~~Confidential~~

Helsinki, 17 May 2023

Addressee(s)
Registrant(s) of JS_97416-84-7 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
10/03/2021

Registered substance subject to this decision ("the Substance")
Substance name: 1,1'-(isopropylidene)bis[3,5-dibromo-4-(2,3-dibromo-2-methylpropoxy)benzene]
EC number/List number: 306-832-3

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 by ***22 August 2025***.

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

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

1. Long-term toxicity testing on aquatic invertebrates, also requested below (triggered by Annex VII, Section 9.1.1., Column 2);

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

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

3. In vitro micronucleus study (Annex VIII, Section 8.4.2.; test method: OECD TG 487) The aneugenic potential of the Substance must be assessed with an additional control group for aneugenicity on top of the control group for clastogenicity, if the Substance induces an increase in the frequency of micronuclei;

4. Justification for an adaptation of the short-term repeated dose toxicity study (28 days) (Annex VIII, Section 8.6.1., Column 2) based on the request 5 below.

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

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

6. 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);

7. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: EU C.20./OECD TG 211).

The reasons for the request(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.

In the requests above, the same study has been requested under different Annexes. This is because some information requirements may be triggered at lower tonnage band(s). In such cases, only the reasons why the information requirement is triggered are provided for the lower tonnage band(s). For the highest tonnage band, the reasons why the standard information requirement is not met and the specification of the study design are provided. Only one study is to be conducted; all registrants concerned must make every effort to reach an agreement as to who is to carry out the study on behalf of the others under Article 53 of REACH.

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 request(s)
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 request(s)

Contents

Reasons common to several requests

0.1. Weight of evidence adaptation rejected

1 You have adapted the following standard information requirements by using Annex XI, Section 1.2. (weight of evidence):

- An *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study (Annex VIII, Section 8.4.2.);
- Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.);
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.).

2 Annex XI, Section 1.2. states that there may be sufficient weight of evidence from several independent sources of information enabling, through a reasoned justification, a conclusion on the information requirement, while the information from each single source alone is insufficient to fulfil the information requirement.

3 The justification must have regard to the information that would otherwise be obtained from the study that must normally be performed for this information requirement.

4 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 on the corresponding information requirement.

5 Your weight of evidence approach has deficiencies that are common to all information requirements under consideration and also deficiencies that are specific for these information requirements individually.

6 The common deficiencies are set out here, while the specific ones are set out under the information requirement concerned in request(s) 3, 4, and 5 below.

0.1.1. Lack of documentation justifying the weight of evidence adaptation

7 Annex XI, Section 1.2. requires that adequate and reliable documentation is provided to describe a 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.

8 You have not included a justification for your weight of evidence adaptation for the information requirement of 28-days and 90-days repeated dose toxicity studies and of in vitro cytogenicity study in mammalian cells or in vitro micronucleus study, 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.

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

0.1.2. Reliability of the information with analogue substances

10 ECHA understands that you use data obtained with the following source substances in a read-across approach as part of your weight of evidence adaptation.

- source substance 1: [1,1'-(isopropylidene)bis[3,5-dibromo-4-(2,3-dibromopropoxy)benzene]], EC 244-617-5 to predict the *in vitro* cytogenicity and repeated dose toxicity properties of the Substance;
- source substance 2: [2,2',6,6'-tetrabromo-4,4'-isopropylidenediphenol], EC 201-236-9, to predict for repeated dose toxicity properties of the Substance.

11 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.

12 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 substances within the group.

13 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).

14 You provide a read-across justification document in IUCLID Section 13.

15 You provide the following reasoning for the prediction of toxicological properties: the three substances are brominated flame retardants having a biphenyl core (tetrabromo bisphenol A, TBBP A) and therefore "The read across is based on the structural similarity between the target substance and the two similar structure proposed." Further you state that the source substance 2 (TBBP A) "can also be considered the main reactive metabolite" of both the Substance and the source substance 1, therefore, "For all the systemic endpoints the results on the metabolite can be regarded as conservative compared to the parent substance. The Read Across approach is applicable"

16 ECHA understands that your read-across hypothesis assumes that different compounds have the same type of effects. More specifically, your read-across hypothesis is based on two arguments:

17 Firstly, based on the common core and similar functional groups you assume that your Substance and the source substance 1 will have similar toxicological profile. Based on this, you predict the properties of your Substance to be quantitatively equal to those of the source substance 1.

18 Secondly, for the systemic effects, you consider that the source substance 2 "can be regarded as conservative compared to the parent substance". Based on this you predict the properties of your Substance from source substance 2 based on a worst-case approach.

19 We have identified the following issues with the predictions of toxicological properties:

0.1.2.1. Missing supporting information to compare properties of the substances and to substantiate worst-case consideration for systemic effects

20 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.).

21 Supporting information must include, among others, information to confirm your claimed worst-case prediction and bridging studies to compare properties of the Substance and source substances.

22 As indicated above, your read-across hypothesis for source substance 1 is based on the assumption that (i) the source substance 1 causes the same type of effects and that (ii) the source substance 2, being reactive metabolite of the Substance, constitutes the worst case for the prediction of the systemic effects of the Substance. In this context, relevant, reliable and adequate information allowing to compare the properties of the substances is necessary to confirm that (i) the source substance 1 causes the same type of effects and (ii) the prediction of the systemic toxicity properties of the Substance is conservative from the data on source substance 2. Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and the source substance(s). In addition, supporting information allowing to establish the rate and extent of biotransformation of your Subsatnce to source substance 2, also needs to be provided.

23 In your dossier, the only toxicological data with your Substance is *in vitro* gene mutation study in mammalian cells. This study does not inform on cytogenicity and chromosomal aberrations in mammalian cells, therefore it cannot be used as bridging data with comparable design and duration to support your read-across hypothesis for this information requirement.

24 As regards the information on systemic toxicity, you have not provided any experimental data with the Substance, that could act as bridging studies with comparable design and duration. In the absence of such information it is not possible to compare the properties of your Substance and source substance 1 and to confirm your hypothesis of worst-case prediction from the source substance 2.

25 Finally, you have not provided any toxicokinetic data on the Substance so it is not possible to establish the rate of its biotransformation to source substance 2, nor the quantity of its formation.

Conclusion on the information from analogue substances

26 In the absence of supporting information, you have not established that the Substance and the source substances 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. Long-term toxicity testing on aquatic invertebrates

27 Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII, Column 1, Section 9.1.1. However, under Column 2, long-term toxicity testing on aquatic invertebrates may be required by the Agency if the substance is poorly water soluble, i.e. solubility below 1 mg/L.

1.1. Triggering of the information requirement

28 Poorly water soluble substances require longer time to reach steady-state conditions. As a result, the short-term tests do not give a true measure of toxicity for this type of substances and the long-term test is required.

29 In the provided OECD TG 105 (2015) the saturation concentration of the Substance in water was determined to be 6.7 µg/L ± 5.4 µg/L.

30 Therefore, the Substance is poorly water soluble and information on long-term toxicity on aquatic invertebrates must be provided.

1.2. Information requirement not fulfilled

31 The information provided, its assessment and the specifications of the study design are addressed under request 7.

2. Growth inhibition study aquatic plants

32 Growth inhibition study on aquatic plants is an information requirement under Annex VII to REACH (Section 9.1.2.).

2.1. Information provided

33 You have adapted this information requirement by using Column 2 of Annex VII, Section 9.1.2. , based on your consideration that the Substance is highly insoluble in water.

2.2. Assessment of the information provided

34 Under Annex VII, Section 9.1.2., Column 2, first indent, the study may be omitted if aquatic toxicity is unlikely, for instance if the Substance is highly insoluble in water. Guidance on IRs and CSA, Section R.7.8.5 explains that there is no scientific basis to define a cut off limit for solubility below which toxicity is unlikely. Therefore, the justification must demonstrate very low water solubility and low likelihood to cross biological membranes. For the latter, the indicators used for low likelihood of a high bioaccumulation potential (Guidance on IRs and CSA, Figure R.11-4) must be considered, including:

- physico-chemical indicators of hindered uptake due to large molecular size (*e.g.* D_{max} > 17.4 Å and MW > 1100 or MML > 4.3 nm) or high octanol-water partition coefficient (Log K_{ow} > 10) or low potential for mass storage (octanol solubility (mg/L) < 0.002 x MW), and

- supporting experimental evidence of hindered uptake (no chronic toxicity for mammals and birds, no chronic ecotoxicity, no uptake in mammalian toxicokinetic studies, very low uptake after chronic exposure).

35 Unless it can reliably be demonstrated that aquatic toxicity is unlikely to occur, the Substance must be considered as poorly water soluble.

36 Your registration dossier provides:

- Information on the water solubility of the Substance based on OECD TG 105: 6.7 µg/L ± 5.4 µg/L.
- Physico-chemical indicators of low likelihood to cross biological membranes based on hindered uptake of the Substance: Dmax > 1.7 nm, molecular weight 971.6 g/mol; and Log Kow > 10.
- No supporting experimental evidence of hindered uptake for the Substance. Your dossier does not contain any toxicokinetic studies, repeated-dose toxicity studies (28-d or 90-d) in rodents, nor any long-term aquatic toxicity studies on the Substance suggesting hindered uptake.

37 Even though the water solubility of the Substance is low, and there are physico-chemical indicators supporting hindered uptake, there is no supporting experimental evidence of hindered uptake (as noted above). Without such evidence it is not possible to reliably conclude that toxicity to aquatic plants will not occur.

38 Therefore, you have not demonstrated that aquatic toxicity is unlikely to occur and your adaptation is rejected. The Substance must be considered to be poorly water soluble.

39 Therefore, the information requirement is not fulfilled.

2.3. Study design and test specifications

40 The Substance is difficult to test due to the low water solubility (6.7 µg/L ± 5.4 µg/L) and adsorptive properties (Log K_{ow} 12.42; Log Koc >5.63). The OECD TG 201 specifies that, for difficult to test substances, you must consider the approach described in the OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in the OECD TG 201. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solution.

41 In your comments on the draft decision you agree to conduct the requested study.

Reasons related to the information under Annex VIII of REACH

3. In vitro micronucleus study

An *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study is a standard information requirement in Annex VIII to REACH.

3.1. Information provided

42 You have adapted this information requirement by using Annex XI, Section 1.2. (weight of evidence) based on the following:

(i) *In vitro* sister chromatid exchange assay in mammalian cells (1984), performed with source substance 1

(ii) The following statement, provided under IUCLID section 7.6 (the endpoint summary): *"Moreover on the NTP database has been reported a result of an in vivo micronucleus test on mice (B6C3F1). The test has been conducted according to the NTP Standard Protocol and negative results have been observed both in male and in female mice (B6C3F1)";*

3.2. Assessment of the information provided

43 We have assessed this information and identified the following issues:

44 As explained under Section 0.1 on Reasons common to several requests, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information.

45 In addition to the deficiencies identified in Section 0.1, ECHA identified endpoint specific issue(s) addressed below.

3.2.1. Missing robust study summary for source (ii)

46 Annex XI, Section 1.2. requires that whenever weight of evidence is used adequate and reliable documentation of the applied method must be provided. Such documentation must include a robust study summary for each source of information used in the adaptations.

47 A robust study summary must provide a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study (Article 3(28)).

48 In addition, for weight of evidence adaptations, the robust study summary must clearly indicate which key parameters of the study normally required for the information requirement are investigated in the study.

49 In your statement, provided under point (ii) you refer to results from an *in vivo* micronucleus test on mice (B6C3F1). However, you have not provided detailed information on the methods, results and conclusions, allowing for an independent assessment of this source of information and how it contributes to the overall weight of evidence for the information requirement under consideration.

50 ECHA concludes that you have failed to provide a robust study summary for source of information (ii) as required by Annex XI, Section 1.2.

51 Consequently, this source of information cannot be considered as contributing to the overall weight of evidence for the information requirement under consideration, as relevance and reliability of its contribution cannot be evaluated.

3.2.2. Assessment of relevance and reliability

52 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.4.2. at Annex VIII includes:

- Detection and quantification of cytotoxicity and the frequency of cells with structural chromosomal aberration(s) or the frequency of micronuclei in cultured mammalian cells *(in vitro*) or in mammals (*in vivo*).

53 A level of information on these aspects similar to that obtained from *in vitro/in vivo* chromosomal aberration tests (OECD TG 473/OECD TG 475) or *in vitro/in vivo* micronucleus tests (OECD TG 487/OECD TG 474) is required.

54 The source of information (i) is neither an *in vitro* chromosomal aberration test nor an *in vitro* micronucleus test. Eventhough, the study provides relevant information on detection and quantification of cytotoxicity, however, it does not provide information on the frequency of cells with structural chromosomal aberration(s). Therefore, it only provides part of the necessary information for this information requirement.

55 However, for the reasons explained in the section 0.1. of the Reasons common to several requests above, you have not established that the information on the analogue substance from study (i) can reliably contribute to your weight of evidence adaptation.

3.2.3. *Conclusion on the weight-of-evidence*

56 In summary, the source of information (i) provides relevant information only on one element of the information requirement on cytogenicity in mammalian cells. Even for this element, the reliability of the provided information is hampered by the deficiency identified related to the use of information on the analogue substance (source (i)).

57 The source of information (ii) does not contribute to the weight of evidence due to missing robust study summary.

58 It is not possible to conclude, based on any of the sources of information alone or considered together, on the information requirement for cytogenicity in mammalian cells.

59 Therefore, the information requirement is not fulfilled.

3.3. Specification of the study design

60 According to the Guidance on IR & CSA, Section R.7.7.6.3., either the *in vitro* mammalian chromosomal aberration ("CA") test (test method OECD TG 473) or the *in vitro* mammalian cell micronucleus ("MN") test (test method OECD TG 487) can be used to investigate chromosomal aberrations *in vitro*. However, while the MN test detects both structural chromosomal aberrations (clastogenicity) and numerical chromosomal aberrations (aneuploidy), the CA test detects only clastogenicity, as the OECD TG 473 is not designed to measure aneuploidy (see OECD TG 473, paragraph 2).Therefore, you must perform the MN test (test method OECD TG 487), as it enables a more comprehensive investigation of the chromosome damaging potential *in vitro*. Moreover, in order to demonstrate the ability of the study to identify clastogens and aneugens, you must include two concurrent positive controls, one known clastogen and one known aneugen [1] (OECD TG 487, paragraphs 33 to 35).

61 In the comments to the draft decision, you agree to perform the requested study.

3.3.1. Assessment of aneugenicity potential

62 If the result of the MN test is positive, i.e. your Substance induces an increase in the frequency of micronuclei, you must assess the aneugenic potential of the Substance.

63 In line with the OECD TG 487 (paragraph 4), you should use one of the centromere labelling or hybridisation procedures to determine whether the increase in the number of micronuclei is the result of clastogenic events (i.e. micronuclei contain chromosome fragment(s)) and/or aneugenic events (i.e. micronuclei contain whole chromosome(s)).

[1] According to the TG 487 (2016) "At the present time, no aneugens are known that require metabolic activation for their genotoxic activity" (paragraph 34).

4. 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)

64 A short-term repeated dose toxicity study (28 days) is an information requirement under Annex VIII, Section 8.6.1. 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 or a general adaptation rule under Annex XI.

4.1. Information provided

65 You have adapted this information requirement by using Annex XI, Section 1.2. (weight of evidence) based on the following experimental data:

66 With the source substance 2 (2,2',6,6'-tetrabromo-4,4'-isopropylidenediphenol; EC 201-236-9):

(i) Short-term (28 day) toxicity study in rats (1972);
(ii) Sub-chronic (90-day) toxicity study in rat (2014a);
(iii) Sub-chronic (90-day) toxicity study in mouse (2014b);
(iv) Sub-chronic (90-day) toxicity study (1975);
(v) Sub-chronic (90-day) toxicity study (1986).

67 With the source substance 1 ([1,1'-(isopropylidene)bis[3,5-dibromo-4-(2,3-dibromopropoxy)benzene]], (EC 244-617-5):

(vi) Sub-chronic (90-day) toxicity study (1987).

4.2. Assessment of the information provided

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

69 As explained under 0.1 Appendix on Reasons common to several requests, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information.

70 In addition to the deficiencies identified in Section 0.1 above on Reasons common to several requests, ECHA identified endpoint specific issue(s) addressed below.

71 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.6.1 at Annex VIII includes similar information that is produced by the OECD TG 407. The following aspects of systemic toxicity in intact, non-pregnant and young adult males and females are covered: 1) in-life observations, 2) blood chemistry, 3) organ and tissue toxicity.

72 We have assessed the individual sources of information with regard to relevance and reliability and identified the following issues:

4.2.1. Aspect 1) in-life observations

73 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).

74 The sources of information (ii) and (iii) provide relevant information on all key elements of in-life observations.

75 The sources of information (i), (iv), (v) and (vi) provide relevant information on some elements of aspect 1), however, they do not cover all key elements of this aspect. More specifically, based on the information reported in your dossier, these sources of information do not inform on functional observations. In addition, the source of information (vi) does not inform on body weight development and food consumption.

76 However, the reliability of all sources of information (i-vi) is significantly affected by the following deficiency:

4.2.1.1. Reliability of the contribution of the information on analogue substances

77 For the reasons explained in the section 0.1 of the Reasons common to several requests above, you have not established that the information from the studies (i), (ii), (iii), (iv), (v) and (vi) can reliably contribute to your weight of evidence adaptation.

4.2.2. Aspect 2) blood chemistry

78 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).

79 The sources of information (i) and (v) do not inform on this aspect.

80 The sources of information (ii) and (iii) provide relevant information on all key elements of aspect 2.

81 The sources of information (iv) and (vi) provide relevant information on some elements of aspect 2, however, they do not cover all key elements of this aspect. More specifically they do not include full-scale haematological and clinical chemistry analysis.

82 However, the reliability of all sources of information is significantly affected by the same deficiency as addressed in 4.2.1.1.

4.2.3. Aaspect 3) organ and tissue toxicity

83 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).

84 The sources of information (ii) and (iii) provide relevant information on all key elements of aspect 3).

85 The sources of information (i), (iv), (v) and (vi) provide relevant information on some elements of aspect 3), however, they do not cover all key elements of this aspect. More specifically, based on the information reported in the dossier, none of these sources inform on histopathology 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).

86 However, the reliability of all sources of information is significantly affected by the same deficiency as addressed in 4.2.1.1.

4.2.4. Conclusion on the weight of evidence

87 Taken together, two sources of information (ii) and (iii) provide relevant information on all elements of aspects 1 (in-life observations), 2 (blood chemistry) and 3 (organ and tissue toxicity), while other sources of information contribute only on some of the elements of all aspects.

88 However, the reliability of this information is hampered by the deficiency identified related to the use of information on the analogue substances.

89 Therefore, it is not possible to conclude, based on any source of information alone or considered together, on the information requirement for short-term repeated toxicity (28 days). Therefore, your adaptation is rejected and the information requirement is not fulfilled.

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

91 The present decision requests the registrants concerned to generate and submit a reliable sub-chronic toxicity study (90 days) (see request 5).

92 According to Annex VIII, Section 8.6.1., Column 2 and to prevent unnecessary animal testing, a short-term toxicity study (28 days) does not need to be conducted. Therefore, to comply with the information requirement in Annex VIII, Section 8.6.1., you are requested to provide a justification for adaptation, as provided in Annex VIII, Section 8.6.1., Column 2.

93 In the comments to the draft decision, you agree to provide a justification for adaptation as requested.

Reasons related to the information under Annex IX of REACH

5. Sub-chronic toxicity study (90 days)

94 A sub-chronic toxicity study (90 days) is an information requirement under Annex IX, Section 8.6.2.

5.1. Information provided

95 You have adapted this information requirement by using Annex XI, Section 1.2. (weight of evidence) based on the following experimental data:

96 With the source substance 2 (2,2',6,6'-tetrabromo-4,4'-isopropylidenediphenol; EC 201-236-9):

(i) 28 days toxicity study in rats (1972);
(ii) Sub-chronic (90-day) toxicity study in rat (2014a);
(iii) Sub-chronic (90-day) toxicity study in mouse (2014b);
(iv) Sub-chronic (90-day) toxicity study (1975);
(v) Sub-chronic (90-day) toxicity study (1986).

97 With the source substance 1 ([1,1'-(isopropylidene)bis[3,5-dibromo-4-(2,3-dibromopropoxy)benzene]], (EC 244-617-5):

(vi) Sub-chronic (90-day) toxicity study (1987).

5.2. Assessment of the information provided

98 We have assessed this information and identified the following issues:

99 As explained under 0.1 Appendix on Reasons common to several requests, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information.

100 In addition to the deficiencies identified in Section 0.1 above on Reasons common to several requests, ECHA identified endpoint specific issue(s) addressed below.

101 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.6.2 at Annex IX includes similar information that is produced by the OECD TG 408. The following aspects of systemic toxicity in intact, non-pregnant and young adult males and females are covered: 1) in-life observations, 2) blood chemistry, 3) organ and tissue toxicity.

102 We have assessed the individual sources of information with regard to relevance and reliability and identified the following issues:

5.2.1. Aspect 1) in-life observations

103 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).

104 The sources of information (ii) and (iii) provide relevant information on all key elements of in-life observations.

105 The sources of information (i), (iv), (v) and (vi) provide relevant information information on some elements of aspect 1), however, they do not cover all key elements of this aspect. More specifically, based on the information reported in your dossier, these sources of information do not inform on functional observations. In addition, source of information (vi) do not inform on body weight development and food consumption.

106 However, the reliability of all sources of information (i-vi) is significantly affected by the following deficiencies:

5.2.1.1. Reliability of the contribution of the information on analogue substances

107 In general, for the reasons explained in the section 0.1 of the Reasons common to several requests above, you have not established that the information from the studies (i), (ii), (iii), (iv), (v) and (vi) can reliably contribute to your weight of evidence adaptation.

5.2.1.2. Reliability of the contribution of the study (i)

108 For a sub-chronic toxicity study, the OECD TG 408 requires dosing of the Substance daily for a minimum of 90 days, i.e. 13 weeks.

109 In study (i), the study specifications are not according to the requirements of the OECD TG 408 since the exposure duration is of 28 days.

110 Therefore, the actual exposure period in study (i) is shorter than the minimum exposure duration expected from a study conducted according to the OECD TG 408. This condition of exposure is essential because the effects observed over the required period of exposure of 90-days might be considerably more pronounced than over a shorter study duration.

111 Therefore, the reliability of the contribution of the results obtained from the study (i) to the weight of evidence is limited. The specifications according to which the results were obtained introduce uncertainty in the results which must be considered.

5.2.2. Aspect 2) blood chemistry

112 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.)

113 The sources of information (i) and (v) do not inform on this aspect.

114 The sources of information (ii) and (iii) provide relevant information on all key elements of aspect 2.

115 The sources of information (iv) and (vi) provide some relevant information, however, they do not cover all key elements of this aspect. More specifically they do not include full-scale of haematological and clinical chemistry analysis. Consequently, the sources of information (iv) and (vi) provide only partially relevant information for aspect 2).

116 However, the reliability of all sources of information is significantly affected by the same deficiencies as addressed in 5.2.1.1. and in 5.2.1.2

5.2.1. Aspect 3) organ and tissue toxicity

117 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).

118 The sources of information (ii) and (iii) provide relevant information on all key elements of aspect 3).

119 The sources of information (i), (iv), (v) and (vi) provide relevant information information on some elements of aspect 3), however, they do not cover all key elements of this aspect. More specifically, based on the information reported in the dossier, none of these sources inform on histopathology 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).

120 However, the reliability of all sources of information is significantly affected by the same deficiencies as addressed in 5.2.1.1. and in 5.2.1.2.

5.2.1. Conclusion on the weight of evidence

121 Taken together, two sources of information (ii) and (iii) provide relevant information on all elements of aspects 1 (in-life observations), 2 (blood chemistry) and 3 (organ and tissue toxicity), while other sources of information contribute only on some of the elements of all aspects.

122 However, the reliability of this information is hampered by the following reliability issues:

- the deficiency identified related to the use of information on the analogue substances and
- related to shorter study duration which increases the uncertainty of the conclusion for the Substance (study (i)).

123 Therefore, it is not possible to conclude, based on any of the sources of information alone or considered together, on the information requirement for sub-chronic toxicity (90 days).

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

5.3. Specification of the study design

125 Following the criteria provided in Annex IX, Section 8.6.2., Column 2, and considering the Guidance on IRs and CSA, Section R.7.5.6.3.2., the oral route is the most appropriate route of administration to investigate repeated dose toxicity of the Substance.

126 According to the OECD TG 408, the rat is the preferred species.

127 Therefore, the study must be performed in rats according to the OECD TG 408 with oral administration of the Substance.

128 In the comments to the draft decision, you agree to perform the requested study.

6. Pre-natal developmental toxicity study in one species

129 A pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is an information requirement under Annex IX, Section 8.7.2.

6.1. Information provided

130 You have adapted this information requirement by using Annex XI, Section 1.5. (grouping of substances and read-across approach) based on the following experimental data:

(i) Prenatal developmental toxicity study in rats (1985) with the source substance 2 (2,2',6,6'-tetrabromo-4,4'-isopropylidenediphenol), (EC: 201-236-9)

6.2. Assessment of the information provided

131 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.

132 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).

133 You provide a read-across justification document in IUCLID section 13.2.

134 You provide the following reasoning for the prediction of toxicological properties: the Substance and the source substance 2 are brominated flame retardants having a biphenyl core (tetrabromo bisphenol A, TBBP A) and the source substance 2 (TBBP A) "can also be considered the main reactive metabolite" of the Substance, therefore, "For all the systemic endpoints the results on the metabolite can be regarded as conservative compared to the parent substance. The Read Across approach is applicable"

135 ECHA understands that your read-across hypothesis assumes that different compounds have the same type of effects. Based on this you predict the properties of your Substance from source substance 2 based on a worst-case approach.

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

6.2.1. Missing supporting information to substantiate worst-case consideration

137 We have identified the following issue(s) with the prediction of toxicological properties:

138 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.).

139 Supporting information must include, among others, information to confirm your claimed worst-case prediction.

140 As indicated above, your read-across hypothesis for the source substance 2, being reactive metabolite of the Substance, constitutes the worst case for the prediction of the systemic effects of the Substance. In this context, relevant, reliable and adequate information allowing to compare the properties of the substances is necessary to confirm that the prediction of the systemic toxicity properties of the Substance is conservative from the data on source substance 2. Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and the source substances. In addition, supporting information allowing to establish the rate and extent of biotransformation of your Subsatnce to source substance 2, also needs to be provided.

141 You have not provided any experimental data with the Substance, in particular bridging studies of comparable design and duration.

142 Further, you have not provided any toxicokinetic data on the Substance to establish the rate of its biotransformation to source subsatnce 2, as well as the quantity of its formation.

143 In the absence of this information it is not possible to compare the properties of the Substance and of the source substance 2 and to confirm your hypothesis of worst-case prediction.

6.2.2. Conclusion on the read-across approach

144 Based on the above,, you have not established that relevant properties of the Substance can be predicted from data on the source substance 2. Your read-across approach under Annex XI, Section 1.5. is rejected.

145 Therefore, the information requirement is not fulfilled.

6.3. Specification of the study design

146 A PNDT study according to the test method OECD TG 414 should be performed in rats or rabbits as preferred species.

147 As the Substance is a solid, the study must be conducted with oral administration of the Substance (Annex IX, Section 8.7.2, Column 1).

148 Therefore, the study must be conducted in rats or rabbits with oral administration of the Substance.

149 In the comments to the draft decision, you agree to perform the requested study. You propose to conduct the study in rats. As mentioned in section 6.3, you may conduct the study in rats or rabbits.

7. Long-term toxicity testing on aquatic invertebrates

150 Long-term toxicity testing on aquatic invertebrates is an information requirement under Annex IX to REACH (Section 9.1.5.).

7.1. Information provided

151 You have adapted this information requirement by using Column 2 of Annex IX, Section 9.1. To support the adaptation, you have provided following statement: '*According to the REACH Regulation (EC n. 1907/2006), Annex IX, Column 2, long-term toxicity testing shall be proposed if the CSA according to Annex I indicates the need to investigate further effects on aquatic organisms. The CSA does not shows any need to test long-term aquatic toxicity, therefore the test has not been conducted*.'

7.2. Assessment of the information provided

7.2.1. Annex IX, Section 9.1., Column 2 is not a valid basis to omit the study

152 Under Annex IX, Section 9.1., Column 2 is not a basis for omitting information on long-term toxicity to aquatic invertebrates referred to under Column 1, Section 9.1.5.

153 Your adaptation is therefore rejected and the information requirement is not fulfilled.

7.3. Study design and test specifications

154 The Substance is difficult to test due to the low water solubility (6.7 µg/L ± 5.4 µg/L) and adsorptive properties (Log K_{ow} 12.42; Log Koc >5.63). The OECD TG 211 specifies that, for difficult to test substances, you must consider the approach described in the OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in the OECD TG 211. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solution.

155 In your comments on the draft decision you agree to conduct the requested study.

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).
Guidance for monomers and polymers; ECHA (2012).
Guidance on intermediates; ECHA (2010).
All guidance documents are 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

The information requirements for an Extended One-Generation Reproductive Toxicity Study (EOGRTS; Annexes IX or X, Section 8.7.3.), a pre-natal developmental toxicity study in a second species (Annex X, Section 8.7.2) and long-term toxicity testing on sediment organisms are not addressed in this decision as your dossier contains testing proposals for these information requirements. These testing proposals will be addressed in separate testing proposal examination decisions. The information requirement for a screening study for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.) is also not addressed in this decision as the proposed EOGRTS will cover the same parameters.

The information requirement for long-term toxicity to fish (Annex IX, Section 9.1.6.) is not addressed in this decision. It may be addressed in a separate decision once the information from the studies requested in the present decisions is provided.

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 01 February 2022.

The deadline of the decision is 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.

In your comments you agree to the draft decision. ECHA took your comments into consideration and did not amend the requests.

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: Addressee(s) 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 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;
- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

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]

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

(2) 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.

(3) 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.

(4) 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[2].

(5) 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

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

[2] https://echa.europa.eu/practical-guides

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.

With that detailed information, ECHA can confirm 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 (https://echa.europa.eu/manuals).