ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 31 March 2017

Addressee: [redacted]

Decision number: TPE-D-2114358498-33-01/F
Substance name: barium titanium trioxide
EC number: 234-975-0
CAS number: 12047-27-7
Registration number: [redacted]
Submission number: [redacted]
Submission date: 05.06.2013
Registered tonnage band: 100-1000T

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA has taken the following decision.

Your testing proposal is rejected and you are requested to carry out:

1. Sub-chronic toxicity study (90-day), inhalation route (Annex IX, Section 8.6.2.; test method: OECD TG 413) including bronchoalveolar lavage (BAL) analysis in rats using the registered substance.

while your originally proposed test(s) for a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (Annex VIII, Section 8.6.1; test method OECD TG 422) is rejected.

Your testing proposal is rejected and you are requested to carry out:

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route using the registered substance.

while your originally proposed test(s) for a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (Annex VIII, Section 8.7.1; test method OECD TG 422) is rejected.

Your testing proposal to comply with the requirement for an Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.) is rejected:

3. Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (Annex VIII, Sections 8.6.1 and 8.7.1; test method OECD TG 422) inhalation route.

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 **8 April 2019**. You shall also 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. Advice and further observations are provided in Appendix 3.

Appeal

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

Authorised[1] by Ofelia Bercaru, Head of Unit, Evaluation E3

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

Appendix 1: Reasons

The decision of ECHA is based on the examination of the testing proposal(s) submitted by you.

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

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.

a) Concerning the testing proposal

You have submitted a testing proposal for a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test by the inhalation route according to OECD TG 422.

ECHA points out that a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test conducted according to the OECD TG 422 does not provide the information required by Annex IX, Section 8.6.2., because the exposure duration is less than 90 days and the number of animals per dose group is significantly lower. Therefore, the sensitivity of such a study as you have proposed is much lower than that of a 90-day study. For these reasons, ECHA considers that the proposed study is not appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

A sub-chronic toxicity study (90 day) is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. Consequently there is an information gap and it is necessary to provide information for this endpoint.

b) Concerning the substance to be tested

Based on the information included in the technical dossier, ECHA understands that you intended to fulfil this information requirement by applying a read-across approach in accordance with the principles set out in Annex XI, Section 1.5. You provided the following read-across hypothesis and justification under section 5.6.3 of the Chemical Safety Report: "*There are reliable in vivo studies available to assess the potential of the analogous test substance barium dichloride dihydrate for repeated dose toxicity after oral administration. For read-across barium chloride is adopted as it is also an inorganic barium salt whose relevant eco-/toxicological nature depends on the common cation barium whereas the toxicological nature of the anion is negligible. The substances differ in solubility. Barium chloride is soluble while barium titanium trioxide is slightly soluble. But this difference is considered as negligible as it is supported by the absence of any adverse findings in acute toxicity for the analogue substance. In conclusion, read-across for the endpoint repeated dose toxicity is justified.*"

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".

According to the requirements of 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 can be predicted from the data for the reference substance(s) by interpolation, and the data should be adequate for the purpose of classification and labelling and/or risk assessment.

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.

ECHA understands that the formation of barium ions as a common compound between the substance subject to this decision and the source substance is an essential element in your read-across approach. However ECHA notes that no information characterizing the formation of this common compound, i.e. the dissociation of the barium titanium trioxide complex, is provided in the technical dossier. In the absence of this information ECHA considers that you have failed to establish a basis according to which the properties of the registered substance can be predicted from data on the source substance, as required by the provisions of Annex XI, section 1.5 of the REACH regulation.

According to your read-across hypothesis, "*the toxicological nature of the anion is negligible*". However, ECHA points out that no scientific evidence is provided to support this claim and to disregard any toxicological property of the titanate anions. In the absence of supporting evidence establishing that the titanate ions do not cause any toxicological effect, ECHA is of the opinion that the read-across approach as currently presented may underestimate the properties of the target substance. Therefore, ECHA considers that you have failed to establish a basis according to which the properties of the registered substance can be predicted from data on the source substance, as required by the provisions of Annex XI, section 1.5 of the REACH regulation.

ECHA further observes that the read-across justification provided in the technical dossier does not account for the impact of exposure to the registered substance in its non-dissociated form. No information on the rate and extent of dissociation of the barium titanium trioxide complex is provided, therefore the possibility that the organism is exposed to the non-dissociated form of the substance cannot be dismissed. In the absence of demonstration that the barium titanium trioxide complex does not cause any toxicological effect in its non-dissociated form, the read-across approach as currently presented may underestimate the properties of the target substance. On the basis of the information provided and considering the absence of consideration of the possible impact of exposure to the registered substance in its non-dissociated form, ECHA considers that you have failed to establish a basis according to which the properties of the registered substance can be predicted from data on the source substance, as required by the provisions of Annex XI, section 1.5 of the REACH regulation.

For the reasons set out above, ECHA notified you a draft decision in which the Agency considered that the read-across adaptation does not comply with the general rules of adaptation as set out in Annex XI, 1.5.
In your comments to the draft decision you have indicated that you see no need to have to perform the requested study and outline the basis on which you intend to revise your read-across approach for this endpoint.

The hypothesis in this revised read-across approach is based on the formation of a common compound between the registered substance and the source substances, i.e. barium ions.

You consider that barium ion concentrations are the most relevant parameter to evaluate barium toxicity, refer to a scientific publication (Journal of the American Ceramic Society, 83: 860-864) to establish that the barium ions are washed out from the crystal lattice and that the remaining titanates are rarely absorbed due to their low solubility. On that basis you conclude that "*the chemical safety assessment for barium titanium trioxide is based on the elemental metal concentration*" and that "*read-across of barium carbonate is plausible as only barium ions are present in aqueous solutions like blood*".

In your comments to the draft decision you also specify that data from a 4-month inhalation study conducted using barium carbonate by Tarasenko *et al.* (Tarasenko, N.Y., et al: Barium compounds as industrial poisons (an experimental study); Journal of Hygiene, Epidemiology, Microbiology and Immunology 21, 1977, No. 4, 361-373.) will be used as source study in this revised read-across approach.

As indicated in the notification letter issued to you alongside the draft decision, for the purpose of the decision-making process, ECHA does not take into account any dossier updates after 8 August 2016, i.e. 30 calendar days after the end of the commenting period under Article 50(1) of the REACH Regulation. ECHA observes that no dossier update reflecting this revision of your read-across approach has been submitted by that deadline. The dossier submission subject to this decision still contains the read-across approach addressed above in this decision, i.e. read-across from an oral 90-day repeated dose toxicity study conducted with barium chloride, and a testing proposal to perform a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test according to the OECD test guideline 422 with the substance subject to this decision. ECHA points out that it has the obligation to examine and to issue a decision on the testing proposal. Therefore in accordance with the provisions of Article 40(3) of the REACH Regulation, ECHA has to proceed with the examination of this testing proposal.

You refer in your comments to a scientific publication with the reference "*Journal of the American Ceramic Society*, 83: 860-864" which ECHA understands corresponds to the publication by Neubrand et al. "*Room-Temperature Solubility Behavior of Barium Titanate in Aqueous Media*". ECHA understands that you consider that the information reported in this scientific publication addresses ECHA's concerns reported in the draft decision on the absence of characterisation of the dissociation of the barium titanium trioxide complex to form the common compound, i.e. barium ions. You consider that this publication characterises the dissolution of the barium titanium trioxide complex by demonstrating that the barium atoms included in the crystals of barium titanium trioxide are washed out and dissolved in aqueous solutions while "*titanates remain unchanged*".

Even though you did not formally provide documentation of this supporting information in your comments, ECHA reviewed the information reported in this publication and observes that it reports leaching of barium ions from the surface of the particles in the conditions of the investigations. It also reports that the observed leaching is dependent on pH and on the particle size and that passivating layers form on the particles that prevent further leaching. ECHA notes that titanium was detected only in amounts comparable to or smaller than the detection limit (5 µg/L), suggesting a low solubility of titanates.

On the basis of this information, ECHA considers that barium titanium trioxide leaches barium ions up to a limited extent and that some titanates and barium ions remain in a complex form. The potential toxicity associated with exposure to this non-dissociated form of the registered substance, already identified in the draft decision issued to you, has not been further addressed in your comments.

ECHA also notes that, according to the information provided in this scientific article, the leaching of the barium ions appears to be dependent on the surface of the particles tested, therefore the impact of particle size on solubility of the barium titanates and the impact of the crystal structure of the substance on properties such as solubility needs to be considered in these read-across approaches. However, ECHA highlights that no information which addresses the particle size and surface chemistry has been reported in your comments. Further, ECHA stresses that the limited solubility of titanates in aqueous media does not constitute evidence of absence of toxicity of these particles.

For the reasons presented above, ECHA considers that the information provided in your comments suggests an incomplete dissolution of the registered substance and indicates that exposure to non-dissolved forms of the registered substance may occur.
The impact of exposure to the registered substance in its non-dissolved form should be assessed. You failed to address the potential local and systemic toxicity of non-dissociated particles of the registered substance by only focusing the chemical safety assessment on the barium ion concentration and dismissing the toxicity of titanates based on their limited solubility. In the absence of demonstration that the barium titanium trioxide complex does not cause any toxicological effect in its non-dissolved form, ECHA considers that the read-across approach as currently presented in your registration dossier and in your comments may underestimate the properties of the target substance.

In your comments you expressed your intentions to use information from a 4-month repeated dose toxicity study conducted via the inhalation route with the analogue substance barium carbonate by Tarasenko et al. that you consider "*suitable for read-across of barium titanium trioxide*". This source substance is different from the source substance mentioned in the submission of your registration dossier on which this decision is based, i.e. barium dichloride. This source study is not included in the submission of your registration dossier on which this decision is based. You have not provided further information on this source study in the format of a robust study summary allowing for an independent assessment of the adequacy and reliability of this data. ECHA notes that this study is included in the registration dossier submitted for barium carbonate who considered that due to imitations in the reporting of methodological details this data cannot be considered reliable.

According to the study summary reported on ECHA's website for this study on barium carbonate, this study was not performed according to a test guideline, only two test doses were used, no information on the particle size of the test material has been reported, no information on the scope of the histopathological investigations conducted is provided and limited information on the nature of the findings is given. In the absence of further information on the design and the results obtained in this study intended to be used a source study in the revised read-across approach as indicated in the comments, ECHA is not in a position to assess the adequacy, relevance and reliability of this source data to predict the properties of the registered substance on the basis of the information provided in the registrant's comments.

For the reasons set out above, ECHA considers that the read-across adaptation as documented in your registration dossier and in your comments to the draft decision does not comply with the general rules of adaptation as set out in Annex XI, 1.5.

ECHA notes that whilst the read-across adaptation proposed by you cannot be accepted for the reasons above, ECHA draws your attention to the note for consideration included in page 2 of this decision referring to the possibility to adapt the information requirement for which testing requested in this decision according to the rules of Annex XI of the REACH Regulation.

c) Concerning the test method

You proposed testing by the inhalation route. In the technical dossier and/or chemical safety report the registered substance is indicated to be handled and used as a dust or a solid. Information provided on granulometry indicates that the substance includes a significant proportion of particles of inhalable size and inhalation exposure of humans to particles of inhalable size is likely. Therefore, ECHA agrees that the inhalation route is the most appropriate route of administration. Hence, the test shall be performed by the inhalation route using the test method OECD TG 413.

You did not specify the species to be used for testing. According to the test method OECD TG 413 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

The registered substance is a solid that is highly insoluble in water. The results of the particle size distribution provided in the registration dossier indicate that approximately 90 % (by mass) of particles are less than 14 µm. Since the provided data on the substance solubility in water and particle size distribution indicate that the lower respiratory tract (i.e., the alveoli) might be the primary site of deposition and retention of the registered substance subject to the present decision and no information is yet available to characterize the risk, ECHA is requesting that bronchioalveolar lavage (BAL) is being performed in the test. BAL fluid shall be analyzed for total and differential cell count, protein content and lactate dehydrogenase. You should consider other parameters taking into account potential effects of the substance in the lung. You should further consider that the preferred mode of exposure is nose-only and that particulate materials should be subjected to mechanical processes. Particle sizing should be performed for all aerosols and for vapours that may condense to form aerosols. To allow for exposure of all relevant regions of the respiratory tract, aerosols with mass median aerodynamic diameters (MMAD) ranging from 1 to 3 µm with a geometric standard deviation (σg) in the range of 1.5 to 3.0 are recommended.

d) Concerning the selection of the test material

ECHA notes that the substance concerned by the registration [redacted], CAS No 12047-27-7, (EC No 234-975-0), identified as barium titanium trioxide, has more than one crystal structure and the registration dossier does not specify the crystal structure(s) covered by the registered substance. In addition, ECHA notes that barium titanium oxide is also known to be manufactured/imported in forms that may fulfil the EU recommendation for nanomaterial[2].

The different crystal structures may have different toxicological properties, and the Registrant has not justified if a certain crystal structure is anticipated to be representative of the hazard properties of all crystal structures. The fact that crystal structure is relevant to determine the hazard of a substance is stressed under the Classification and labelling regulation (CLP).

The Article 5.1 of the CLP regulation (Substances) and Article 6.1 (Mixtures) specify: "Manufacturers, importers and downstream users of a substance shall identify the relevant available information for the purposes of determining whether the substance entails a physical, health or environmental hazard [...]The information shall relate to the forms or physical states in which the substance (mixture) is placed on the market [...]" .[3]

[2] "Commission recommendation of 18 October 2011on the definition of nanomaterial" L 275/38 Official Journal of the European Union; available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:275:0038:0040:EN:PDF
[3] Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures.

In addition, the ECHA Guidance on the application of CLP criteria (version 4.1, June 2015)[4] mentions that "Different forms or physical states of a substance or mixture may result in different physical properties and hazards with possible consequences for the hazard classification of a substance or mixture. Putative forms comprise properties such as crystal structure, particle size, [...]."

As different crystal structures of the same substance may result in different hazard properties, data generated on one crystal structure according to Annex VII- XI may not be relevant and appropriate for a different crystal structure.

Similarly, current scientific knowledge establishes that the risks of nanoforms of substances would require separate assessment. Indeed, the specific risks of nanoforms are not founded on mere hypotheses that have not been scientifically confirmed. These risks have been demonstrated by the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR).[5] Where appropriate, registrants are compelled to scientifically assess the potentially adverse effects of nanomaterial forms of the substance they register.

The purpose of the REACH Regulation is to ensure a high level of protection of human health and the environment. In order to achieve this objective, the REACH Regulation imposes the determination of hazards and risks of substances manufactured or imported into the European Union. The determination of hazards and risks is irrespective of the crystal structures or nanomaterial forms of the substances concerned. It is therefore of utmost importance that the data generated with the test proposed allows the determination of the actual hazards posed by the registered substance, irrespective of its crystal structures or nanomaterial forms.

Specifically, and in view that the registered substance is known to exist as crystal structures, and possibly in nanomaterial forms, the proposed test shall aim at identifying all the actual human health hazards of the registered substance, and shall preclude underestimation of hazards. Indeed, it should be noted that the difference in crystal structures and nanomaterial forms of the registered substance does not relieve the Registrant from complying with the obligation to identify accurately hazards posed by the substance, irrespective of these crystal structures or nanomaterial forms.

Accordingly, when a registration dossier concerns a substance subject to different crystal structures or nanomaterial forms, which may result in different hazards and risks, the Registrant is compelled to determine the specific hazards and risks relevant for each specific crystal structure or nanomaterial form.

In that context, the REACH Regulation also promotes alternative methods for the assessment of hazards of substances, including the specific crystal structure or nanomaterial forms of these substances. As a result, the REACH Regulation allows the Registrant to identify the hazards of these specific crystal structures or nanomaterial forms by alternative means offering equivalence to test methods.

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[4] Available at http://echa.europa.eu/documents/10162/13562/clp_en.pdf

[5] "*There is sufficient evidence that there can be a change in some properties of the material at the nanoscale which is, for instance, due to the increase in surface-to-volume ratio. These nanospecific properties raise concerns over their potential to cause harm to humans and the environment. The chemical reactivity of nanoparticles often relates to the surface area. Consequently, the chemical reactivity per mass dose increases for smaller particles of the same type. This effect may or may not be associated with an increase in biological activity or toxicity*". SCENIHR, Opinion of 8 December 2010 on *Scientific Basis for the Definition of the Term «nanomaterial »*, page 31.

In the present case, ECHA notes that the Registrant has not identified which crystal structure he intended to test in this testing proposal. More specifically, the Registrant has not demonstrated in the dossier that a test performed with one of the crystal structure of the substance would allow identifying the hazards of all crystal structures of the substance in such a way that an underestimation of hazard, that may be associated with the different crystal structure, is excluded.

The responsibility to decide which crystal structures of the substance to test falls to the Registrant. Based on the above and on his knowledge of the substance identity, the Registrant may consider necessary to test all the crystal structures in order to determine their specific hazards. Alternatively, the Registrant may decide to test only one or some of these crystal structures. This approach may fulfil the information requirement only if the Registrant can scientifically justify why he considers a particular crystal structure to be representative of the toxicological hazards of other crystal structures of the substance and documents that this choice would not lead to an underestimation of the hazards. The same applies to the testing of nanomaterial forms of the substance, if any.

If, upon further consideration of the documentation provided, ECHA considers the justification inadequate to exclude an underestimation of the hazards, it reserves the right to request additional tests necessary to fulfil the fundamental objectives of the REACH Regulation.

Finally, should the Registrant decide to test more than one crystal structure of the substance in order to identify its specific hazard, he shall submit a new testing proposal for each additional experimental study planned to fulfil Annex IX or X information requirements. Similarly, should the substance be in different forms, including nanomaterial form(s), for which the Registrant would envision further testing in order to identify a specific hazard, he shall submit a new testing proposal for each additional experimental study planned to fulfil Annex IX or X information requirements.

e) Conclusion

Therefore, pursuant to Article 40(3)(b) and (c) of the REACH Regulation, you are requested to carry out the study with the registered substance subject to the present decision: Sub-chronic toxicity study (90-day) in rats, inhalation route (test method: OECD TG 413) including bronchoalveolar lavage (BAL) analysis, while your originally proposed test for a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method OECD TG 422) on the analogue substance barium dichloride dehydrate is rejected.

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

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.
A pre-natal developmental toxicity study for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test by the inhalation route according to the OECD TG 422 with the following justification: "*We propose a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD 422) as the NOAEL on developmental toxicity (no guideline followed, Dietz et al., 1992) of 4,000 ppm in the fertility study is of limited value to evaluate the potential for barium to induce developmental effects. The reason for this limitation is based on the fact that the premating study design did not include exposure of female animals during the gestational period to barium chloride. Therefore, the premating study has to be considered as an inadequate study of developmental toxicity and cannot be used to determine the occurrence of developmental toxicity.*"

ECHA points out that a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test conducted according to the OECD TG 422 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. Therefore, ECHA considers that the proposed study is not appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

You did not specify the species to be used for testing. According to the test method EU B.31/OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed with rats or rabbits as a first species.

You proposed testing by the inhalation route. 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 dust, ECHA concludes that testing should be performed by the oral route.

Concerning the selection of the test material, as explained in section 1.d) of the present Appendix, the responsibility to decide which crystal structures of the substance to test falls to the Registrant. Based on his knowledge of the substance identity, the Registrant may consider necessary to test all the crystal structures in order to determine their specific hazards. Alternatively, the Registrant may decide to test only one or some of these crystal structures.

This approach may fulfil the information requirement only if the Registrant can scientifically justify why he considers a particular crystal structure to be representative of the toxicological hazards of other crystal structures of the substance and documents that this choice would not lead to an underestimation of the hazards. If the Registrant decide to test more than one crystal structure of the substance in order to identify its specific hazard, he shall submit a new testing proposal for each additional experimental study planned. Similarly, should the substance be in different forms, including nanomaterial form(s), for which the Registrant would envision further testing in order to identify a specific hazard, he shall submit a new testing proposal for each additional experimental study planned.

In your comments to the draft decision you have indicated that you see no need to have to perform the requested study and outline the basis on which you intend to revise your read-across approach for this endpoint.

The hypothesis in this revised read-across approach is based on the formation of a common compound between the registered substance and the source substances, i.e. barium ions. You consider that barium ion concentrations are the most relevant parameter to evaluate barium toxicity, refer to a scientific publication (Journal of the American Ceramic Society, 83: 860-864) to establish that the barium ions are washed out from the crystal lattice and that the remaining titanates are rarely absorbed due to their low solubility. On that basis you conclude that "*the chemical safety assessment for barium titanium trioxide is based on the elemental metal concentration*" and that "*read-across of barium carbonate is plausible as only barium ions are present in aqueous solutions like blood*". In your comments to the draft decision you also specify that data from a pre-natal developmental toxicity study performed with barium chloride exists and will be used as source study in this revised read-across approach.

As indicated in the notification letter issued to you alongside the draft decision, for the purpose of the decision-making process, ECHA does not take into account any dossier updates after 8 August 2016, i.e. 30 calendar days after the end of the commenting period under Article 50(1) of the REACH Regulation. ECHA observes that no dossier update reflecting this revision of your read-across approach has been submitted by that deadline. The dossier submission subject to this decision still contains a testing proposal to perform a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test according to the OECD test guideline 422 with the substance subject to this decision. ECHA points out that it has the obligation to examine and to issue a decision on the testing proposal. No read-across adaptation is included in this dossier submission for the information requirement of Annex IX, section 8.7.2 for a pre-natal developmental toxicity study. Therefore, in accordance with the provisions of Article 40(3) of the REACH Regulation, ECHA has to proceed with the examination of this testing proposal.

You refer in your comments to a scientific publication with the reference "*Journal of the American Ceramic Society*, 83: 860-864" which ECHA understands corresponds to the publication by Neubrand et al. "*Room-Temperature Solubility Behavior of Barium Titanate in Aqueous Media*". ECHA understands that you consider that the information reported in this scientific publication addresses ECHA's concerns reported in the draft decision on the absence of characterisation of the dissociation of the barium titanium trioxide complex to form the common compound, i.e. barium ions. You consider that this publication characterises the dissolution of the barium titanium trioxide complex by demonstrating that the barium atoms included in the crystals of barium titanium trioxide are washed out and dissolved in aqueous solutions while "*titanates remain unchanged*".

For the reasons presented in section 1.1.b above, ECHA considers that the information provided in your comments suggests an incomplete dissolution of the registered substance and indicates that exposure to non-dissolved forms of the registered substance may occur. The impact of exposure to the registered substance in its non-dissolved form should be assessed. You failed to address the potential local and systemic toxicity of non-dissociated particles of the registered substance by only focusing the chemical safety assessment on the barium ion concentration and dismissing the toxicity of titanates based on their limited solubility. In the absence of demonstration that the barium titanium trioxide complex does not cause any toxicological effect in its non-dissolved form, ECHA considers that the read-across approach as currently presented in your registration dossier and in your comments may underestimate the properties of the target substance.

In your comments you expressed your intention to use information from a pre-natal developmental toxicity study performed with barium chloride to support your read-across approach. You refer to the study report provided by the registrant of barium chloride and you consider that study to be "*suitable for read-across of barium titanium trioxide*". You did not provide further information or documentation on this source study in your comments or in your registration dossier.

Based on the information provided in the registration dossier submitted for the substance barium chloride and disseminated on ECHA's website, this study appears to provide adequate and reliable information on the pre-natal developmental toxicity of barium chloride. However, ECHA considers that cross-referencing data reported in another registration dossier, as suggested by your reference to information from an existing pre-natal developmental toxicity study on barium chloride, does not constitute an adequate and reliable documentation of a source study.

For the reasons set out above, ECHA considers that the read-across adaptation as documented in your comments to the draft decision does not comply with the general rules of adaptation as set out in Annex XI, 1.5. Whilst the read-across adaptation proposed by you cannot be accepted for the reasons above, ECHA draws your attention to the note for consideration included in Section II.A of this decision referring to the possibility to adapt the information requirement for which testing requested in this decision according to the rules of Annex XI of the REACH Regulation.

Therefore, pursuant to Article 40(3)(b) and (c) of the REACH Regulation, you are requested to carry out the study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in a first species (rats or rabbits), oral route (test method: EU B.31/OECD TG 414) while your originally proposed test for a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method OECD TG 422) is rejected.

Notes for your consideration

For the selection of the appropriate species you are advised to consult ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015), Chapter R.7a, section R.7.6.2.3.2.

3. Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.)

Pursuant to Article 40(3)(d) of the REACH Regulation, ECHA may reject a proposed test.

You have submitted a testing proposal for a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method OECD TG 422) with the registered substance.

ECHA outlines that testing proposals can be only made for the provision of the information specified in Annexes IX and X of the REACH Regulation. A test covering an endpoint of Annex VIII as proposed by you does not fall within the scope of the examination of a testing proposal under Articles 40 and 10(a)(ix) of the REACH Regulation. In case the provision of the information specified in Annexes VII and VIII requires generating new data, it is your responsibility to perform the relevant test in accordance with the test methods laid down in a Commission regulation or in accordance with other international test methods recognised by the Commission or the Agency as being appropriate, as referred to in Article 13(3).

According to Annex IX, Section 8.7.3., as amended by Commission Regulation (EU) 2015/282 (entered into force on 13 March 2015), a two-generation reproductive toxicity study is no longer an information requirement. However, the requirement according to Annex IX, Section 8.7.3., i.e. the extended one-generation reproductive toxicity study, is only an information requirement if adverse effects on reproductive organs or tissues have been observed in the available repeated dose toxicity studies (e.g. a 28-day or 90-day repeated dose toxicity study, OECD TG 421 or 422 screening studies) or if they reveal other concerns in relation with reproductive toxicity.

ECHA notes that there is no repeated dose toxicity study available in the registration dossier, while you have proposed to perform a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method OECD TG 422). As detailed in section 1 of this Appendix, ECHA has examined this testing proposal and concluded that a sub-chronic (90-day) toxicity study shall be conducted according to the OECD TG 413 using the registered substance.

ECHA considers that the proposed study is at this stage not necessary to fulfil the information requirement of Annex IX, Section 8.7.3. of the REACH Regulation because no repeated dose toxicity study is currently available to evaluate if performance of such a reproductive toxicity study is required at that tonnage level.

ECHA concludes that at this stage there is no information gap for the information requirement of Annex IX, Section 8.7.3. Therefore, pursuant to Article 40(3)(d) of the REACH Regulation, the proposed combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method OECD TG 422) is rejected.

Notes for your consideration

Once the results from the sub-chronic toxicity study (Appendix 1, section 1. above) are available, you should reconsider the information requirement of Annex IX, Section 8.7.3. If the sub-chronic toxicity study indicates adverse effects on reproductive organs or tissues, or reveals other concerns in relation with reproductive toxicity, a new testing proposal for the present endpoint would – in accordance with the REACH Regulation – have to be submitted, unless compliance with this information requirement is scientifically justified and documented by means of specific or general rules of adaptation.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposal(s) for examination pursuant to Article 40(1) on 5 February 2013.

ECHA held a third party consultation for the testing proposal(s) from 17 April 2015 until 4 June 2015. ECHA did not receive information from third parties.

This decision does not take into account any updates after 8 August 2016, 30 calendar days after the end of the commenting period.

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 proposal(s) for amendment.

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

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

ECHA referred the draft decision to the Member State Committee.

You did not provide any comments on the proposed amendment(s).

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-52 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided in your registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the registration at a later stage.

2. 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 the Member States.

3. 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. It is also the responsibility of each registrant to document the necessary information on the composition(s) specifically covered by their individual submission. 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 compositions of the substance as actually manufactured or imported by each registrant including any other parameters relevant for determination of the properties of the substance, such as morphology when appropriate. If the registration of the substance by any registrant covers different compositions, the sample used for the new test(s) must be suitable to assess these compositions. Finally there must be adequate information on the composition for the sample tested and compositions registered to enable the relevance of the test(s) to be assessed.