~~Confidential~~

Helsinki, 16 November 2022

Addressees
Registrant(s) of TEC_201-070-7_JS as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
14/05/2019

Registered substance subject to this decision ("the Substance")
Substance name: Triethyl citrate
EC number: 201-070-7

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 ***23 February 2026***.

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

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

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: OECD TG 471, 2020)

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. If negative results are obtained in tests performed for the information requirement of Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. then: In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490)

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) requested below (Annex VIII, Section 8.6.1.)

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)

8. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: EU C.47./OECD TG 210)

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

9. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: OECD TG 414) by oral route, in a second species (rat/rabbit)

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 weight of evidence adaptations

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

- *In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- *In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- Short-term repeated dose toxicity (28 day) (Annex VIII, Section 8.6.1.)
- Sub-chronic toxicity (90-day) (Annex IX, Section 8.6.2)
- Pre-natal developmental toxicity study, one species (Annex IX, Section 8.7.2)
- Pre-natal developmental toxicity study in a second species (Annex X, Section 8.7.2.).

2 Your weight of evidence adaptations are based on information obtained from the Substance itself and/or an analogue substance structurally similar to the Substance.

3 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.

4 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.

5 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.

6 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.

7 You have not included a justification for your weight of evidence adaptation for each of the relevant information requirement, 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.

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

The common deficiencies are set out here, while the specific ones are set out under the information requirement concerned in the Sections below.

0.1.1. Reliability of the information provided from analogue substance

ECHA understands that you use data obtained with the following analogue substance in a read-across approach as part of your weight of evidence adaptation:

- tributyl 2-acetoxypropane-1,2,3-tricarboxylate, (ATBC), EC 201-067-0.

9 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.

10 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).

11 You provide a read-across justification document in IUCLID Section 13.2.

12 Within this document you state that "*it is proposed to group the chemicals into a category and perform read-across for the endpoints where data is lacking*", referring to the substances triethyl citrate (EC 201-070-7), tributyl citrate (EC 201-071-2), tris(2-ethylhexyl)-Oacetylcitrate (ATEHC) (EC 205-617-0), tributyl-O-acetylcitrate (ATBC) (EC 201-067-0) and triethyl-O-acetylcitrate (ATEC) (EC 201-066-5).

13 However, for the endpoints listed above, you only refer to one "*near analogue*" in your dossier. You provide the following reasoning for the prediction of toxicological properties: *"It can be assumed that the same [toxicological property] applies to triethyl citrate as it is a near analogue to the test substance acetyl tributyl citrate."*

14 Therefore ECHA understands that you are using an analogue approach for predicting the toxicological properties of the Substance from the analogue substance ATBC for the endpoints listed above, using the reasoning described in the read-across justification document.

15 You reason that the substances have common structural moieties which determine a common functionality, and that they are similar by closely related breakdown/metabolite products. You state that they are expected to have similar biological activity and behave in a comparable way in living organisms.

16 ECHA understands that your read-across hypothesis assumes that different compounds have the same type of effects. You predict the properties of your Substance to be quantitatively equal to those of the source substance.

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

0.1.1.1. Missing supporting information

18 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.).

19 As indicated above, your read-across hypothesis is based on the assumption that the

structurally similar substances cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the Substance and of the source substance(s) is necessary to confirm that both substances cause the same type of effects and that structural differences would not affect the predicted properties of the substances. Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and of the source substance(s).

20 You have provided the following information on the Substance and analogue to support your hypothesis:

- structural information
- information on structural alerts and estimation of metabolic fate using the software Toxtree v2.5.0
- similarity indices obtained using the Toxmatch tool (v.1.07)
- structural characteristics and mechanistic alerts obtained from the OECD QSAR Toolbox v2.2
- information on physicochemical, and absorption, distribution, metabolism, excretion properties
- data on acute toxicity, skin irritation, eye irritation, skin sensitisation, gene mutation in bacteria, repeated dose toxicity to compare the toxicological properties of the substances.

21 ECHA has assessed the provided supporting information and identified the following issues:

22 The Substance and source substance have a triester backbone as common structural element, i.e. tricarboxylic acid with three short-chain alkyl esters. However, the substances differ structurally in the chain length of the alkyl groups (ethyl for the Substance vs. butyl for the analogue substance) as well as by having either a hydroxyl or acetyl moiety, respectively.

23 You have assessed the impact of these structural differences using a set of physico-chemical and (abiotic and biotic) degradation properties, structural characteristics and mechanistic alerts obtained from Toxtree v2.5.0 and the OECD QSAR Toolbox v2.2 for the Substance and the analogue substance.

Similarity indices, structural and mechanistic alerts

24 Regarding the structural and descriptor based similarity (Toxmatch), you have identified a "*little change in similarity […] accounted by the acetyl group*".

25 You state that the results obtained with the OECD QSAR Toolbox v2.2 show that "*endpoint specific mechanisms/modes of action, structural alerts, functional groups etc. are very similar*". The profiles of structural alerts for the Substance and the source substance are consistent, except a difference, that you have also identified, between the Substance and the source substance for the structural alert for DNA binding: the non-acetylated Substance is indicated as non-binder to DNA, whereas the acetylated source substance might bind to DNA (structural alert for "acetoxy compounds"), pointing at different chemical mechanisms. This difference in the structural alerts for DNA binding indicates that the substances may have different reactivity, which is directly relevant for gene mutation. Therefore the information on the structural alerts provided does not support the similar toxicological profile for the Substance and analogue substance.

26 Furthermore, ECHA notes that while the similarity in presence or absence of structural alerts may indicate that the differences do not influence the reactivity of the substance e.g. on proteins, this information does not confirm, on its own, that the Substance and the source substances have similar toxicological properties such as repeated dose toxicity and

reproductive toxicity. The complexity of the systemic interactions and the reproductive process and the large number of targets/mechanisms associated with those broad areas of toxicity is not covered by computational tools. Therefore, the structural alerts reported in the justification document do not represent adequate information on the above-mentioned properties of the Substance and the source substance, e.g. bridging studies of comparable design and duration.

Physicochemical and toxicokinetic properties

27 You also state that the "*acetyl group implicates a certain influences of physicochemical properties of citrates*" although you claim that "*the differences between non-acetylated and acetylated citrates follow a predictable pattern of changes*" and "*the toxicity level of non-acetylated and acetylated chemicals would not deviate significantly from each other*".

28 The physicochemical properties such as water solubility, hydrophobicity and vapour pressure differ depending on the length of the linear alkyl rests and acetylation. In contrast to ATBC, triethyl citrate is highly water soluble and easily absorbed. Triethyl citrate is "*expected to be mainly available in the circulatory system*", compared to the analogue substance which is "*expected to be better distributed into the cells*" since more hydrophobic. Hydrophobicity increases with the length of the alkyl chain; acetylated citrates are more hydrophobic than non-acetylated citrates. Therefore the physicochemical properties indicate differences in the toxicokinetics behaviour of the substances in the organism which could have an impact on toxicologoical effects.

Hydrolysis and breakdown products

29 Both substances are likely to be hydrolysed in the stomach. Despite potentially having similar hydrolysis properties, with the common hydrolysis product citric acid, they form non-common hydrolysis products. The non-common hydrolysis products are, amongst others, ethanol for the Substance and butanol for the source substance, which differ structurally, in analogy to the substances. Further non-common hydrolysis products for the source substance include acetyl citrate and acetic acid.

30 Furthermore, in your justification document it is stated that ATBC "*was hydrolysed relatively slowly in human serum (half-life ca. 7 hours)*". Therefore, the contribution of the parent substance has also to be taken into account. There is no other information on the hydrolysis of the Substance.

Comparison of toxicological properties

31 You have indicated that based on available experimental data the substances are both not acutely toxic and that "*they are not a skin or eye irritant*", however "*triethylcitrate is presumed to be slightly eye irritating*". You also indicate that "*ethyl citrates were found to be more toxic than their butyl analogues but a little change was caused by the acetyl group. A possible explanation can be a more rapid hydrolysis of triethyl citrates in comparison to their butyl- analogues.*" This indicates different reactivity between the Substance and the source substance.

32 ECHA further notes that studies on acute toxicity, skin irritation, eye irritation, skin sensitisation do not inform on the mutagenicity, repeated dose and developmental toxicity properties of the Substance and of the source substance. Accordingly, this information is not considered as relevant to support your read-across hypothesis.

33 In conclusion, you have not provided adequate supporting information demonstrating that the structural differences between the Substance and the source substance do not influence the toxicological properties and have no impact on the read-across prediction between these two substances.

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

35 In the absence of reliable read-across from the analogue substance, the properties of your Substance cannot be predicted from the data on the analogue substance. Therefore the information from the analogue substance cannot reliably contribute to your weight of evidence adaptations.

Reasons related to the information under Annex VII of REACH

1. In vitro gene mutation study in bacteria

36 An *in vitro* gene mutation study in bacteria is an information requirement under Annex VII, Section 8.4.1.

1.1. Information provided

37 You have adapted this information requirement by using weight of evidence based on the following experimental data:

(i) *in vitro* gene mutation in bacteria (1976) with the Substance;

(ii) *in vitro* gene mutation in bacteria (1982) with the analogue substance tributyl 2-acetoxypropane-1,2,3-tricarboxylate (ATBC), EC 201-067-0;

(iii) *in vivo* chromosomal aberration study in rats (2002) with the analogue substance ATBC;

(iv) *in vitro* gene mutation study in mammalian cells (1991) with the analogue substance ATBC.

You justify the weight of evidence as follows: "*Based on all pieces of weight of evidence it is clear that triethyl citrate is not mutagenic.*"

1.2. Assessment of the information provided

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

39 As explained under Section 0.1. of the Reasons common to several requests, 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 on the information requirement under consideration.

40 As explained in Section 0.1. of the Reasons common to several requests, your documentation of the weight of evidence is not in line with the requirements of Annex XI, Section 1.2. Therefore, your adaptation is rejected. In addition, ECHA identified endpoint-specific issue(s) regarding the weight of evidence. These are addressed below.

41 Relevant information that can be used to support weight of evidence adaptation for the information requirement of Annex VII, Section 8.4.1 includes similar information that is produced by the OECD TG 471. The following aspects are covered:

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

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

Sources of information (iii) and (iv) do not provide relevant information on the detection and quantification of gene mutations (base pairs, substitution or frame shift) in cultured bacteria. More specifically, study (iii) provides information on the detection and quantification of structural or numerical chromosomal aberrations in cultured mammalian cells and study (iv) provides information on the detection and quantification of gene mutations in cultured mammalian cells. Consequently, these studies do not provide relevant information for this information requirement.

42 The sources of information (i) and (ii) provide relevant information on detection and quantification of gene mutations in bacteria. However, study (i) provides this information only on 2 strains (S. typhimurium TA 1535 and TA 1537) while study (ii) provides such information only on 4 strains (S. typhimurium TA 1535, TA 1537, TA 98 and TA 100). The fifth strain S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101) is missing from the study (i) and from the study (ii). Therefore information on a strain which is capable of detecting oxidising mutagens, cross-linking agents and hydrazines is missing. Consequently, the sources of information (i) and (ii) only provide partially relevant information on gene mutation in bacteria.

43 The reliability of the source of information (ii) is significantly affected by the following deficiency:

1.2.1. Reliability of the contribution of the information on the analogue substance

44 For the reasons explained in the section 0.1.1. of the Reasons common to several requests above, you have not established that the information from study (ii) can reliably contribute to your weight of evidence adaptation.

45 In addition, the reliability of the sources of information (i). and (ii.) is also affected by the following issues:

1.2.2. Reliability of the contribution of the studies (i) and (ii)

46 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.

47 The studies (i) and (ii) were conducted following the OECD TG 471. This test guideline requires that:

- two separate test conditions are assessed: in absence of metabolic activation and in presence of metabolic activation;
- the maximum dose tested induces a reduction in the number of revertant colonies per plate compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test dose corresponds to 5 mg/plate or 5 µl/plate;
- at least 5 doses are evaluated, in each test condition.

48 In the source of information (i), the following investigation/specification is not to the requirements of OECD TG 471:

- Three doses were evaluated in absence and presence of metabolic activation, i.e. less then 5 doses.

49 In the source of information (ii), the following investigations/specifications are not to the requirements of OECD TG 471:

- The study was performed only in absence of metabolic activation.
- The highest concentration was 495µg/plate, i.e. lower than 5 mg/plate, without a

justification.

~~50~~ Based on the above, the reliability of the contribution of the results obtained from the studies (i) and (ii) 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.

1.3. Conclusion on the weight of evidence

51 Taken together, the sources of information (i) and (ii) provide relevant information. However, neither of the sources of information (i) and (ii) provides relevant information on all five strains of bacteria. Information on the 5th strain, and therefore information obtained in a strain capable of detecting oxidising mutagens, cross-linking agents and hydrazines, is missing.

52 Furthermore, the reliability of the contribution of the information is hampered by:

- the deficiency identified related to the use of information on the analogue substance (study (ii)) and
- limitations of the study design and/or reporting listed above affecting directly the reliability of the results of studies (i) and (ii) and their contribution to the weight of evidence adaptation, since they introduce uncertainty in the results.

53 Therefore, it is not possible to conclude, based on any source of information alone or considered together, on the information requirement for gene mutations in bacteria. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

1.4. Specification of the study design

54 To fulfil the information requirement for the Substance, the *in vitro* gene mutation study in bacteria (OECD TG 471, 2020) is considered suitable.

55 In the comments to the draft decision, one registrant indicates that it expects the lead registrant to provide a suitable adaptation for this information requirement.

56 As this potential strategy seems to rely on weight of evidence and read-across approaches that have not yet been further described and justified, no conclusion on the compliance of the adaptation can be made.

57 ECHA understands that in case an adaptation cannot be made, the registrant agrees to perform the requested study.

58 You remain responsible for complying with this decision by the set deadline.

Reasons related to the information under Annex VIII of REACH

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

59 An *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study is an information requirement under Annex VIII, Section 8.4.2.

2.1. Information provided

60 You have adapted this information requirement by using Column 2 of Annex VIII, Section 8.4.2. To support the adaptation, you have provided following information:

(i) a justification stating that "*in accordance with Column 2 adaptation statement of REACH Annex VIII, the study does not need to be conducted if adequate data from a reliable in vivo mammalian gene mutation test are available. From a valid in vivo study […] according to OECD Guideline 475 as well as a valid carcinogenicity study it can be concluded, that adverse effects concerning mutagenicity/genotoxicity are not to be expected.*";

(ii) an *in vivo* chromosomal aberration study in rats (2002) with the analogue substance tributyl 2-acetoxypropane-1,2,3-tricarboxylate (ATBC), EC 201-067-0.

2.2. Assessment of the information provided

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

2.2.1. The provided adaptation does not meet the criteria of Annex VIII, Section 8.4.2., Column 2

62 Under Annex VIII, Section 8.4.2., Column 2, the study usually does not need to be conducted "*if adequate data from an in vivo cytogenicity test are available*". The Guidance on IRs and CSA, Section R.7.7.6.3 and Table R.7.7–3 clarifies that the *in vivo* somatic cell cytogenicity test must be either a micronucleus test or a chromosomal aberration test, performed according to the OECD TG 474 or 475, respectively.

63 The carcinogenicity study mentioned in your justification above is neither a micronucleus test nor a chromosomal aberration test. Therefore, it does not meet the requirements of Column 2.

64 The study (ii) provided is described as a mammalian bone marrow chromosome aberration test, performed with the analogue substance ATBC.

65 The test material in study (ii) 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.

Assessment of the read-across approach

66 For this information (study (ii)) to reliably contribute to the Coumn 2 adaptation, it would have to meet the requirements for Grouping of substances and read-across approaches.

67 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.

68 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).

69 You use data obtained with the analogue substance ATBC to predict *in vivo* mammalian bone marrow chromosome aberration for the Substance.

70 You provide a read-across justification document in IUCLID Section 13.2.

71 Within this document you state that "*it is proposed to group the chemicals into a category and perform read-across for the endpoints where data is lacking*", referring to the substances triethyl citrate (EC 201-070-7), tributyl citrate (EC 201-071-2), tris(2-ethylhexyl)-Oacetylcitrate (ATEHC) (EC 205-617-0), tributyl-O-acetylcitrate (ATBC) (EC 201-067-0) and triethyl-O-acetylcitrate (ATEC) (EC 201-066-5).

72 However, for this information requirement, among other, you only refer to one "*near analogue*" in your dossier. You provide the following reasoning for the prediction of toxicological properties: *"It can be assumed that the same [toxicological property] applies to triethyl citrate as it is a near analogue to the test substance acetyl tributyl citrate."*

73 Therefore ECHA understands that you are using an analogue approach for predicting the toxicological properties of the Substance from the analogue substance ATBC for this information requirement, using the reasoning described in the read-across justification document.

74 You reason that the substances have common structural moieties which determine a common functionality, and that they are similar by closely related breakdown/metabolite products. You state that they are expected to have similar biological activity and behave in a comparable way in living organisms.

75 ECHA understands that your read-across hypothesis assumes that different compounds have the same type of effects. You predict the properties of your Substance to be quantitatively equal to those of the source substance.

76 As already explained in more detail in Section 0.1.1. of the Reasons common to several requests, you have not provided supporting information to strengthen the rationale for the read-across and you have not established that the Substance and the source substance are likely to have similar properties. The shortcomings identified and explained under Section 0.1.1. equally apply to the read-across approach submitted under your Column 2 adaptation. Your adaptation based on grouping of substances and read-across under Annex XI, Section 1.5 is rejected.

77 Based on this, you have not established that *in vivo* mammalian bone marrow chromosome aberration properties of the Substance can be predicted from data on the source substance ATBC. Therefore the information from the analogue substance cannot contribute to your Column 2 adaptation.

78 Since the Column 2 criteria are not met, your adaptation is rejected and the information requirement is not fulfilled.

2.3. Specification of the study design

79 To fulfil the information requirement for the Substance, either *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) are considered suitable.

80 In the comments to the draft decision, one registrant indicates that it expects the lead registrant to provide a suitable adaptation for this information requirement.

81 As this potential strategy seems to rely on a read-across approach that has not yet been further described and justified, no conclusion on the compliance of the adaptation can be made.

82 ECHA understands that in case an adaptation cannot be made, the registrant agrees to perform the requested study.

83 You remain responsible for complying with this decision by the set deadline.

3. In vitro gene mutation study in mammalian cells

84 An *in vitro* gene mutation study in mammalian cells is an information requirement under Annex VIII, Section 8.4.3., in case of a negative result in the *in vitro* gene mutation test in bacteria and the in vitro cytogenicity test.

3.1. Triggering of the information requirement

85 Your dossier contains an adaptation for an *in vitro* gene mutation study in bacteria, and an adaptation for an *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study.

86 The information for the *in vitro* gene mutation study in bacteria and for the *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study provided in the dossier are rejected for the reasons *provided in requests 1 and 2.*

87 *The result of the requests for an in vitro gene mutation study in bacteria and for an in vitro cytogenicity study in mammalian cells or an in vitro micronucleus study will determine whether the present requirement for an in vitro* mammalian cell gene mutation study in accordance with Annex VIII, Section 8.4.3 is triggered.

88 Consequently, you are required to provide information for this information requirement, if the *in vitro* gene mutation study in bacteria and the *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study provide a negative result.

3.2. Information provided

89 You have adapted this information requirement by using weight of evidence based on the following experimental data:

(i) *in vitro* gene mutation in bacteria (1976) with the Substance;

(ii) *in vitro* gene mutation in bacteria (1982) with the analogue substance tributyl 2-acetoxypropane-1,2,3-tricarboxylate (ATBC), EC 201-067-0;

(iii) *in vivo* chromosomal aberration study in rats (2002) with the analogue substance ATBC;

(iv) *in vitro* gene mutation study in mammalian cells (1991) with the analogue substance ATBC.

You justify the weight of evidence as follows: "*Based on all pieces of weight of evidence it is clear that triethyl citrate is not mutagenic.*"

3.3. Assessment of the information provided

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

91 As explained under Section 0.1. of the Reasons common to several requests, 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 on the information requirement under consideration.

92 As explained in Section 0.1. of the Reasons common to several requests, your documentation of the weight of evidence is not in line with the requirements of Annex XI, Section 1.2. Therefore, your adaptation is rejected. In addition, ECHA identified endpoint-specific issue(s) regarding the weight of evidence. These are addressed below.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.4.3 at Annex VIII includes similar information that is produced by the OECD TG 476/490 and OECD TG 488. This includes:

- Detection and quantification of gene mutations (point mutations, frame-shift mutations, small deletions, etc.) including data on the frequency of mutant colonies in cultured mammalian cells (*in vitro*) or mutant frequency for each tissue in mammals (*in vivo*).

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

94 Sources of information (i) to (iii) do not provide relevant information on the detection and quantification of gene mutations (point mutations, frame-shift mutations, small deletions, etc.) in cultured mammalian cells (*in vitro*) or mutant frequency for each tissue in mammals (*in vivo*). More specifically, studies (i) and (ii) provide information on the detection and quantification of gene mutations in bacteria and study (iii) provides information on the detection and quantification of structural or numerical chromosomal aberrations in cultured mammalian cells. Consequently, these studies do not provide relevant information for this information requirement.

95 The source of information (iv) provides relevant information on gene mutation in mammalian cells.

96 However, there are deficiencies affecting its reliability:

3.3.1. Reliability of the contribution of the information on the analogue substance

97 For the reasons explained in the section 0.1.1. of the Reasons common to several requests above, you have not established that the information from study (iv) can reliably contribute to your weight of evidence adaptation.

3.3.2. Reliability of the contribution of the study (iv)

98 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.

99 The study (iv) was conducted following the OECD TG 476. This test guideline requires that:

- at least 4 concentrations are evaluated, in absence and in presence of metabolic activation;
- the maximum concentration tested induces 80-90% of cytotoxicity compared to

the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test concentration corresponds to 10 mM, 2 mg/mL or 2 µL/mL, whichever is the lowest;

- data on the cytotoxicity and the mutation frequency for the treated and control cultures are reported.

100 In the source of information (iv), the following investigation/specification is not to the requirements of OECD TG 476:

- no information on the number and level of concentrations used is reported
- no data on the cytotoxicity and the mutation frequency for the treated and control cultures is provided.

101 Based on the above, the reliability of the contribution of the results obtained from this study to the weight of evidence is limited. The unclarity regarding how the results were obtained introduces uncertainty in the results which must be considered.

3.4. Conclusion on the weight of evidence

102 Taken together, only one source of information (study (iv)) provides relevant information on gene mutation in mammalian cells.

103 However, the reliability of this information is hampered by:

- the deficiency identified related to the use of information on the analogue substance and
- issues related to how the results were obtained in the studies which increases the uncertainty of the conclusion for the Substance.

104 Therefore, it is not possible to conclude, based on any source of information alone or considered together, on the information requirement for gene mutations in mammalian cells. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

3.5. Specification of the study design

105 To fulfil the information requirement for the Substance, either the *in vitro* mammalian cell gene mutation tests using the hprt and xprt genes (OECD TG 476) or the thymidine kinase gene (OECD TG 490) are considered suitable.

106 In the comments to the draft decision, one registrant indicates that it expects the lead registrant to provide a suitable adaptation for the information requirements of Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2..

107 The registrant considers that when those requests have been addressed adequately by adaptations or alternatively by new tests as stated in Sections 1 and 2, "*it can be decided if further testing according to [OECD TG 476 or 490] is necessary*".

108 You remain responsible for complying with this decision by the set deadline.

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)

109 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 of Annex

VIII or a general adaptation rule under Annex XI.

4.1. Information provided

110 You have adapted this information requirement by using weight of evidence based on the following experimental data:

(i) a repeated dose 90-day oral toxicity study in rats (2003) with the analogue substance tributyl 2-acetoxypropane-1,2,3-tricarboxylate, EC 201-067-0;

(ii) a 8-week-study in cat (2010) with the Substance;

(iii) a 2-year-study in rat (1954) with the Substance;

(iv) a 6-week-study in rat (1959) with the Substance;

(v) a 8-week-study in cat (1959) with the Substance;

(vi) a 6-month-study in beagle dog (1954) with the Substance.

You justify the weight of evidence as follows: "*Based on all pieces of weight of evidence it is clear that triethyl citrate is of very low toxicity after repeated administrations.*"

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

4.2. Assessment of the information provided

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

112 As explained under Section 0.1. Reasons common to several requests, 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 on the information requirement under consideration.

113 As explained in Section 0.1. of the Reasons common to several requests, your documentation of the weight of evidence is not in line with the requirements of Annex XI, Section 1.2. Therefore, your adaptation is rejected. In addition, ECHA identified endpoint-specific issue(s) regarding the weight of evidence. These are addressed below.

114 Relevant information that can be used to support weight of evidence adaptation for the information requirement of Annex VIII, Section 8.6.1 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.

115 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

116 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).

117 The sources of information (i) to (vi) provide some relevant information, however they do not cover all of the 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 (iii) does not inform on survival and clinical signs, while the source of information (vi) does not report clinical signs. For the source of information (ii) in your dossier only some clinical observations and no other information are reported.

118 Consequently, the sources of information (i) to (vi) only provide partially relevant information on aspect 1).

119 In addition, the sources of information have deficiencies affecting their reliability:

4.2.1.1. Reliability of the contribution of the information on the analogue substance (study (i))

120 For the reasons explained in the section 0.1.1 of the Reasons common to several requests above, you have not established that the information from study (i) can reliably contribute to your weight of evidence adaptation.

4.2.2. Aspect 2) blood chemistry

121 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.)

122 The sources of information (i), (iv), (v) and (vi) provide relevant information on some of the elements of aspect 2). However, they do not provide information on the following aspects to address relevant physiological systems: circulatory digestive/excretory, endocrine, immune and musculoskeletal systems.

123 According to the information reported in your dossier the sources of information (ii) and (iii) do not provide relevant information on blood chemistry.

124 Consequently, only the sources of information (i), (iv), (v) and (vi) provide partially relevant information on aspect 2).

125 In addition, the sources of information have deficiencies affecting their reliability:

4.2.2.1. Reliability of the contribution of the information on the analogue substance (study (i))

126 For the reasons explained in the section 0.1.1. of the Reasons common to several requests above, you have not established that the information from study (i) can reliably contribute to your weight of evidence adaptation.

4.2.3. Aspect 3) organ and tissue toxicity

127 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).

128 The source of information (i) provides relevant information on organ weight and gross pathology. However, not all required information on histopathology is covered, as also stated in your dossier: "*only limited histopathology performed and no special neurotoxicity examination included.*" Based on the information provided in the study record, the histopathology of the following organs was not investigated: heart, gastrointestinal tract, spleen, brain, spinal cord, pituitary, adrenal gland, trachea and lungs, uterus, cervix vagina,

epididymides, prostate, seminal vesicle, coagulation glands, mammary glands, urinary bladder, lymph nodes, peripheral nerves, skeletal muscle, bone, bone marrow.

129 The source of information (iv) provides relevant information on some of the elements of aspect 3) but do not cover all the required information on gross pathology and full histopathology. Based on the information provided in the study record, the following organs were not investigated: brain, spinal cord, pituitary, adrenal gland, stomach, trachea, ovaries, uterus, cervix vagina, epididymides, prostate, testes, seminal vesicle, coagulation glands, mammary glands, urinary bladder, lymph nodes, peripheral nerves, skeletal muscle, bone, bone marrow.

130 The source of information (vi) only mentions liver as organ examined. The study record for the source of information (v) indicates that histopathology was performed, however, no details on which organs were examined an no results are reported.

131 Therefore, the studies (i), (iv), (v) and (vi) do not cover all the necessary information on gross pathology and full histopathology, as specified in the OECD TG 407.

132 The study records for the sources of information (ii) and (iii) do not mention any organs and tissues investigated, therefore, they do not provide relevant information for aspect 3).

133 Consequently, only the sources of information (i), (iv), (v) and (vi) provide partially relevant information on aspect 3).

134 In addition, the sources of information have deficiencies affecting their reliability:

4.2.3.1. Reliability of the contribution of the information on analogue substances (study (i))

135 In general, for the reasons in the section 0.1.1. of the Reasons common to several requests above, you have not established that the information from study (i) can reliably contribute to your weight of evidence adaptation.

4.2.4. Conclusion on the weight of evidence

136 Taken together, all sources of information (i) to (vi) provide relevant information 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 all aspects 1) to 3), as described above.

137 Furthermore, any robust conclusion on any of the 3 aspects is hampered by the reliability issue related to the use of information on the analogue substance (study (i)).

138 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.

139 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.

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

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

142 In the comments to the draft decision, one registrant takes note of the request to provide a justification for the adaptation of a Short-term repeated dose toxicity study (28 days) after generating and submitting a reliable Sub-chronic toxicity study (90 days).

Reasons related to the information under Annex IX of REACH

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

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

5.1. Information provided

144 You have adapted this information requirement by using weight of evidence based on the following experimental data:

(i) a repeated dose 90-day oral toxicity study in rats (2003) with the analogue substance tributyl 2-acetoxypropane-1,2,3-tricarboxylate, EC 201-067-0;

(ii) a 8-week-study in cat (2010) with the Substance;

(iii) a 2-year-study in rat (1954) with the Substance;

(iv) a 6-week-study in rat (1959) with the Substance;

(v) a 8-week-study in cat (1959) with the Substance;

(vi) a 6-month-study in beagle dog (1954) with the Substance.

You justify the weight of evidence as follows: "*Based on all pieces of weight of evidence it is clear that triethyl citrate is of very low toxicity after repeated administrations.*"

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

5.2. Assessment of the information provided

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

146 As explained under Section 0.1. Reasons common to several requests, 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 on the information requirement under consideration.

147 As explained in Section 0.1. of the Reasons common to several requests, your documentation of the weight of evidence is not in line with the requirements of Annex XI, Section 1.2. Therefore, your adaptation is rejected. In addition, ECHA identified endpoint-specific issue(s) regarding the weight of evidence. These are addressed below.

148 Relevant information that can be used to support weight of evidence adaptation for the information requirement of Annex IX, Section 8.6.2 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.

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

5.2.1. General consideration

150 According to Column 1 of Annex IX, Section 8.6.2., a sub-chronic toxicity (90-day) study has to be performed in one species, rodent, via most appropriate route of administration. The sources of information (ii), (v) and (vi) provide information on other species than rodent, more specifically cat and dog.

151 Therefore, the sources of information (ii), (v) and (vi) do not provide relevant information.

152 In the following the relevance of the information provided by studies (i), (iii) and (iv) regarding the aspects 1) in-life observations, 2) blood chemistry and 3) organ and tissue toxicity is assessed.

5.2.2. Aspect 1) in-life observations

153 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).

154 The sources of information (i), (iii) and (iv) provide some relevant information, however they do not cover all of the 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 (iii) does not inform on survival and clinical signs.

155 Consequently, the sources of information (i), (iii) and (iv) only provide partially relevant information on aspect 1).

156 In addition, these sources of information have deficiencies affecting their reliability:

5.2.2.1. Reliability of the contribution of the information on the analogue substance (study (i))

157 For the reasons explained in the section 0.1.1 of the Reasons common to several requests above, you have not established that the information from study (i) can reliably contribute to your weight of evidence adaptation.

5.2.2.2. Reliability of the contribution of the study (iv)

158 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
- at least 10 male and 10 female animals for each test and control group.

159 In study (iv), the following specifications are not according to the requirements of the OECD TG 408:

- an exposure duration of 6 weeks
- according to the information provided in your dossier, the study (iv) included "*about 7 animals per group*".

160 Therefore, the actual exposure period in study (iv) 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.

161 Furthermore, the study (iv) has not investigated the hazardous property at the similar range of the statistical power (e.g. number of animals or number of samples) as required in the OECD TG 408.

162 Therefore, the the reliability of the contribution of the results obtained from the studies (i)

and (iv) 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.

5.2.3. Aspect 2) blood chemistry

163 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.)

164 The sources of information (i) and (iv) provide relevant information on some of the elements of aspect 2). However, they do not provide information on the following aspects to address relevant physiological systems: circulatory digestive/excretory, endocrine, immune and musculoskeletal systems.

165 According to the information reported in your dossier the source of information (iii) does not provide relevant information on blood chemistry.

166 Consequently, only the sources of information (i) and (iv) provide partially relevant information on aspect 2).

167 In addition, the sources of information have deficiencies affecting their reliability:

5.2.3.1. Reliability of the contribution of the information on the analogue substance (study (i))

168 For the reasons explained in the section 0.1.1. of the Reasons common to several requests above, you have not established that the information from study (i) can reliably contribute to your weight of evidence adaptation.

5.2.3.2. Reliability of the contribution of the study (iv)

169 The reliability issues identified in section 5.2.2.2. above, related to exposure duration and statistical power (study iv)), equally apply to the aspect 2).

170 As a result, the reliability of the contribution of the results obtained from the studies (i) and (iv) 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.

5.2.4. Aspect 3) organ and tissue toxicity

171 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).

172 The source of information (i) provides relevant information on organ weight and gross pathology. However, not all required information on histopathology is covered, as also stated in your dossier: "*only limited histopathology performed and no special neurotoxicity examination included.*" Based on the information provided in the study record, the histopathology of the following organs was not investigated: heart, gastrointestinal tract, pancreas, spleen, brain, spinal cord, pituitary, adrenal gland, thyroid, parathyroid, oesophagus, salivary glands, trachea and lungs, aorta, uterus, cervix vagina, epididymides, prostate, seminal vesicle, coagulation glands, mammary glands, urinary bladder, gall bladder, lymph nodes, peripheral nerves, skeletal muscle, bone, bone marrow.

173 The source of information (iv) provides relevant information on some of the elements of aspect 3) but do not cover all the required information on gross pathology and full

histopathology. Based on the information provided in the study record, the following organs were not investigated: brain, spinal cord, pituitary, adrenal gland, thyroid, parathyroid, oesophagus, salivary glands, stomach, trachea, aorta, ovaries, uterus, cervix vagina, epididymides, prostate, testes, seminal vesicle, coagulation glands, mammary glands, urinary bladder, gall bladder, lymph nodes, peripheral nerves, skeletal muscle, bone, bone marrow.

174 Therefore, the studies (i) and (iv) do not cover all the necessary information on gross pathology and full histopathology, as specified in the OECD TG 408.

175 The study record for the source of information (iii) does not mention any organs and tissues investigated, therefore it does not provide relevant information for aspect 3).

176 Consequently, only the sources of information (i) and (iv) provide partially relevant information on aspect 3).

177 In addition, the sources of information have deficiencies affecting their reliability:

5.2.4.1. Reliability of the contribution of the information on analogue substances (study (i))

178 In general, for the reasons in the section 0.1.1. of the Reasons common to several requests above, you have not established that the information from study (i) can reliably contribute to your weight of evidence adaptation.

5.2.4.2. Reliability of the contribution of the study (iv)

179 The reliability issues identified in section 5.2.2.2. above, related to exposure duration and statistical power (study iv)), equally apply to the aspect 3).

180 As a result, the the reliability of the contribution of the results obtained from the studies (i) and (iv) 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.

5.2.5. Conclusion on the weight of evidence

181 Taken together, only the sources of information (i), (iii) and (iv) provide partially relevant information and in particular: studies (i), and (iv) provide relevant information on some elements of aspects 1) in-life observations, 2) blood chemistry and 3) organ and tissue toxicity, while study (iii) provides relevant information only on some elements of aspect 1). However, the three studies do not cover the entire set of elements expected to be obtained from the OECD TG 408 for all aspects 1) to 3), as described above.

182 Furthermore, any robust conclusion on any of the 3 aspects is hampered by the following reliability issues:

- the deficiency identified related to the use of information on the analogue substance (study (i)) and
- issues related to how the results were obtained in the studies which increases the uncertainty of the conclusion for the Substance (study (iv)).

183 Therefore, it is not possible to conclude, based on any source of information alone or considered together, on the information requirement for sub-chronic toxicity (90 days). Therefore, your adaptation is rejected and the information requirement is not fulfilled.

5.3. Specification of the study design

184 Following the criteria provided in Annex IX, Section 8.6.2, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity of the

Substance; Guidance on IRs and CSA, Section R.7.5.6.3.2.

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

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

187 In the comments to the draft decision, one registrant "*notes ECHA's request regarding the need to fulfil the data requirements for this endpoint*".

188 The registrant's comments regarding an extension of the deadline are addressed in Appendix 2 of this decision.

6. Pre-natal developmental toxicity study in one species

189 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

190 You have adapted this information requirement by using weight of evidence based on the following experimental data:

(i) 12-month toxicity study in rats via diet with pairing of animals in the ninth month (1977) with the analogue substance tributyl 2-acetoxypropane-1,2,3-tricarboxylate, EC 201-067-0;

(ii) 12-month toxicity study in mice via diet with pairing of animals in the ninth month (1977) with the analogue substance tributyl 2-acetoxypropane-1,2,3-tricarboxylate, EC 201-067-0.

6.2. Assessment of the information provided

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

192 As explained under Section 0.1. of the Reasons common to several requests, 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 on the information requirement under consideration.

193 As explained in Section 0.1. of the Reasons common to several requests, your documentation of the weight of evidence is not in line with the requirements of Annex XI, Section 1.2. Therefore, your adaptation is rejected. In addition, ECHA identified endpoint-specific issue(s) regarding the weight of evidence. These are addressed below.

194 Relevant information that can be used to support weight of evidence adaptation for the information requirement of Annex IX, Section 8.7.2 includes similar information that is produced by the OECD TG 414 with a design as specified in this decision. The OECD TG 414 requires the study to investigate the following key elements: 1) pre-natal developmental toxicity, 2) maternal toxicity, 3) maintenance of pregnancy.

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

6.2.1. Aspect 1) Pre-natal developmental toxicity

196 Pre-natal developmental toxicity includes information after pre-natal exposure on

embryonic/foetal survivial (number of live foetuses; number of resorptions and dead foetuses, postimplantation loss), growth (body weights and size) and structural malformations and variations (external, visceral and skeletal).

197 The sources of information (i) and (ii) are described as 12-month toxicity studies, via diet, with pairing of animals in the ninth month and subsequent examination of reproductive parameters and offspring. ECHA understands from the information in your dossier that the provided studies investigate post-natal effects on the offspring after natural delivery instead of caesarean section. The studies provide limited relevant information on embryonic survival (early and late embryonic death). However, the studies do not provide relevant information on foetal survival (number of live foetuses), growth (body weights and size) and structural malformations and variations (external, visceral and skeletal). Consequently, the studies provide partially relevant information on aspect 1).

198 In addition, the reliability of these sources of information is significantly affected by the following deficiencies:

6.2.1.1. Reliability of the contribution of the information on the analogue substance

199 For the reasons explained in the section 0.1.1. of the Reasons common to several requests, you have not established that the information from studies (i) and (ii) can reliably contribute to your weight of evidence adaptation.

6.2.1.2. Reliability of the contribution of the studies (i) and (ii)

200 Investigations/specifications in a developmental toxicity study (OECD TG 414) include at least 20 female animals with implantation sites for each test and control group.

201 In your dossier no information on the numbers of animals is reported. Therefore, it cannot be concluded whether the statistical power of the information from the studies (i) and (ii) is equivalent to the OECD TG 414.

202 Based on the above, the reliability of the contribution of the results obtained from these studies to the weight of evidence is limited. The unclarity regarding how the results were obtained introduces uncertainty in the results which must be considered.

6.2.2. Aspect 2) Maternal toxicity

203 Maternal toxicity includes information after gestational exposure on maternal survival, body weight and clinical signs and other potential aspects of maternal toxicity in dams.

204 The sources of information (i) and (ii) provide relevant information on maternal toxicity.

205 However, the reliability of these sources of information is significantly affected by the following deficiencies:

6.2.2.1. Reliability of the contribution of the information on the analogue substance

206 For the reasons explained in the section 0.1.1 of the Reasons common to several requests, you have not established that the information from studies (i) and (ii) can reliably contribute to your weight of evidence adaptation.

6.2.2.2. Reliability of the contribution of the studies (i) and (ii)

207 The reliability issue identified in section 6.2.1.2. above related to statistical power equally applies to the aspect 2).

208 Based on the above, the reliability of the contribution of the results obtained from these studies to the weight of evidence is limited. The unclarity regarding how the results were obtained introduces uncertainty in the results which must be considered.

6.2.3. Aspect 3) Maintenance of pregnancy

209 Maintenance of pregnancy includes information on abortions and/or early delivery as a consequence of gestational exposure and other potential aspects of maintenance of pregnancy.

210 The sources of information (i) and (ii) provide relevant information on maintenance of pregnancy, according to the examinations that are stated in your dossier as performed for the studies, i.e. placental weight, number of normal, resorptive and deformed tissues.

211 However, the reliability of these sources of information is significantly affected by the following deficiencies:

6.2.3.1. Reliability of the contribution of the information on the analogue substance

212 For the reasons explained in the section 0.1.1. of the Reasons common to several requests, you have not established that the information from studies (i) and (ii) can reliably contribute to your weight of evidence adaptation.

6.2.3.2. Reliability of the contribution of the studies (i) and (ii)

213 The reliability issue identified in section 6.2.1.2. above related to statistical power equally applies to the aspect 3).

214 Based on the above, the reliability of the contribution of the results obtained from these studies to the weight of evidence is limited. The unclarity regarding how the results were obtained introduces uncertainty in the results which must be considered.

6.3. Conclusion on the weight of evidence

215 Taken together, the sources of information provide relevant information on maternal toxicity and maintenance of pregnancy. However, they provide only partially relevant information on pre-natal developmental toxicity. More specifically, they do not provide information on foetal survival, growth and on external, skeletal and visceral malformations/ variations/ abnormalities.

216 Furthermore, any robust conclusion on any of the 3 aspects is hampered by reliability issues affecting all sources of information (studies (i) and (ii)):

- related to the use of information on the analogue substance
- related to how the results were obtained in the studies which increases the uncertainty of the conclusion.

217 Therefore, it is not possible to conclude, based on any source of information alone or considered together, on the information requirement for pre-natal developmental toxicity in one species. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

6.4. Specification of the study design

218 A PNDT study according to the test method OECD TG 414 should be performed in rat or rabbit as preferred species.

219 The study must be performed with oral administration of the Substance (Guidance on IRs

and CSA, Section R.7.6.2.3.2.).

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

221 In the comments to the draft decision, one registrant "*notes ECHA's comments regarding the need to fulfil the endpoint*".

222 The registrant's comments regarding an extension of the deadline are addressed in Appendix 2 of this decision.

7. Long-term toxicity testing on aquatic invertebrates

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

7.1. Information provided

224 You have provided following justification to omit this information requirement claiming that "*According to reliable study results, the substance is considered to be readily degraded in aquatic compartments; the bioaccumulation potential is regarded to be low [BCF estimated with BCFBAF v3.01 (EPI suite v4.1): 2.475 L/kg]. Furthermore, from metabolism studies in animals no metabolites are expected to occur that pose a significant risk to aquatic organisms. Therefore, a chronic invertebrate study is assumed to be not justifiable.*"

7.2. Assessment of the information provided

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

7.2.1. Your justification to omit the study has no legal basis

226 A registrant may only adapt this information requirement based on the general rules set out in Annex XI. It is noted that Column 2 of Annex IX, Section 9.1, does not allow omitting the need to submit information on long-term toxicity to aquatic invertebrates under Column 1 (Decision of the Board of Appeal in case A-011-2018).

227 Your justification to omit this information does not refer to any legal ground for adaptation under Annex XI to REACH.

228 Therefore, you have not demonstrated that this information can be omitted.

On this basis, the information requirement is not fulfilled.

229 In the comments to the draft decision, one registrant indicates that it expects the lead registrant to first attempt to provide a suitable adaptation for this information requirement by means of grouping and read-across according to Annex XI, Section 1.5, of the REACH Regulation. In case an adaptation cannot be made, the member registrant agrees to perform the requested study.

230 As this strategy relies on a read-across approach that has not yet been described and justified, no conclusion on the compliance of the proposed adaptation can be made. You remain responsible for complying with this decision by the set deadline.

231 Comments regarding dedline extension requests are addressed in Appendix 2 of this decision.

8. Long-term toxicity testing on fish

232 Long-term toxicity testing on fish is an information requirement under Annex IX to REACH (Section 9.1.6.).

8.1. Information provided

233 You have provided following a justification to omit this information requirement claiming that "*According to reliable study results, the substance is considered to be readily degraded in aquatic compartments; the bioaccumulation potential is regarded to be low [BCF estimated with BCFBAF v3.01 (EPI suite v4.1): 2.475 L/kg]. Furthermore, from metabolism studies in animals no metabolites are expected to occur that pose a significant risk to aquatic organisms. Therefore, with respect to animal welfare the performance of a chronic fish study is assumed to be not justifiable.*"

8.2. Assessment of the information provided

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

8.2.1. Your justification to omit the study has no legal basis

235 A registrant may only adapt this information requirement based on the general rules set out in Annex XI. It is noted that Column 2 of Annex IX, Section 9.1, does not allow omitting the need to submit information on long-term toxicity to fish under Column 1 (Decision of the Board of Appeal in case A-011-2018).

236 Your justification to omit this information does not refer to any legal ground for adaptation under Annex XI to REACH.

237 Therefore, you have not demonstrated that this information can be omitted. Minimisation of animal testing is not on its own a legal ground for adaptation under the general rules of Annex XI.

238 On this basis, the information requirement is not fulfilled.

8.3. Study design and test specifications

239 To fulfil the information requirement for the Substance, the Fish, Early-life Stage Toxicity Test (test method OECD TG 210) is the most appropriate (Guidance on IRs and CSA, Section R.7.8.2.).

240 In the comments to the draft decision, one registrant indicates that it expects the lead registrant to first attempt to provide a suitable adaptation for this information requirement by means of grouping and read-across according to Annex XI, Section 1.5, of the REACH Regulation. ECHA understand that in case an adaptation cannot be made, the member registrant agrees to perform the requested study.

241 As this strategy relies on a read-across approach that has not yet been described and justified, no conclusion on the compliance of the proposed adaptation can be made. You remain responsible for complying with this decision by the set deadline.

242 Comments regarding dedline extension requests are addressed in Appendix 2 of this decision.

Reasons related to the information under Annex X of REACH

9. Pre-natal developmental toxicity study in a second species

243 Pre-natal developmental toxicity (PNDT) studies (OECD TG 414) in two species is an information requirement under Annex X, Section 8.7.2.

9.1. Information provided

244 You have adapted this information requirement by using weight of evidence based on the following experimental data, as also described under section 6.1 above:

(iii) 12-month toxicity study in rats via diet with pairing of animals in the ninth month (1977) with the analogue substance tributyl 2-acetoxypropane-1,2,3-tricarboxylate, EC 201-067-0;

(iv) 12-month toxicity study in mice via diet with pairing of animals in the ninth month (1977) with the analogue substance tributyl 2-acetoxypropane-1,2,3-tricarboxylate, EC 201-067-0.

9.2. Assessment of the information provided

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

246 As explained under Section 0.1. of the Reasons common to several requests, 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 on the information requirement under consideration.

247 As explained in Section 0.1. of the Reasons common to several requests, your documentation of the weight of evidence is not in line with the requirements of Annex XI, Section 1.2. Therefore, your adaptation is rejected. In addition, ECHA identified endpoint-specific issue(s) regarding the weight of evidence. These are addressed below.

248 Relevant information that can be used to support weight of evidence adaptation for the information requirement of Annex X, Section 8.7.2 includes similar information that is produced by the OECD TG 414 on a second species (two species taking the first species into account to address the potential species differences). The following aspects are covered: 1) prenatal developmental toxicity in two species, 2) maternal toxicity in two species, and 3) maintenance of pregnancy in two species.

249 1) Prenatal developmental toxicity: Prenatal developmental toxicity includes information after prenatal exposure on embryonic/foetal survivial (number of live foetuses; number of resorptions and dead foetuses, postimplantation loss), growth (body weights and size) and structural malformations and variations (external, visceral and skeletal) and other potential aspects of developmental toxicity due to in utero exposure. This information in two species should be covered to address the potential species differences.

250 2) Maternal toxicity: Maternal toxicity inlcudes information after gestational exposure on maternal survival, body weight and clinical signs and other potential aspects of maternal toxicity in the pregnant dam. This information in two species should be covered to address the potential species differences.

251 3) Maintenance of pregnancy: Maintenance of pregnancy includes information on abortions and/or early delivery as a consequence of gestational exposure. This information in two

species should be covered to address the potential species differences.

252 We have assessed the information provided, which is the same as for the pre-natal developmental toxicity in the first species. For the same reasons as already presented in sections 6.2 and 6.3 above it is not possible to conclude whether the Substance has or has not hazardous properties in relation to PNDT in the second species. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

9.3. Specification of the study design

A PNDT study according to the test method OECD TG 414 should be performed in rabbit or rat as preferred second species, depending on the species tested in the first PNDT study (request 6 in this decision).

253 The study must be performed with oral administration of the Substance (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

254 Based on the above, the study must be conducted in rabbit or rat with oral administration of the Substance.

255 In the comments to the draft decision, one registrant at Annex IX indicates that it considers to upgrade its tonnage band to Annex X and it already provides comments for this information requirement in anticipation of its possible tonnage band change.

256 In its comments, the registrant disagrees with this request.

257 The registrant claims that "*no gain in information is expected when testing the second species*" and that "*a pre-natal developmental toxicity study in a second species will result in unnecessary death of animals, being against the best interest of animal welfare*".

258 The registrant is also of the view that the need for a pre-natal developmental toxicity study in a second species can only be decided after conducting the pre-natal developmental toxicity study in the first species. In support of its opinion, the registrant refers to an alleged adaptation possibility under Annex IX, Section 8.7.2., Column 2. It considers that if the study in a second species was still requested to be performed, it would need to be performed sequentially after the study in the first species, because "*data obtained to address request [6]* […] *must be generated before a decision on the necessity of a study in a second species can be made*".

259 In this context, the registrant refers to a possible adaptation of the information requirement of the second species, in case the results of the study in the first species would lead to classification.

260 With respect to the registrant's comments on the information requirement, although not pertinent, ECHA addresses them for the sake of administrative efficiency.

261 First, the registrant refers in its comments to an adaptation under Annex IX, Section 8.7.2., Column 2.

262 However, in order to be compliant and enable concluding if the Substance is a developmental toxicant, information provided has to meet the requirements of OECD TG 414 in two species. The studies with two species provide complementary information.

263 A pre-natal developmental toxicity study in a second species is a standard information requirement at Annex X unless one or more of the adaptations in Section 8.7 of Annex X or Annex XI apply, taking into account the results of the test in the first species or any other relevant avalable information.

264 It has not been demonstrated that the results of tests in the first species or any other relevant available information enable adaptations in accordance with Section 8.7 of Annex X or Annex XI.

265 Thus, the adaptation referred to in the registrant's comments is rejected.

266 Second, the registrant seems to point to Annex X, Section 8.7., Column 2 in case that the results of the study in the first species would lead to classification. However, this adaptation relies on data not yet generated and therefore, no conclusion on its compliance can be made.

267 In any event, the deadline set in this decision allows for sequential testing for the two requested studies on pre-natal developmental toxicity.

268 Third, minimisation of vertebrate animal testing is not on its own a legal ground for adaptation under the general rules of Annex XI. When the conditions for an adaptation are not met and there is a data gap, ECHA has the duty to request the missing study, which is a standard information requirement and ECHA does not breach the principle of testing as last resort in Article 25(1) of the REACH Regulation by requesting the study.

269 The registrant's comments on a deadline extension are addressed in Appendix 2 of this decision.

270 In any event, ECHA notes that this information requirement only concerns registrants with a registration at Annex X.

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

The information requirement for an Extended one-generation reproductive toxicity study (EOGRTS; Annexes IX or X, Section 8.7.3.) is not addressed in this decision. This may be addressed in a separate decision once the information from the Sub-chronic toxicity study (90-day) requested in the present decision is provided; due to the fact that the results from the 90-day study is needed for the design of the EOGRTS. Similarly the information requirement for a Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.) is not addressed in this decision; as the EOGRTS will cover the same parameters.

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 27 September 2021.

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

ECHA took into account your comments and did not amend the requests, but amended the deadlines.

Deadlines to submit the requested information in this decision

Environmental information requirements

In its comments on the draft decision, one registrant requests an extension of the deadline to provide the requested information on long-term toxicity to aquatic invertebrates and fish (Requests 7 and 8 of this decision), from 24 to 36 months from the date of adoption of the decision.

In support of this request the registrant has provided an email exchange with the laboratory by which the studies are claimed to be conducted.

ECHA considers the extension of the deadline to perform the required aquatic chronic toxicity studies by an additional 12 months justified on the basis of low laboratory capacity.

Human health information requirements

In its comments on the draft decision, one registrant requests an extension of the deadline to provide information for the Sub-chronic toxicity study (90 day) from 12 to 23 months from the date of adoption of the decision. The extension request is supported by evidence on limited laboratory capacities, as well as by the time needed to perform preliminary analytical studies, a comprehensive dose-range finding study and the main study as well as a time buffer needed for "*unforeseeable events*". On the basis of the provided information in particular regarding limited laboratory capacities ECHA considers the extension of the deadline for this information request justified.In addition, the registrant requests in its comments on the draft decision an extension of the deadline to provide information for the Pre-natal developmental toxicity study in two species from 24 to 41 months from the date of adoption of the decision. The registrant aims to justify the extension request with evidence on limited laboratory capacities, as well as by the time needed to perfom the two PNDT studies in two species in sequential order, and by the "*waiting time for results from RDT dose range finder*", i.e. sequential performance of the OECD TG 408 and OECD TG 414 studies, in order to "*to use data from the study according to OECD 408 for optimising the selection of the dose levels*" for the OECD TG 414 studies.

ECHA notes that usually 24 months is the standard deadline for the Pre-natal developmental toxicity studies in two species which is based on the standard practice for carrying out OECD TG tests and allows for sequential performance of the studies in both species. In the present case, ECHA considers an extension of the deadline to perform the required pre-natal developmental toxicity studies justified on the basis of low laboratory capacity.However, the doses for the OECD TG 414 studies should be selected according to the principles of EU Test Method B.31, OECD TG 414, which states that "*the highest dose should be chosen with the aim to induce some developmental and/or maternal toxicity (clinical signs or a decrease in body weight) but not death or severe suffering*". The OECD TG 408 in rats only informs on toxicological effects on adult non-pregnant rats. Therefore, OECD TG 408 is not adequate to inform on the dose level setting for the PNDT study which uses pregnant animals only and in particular for the PNDT in rabbits due to interspecies differences. Hence, the Sub-chronic toxicity study (90 day) shall be conducted in parallel to the OECD TG 414 studies.

Standard extension of the deadlines

Irrespective of the above, the deadlines have been exceptionally extended by 12 months from the standard deadlines granted by ECHA to take into account currently longer lead times in contract research organisations.

On this basis, ECHA has extended all information requests, besides request 5, to ***36 months*** *from the date of the decision*.

For request 5 it has been also exceptionally extended to 36 months *from the date of the decision*, however, to be the same as the deadline of a decision sent to another registrants of the Substance requesting the same study.

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 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]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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

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[2].

(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

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

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

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

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

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[3].

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