 1978), assigned a reliability score of 4 (not assignable), following no test guidelines and not conducted in accordance with good laboratory practice (GLP). Due to the limited reliability of these studies it is difficult to determine the validity of these tests and their adequacy for the specific endpoint, hence the results cannot be used to determine the comparability of the toxicological data among the target and source substances.

For the developmental toxicity endpoint of the target substance, read-across from ethylparaben (EC no. 204-399-4) is being proposed; ECHA notes that the study provided for this source substance (Moriyama, 1975) cannot be considered as an adequate study for this endpoint. The study provided not only does not follow any test guideline (non-GLP and reliability 2), but it also has some important deviations from OECD TG 414, namely the number of pregnant rats used per dose group which is less than 20, and the exposure duration which lasted only from day 8 to day 15 of the gestation period, that is 6 days before the delivery. According to the TG 414, maternal exposure should last at least from implantation to 1 or 2 days before expected delivery. ECHA also notes that some foetal anomalies were observed, though without a clear dose-response relationship. The other read-across studies provided for the other source substance (methylparaben (EC no. 202-785-7)) have also a shorter exposure duration, deviating from the TG 414. Due to the limited reliability of these studies they do not provide a sufficient basis to assess the developmental toxicity endpoint by means of the analogue approach and therefore the read-across from these source substances to the registered substance cannot be justified.

0.3 Conclusion on the read-across approach

In view of the reasons presented, and considering all the arguments you have provided in the technical dossier on the proposed read-across approach examined above, the adaptation of the standard information requirement for the *in vitro* gene mutation in bacteria, the *in vitro* cytogenicity in mammalian cells and the pre-natal developmental toxicity endpoints cannot be accepted.

In the comments to the draft decision you disagree with ECHA's conclusion rejecting the read-across justification. However, ECHA notes that the information on the read-across approach as provided within the comments does not address the shortcomings listed above by ECHA. More specifically, in your justification you fail to provide information on the potential different metabolites that might influence the toxicological properties of the registered substance; establish whether similar toxicokinetic behaviour cause similar toxicological behaviour; and explain the differences in the toxicological data provided for the source and target substances.

Moreover, ECHA notes that in your comments you refer to two studies (*in vitro* gene mutation study in bacteria and pre-natal developmental toxicity study) performed with another analogue substance (butylparaben (EC no. 202-318-7)). However, these studies have not been provided in the technical dossier. As already stated in this section, ECHA notes that the use of this potential source substance has only been mentioned in the read-across justification document, however, no data and explanation has been provided to substantiate the read-across justification with this specific longer alkyl chain paraben.

You also mention that similarity of parabens has been "*acknowledged by many other regulatory agencies, in particular SCCS, SCCP, EMA, WHO.*" However, no further supporting information has been provided for this statement.

Hence, ECHA considers that the explanations concerning the missing information on the points provided above have not been adequately addressed and are still valid, thus the read-across approach as currently provided in the dossier cannot be accepted.

ECHA does not consider the read-across justification to be a reliable basis to predict the properties of the registered substance for the reasons set out above. Thus, the adaptation does not comply with the general rules of adaptation as set out in Annex XI, 1.5. Therefore, ECHA rejects all adaptations in the technical dossier that are based on Annex XI, 1.5.

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of 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 bacteria" is a standard information requirement as laid down in Annex VII, Section 8.4.1. 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.

According to Article 13(3) of the REACH Regulation, tests required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods recognised by the Commission or ECHA. Other tests may be used if the conditions of Annex XI are met. More specifically, Section 1.1.2 of Annex XI provides that existing data on human health properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3) may be used if the following conditions are met:

(1) Adequacy for the purpose of classification and labelling and/or risk assessment;
(2) Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
(3) Exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and
(4) Adequate and reliable documentation of the study is provided.

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 Reverse Mutation Assay using Bacteria (*Salmonella typhimurium*) (OECD TG 471) with the analogue substance Ethylparaben (EC no 120-47-8) with the following strains: *S. typhimurium* TA 1535, TA 1537, TA 98, TA 100 and TA 102. However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

In the technical dossier you have also provided three study records with the registered substance for the *in vitro* gene mutation study in bacteria. However, ECHA notes that these studies do not provide the information required by Annex VIII, Section 8.4.1., because of the following reasons:

(1) The supporting study ([redacted] 1975), assigned a reliability score of 2, is not in line with OECD TG 471 (since the first test guideline was published in 1983) and has not been conducted according to GLP. Moreover, it has only been conducted on three *S. typhimurium* strains (TA 1535, TA 1537, TA 1538) instead of the required five strains. There are also other deviations to the OECD TG 471, namely:
   a. The number of doses levels used, where according to the data provided a range-finding study has been performed at concentrations from 0.0005 to 5% of the test substance, however, data was only provided for one concentration (0.075%) instead of three different concentrations.
   b. Duplicate plating instead of triplicate plating was used, without providing any justification.
   c. Incubation period time for the plate incorporation assay was 96 hours instead of 48-72 hours.

(2) The other two studies (McCann, 1975 and Sugimura, 1976), with restricted reliability (assigned reliability score of 4 and 3, respectively), do not follow any test guidelines and have not been conducted according to GLP. The McCann study (1975) tested four strains of bacteria (*S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100) while three strains (TA 100, TA 98, and *E. coli* WP2) were tested in the Sugimura study (1976). Even though between the two studies the five strains have been examined, due to the limited information provided and the lack of details on the study design of the McCann study (1975), it makes it difficult to determine whether the studies are adequate and reliable for assessing the *in vitro* gene mutation in bacteria endpoint.

In your comments on the draft decision you argue that the Ames study does not need to be conducted as this "*endpoint is fulfilled by a weight of evidence approach*". However, ECHA notes that the weight of evidence cannot be accepted since the read-across justification is still not acceptable, hence the studies with the ethylparaben (EC no. 120-47-8)) cannot be used to cover the information requirement for this particular endpoint. In your comments you also mention a negative Ames test performed with butylparaben (EC no. 202-318-7) as part of this weight of evidence adaptation. However, this study has not been provided in the technical dossier. ECHA also notes that the use of this potential source substance has only been mentioned in the read-across justification document and no data and explanation has been provided to substantiate the read-across justification with this specific longer alkyl chain paraben.

In your comments you also claim that the negative *in vitro* gene mutation in mammalian cells provided in the technical dossier may be "considered as more sensitive" than the Ames test. However, ECHA notes that you did not provide any form of evidence and/or justification to support your claim.

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 considers that the bacterial reverse mutation test (test method EU B.13/14. / OECD TG 471) is appropriate to address the standard information requirement of Annex VII, Section 8.4.1. 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: Bacterial reverse mutation test (test method: EU B.13/14. / OECD TG 471).

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

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of 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.

You have not provided any study record of an *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study in the dossier that would meet the information requirement of Annex VIII, Section 8.4.2.

In the technical dossier you have provided a study record for an *in vitro* chromosome aberration study (Ishidate, 1978) with the registered substance. The study does not follow any test guidelines and was not conducted in accordance to GLP requirements; hence, the assigned reliability Klimisch score of 4. ECHA considers that a study with a Klimisch score of 4 cannot provide reliable information for an endpoint. Additionally, this study does not provide the information required by Annex VIII, Section 8.4.2., because it fails to provide (i) adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3), and (ii) adequate and reliable documentation of the study, according to Annex XI, Section 1.1.2.(4).

ECHA notes that there are multiple shortcomings. The first deviation noted, from test methods 473 and 487, is the lack of data with metabolic activation. The study did not use a metabolising system and no explanation is given to justify the absence of this testing parameter. Both OECD test guidelines 473 and 487 clearly state that "*Tests conducted in vitro generally require the use of an exogenous source of metabolic activation unless the cells are metabolically competent with respect to the test substances.*" For *in vitro* testing there is the need for use of a metabolising system as it is often the metabolite and not the parent which causes the effect. Secondly, as regards the test concentration, it was only reported that "*up to 0.125 mg/mL (maximum tolerated concentration on cells)*" was tested, however no further information was provided. ECHA cannot verify whether at least three test concentrations were used in the study, as required by the Test Guideline. Additionally, you only provide the following statement under the results' section: "*After 48 h, in 3% of the cells chromosome aberration was noticed.*" Specifically, because of your limited data concerning the results and conclusions of the study, ECHA considers that this endpoint study record does not meet the requirements of a robust study summary (as defined under Article 3(28)), which is required pursuant to Article 10(a)(vii) and Annex I, Section 1.1.4. ECHA's "*Practical Guide 3: How to report robust study summaries*" (version 2.0, November 2012), sets out what is required for a robust study summary for this endpoint.

Two *in vivo* studies (Dominant Lethal Assay and Chromosome Aberration Assay) provided in the dossier are not with the registered substance but with the source substance, methylparaben. However, as already mentioned above in Appendix 1, section 0 of this decision, the read-across approach fails to meet the requirements of Annex XI, 1.5 and the adaptation for column 2, Annex VIII, Section 8.4.2., is not accepted.

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

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

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of 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 not provided any study record of a sub-chronic toxicity study (90 day) in the dossier that would meet the information requirement of Annex IX, Section 8.6.2.

In the technical dossier you have provided a study record for a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" ([redacted], 2012) (test method: OECD TG 422) on the registered substance. However, this study does not provide the information required by Annex IX, Section 8.6.2., because exposure duration is less than 90 days. In the study by [redacted] (2012), male rats were exposed to a "*minimum*" of 4 weeks while female rats were exposed for "*approximately 7 weeks*". Moreover, this study does not meet the conditions according to Annex XI, Section 1.1.2. concerning existing data, since the exposure duration is not "*comparable to or longer than than the corresponding test methods*" (OECD TG 408).

In the technical dossier you have also provided a 96-day chronic study on rats on the registered substance (Matthews, 1956). Though this study may have been assigned a reliability score of 1, there are some significant deviations from the OECD TG 408 on repeated dose toxicity study in rats, namely:

(i) Number of doses: in this study only two doses plus control have been used instead of three plus control;
(ii) Number of test animals used: Only six animals per sex per dose used instead of ten males and females per group; and

(iii) The only information reported is on body weight. No data has been reported on the following endpoints: clinical signs and mortality, opthalmoscopic examination, haematology, clinical chemistry, urinalysis, neurobehaviour and organ weights.

Due to these important deviations from OECD TG 408 and the omitted data, the study by Matthews (1956) is not adequate to provide the information required by Annex IX, Section 8.6.2. Hence it also fails to meet the conditions according to Annex XI, Section 1.1.2., since there is no adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3) (please refer to points (i)-(iii) above).

You have also provided another two older studies on dogs and rabbits on the registered substance (Schubel and Manger, 1929). These studies are assigned a reliability score of 4 (i.e. not assignable), and hence cannot be considered as reliable information to fulfil the information requirement.

In your comments to the draft decision you argue that in the technical dossier there are several repeated dose toxicity studies with the registered substance to fulfill this endpoint. However, ECHA notes that there is no reliable repeated dose toxicity study available in the dossier that covers the 90-day exposure duration with the test substance. The assumption you state in your comments, that is, "*extrapolation of the study duration to 12 weeks is likely to lead to no severe systemic effects*", cannot be supported from the other studies available in the technical dossier. In the OECD TG 422 study ([redacted], 2012) only female rats were exposed for "*approximately 7 weeks*" as males were only exposed to a "*minimum*" of 4 weeks. As already mentioned above, the data provided in the other studies (Matthews, 1956; Schubel and Manger, 1929) cannot be considered to be equivalent to the data generated by the corresponding test method for the sub-chronic toxicity study (OECD TG 408). The studies fail to provide adequate and reliable coverage of key parameters and reliable documentation. In your comments you fail to address the shortcomings noted above regarding the coverage of these key parameters. Hence, these studies cannot provide support to the hypothesis proposed in your comments.

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 4.1, October 2015) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration. More specifically, the substance, which is a white crystalline solid, is not used in spray processes and in the case of dust formation, an exposure to the test substance cannot be excluded, however only during the blending of this substance. In such processes, the use of general risk management measures (RMMs) and operational conditions (OCs) including personal protection equipment (PPE) are recommended. According to the CSR, "*Local hazard via inhalation route is unlikely, since dust exposure during production processes is strictly regulated*". As regards the consumer uses, in cosmetic products or pharmaceuticals, the substance is supplied in the form of a mixture. 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.

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

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of 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.

You have not provided any study record of a pre-natal developmental toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.7.2.

You have sought to adapt this information requirement according to Annex XI, Section 1.2. of the REACH Regulation. This adaptation requires that there may be 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. However, from the information provided it cannot be assumed or concluded that the substance will not lead to pre-natal developmental toxicity.

As part of a weight of evidence analysis you have provided one study record for oestrogenicity of parabens on mice (Shaw and de Catanzaro, 2009) with the registered substance and five study records for teratogenic effects in rats (Moriyama *et al.*, 1975; [redacted] 1972), mice and hamsters ([redacted] 1972), and rabbits ([redacted] 1973) with the analogue substances Methylparaben (EC no. 202-785-7) and Ethylparaben (EC no. 120-47-8). You have also provided the following justification, under IUCLID Section 7.8, for the adaptation: "*There are no further data available on the developmental toxicity of propylparaben. However, there are reliable data for methylparaben and ethylparaben which are structurally related to propylparaben. Therefore, read-across was performed based on an analogue approach.*". You also conclude that the observed findings in the Moriyama study (1975) with ethylparaben in rats "*are not supported by reliable studies on propylparaben and methylparaben*" hence the NOAELs for developmental toxicity of methylparaben of 550 mg/kg bw/d for rats and 300 mg/kg bw/d for rabbits were taken forward for hazard assessment.

Regarding the weight of evidence arguments, ECHA notes the following:

(i) In the discussion summary, under IUCLID section 7.8, you have provided a summary of the studies and a summary of the read-across justification. You have also discussed the choice of NOAEL values for the developmental toxicity endpoint. However, you failed to provide any argument on how all the evidence presented in the dossier adds up for the weight of evidence analysis. ECHA considers that this is a failure to provide adequate and reliable documentation, as required by Annex XI, 1.2.

(ii) The only study available with the registered substance (Shaw and deCatanzaro, 2009) does not follow any test guidelines and has not been conducted in accordance to GLP. The study has been performed on mice, subcutaneously, with only two doses plus the control. Six animals were used in one dose group and in the control while in the other dose group only five animals were used. These conditions deviate from the pre-natal developmental toxicity study according to OECD TG 414, as in this study three dose levels plus the control should be used. Furthermore, the preferred species is rat or rabbit and the oral route is preferred, and at least twenty pregnant females should be used per dose group. In addition, this study does not look at the developmental endpoints, as, according to IUCLID section 7.8.2., it is only reported that "*the number of visible intrauterine implantation sites was counted*" and that "*no apparent impact of propylparaben on the number of implantation sites was observed in any dose group*." ECHA considers that this study does not meet the requirement of Annex XI, Section 1.1.2., that there is adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3), because of the shortcomings set out above.

(iii) Moreover, the read-across from the two analogue substances to the registered substance for the pre-natal developmental toxicity does not meet the requirements of Annex XI, 1.5, as explained above in Appendix 1, section 0 of this decision.

ECHA thus considers that the individual studies provided are each insufficient to meet the information requirement of Annex IX, 8.7.2, for the reasons set out above. ECHA considers that you have not set out a basis for considering how the individual, independent sources of information add up to provide a sufficient weight of evidence, and ECHA considers that there is not sufficient weight of evidence from the totality of these sources of information that could lead to the reliable conclusion that the registered substance does not have developmental toxicity effects. Consequently, ECHA notes that your adaptation does not meet the general rule for adaptation of Annex XI; Section 1.2. hence your adaptation of the information requirement is rejected.

Furthermore, ECHA notes that in the discussion summary, under IUCLID section 7.8, you also make reference to the Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test with the registered substance ([redacted], 2012) (test method: OECD TG 422). However, this study 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 like examinations of foetuses for skeletal and visceral alterations.

In your comments to the draft decision you argue that the test substance "*is considered to have no adverse properties with reference to embryonic/fetal development*" since no developmental effects resulted from the pre-natal developmental toxicity studies performed with the analogue substances (methylparaben (EC no. 202-785-7) and butylparaben (EC no. 202-318-7)). You also state that this can be further sustained since a negative result was obtained in the Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test when performed with the registered substance (Harlan, 2012) (test method: OECD TG 422).

ECHA notes that the study performed with butylparaben (EC no. 202-318-7) has not been provided in the dossier and the use of this potential source substance has only been mentioned in the read-across justification document and no data and explanation has been provided to substantiate the read-across justification with this specific longer alkyl chain paraben. Furthermore, the read-across justification is not acceptable, hence the studies with the methylparaben (EC no. 202-785-7) cannot be used to cover the information requirement for this particular endpoint.

Moreover, as indicated above, ECHA notes that the screening study ([redacted], 2012) (test method: OECD TG 422) does not provide the information required by Annex IX.

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 4.1, October 2015) 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.

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 1 July 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.

In your comments you agreed with request 2 to the draft decision. ECHA took your comments into account and did not amend requests 1, 3 and 4.

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. The substance subject to the present decision was listed in the Community rolling action plan (CoRAP) for start of substance evaluation in 2015, and Substance Evaluation is ongoing as of June 2016.

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

3. Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

4. In relation to the information required by the present decision, the sample of the substance used for the new test(s) must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants. It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new test(s) is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new test(s) must be suitable to assess these grades. Finally, there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.