~~Confidential~~

Helsinki, 25 October 2022

Addressees
Registrant(s) of 210-288-1_JS as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
14 April 2018

Registered substance subject to this decision ("the Substance")
Substance name: 4,4'-dihydroxybenzophenone
EC number: 210-288-1

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 ***4 November 2024***.

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

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

1. Skin sensitisation (Annex VII, Section 8.3.; test method:

i) In vitro/in chemico skin sensitisation information on molecular interaction with skin proteins and inflammatory response in keratinocytes and activation of dendritic cells (OECD TG 442C and OECD TG 442D and EU B.71/OECD TG 442E); and

ii) Only in case no conclusion on the skin sensitisation potency can be made for the Substance based on the newly generated in vitro/in chemico data, in vivo skin sensitisation study must be performed and the murine local lymph node assay (EU Method B.42/OECD TG 429) is considered as the appropriate study for the potency estimation.

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

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

3. Short-term repeated dose toxicity (28 days; Annex VIII, Section 8.6.1.) to be combined with the Screening for reproductive/developmental toxicity below;

4. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: EU B.64/OECD TG 422) by oral route, in rats;

5. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: EU C.1./OECD TG 203).

The reasons for the decision(s) are explained in Appendix 1.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you in accordance with Articles 10(a) and 12(1) of REACH. The addressees of the decision and their corresponding information requirements based on registered tonnage band are listed in Appendix 3.

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 requirements for testing and reporting new tests under REACH, see Appendix 4.

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 Mike Rasenberg, Director of Hazard Assessment

Appendix 1: Reasons for the decision
Appendix 2: Procedure
Appendix 3: Addressees of the decision and their individual information requirements
Appendix 4: Conducting and reporting new tests under REACH

[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 for the decision

Contents

0. Reasons common to several requests

0.1. *Assessment of the read-across approach*

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

- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Short-term toxicity to fish (Annex VIII, Section 9.1.3.)

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

Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group.

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance R.6. and related documents.

0.1.1. Predictions for (eco)toxicological properties

You read-across between the Substance as target substance and the following structurally similar substances as source substances:

- source substance 1: Benzophenone (EC: 204-337-6) for toxicity to reproduction and short-term toxicity to fish;
- source substance 2: Oxybenzone (Benzophenone-3; EC: 205-031-5) for genotoxicity;
- source substance 3: 2,4-dihydroxybenzophenone (EC: 205-029-4) for repeated dose toxicity, used under weight of evidence.

ECHA notes the following deficiencies with regards to predictions of (eco)toxicological properties.

Absence of justification for use of information on source substances 2 and 3

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 summary(ies) of the source study(ies).[2]

You have provided studies conducted with other substances than your Substance in order to comply with the REACH information requirements. You have not provided documentation or any other explanation as to why the information on source substances 2 and 3 is reliable and relevant for your Substance.

In the absence of such documentation, ECHA cannot verify that the properties of the Substance can be reliably predicted from the data on the source substance 2 and source substance 3.

Missing supporting information to compare properties of the Substance with source substance 1

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 supporting information to scientifically justify the read-across explanation for prediction of properties. The set of supporting information should strengthen the rationale for the read-across in allowing to verify the crucial aspects of the read-across hypothesis and establishing that the properties of the Substance can be predicted from the data on the source substance(s) (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.). Supporting information must include bridging studies to compare properties of the Substance and source substances.

You provided the following reasoning for using information from source substance 1: "The substance benzophenone (BP), which is the parent molecule for the di hydroxy species 4,4 -dihydroxybenzophenone, is used widely in personal care products and has been evaluated for both toxicology and ecotoxicology. It has been assessed that in the absence of other specific data on 4,4 -dihydroxybenzophenone that benzophenone can be used as a suitable surrogate molecule for evaluation of this end point". Further, you refer to the EFSA "Scientific opinion on toxicological evaluation of benzophenone" (May, 2009) that concludes that "benzophenone has no genotoxic potential", "liver and kidney were identified as primary target organs" in rats and mice and identified a TDI of 0.03 mg/kg bw/day.

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. The properties of your Substance are predicted to be quantitatively equal to those of the source substance.

In this context, relevant, reliable and adequate information allowing to compare the properties of the Substance and of the source substance 1 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 and duration for the Substance and of the source substance 1. In addition, with regards to your statement that the source substance 1 (Benzopehnone, EC: EC: 204-337-6) is a "*parent molecule*" of your Substance, supporting information, allowing to establish the rate and extent of biotransformation of the source substance 1 to your Substance, also needs to be provided.

You have not provided bridging studies allowing to compare the properties of the Substance and the source substance. Further, you have not provided any data on the source substance 1, to establish the rate of biotransformation as well as the quantity of the Substance, formed as metabolte. In the absence of such information, you have not established that the properties of the Substance can be reliably predicted from information on the source substance 1.

[2] ECHA Guidance R.6

Furthermore, ECHA notes that the source substance 1 (Benzophenone, EC 204-337-6) has hazardous properties as identified in the opinion of the Committee for Risk Assessment proposing a harmonised classification and labelling at EU level of Benzophenone (EC 204-337-6)[3]. Due to the lack of supporting information on the Substance, it is not possible to determine if other and/or more severe effects would be observed with the Substance than with the source substance 1, and your predictions may underestimate the hazards of the Substance.

In the comments to the draft decision you state that "*The read-across approach will be bolstered and made more robust, in compliance with general comments raised by ECHA*".

ECHA notes that in your comments you did not provide any further information and/or documentation to support your intention to improve the adaptation. Therefore, no conclusion on the compliance of the adaptation can be made.

0.1.2. Conclusions on the read-across approach

As explained above, you have not established that relevant properties of the Substance can be predicted from data on the source substances. Therefore, the read-across approach does not comply with the general rules as set out in Annex XI, Section 1.5.

0.2. *Assessment of weight of evidence adaptations*

You have adapted the following standard information requirements by applying weight of evidence (WoE) adaptation in accordance with Annex XI, section 1.2:

- Skin sensitisation (Annex VII, Section 7.4.1)
- Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.)

Your weight of evidence adaptations are based on information obtained from analogue substances, structurally similar to the Substance. The details of the set of information provided for each of the information requirements listed above are provided in the endpoint-specific sections of this document.

Your weight of evidence approach raises the same deficiencies irrespective of the information requirement for which it is invoked. Accordingly, ECHA addressed these deficiencies in the present Section, before assessing the specific standard information requirements in the following Sections.

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, 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 and coverage of the information for the given regulatory information requirement. Subsequently, relevance, reliability, coverage, 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.

[3] Committee for Risk Assessment, RAC. Opinion proposing harmonised classification and labelling at EU level of Benzophenone. EC Number: 204-337-6; CAS Number: 119-61-9. CLH-O-0000006808-62-01/F. Adopted 11 June 2020

Annex XI, section 1.2 requires that adequate and reliable documentation is provided to describe your weight of evidence approach. This documentation must include robust study summaries of the studies used as sources of information and a justification explaining why the sources of information together provide a conclusion on the information requirement.

You have not included a justification for your weight of evidence adaptation for each of the relevant information requirements, which would include an adequate and reliable (concise) documentation as to why the sources of information provide sufficient weight to conclude on the information requirements under consideration.

0.2.1. Reliability of the information with analogue substances

In particular, ECHA understands that you use data obtained with analogue substances in a read-across approach as part of your weight of evidence adaptation. For this information to reliably contribute to the weight of evidence approaches, it would have to meet the requirements for Grouping of substances and read-across approaches.

Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group.

Additional information on what is necessary when justifying a read-across approach can be found in the Guidance on IRs and CSA, Chapter R.6. and related documents (RAAF, 2017; RAAF UVCB, 2017).

For (eco)toxicological properties you use information on the following analogue substances:

- source substance 1: Benzophenone (EC: 204-337-6), to predict for repeated dose toxicity;
- source substance 2: Oxybenzone (Benzophenone-3; EC: 205-031-5), to predict for skin sensitization;
- source substance 3: 2,4-dihydroxybenzophenone (EC: 205-029-4), to predict for repeated dose toxicity.

As already explained in more detail in Section 0.1 of the present Appendix, you would need to provide information in support of the grouping and read-across approach. No such information has been provided by you in support of the predictions from the sources of information 1 to 3 submitted for your weight of evidence adaptations.

In the comments to the draft decision you state that *"The existing weight of evidence approach will be bolstered and made more robust, in compliance with general comments raised by ECHA".*

ECHA notes that in your comments you did not provide any further information and/or documentation to support your intention to improve the adaptation. Therefore, no conclusion on the compliance of the adaptation can be made.

0.2.2. *Conclusion on the information from analogue substances*

In the absence of supporting information, you have not established that the Substance and the source substance(s) are likely to have similar properties. Therefore the information from the analogue substances cannot reliably contribute to your weight of evidence adaptations

Reasons related to the information under Annex VII of REACH

1. Skin sensitisation

Skin sensitisation is an information requirement under Annex VII to REACH (Section 8.3.). Under Section 8.3., Column 1, the registrants must submit information allowing A) a conclusion whether the substance is a skin sensitiser and B) whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A), and (2) risk assessment, where required.

1.1. *Information provided*

In your IUCLID dossier you have reported the following information, relevant for this endpoint:

(i) *In vivo* in guinea pigs maximization test (key study, 1983), performed with an analogue substance. It is not clear from the robust study summary whether the test was performed with source substance 2 (Oxybenzone, EC: 205-031-5) or with source substance 1 (Benzophenone, EC: 204-337-6) which is given as test material.
(ii) Human Repeated insult patch test (HRIPT) (weight of evidence, 1983), performed with source substance 2 (Oxobenzone, EC: 205-031-5).

In addition, in the endpoint summary in IUCLID, section 7.4.1., you refer to the Cosmetic Ingredient Review (CIR) on Benzophenones and mention other (four) HRIPT on benzophenone-3 (oxybenzone) (without providing any details). You provide the conclusion of CIR that "this substance did not have a sensitising effect on humans".

Based on all this information, you consider that "*The data is quite comprehensive and on the basis of the available animal data and clinical human experience, it is concluded that Benzophenone-1, -3, -4, -5, -9, and -11. are safe for topical application to humans in the present practices of use and concentration in cosmetics"*

While you have not provided a specific legal reference for the adaptation rule which you apply, ECHA understands from the above that you use this information in a weight of evidence approach to cover for this information requirement.

1.2. Assessment of the information provided

We have assessed this information and identified the following issues:

1.2.1. Assessment whether the Substance causes skin sensitation

As explained in Section 0.2 of the Reasons common to several requests above, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Information that can be used to support a weight of evidence adaptation for the information requirements of Section 8.3 at Annex VII includes similar information to that investigated by the internationally recognised in vitro, in chemico and/or in vivo test methods on skin sensitisation. The key investigations of such test methods address each

of the 3 key events of skin sensitisation, either individually or in an integrated approach as follows:

1. investigation of cell proliferation in the draining lymph nodes (local lymph node assay), or
2. investigation of local responses in animals or humans (guinea pig assays or human studies), or
3. investigation of molecular interaction with proteins, inflammatory response in keratinocytes and activation of dendritic cells (*in vitro* and *in chemico* assays).

The sources of information (i) and (ii) provide relevant information, as they aim to provide information on these key investigations. However, these sources of information have the following deficiencies affecting the reliability of their contribution to the weight of evidence approach.

Reliability of the contribution of the information on the analogue substances

For the reasons explained in Section 0.2 of the Reasons common to several requests above, you have not established that the information from studies (i) and (ii) can reliably contribute to your weight of evidence adaptation.

Methodological deficiencies of experimental studies

In addition, ECHA notes the following methodological deficiency regarding the above source of information (i).

The evaluation of the reliability of the contribution of each relevant line of information to the weight of evidence approach includes an assessment of each source of information against the specifications of the test guideline followed.

The source of information (i) is a guinea pigs maximization test. The OECD TG 406, paragraph 11 requires that positive and negative controls establish the sensitivity and reliability of the experimental technique.

In the provided study (i), no information on positive and negative controls was provided.

In the absence of such information, the effective performance of the study is not demonstrated and the results obtained from the study (i) cannot be considered as reliable.

Based on the above, the reliability of the contribution of the results obtained from the study (i) to the weight of evidence is limited.

Adequacy of the study for hazard identification

Further, a study must be adequate for the corresponding information requirement. According to the ECHA Guidance (ECHA Guidance, Chapter R.4, page 1), "The evaluation of data quality includes assessment of adequacy of the information for hazard/risk assessment and C&L purposes". The ECHA Guidance defines adequacy as "the usefulness of data for hazard/risk assessment purposes". As a consequence, a study must be relevant for hazard assessment and for classification and labelling purposes.

The source of information (ii) is a Human Repeated insult patch test (HRIPT) where the source substance 2 (Oxobenzone, EC: 205-031-5) was applied at concentration of [redacted]% in a sunscreen preparation. You state that the study "has been caried out as part of a cosmetics review in 1983".

The study (ii) appears to have been designed to establish safe levels for specific intended uses - UV filter in sunscreens, rather than to investigate the intrinsic properties of the Substance as required for the purpose of hazard identification. In particular, the dose

levels used in this study are far lower than the doses expected to be used for hazard assessment purposes, as the method (HRIP) is intended to confirm the absence of irritation and sensitisation potential. Therefore, the study does not allow to make a conclusion whether the source substance 2 (Oxobenzone, EC: 205-031-5) causes skin sensitisation.

This deficiency significantly affects the reliability of this source of information and therefore its ability to predict the properties of the Substance.

1.3. *Conclusion on the weight of evidence*

Taken together, the sources of information as indicated above, provide relevant information, as they investigate local effects in animals and humans (guinea pig assay and HRIPT).

However, the reliability of the contribution of the information is hampered by:

- the use of information on analogue substance (studies (i) and (ii))
- methodological deficiencies in the study design and/or reporting listed above affecting directly the reliability of the results of study (i) and its contribution to the weight of evidence
- inadequacy for hazard identification explained above affecting directly the reliability of the results of study (ii) and its contribution to the weight of evidence

Therefore, 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 properties foreseen to be investigated in skin sensitisation studies.

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

1.4. *Assessment whether the Substance can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A).*

No assessment of potency

To be considered compliant and enable a conclusion in cases where the substance is considered to cause skin sensitisation, the information provided must also allow a conclusion whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A).

As the currently available data does not allow to conclude whether the Substance causes skin sensitisation (see section 1.2.1) above), this condition cannot be assessed.

On this basis, the information requirement is not fulfilled.

1.5. *Information provided in your comments on the draft decision*

In the comments to the draft decion you state that for "*The existing endpoint and weight of evidence approach will be bolstered and made more robust, in compliance with general comments raised by ECHA and the key parameter requirements for the study in question. In the event that robust data cannot be provided, a new study will be commissioned"*.

ECHA notes that in your comments you did not provide any further information and/or documentation to support your intention to improve the weight of evidance approach. Therefore, there is currently no information to assess and no conclusion on the compliance of the adaptation can be made. You remain responsible for complying with this decision by the set deadline.

1.6. *Specification of the study design*

To fulfil the information requirement for the Substance, information on molecular interaction with skin proteins and/or inflammatory response in keratinocytes and/or activation of dendritic cells (OECD TG 442C and OECD TG 442D and EU B.71/OECD TG 442E) must be provided. Furthermore an appropriate risk assessment is required if a classification of the Substance as a skin sensitiser (Cat 1A or 1B) is warranted.

In case no conclusion on the skin sensitisation potency can be made for the Substance based on the existing data or newly generated data, in vivo skin sensitisation study must be performed and the murine local lymph node assay (EU Method B.42/OECD TG 429) is considered as the appropriate study for the potency estimation

Reasons related to the information under Annex VIII of REACH

2. In vitro cytogenicity study in mammalian cells or In vitro micronucleus study

An in vitro cytogenicity study in mammalian cells or an in vitro micro-nucleus study is an information requirement under Annex VIII to REACH (Section 8.4.2.).

2.1. Information provided

In your IUCLID dossier, you do not excplicitly refer to a specific or general adaptation rule under the REACH provisions. In section 7.6.2. (Genetic toxicity in vivo) of the dossier you have provided a single source of information:

(i) In vivo mammalian bone marrow CA test (1994), performed with source substance 2 (Oxybenzone, EC: 205-031-5), giving negative results.

Despite the fact that you flagged the adequacy of the study as "weight of evidence", ECHA did not consider the information as a weight of evidence adaptation under Annex XI, Section 1.2, as this general adaptation rule presupposes evidence "from several independent sources of information […] while information from a single source alone is insufficient to support this notion."

The test material in study (i) is different than the Substance. Therefore, even if you have not provided a specific legal reference for your adaptation of this information requirement, ECHA has evaluated the study as read-across adaptation under Annex XI, Section 1.5. of REACH and identified the following issues.

2.1. *Assessment of the information provided*

As explained under Section 0.1 of the Reasons common to several request above, your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5 lacks adequate documentation and is therefore rejected.

Therefore, the information requirement is not fulfilled.

2.2. *Information provided in your comments on the draft decision*

In the comments to the draft decion you state that for "*The existing endpoint and weight of evidence approach will be bolstered and made more robust, in compliance with general comments raised by ECHA and the key parameter requirements for the study in question. In the event that robust data cannot be provided, a new study will be commissioned"*.

ECHA notes that in your comments you did not provide any further information and/or documentation to support your intention to improve the weight of evidance approach. Therefore, there is currently no information to assess and no conclusion on the compliance of the adaptation can be made. You remain responsible for complying with this decision by the set deadline.

2.3. *Specification of the study design*

To fulfil the information requirement for the Substance, the in vitro cytogenicity study in mammalian cells (OECD TG 473, 2016) or the in vitro micronucleus study (OECD TG 487, 2016) are considered suitable.

3. Short-term repeated dose toxicity (28 days)

A short-term repeated dose toxicity study (28 days) is an information requirement under Annex VIII to REACH (Section 8.6.1.).

3.1. Information provided

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

i) Repeated dose (90-day) toxicity study in rat (1983), performed with source substance 1 (Benzophenone, EC: 204-337-6);
ii) Repeated dose (90-day) toxicity study in rat (1991), performed with source substance 3 (2,4-dihydroxybenzophenone, EC: 205-029-4).

You consider that the information that you have provided on the analogue substances, when taken together, is adequate to fulfil the information requirement under consideration.

3.2. Assessment of the information provided

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

As explained in Sections 0.2 of the Reasons common to several request above, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.6.1. at Annex VIII includes, at general level, information on systemic toxicity in intact, non-pregnant and young adult males and females from: 1) in-life observations, 2) blood chemistry, 3) organ and tissue toxicity. Information should address effects on the following physiological systems: circulatory system, digestive/excretory system, endocrine system, immune system, integumentary system, musculoskeletal system, nervous system, renal/urinary system, reproductive system, and respiratory system.

We have assessed the individual sources of information with regard to relevance and reliability and identified the following issue(s):

3.2.1. Aspect 1) in-life observations

In-life observations must include information on survival, body weight development, clinical signs, functional observations, food/water consumption and other potential aspects of in life observations on the relevant physiological systems (circulatory, digestive/excretory, integumentary, musculoskeletal, nervous, renal/urinary, and respiratory).

The source of information (i) provides some relevant information, however it does not cover all of the key elements of this aspect. Moore specifically, based on the information provided in your dossier, this study does not inform on survival, clinical signs and functional observations.

According to the information provided in your dossier, the source of information (ii) provides relevant information, limited to the body weight development. It does not provide information on the other elements of aspect 1).

However, these sources of information have deficiencies affecting ther reliability:

Reliability of the contribution of the information on analogue substances

In general, for the reasons explained in the section 0.2 of the Reasons common to several requests above, you have not established that the information from the studies (i) and (ii) can reliably contribute to your weight of evidence adaptation.

3.2.2. Aspect 2) blood chemistry

Information on blood chemistry must include haematological (full-scale) and clinical chemistry analysis (full-scale), and other potential aspects related to blood chemistry to address relevant physiological systems (circulatory digestive/excretory, endocrine, immune, musculoskeletal, and renal/urinary).

The source of information (i) provides relevant information on some of the elements of aspect 2. However, it does not provide information on the following aspects: circulatory digestive/excretory, endocrine, immune and musculoskeletal systems.

According to the information provided in your dossier the source of information (ii) does not provide relevant information on blood biochemistry.

The source of information (i) has deficiencies affecting its reliability:

Reliability of the contribution of the information on analogue substance

In general, for the reasons explained in the section 0.2 of the Reasons common to several requests above, you have not established that the information from the study (i) can reliably contribute to your weight of evidence adaptation.

3.2.3. Aspect 3) organ and tissue toxicity

Organ and tissue toxicity must include information on terminal observations on organ weights, gross pathology and histopathology (full-scale) and other potential aspects related to organ and tissue toxicity to address relevant physiological systems (circulatory, digestive/excretory, endocrine, immune, integumentary, musculoskeletal, nervous, renal/urinary system, reproductive, and respiratory).

The sources of information (i) and (ii) provide relevant but very limited information on some elements of aspect 3). In the study summaries, liver and kidney are the only organs mentioned. Therefore, the studies (i) and (ii) do not cover all the necessary information on gross pathology and full histopathology, as specified in the OECD TG 407.

In addition, there are deficiencies affecting their reliability:

Reliability of the contribution of the information on analogue substances

In general, for the reasons explained in the section 0.2 of the Reasons common to several requests above, you have not established that the information from the studies (i) and (ii) can reliably contribute to your weight of evidence adaptation.

In the comments to the draft decision you state that "*The existing endpoint will be reviewed in terms of read-across versus a weight of evidence approach*". Further, you indicate that "*an exposure-based waiver will also be explored. Since the exit of the UK from the EU, there may be no applicable exposure of the monomer in the EU since it is*

the polymer which is imported. Tonnage remains below 100 TPA and so the registrant may seek to waive this study based on Annex XI, Section 3".

Conclusion

Taken together, the sources of information as indicated above, provide relevant information only on some elements of aspects 1 (in-life observations), 2 (blood chemistry) and 3 (organ and tissue toxicity, however they do not cover the entire set of elements, expected to be obtained from the OECD TG 407 for any of the aspects 1 to 3.

Furthermore, any robust conclusion on any of the 3 aspects is hampered by the use of information on analogue substances (source of information (i) and (ii)).

Therefore, 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 properties foreseen to be investigated in a study conducted according to the OECD TGs 407. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

3.3 Information provided in your comments

In your comments you did not provide any further information and/or documentation to support the read-across or weight of evidence approach.

Further, with regards to your intention to explore possibilities for applying exposure-based waiver, in accordance with Annex XI, section 3.2. you are required to provide a thorough and rigorous exposure assessment of the Substance covering all relevant exposures throughout the life-cycle of the Substance including the potential exposure to the monomer as an unreacted monomer in, or as a degradation product of, polymer. Based on the information provided in the comments, there is currently no information to assess whether your adaptation fulfils the requirements of Section 3 of Annex XI to the REACH Regulation. You remain responsible for complying with this decision by the set deadline.

3.4 Specification of the study design

When there is no information available neither for the 28-day repeated dose toxicity endpoint (OECD TG 407), nor for the screening study for reproductive/developmental toxicity (OECD TG 421 or TG 422), the conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) is preferred to ensure that unnecessary animal testing is avoided. Such an approach offers the possibility to avoid carrying out a 28-day study according to the OECD TG 407, because the OECD TG 422 can at the same time fulfil the information requirement of REACH Annex VIII, 8.6.1 and that of REACH Annex VIII, 8.7.1. (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

Therefore, a study according to the test method EU B.64/OECD TG 422 must be performed in rats with oral administration of the Substance.

4. Screening for reproductive/developmental toxicity

A Screening for reproductive/developmental toxicity study (test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) is a standard information requirement under Annex VIII to REACH, if there is no evidence from analogue substances, QSAR or in vitro methods that the Substance may be a developmental toxicant. There is no information available in your dossier indicating that your Substance may be a developmental toxicant.

4.1. Information provided

In your IUCLID dossier, section 7.8.1. (Toxicity to reproduction) you have provided:

(i) Two-generation reproductive toxicity study (key study, 2005), performed with source substance 1 (Benzophenone, EC: 204-337-6)

While you have not provided a specific legal reference for an adaptation of this information requirement, ECHA understands that you use this information in a read-across approach, since the test material is different than the Substance under Annex XI, Section 1.5. of REACH.

4.2. Assessment of the information provided

We have assessed this information and identified the following issues:

As explained in section 0.1 of the Reasons common to several requests above, your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5 is not adequately documented and therefore rejected. Therefore, the information requirement is not fulfilled.

4.3. Information provided in your comments on the draft decision

In the comments to the draft decision you state that "*an exposure-based waiver will also be explored. Since the exit of the UK from the EU, there may be no applicable exposure of the monomer in the EU since it is the polymer which is imported. Tonnage remains below 100 TPA and so the registrant may seek to waive this study based on Annex XI, Section 3".*

In accordance with Annex XI, section 3.2. you are required to provide a thorough and rigorous exposure assessment of the Substance covering all relevant exposures throughout the life-cycle of the Substance including the potential exposure to the monomer as an unreacted monomer in, or as a degradation product of, polymer. Based on the information provided in the comments, there is currently no information to assess whether your adaptation fulfils the requirements of Section 3 of Annex XI to the REACH Regulation. You remain responsible for complying with this decision by the set deadline.

4.4. Specification of the study design

When there is no information available neither for the 28-day repeated dose toxicity endpoint (OECD TG 407), nor for the screening study for reproductive/developmental toxicity (OECD TG 421 or TG 422), the conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) is preferred to ensure that unnecessary animal testing is avoided (see also section 4 above). Such an approach offers the possibility to avoid carrying out a 28-day study according to the OECD TG 407, because the OECD TG 422 can at the same time fulfil the information requirement of REACH Annex VIII, 8.6.1 and that of REACH Annex VIII, 8.7.1. (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

Therefore, a study according to the test method EU B.64/OECD TG 422 must be performed in rats with oral administration of the Substance.

5. Short-term toxicity testing on fish

Short-term toxicity testing on fish is an information requirement under Annex VIII to REACH (Section 9.1.3.).

5.1. *Information provided*

In your IUCLID dossier, you do not explicitly refer to a specific or general adaptation rule under the REACH provisions. In section 6.1.1. (Short-term toxicity to fish) of the dossier you have provided a single source of information:

(i) Fish, Acute Toxicity Test (Chinese National Standards: GB/T 27861-2011 equivalent or similar to OECD TG 203, GLP not specified), performed with source substance 1 (Benzophenone)

In addition, in section 6.1.1., you have provided references to data provided to fulfil other standard information requirements (daphnia, algae and aquatic microorganisms) but which do not provide further sources of information on short-term toxicity to fish

Despite the fact that you flagged the adequacy of study (i) as "weight of evidence" in the IUCLID dossier, ECHA did not consider the information as a weight of evidence adaptation under Annex XI, Section 1.2 because this general adaptation rule presupposes evidence "from several independent sources of information […] while information from a single source alone is insufficient to support this notion."

The test material in study (i) is different than the Substance. Therefore, even if you have not provided a specific legal reference for your adaptation of this information requirement, ECHA has evaluated the study as read-across approach adaptation under Annex XI, Section 1.5. of REACH and identified the following issues:

Lack of supporting information

As explained in Section 0.1 of the Reasons common to several requests above, your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5 is not adequately documented and therefore rejected. In addition, ECHA identified endpoint specific issue(s) addressed below.

Source study not adequate for the information requirement

Under Annex XI, Section 1.5., the study to be read across must have an adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this case test method equivalent or similar to the OECD TG 203. Therefore, the following specifications must be met:

a. the analytical measurement of test concentrations is conducted;
b. the test is conducted on juveniles of similar age (or size);
c. mortalities and sub-lethal effects (*e.g.* with regard to equilibrium, appearance, ventilator and swimming behaviour) are reported. The frequency of observations includes at least 2 observations within the first 24 hours and at least two observations per day from day 2 to 4.

The study (i) is described as short-term toxicity study in fish. However, the following specifications are not according to the requirements of OECD TG 203/EU Method C.1:

a. no analytical measurement of test concentrations was conducted;
b. the mean size of fish was 2.60 ± 0.20 cm, which does not correspond to juveniles for Zebrafish, *Danio rerio*;
c. tabulated data on mortalities and sub-lethal effects (*e.g.* with regard to equilibrium, appearance, ventilator and swimming behaviour) obtained on at least 2 observations within the first 24 hours and at least two observations per day

from day 2 to 4 for each treatment group and control are not reported.

Based on the above, the study does not provide an adequate and reliable coverage of the key parameter(s) addressed by the OECD TG 203 and this study is not an adequate basis for your read-across predictions. On this basis, the information requirement is not fulfilled.

5.2. *Information provided in your comments on the draft decision*

In the comments to the draft decision you state that "*The existing endpoint […..] will be bolstered and made more robust, in compliance with general comments raised by ECHA and the key parameter requirements for the study in question.*" Further, you indicate that "*An exposure-based waiver will also be explored*" and you conclude that "*In the event that robust data cannot be provided, a new study will be commissioned but only as a last resort in line with our obligations under the 3R's framework.*"

In your comments you did not provide any further information and/or documentation to support your intention to improve the weight of evidance approach.

Further, with regards to your intention to explore possibilities for applying exposure-based waiver, in accordance with Annex XI, section 3.2. you are required to provide a thorough and rigorous exposure assessment of the Substance. This should cover all relevant exposures throughout the life-cycle of the Substance including, in case of monomers incorporated into polymers which are imported in the EU, the potential exposure to the monomer as an unreacted monomer in, or as a degradation product of, polymer. Based on the information provided in the comments, there is currently no information to assess whether your adaptation fulfils the requirements of Section 3 of Annex XI to the REACH Regulation. You remain responsible for complying with this decision by the set deadline.

References

The following documents may have been cited in the decision.

Guidance on information requirements and chemical safety assessment (Guidance on IRs & CSA)

Chapter R.4 Evaluation of available information; ECHA (2011).
Chapter R.6 QSARs, read-across and grouping; ECHA (2008).
Appendix to Chapter R.6 for nanoforms; ECHA (2019).
Chapter R.7a Endpoint specific guidance, Sections R.7.1 – R.7.7; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Chapter R.7b Endpoint specific guidance, Sections R.7.8 – R.7.9; ECHA (2017).
Appendix to Chapter R.7b for nanomaterials; ECHA (2017).
Chapter R.7c Endpoint specific guidance, Sections R.7.10 – R.7.13; (ECHA 2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Appendix R.7.13-2 Environmental risk assessment for metals and metal compounds; ECHA (2008).
Chapter R.11 PBT/vPvB assessment; ECHA (2017).
Chapter R.16 Environmental exposure assessment; ECHA (2016).

Guidance on data-sharing; ECHA (2017).

All Guidance on REACH is available online: https://echa.europa.eu/guidance-documents/guidance-on-reach

Read-across assessment framework (RAAF)

RAAF, 2017 Read-across assessment framework (RAAF), ECHA (2017)
RAAF UVCB, 2017 Read-across assessment framework (RAAF) – considerations on multi- constituent substances and UVCBs), ECHA (2017).

The RAAF and related documents are available online:
https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

***OECD Guidance documents* (OECD GDs)**

OECD GD 23 Guidance document on aquatic toxicity testing of difficult substances and mixtures; No. 23 in the OECD series on testing and assessment, OECD (2019).
OECD GD 29 Guidance document on transformation/dissolution of metals and metal compounds in aqueous media; No. 29 in the OECD series on testing and assessment, OECD (2002).
OECD GD 150 Revised guidance document 150 on standardised test guidelines for evaluating chemicals for endocrine disruption; No. 150 in the OECD series on testing and assessment, OECD (2018).
OECD GD 151 Guidance document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test; No. 151 in the OECD series on testing and assessment, OECD (2013).

Appendix 2: 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 11 October 2021.

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

In the comments on the draft decision, you requested an extension of the deadline from 12 to 24 months from the date of adoption of the decision. You have provided the following argumentation for the extension: "*Since the reproductive / developmental toxicity test may be waived if the substance is known to exhibit some toxicity which may be indicated in the results of a cytogenicity study then the studies, if required, would be undertaken sequentially".*

Under Annex VIII, Section 8.7.1., column 2, the Screening study for reproductive/developmental toxicity does not need to be conducted if the substance is known to be a germ cell mutagen and appropriate risk management measures are implemented.

ECHA notes that, currently, your Substance does not meet the criteria for classification as germ cell mutagenic category 1A, 1B or 2, since your dossier contains negative results for the *in vitro* gene mutation in bacteria ([redacted], 2006) and *in vitro* gene mutation in mammalian cells ([redacted] 2006).

Note that this decision is based on the information currently available in the registration dossier for the Substance. As indicated in Appendix 1 Section 4 of this decision, your adaptation for the information requirement screening study for reproductive/developmental toxicity is rejected and you are requested to perform the study to fulfil the information requirement. Whilst ECHA takes note of your intention to submit a new adaptation for this information requirement, this does not justify extending the set deadline.

Therefore, ECHA considers that the timeline of 12 months set in the decision, allows for generating the required data on the Substance.

However, the deadline of the decision was set based on standard practice for carrying out OECD TG tests. It has been exceptionally extended by 12 months from the standard deadline granted by ECHA to take into account currently longer lead times in contract research organisations.

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

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix 3: Addressees of this decision and their corresponding information requirements

In accordance with Articles 10(a) and 12(1) of REACH, the information requirements for individual registrations are defined as follows:

- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa;

Registrant Name	Registration number	Highest REACH Annex applicable to you
[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.

Appendix 4: Conducting and reporting new tests for REACH purposes

1. Requirements when conducting and reporting new tests for REACH purposes

1.1. 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[4].

(4) Under the introductory part of Annexes VII/VIII/IX/X to REACH, where a test method offers flexibility in the study design, for example in relation to the choice of dose levels or concentrations, the chosen study design must ensure that the data generated are adequate for hazard identification and risk assessment.

1.2. Test material

(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 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.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[5].

[4] https://echa.europa.eu/practical-guides
[5] https://echa.europa.eu/manuals