EUROPEAN CHEMICALS AGENCY

Helsinki, 21 January 2021

Addressees
Registrant(s) of JS_202-259-7 as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
08/05/2015

Registered substance subject to this decision ("the Substance")
Substance name: Methyl benzoate
EC number: 202-259-7
CAS number: 93-58-3

Decision number: Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/F)

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***28 April 2023***.

Requested information must be generated using the Substance unless otherwise specified.

A. Information required from all the Registrants subject to Annex VII of REACH

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: EU B.13/14. /OECD TG 471) using one of the following strains: *E. coli* WP2 uvrA*, or E. coli WP2* uvrA (pKM101), or *S. typhimurium* TA102

2. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: EU C.3./OECD TG 201)

B. Information required from all the Registrants subject to Annex VIII of REACH

1. Justification for an adaptation of a Short-term repeated dose toxicity (28 days) based on the results of the Sub-chronic toxicity study (90 days) requested below (Annex VIII, Section 8.6.1.)

C. Information required from all the Registrants subject to Annex IX of REACH

1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.; test method: OECD TG 408) by oral route, in rats

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) by oral route, in one species (rat or rabbit)

Reasons for the request(s) are explained in the following appendices:

- Appendix on Reasons common to several requests

- Appendices entitled "Reasons to request information required under Annexes VII to IX of REACH", respectively.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

- the information specified in Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa;
- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;

You are only required to share the costs of information that you must submit to fulfil your information requirements.

How to comply with your information requirements

To comply with your information requirements you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information.

You must follow the general testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[1] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

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

Appendix on Reasons common to several requests

- **Assessment of your read-across approach under Annex XI, Section 1.5.**

You seek to adapt the following standard information requirements by applying a read-across approach in accordance with Annex XI, Section 1.5:

A. Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
B. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

ECHA has considered the scientific and regulatory validity of your read-across approach(es) in general before assessing the specific standard information requirements in the following appendices.

Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide a justification for the read-across including a hypothesis, explanation of the rationale for the prediction of properties and robust study summaries of the source studies.[2]

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance[3] and related documents[4, 5].

- **Predictions for properties**

  - **Prediction for toxicological properties**

You have provided the following reasoning for the prediction of toxicological properties (in the IUCLID section 13.21):
"*Methyl benzoate is likely to be rapidly transformed into benzoic acid via enzymatic cleavage by non-specific esterases in the gastrointestinal tract and when absorbed through the skin. Benzoic acid has a pKa of 4.2 ([redacted] 2010) and therefore it is available in the dissociated form in the blood (blood pH 7.4). Also sodium benzoate is dissociated to benzoate in the body and therefore considered as additional read-across substance.*
Methyl benzoate, benzoic acid and sodium benzoate have a common metabolism and will be excreted in mammals as hippuric acid or glucuronic acid conjugate. It could also be shown that the acute toxicity of all three substances has relatively low acute toxicity via the oral and dermal routes.
In summary, the chemicals will have a comparable mode of action in the covered endpoints:
- Repeated dose toxicity, Reproductive toxicity/developmental toxicity"

ECHA understands that you predict the properties of the Substance using a read-across hypothesis, which assumes that different compounds have the same type of effects. More precisely, you claim the Substance is transformed to one of the source substances (benzoic acid). The properties of your Substance are predicted to be qualitatively and quantitatively equal to those of the source substance.

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[2] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.6.1
[3] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals. 2008 (May) ECHA, Helsinki. 134. pp. Available online: https://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf/77f49f81-b76d-40ab-8513-4f3a533b6ac9
[4] Read-Across Assessment Framework (RAAF). 2017 (March) ECHA, Helsinki. 60 pp. Available online: Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across)
[5] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 (March) ECHA, Helsinki. 40 pp. Available online: https://doi.org/10.2823/794394

ECHA notes the following shortcomings with regards to prediction of toxicological properties.

Missing supporting information on the target substance

Annex XI, Section 1.5 of the REACH Regulation states that "*physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s)*". For this purpose "*it is important to provide supporting information to strengthen the rationale for the read-across*"[6]. The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on other category members.

Supporting information must include bridging studies to compare properties of the category members and to support your prediction, which is based on similarity of the relevant toxic properties.

As indicated above, your read-across hypothesis is based on the assumption that the structurally similar target and source substances cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the target and source substance is necessary to confirm that both substances cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design for the target and the source substances.

In your comments to the draft decision you state that information from studies with group members were provided for several toxicological endpoints, but not for repeated dose toxicity or developmental toxicity. You conclude that if ECHA considers data on repeated dose toxicity or reproductive/developmental toxicity as mandatory bridging studies, it would mean that for substances of Annex VIII the OECD 422 or 421 and OECD 407 become mandatory tests, and that you cannot find such an assessment or requirement in either ECHA's guidance nor in REACH.

Read-across is a case-by-case process, dependent on the read-across hypothesis made.

For cases where the read-across hypothesis for repeated dose toxicity or reproductive toxicity is based on the assumption that the structurally similar target and source substances cause the same type of effect(s), bridging information is likely to bring confidence that the source and target substances in fact share the same toxic properties. For categories the possibility to demonstrate that properties can be predicted from data on other category members depends on several parameters, such as the structural characteristics and data density of the family members in a category.

Different considerations would apply for read-across hypothesis solely based on the formation of common (bio)transformation products. Therefore, ECHA disagrees with your statement that for substances of Annex VIII the OECD 422 or 421 and OECD 407 are mandatory tests.

You furthermore state that you find it premature to request higher tier studies such as OECD TGs 408 and 414, and that ECHA instead should request bridging studies such as OECD TGs 407, 421 or 422. ECHA would like to stress that it is the responsibility of the Registrant to decide on a testing strategy for their substance, if there are data gaps, and that ECHA under Article 41 of REACH may only request information to fulfil the legal information requirements

[6] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.2.1.f

for the respective tonnages.

The data set reported in the technical dossier does not include relevant, reliable and adequate information for the Substance to support your read-across hypothesis. More notably, you have not provided any information on repeated dose toxicity or developmental toxicity for the target substance, which could be considered as bridging studies to demonstrate toxicological similarity between the source and target substance.

In the absence of such information, you have not established that the target and the source substances are likely to have similar properties. Therefore, you have not provided sufficient supporting information to strengthen the rationale for the read-across.

Missing information on the formation of common compound

As indicated above, your read-across hypothesis is based on the transformation of the Substance to one of the source substances (benzoic acid). In this context, information characterising the rate and extent of the break-down of the Substance and of the source substance(s) is necessary to confirm the formation of the proposed common break-down product and to assess the impact of the exposure to the parent compounds.

You have not provided any experimental data to document the presumed rapid transformation of the Substance.

In your comments to the draft decision, you provide the following information: *"Hydrolysis rates were measured in 80% human plasma and showed similar rates between ethyl benzoate (target) and methyl benzoate (source substance 1). The rates were 3.3 x 10^{-2}/min and 6.4 x 10^{-3}/min respectively. The half-lives ($t_{1/2}$) were 210 and 108 minutes."*

ECHA concludes that the information provided does not demonstrate rapid hydrolysis of your Substance. On the contrary the $t_{1/2}$ of 108 minutes shows that significant exposure to the parent compound occurs.

Therefore, your hypothesis based on formation of common (bio)transformation products and predicting the toxicity of the Substance based on information on the common products only is rejected.

In your comments to the draft decision, you also indicate that you intend to reconsider the kinetic data and consider whether or not additional information is needed. It is not possible, however, to take into account future studies.

Missing information on the impact of non-common compounds

As indicated above, your read-across hypothesis is based on the (bio)transformation of the Substance to one of the source substances (benzoic acid). In this context, exposure to the Substance may also lead to exposure to other compounds than the source substance. The impact of exposure to these other compounds on the prediction of properties of the target needs to be assessed to ensure that a reliable prediction can be made.

You state that *"potential adverse effects due to exposure to methanol should be taken into account when assessing the potential toxicity of methyl benzoate"* and compare methyl benzoate and methanol DNELs. You have not provided experimental data or other adequate and reliable information addressing the repeated dose toxicity or developmental toxicity of the dissociation/transformation product, methanol.

In your comments to the draft decision you raise the issue with data on the metabolite methanol and explain that, although studies were not provided in your documentation, such information was already taken into account in your DNEL derivations and can be included in the dossier. You also stress that methanol has been comprehensively investigated for developmental toxicity and that the relatively low content of methanol in the Substance is unlikely to present a hazard for that endpoint.

You also refer to the classification of methanol as STOT SE 1 and whether or not this is of relevance for the endpoints for which read-across has been used in this decision. ECHA agrees that read-across is endpoint specific and that information on acute toxicity has limited relevance for the present case. We have therefore deleted our statement on the STOT SE 1 classification.

ECHA notes, however, that if you wish to base your read-across hypothesis on the formation of common (bio)transformation products, sufficient hazard data on the (bio)transformation products to fulfil the information requirements for the endpoint in question is required.

In the absence of such experimental data or other adequate and reliable information, you have not established that a reliable prediction of the property under consideration of the target substance can be derived on the basis of your read-across hypothesis. Therefore, you have not provided sufficient supporting information to strengthen the rationale for the read-across.

Adequacy and reliability of source studies

According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across should:
1. have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3);
2. cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter.

The studies that you provided for the endpoints on sub-chronic toxicity and developmental toxicity in first species do not provide an adequate coverage of some key parameters expected to be investigated and do not meet the requirement for adequacy and reliability under Section 1.5, Annex XI to REACH for the reasons provided under Appendix B, section 1, Appendix C, sections 1 and 2.

- **Conclusions on the read-across approach**

As explained above, your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. Therefore, your adaptation is rejected and it is necessary to perform testing on your Substance.

Appendix A: Reasons to request information required under Annex VII of REACH

1. In vitro gene mutation study in bacteria

An *in vitro* gene mutation study in bacteria is an information requirement in Annex VII to REACH (Section 8.4.1.).

You have adapted this information requirement according to Annex XI, Section 1.2. of REACH (weight of evidence). In support of your adaptation, you have provided the following sources of information with the Substance:

i. Bacterial Reverse Mutation study ([redacted] 1987)
ii. Bacterial Reverse Mutation study (Szybalski, 1958)

In your comments to the proposal for amendment (PfA) submitted by one of the Member States competent authorities you also refer to the following studies:

iii. an *in vitro* gene mutation study in bacteria (OECD TG 471) with the analogue substance, ethyl benzoate [Salmonella mutagenicity tests: V. Results from testing 311 chemicals, Zeiger E, Anderson B, Haworth S, Lawlor T, Environmental and Molecular Mutagenesis 1988, 19(suppl. 21), 2-141.]; and
iv. *in vitro* HPRT test in mammalian cells with the Substance (OECD TG 476).

We have assessed this information and identified the following issues:

Annex XI, Section 1.2 states that there may be sufficient weight of evidence from several independent sources of information leading to assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

According to ECHA Guidance R.4.4, a weight of evidence adaptation involves an assessment of the relative values/weights of different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance of the information for the given regulatory information requirement. Subsequently, relevance, reliability, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Annex XI, section 1.2 requires that adequate and reliable documentation is provided to describe your weight of evidence approach.

However, you have not submitted any explanation why the sources of information provide sufficient weight of evidence leading to the conclusion/assumption that the Substance has or has not a particular dangerous property.

In spite of this critical deficiency, ECHA has nevertheless assessed the validity of your adaptation and identified the following issue:

Relevant information that can be used to support your weight of evidence adaptation for information requirement of Section 8.4.1 at Annex VII includes:

- Detection and quantification of gene mutations (base pairs, substitution or frame shift) in cultured bacteria including data on the number of revertant colonies; and
- Data provided on 5 bacterial strains: four strains of *S. typhimurium* (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101).

The sources of information (i.) and (ii.) provide information on detection and quantification of gene mutation in 4 bacterial strains (TA1535, TA1537, TA 100 and TA 98). However, the sources of information do not inform on detection and quantification of gene mutation in the 5th bacterial strain (either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101)).

As regards source of information (iii.) you indicate that all the required 5 bacterial strains have been tested. However, you have neither provided the referred study in your registration dossier nor submitted it to ECHA with your comments to the PfA. In addition, you have not provided a read-across adaptation for this endpoint. Therefore, ECHA is not in the position to assess the referred information. Therefore source of information (iii.) cannot be used to contribute to the weight of evidence for this information requirement.

Source of information (iv) does not provide information on bacterial cells therefore this study cannot contribute to the conclusion on gene mutations in bacterial cells.

Therefore, an essential investigation that would inform on *in vitro* gene mutation in bacteria is lacking.

In your comments to the PfA you confirmed that studies (i.) and (ii.) above do not include testing on *E. coli* WP2 uvrA, *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102. Nevertheless, you claim that this is not relevant as the Substance is neither a hydrazine nor an oxidizing agent.

As indicated in OECD TG 471, this information is required as the fifth strain may detect certain oxidising mutagens, cross-linking agents and hydrazines, which the other four strains cannot detect. In addition the fifth strain detects mutations at AT base pairs (the four strains detect mutations at GC base pairs). Thus, testing of all strains provides full information on the genotoxic mode of action in this test system.

Therefore, in absence of information of the fifth strain, the provided studies cannot be considered as reliable sources of information that could contribute to the conclusion on gene (point) mutations in the five bacterial strains.

On this basis, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous property foreseen to be investigated in an OECD TG 471.

Therefore, your adaptation is rejected and the information requirement is not fulfilled.

In your comments to the PfA you also indicate your intention to update the dossier with regard to the additional information of the alkyl benzoates to strengthen the weight of evidence.

We acknowledge your intention to strengthen and update the weight of evidence justification. However, currently, the weight of evidence adaptation cannot be accepted.

Consequently, the information provided in your dossier and your comments to the PfA is not sufficient to fulfil the information requirement.

Outcome

To fulfil the information requirement for the Substance, the *in vitro* gene mutation study in bacteria (OECD TG 471) should be performed using one of the following strains: *E. coli* WP2

uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102.

2. Growth inhibition study aquatic plants

Short-term toxicity testing on aquatic invertebrates is a standard information requirement in Annex VII to REACH.

You have provided a key study (1992) conducted according to the EU method C.3 (equivalent to OECD TG 201) with the Substance.

We have assessed this information and identified following issue:

To comply with this information requirement, an OECD TG 201 study must fulfil the validity criteria of the corresponding TG (Article 13(3) of REACH), which include (among others):

- The mean coefficient of variation for section-by-section specific growth rate in the control cultures not exceeding 35%
- The coefficient of variation of average specific growth rates during the whole test period in replicate control cultures must not exceed 7% in tests with Desmodesmus subspicatus

You have provided a key study conducted according to the EU Method C.3 (equivalent to OECD TG 201) showing the following:

- You stated that validity criteria were fulfilled. However there is no raw data to verify that the two of validity criteria listed above were met.

In your comments to the draft decision, you provide the calculated values for the validity criteria (as table 1 in the comments). You argue that the calculated results fulfils all three validity criteria of the OECD TG 201, and thus you consider the key study fulfils the information requirement. However, you also state that you are not the owner of the study and you still do not provide data used for the calculation.

In the absence of raw data, however, you still did not demonstrate that the validity criteria were fulfilled for the submitted key study. You are responsible to provide the necessary information to comply with the decision by the set deadline.

The information provided does not allow ECHA to confirm the fulfilment of the validity criteria.

Therefore, you did not demonstrate that the validity criteria are met.

Based on the above, the information you provided does not fulfil the information requirement and therefore a study according to TG 201 must be performed with the Substance.

Appendix B: Reasons to request information required under Annex VIII of REACH

1. Justification for an adaptation of a Short-term repeated dose toxicity (28 days) based on the results of the Sub-chronic toxicity study (90 days)

A Short-term repeated dose toxicity study (28 days) is a standard information requirement in Annex VIII to REACH. This information may take the form of a study record or a valid adaptation in accordance with either a specific adaptation rule under Column 2 of Annex VIII or a general adaptation rule under Annex XI.

You have provided the following studies for this endpoint in your dossier:

1. A multi-generation reproductive toxicity study in rat, with analogue substance benzoic acid (EC 200-618-2). No guideline (1960).
2. A repeated dose toxicity study (45 day) in rat, with the Substance. No guideline (1970).
3. A combined chronic toxicity/carcinogenicity study in mouse, with the analogue substance sodium benzoate (208-534-8). No guideline (1984).

As explained in the Appendix on Reasons common to several requests, your read-across adaptation is rejected. In addition we have identified the following deficiencies:

A. QUALITY OF READ-ACROSS STUDIES

As specified under Appendix on Reasons common to several requests, in the Assessment of your read-across approach, your study needs to have adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3), in this case OECD TG 407, including at least three dose levels, and at least 10 animals per dose group, clinical observations, ophthalmological examination, haematology, clinical biochemistry, and urinalysis.

The studies 1 and 3 you have provided deviate from the OECD TG 407 in the following ways:

- studies were conducted with less than three dose levels, and therefore they do not fulfil the criterion set in OECD TG 407.
- studies were not performed according to the criteria of the OECD TG 407, since the following key parameters are missing: clinical observations, ophthalmological examination, haematology, clinical biochemistry, urinalysis.

B. QUALITY OF STUDY WITH THE SUBSTANCE

As explained above, to comply with this information requirement, studies must cover the key parameters of OECD TG 407. The study 2 you have provided deviates from the OECD TG 407 in the following ways:

- study was conducted with less than three dose levels, and therefore does not fulfil the criterion set in OECD TG 407.
- study was conducted with less than 10 animals per sex per test dose group (7 rats per group were tested).
- the following key parameters are missing: ophthalmological examination and urinalysis,

Moreover, you have assigned reliability score 3 (not reliable) and therefore the information of that study is not considered relevant.

Therefore, the studies 1-3 were not performed according to the criteria of the OECD TG 407, and you did not justify why deviations from the OECD TG 407 can be considered acceptable.

Based on the above, the information you provided do not fulfil the information requirement.

Column 2 of Annex VIII, Section 8.6.1. provides that an experimental study for this endpoint is not needed if a reliable sub-chronic (90 days) or chronic toxicity study is available.

The present decision requests the registrants concerned to generate and submit a reliable sub-chronic toxicity study (90 days) (see Section 1 of Appendix C). According to Column 2 of Annex VIII, Section 8.6.1., and to prevent unnecessary animal testing, a short term toxicity study (28 days) does not therefore need to be conducted.

Because you still must comply with the information requirement in Annex VIII, Section 8.6.1., you are requested to submit a justification for the adaptation provided in Column 2 of that provision.

Appendix C: Reasons to request information required under Annex IX of REACH

1. Sub-chronic toxicity study (90-day)

A Sub-chronic toxicity study (90 day) is a standard information requirement in Annex IX to REACH. You have adapted the standard information requirement by applying read-across adaptation in accordance with Annex XI, section 1.5.

You have provided the following studies for this endpoint in your dossier:

1. A multi-generation reproductive toxicity study in rat, with the analogue substance benzoic acid (EC 200-618-2). No guideline (1960).
2. A repeated dose toxicity study (45 day) in rat, with the Substance. No guideline (1970).
3. A combined chronic toxicity/carcinogenicity study in mouse, with the analogue substance sodium benzoate (EC 208-534-8). No guideline (1984).

We have assessed this information and identified the following issue(s):

As explained in the Appendix on Reasons common to several requests, your read-across adaptation is rejected. In addition we have identified the following deficiencies:

A. QUALITY OF READ-ACROSS STUDIES

As specified under Appendix on Reasons common to several requests, in the Assessment of your read-across approach, your study needs to have adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3), in this case OECD TG 408, including at least three dose levels, clinical observations, ophthalmological examination, haematology, clinical biochemistry, urinalysis, and at least 20 animals per dose group and exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3), in this case 90 days.

The studies 1 and 3 you have provided deviate from the OECD TG 408 in the following ways:

- studies were conducted with less than three dose levels, and therefore they do not fulfil the criterion set in OECD TG 408.
- studies were not performed according to the criteria of the OECD TG 408, since the following key parameters are missing: clinical observations, ophthalmological examination, haematology, clinical biochemistry, urinalysis.

In your comments to the draft decision, you agree that the studies provided for this endpoint do not address all key parameters of an OECD TG 408 study. You argue, however, that the longer duration and the high number of animals used in the studies could in part compensate for the fact that only two doses were used.

ECHA notes that there is at present no adaptation according to Annex XI Section 1.2. (Weight of Evidence) in your dossier to justify how the studies presently included in your dossier may fulfil this information requirement.

You also indicated that the 4-generation study has been accepted in other registration dossiers. ECHA notes that the current compliance check can only consider the information on that study submitted for the registration for the Substance.

B. QUALITY OF STUDY WITH THE SUBSTANCE

As explained above, to comply with this information requirement, studies must cover the key parameters of OECD TG 408. The study 2 you have provided deviates from the OECD TG 408 in the following ways:

- study was conducted with less than three dose levels, and therefore they do not fulfil the criterion set in OECD TG 408,
- the following key parameters are missing: ophthalmological examination and urinalysis.
- study was conducted with less than 10 animals per sex per test dose group (7 rats per group were tested), and
- exposure duration of the study was only 45 days.

Moreover, you have assigned reliability score 3 (not reliable) and therefore the information of that study is not considered relevant.

Therefore, the studies were not performed according to the criteria of the OECD TG 408, and you did not justify why deviations from the OECD TG 408, can be considered acceptable.

Based on the above, the information you provided do not fulfil the information requirement.

Information on the design of the study to be performed (route/ species/ strain)

Referring to the criteria provided in Annex IX, Section 8.6.2, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity, because although the information indicates that human exposure to the Substance by the inhalation route is likely, potential inhalation-specific effects are already addressed by deriving a long-term DNEL for inhalation, local effects and by performing a qualitative assessment for inhalation, local effects.

Therefore the sub-chronic toxicity study must be performed according to the OECD TG 408, in rats and with oral administration of the Substance.

2. Pre-natal developmental toxicity study in one species

A Pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is a standard information requirement under Annex IX to REACH. You have adapted the standard information requirement by applying weight of evidence and read-across adaptations in accordance with Annex XI, sections 1.2. and 1.5.

You have provided the following studies all made with the analogue substance sodium benzoate (EC 208-534-8):

1. Weight of evidence, Prenatal Developmental Toxicity Study in rat, equivalent or similar to OECD TG 414 ([redacted], 1972)
2. Weight of evidence, Prenatal Developmental Toxicity Study in mouse, equivalent or similar to OECD TG 414 ([redacted], 1972)
3. Weight of evidence, Prenatal Developmental Toxicity Study in hamster, equivalent or similar to OECD TG 414 ([redacted], 1972)
4. Weight of evidence, Prenatal Developmental Toxicity Study in rabbit, equivalent or similar to OECD TG 414 ([redacted], 1972)
5. Supporting study in rat, Studies on effects of sodium benzoate on fetuses and offspring of Wistar rats (Onodera, 1978)

We have assessed this information and identified the following issue(s):

A. READ-ACROSS

As explained in the Appendix on reasons common to several requests, your read-across adaptation with study 5 is rejected.

B. WEIGHT OF EVIDENCE

You have adapted the standard information requirement for Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) by applying weight of evidence (WoE) adaptation in accordance with Annex XI, section 1.2. You have indicated studies 1-4 of being relevant information to be considered under WoE adaptation.

Annex XI, Section 1.2 states that there may be sufficient weight of evidence weight of evidence from several independent sources of information leading to assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

According to ECHA Guidance R.4.4, a weight of evidence adaptation involves an assessment of the relative values/weights of the different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance of the information for the given regulatory information requirement. Subsequently, relevance, reliability, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the (dangerous) property investigated by the required study.

Annex XI, section 1.2 requires that adequate and reliable documentation is provided to describe your weight of evidence approach.

However, for this information requirement, you have not submitted any explanation why the sources of information provide sufficient weight of evidence leading to the conclusion/assumption that the Substance has or has not a particular dangerous property.

In spite of this critical deficiency, ECHA has have nevertheless assessed the validity of your adaptation.

Section 1 of the Appendix Reasons common to several requests identifies deficiencies of the grouping and read-across approach, which leads to rejection of your read-across adaptation. These deficiencies apply equally to all the sources of information relating to analogue substance sodium benzoate submitted under your weight of evidence adaptations.

It is therefore not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not a particular dangerous property (i.e. toxicological endpoints listed above).

As explained above, your adaptations according to Annex XI 1.2. and 1.5. are rejected and the information requirement is not fulfilled.

A PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit as preferred species with oral[7] administration of the Substance.

Therefore, the pre-natal developmental toxicity study must be performed according to the OECD TG 414, in rats and with oral administration of the Substance.

[7] ECHA Guidance R.7a, Section R.7.6.2.3.2.

Appendix D: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. Test methods, GLP requirements and reporting

1. Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.

2. Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[8].

B. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

1. Selection of the Test material(s)

   The Test Material used to generate the new data must be selected taking into account the following:
   - the variation in compositions reported by all members of the joint submission,
   - the boundary composition(s) of the Substance,
   - the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

2. Information on the Test Material needed in the updated dossier
   - You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
   - The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[9].

[8] https://echa.europa.eu/practical-guides
[9] https://echa.europa.eu/manuals

Appendix E: Procedure

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

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The compliance check was initiated on 9 July 2019.

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).

In your comments to the draft decision you seek confirmation by ECHA on how the data use of the higher tier studies requested from the Annex IX registrants are to be handled in line with transparent and fair cost sharing concept among the Annex VIII registrants of the joint submission.

At Annex VIII, a request for a justification for an adaptation of a Short-term repeated dose toxicity (28 days) based on the results of the Sub-chronic toxicity study (90 days) is made because unnecessary animal testing must be avoided (Article 25 of REACH). In all cases registrants are responsible for data-sharing and cost-sharing, following REACH (see a.o. Title III) and the Commission Regulation 2016/9.

In response to your comment on the absence of request for screening test, ECHA notes also that the information requirement for a Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1) is not addressed in this decision. This may be addressed at a later stage.

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

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

ECHA invited you to comment on the proposed amendment(s) and referred the modified draft decision to the Member State Committee.

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

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

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-72 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix F: List of references - ECHA Guidance[10] and other supporting documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)[11]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[11]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents[12]

[10] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[11] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[12] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

Appendix G: Addressees of this decision and the corresponding information requirements applicable to them

You must provide the information requested in this decision for all REACH Annexes applicable to you.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.