~~Confidential~~

Helsinki,16 November 2022

Addressees
Registrant(s) as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
24 July 2017

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);

2. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method: EU C.2./OECD TG 202);

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

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

4. 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);

5. 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);

6. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) by oral route, in rats;

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

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

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

9. 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);

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

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

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

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

Appendix 1: Reasons for the decision

Contents

0. Reasons common to several requests 5

Reasons related to the information under Annex VII of REACH 11

1. In vitro gene mutation study in bacteria 11
2. Short-term toxicity testing on aquatic invertebrates 13
3. Growth inhibition study aquatic plants 14

Reasons related to the information under Annex VIII of REACH 16

4. In vitro cytogenicity study in mammalian cells or In vitro micronucleus study 16
5. In vitro gene mutation study in mammalian cells 19
6. Screening for reproductive/developmental toxicity 22
7. Short-term toxicity testing on fish 23

Reasons related to the information under Annex IX of REACH 26

8. Sub-chronic toxicity study (90-day) 26
9. Pre-natal developmental toxicity study in one species 30
10. Long-term toxicity testing on aquatic invertebrates 32
11. Long-term toxicity testing on fish 32

References 35

0. Reasons common to several requests

0.1. Assessment of the read-across approach

1 You have adapted the following standard information requirements by using grouping and read-across approach under Annex XI, Section 1.5:

- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.);
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.).

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

3 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.

4 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).

5 You provide a read-across justification document in separate endpoint study records under sections 7.8.1 and 7.8.2 in IUCLID and in the respective section of your Chemical Safety Report.

6 You predict the properties of the Substance from information obtained from the source substance tributyl 2-acetoxypropane-1,2,3-tricarboxylate (ATBC), EC 201-067-0.

7 You provide the following reasoning for the prediction of toxicological properties: *"The analogue approach is based on common breakdown products via physical and biological processes, and similar functional groups"*, adding that "*for each of these endpoints, filling of data by read-across is supported by the established common route of metabolism"*.

8 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.

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

0.1.1. Missing supporting information

10 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.).

11 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).

12 You state that "*substances have common breakdown products via physical and biological processes, which reflects the similar functional groups in their chemical structure*" as well as that "*other than the acetyl group, there are no other functional groups which may introduce additional toxicities*".

13 You have provided the following information on the Substance and analogue substance ATBC to support your hypothesis:

- structural information
- information on physical form, vapour pressure, metabolism
- information on available data on acute toxicity, skin and eye irritation, skin sensitisation, gene mutation, repeated dose toxicity.

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

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

16 You have assessed the impact of these structural differences referring to degradation properties and available information on toxicological properties for the Substance and the analogue substances.

Comparison of toxicological properties

17 You have provided information on available data on acute toxicity, skin irritation, eye irritation, skin sensitisation for both the Substance and the source substance ATBC. ECHA notes that studies on acute toxicity, skin irritation, eye irritation, skin sensitisation do not inform on the reproductive and developmental toxicity as well as mutagenicity and repeated dose properties of the Substance and of the source substance. Information provided on repeated dose toxicity and mutagenicity for the Substance are indicated as inconclusive or with varying results.

18 Accordingly, this information is not considered as relevant to compare these toxicological properties of the substances.

19 Therefore you have not provided any adequate and reliable information in the documentation of your read-across approach addressing the impact of the structural differences of the Substance and analogue substance on the toxicological profile.

Hydrolysis and breakdown products

20 Furthermore, you state that the Substance "breaks down stoichiometrically to citric acid and ethanol", via metabolites such as diethyl citrate and monoethyl citrate which are further metabolised. You also state that the analogue substance ATBC is hydrolysed to monobutyl citrate, acetyl citrate, acetyl monobutyl citrate, dibutyl citrate, and acetyl dibutyl citrate. You claim that the metabolic profile of ATBC is similar to that of the Substance.

21 However, ECHA notes that citric acid is the only common break-down product. Despite potentially having similar hydrolysis properties, with the common hydrolysis product citric acid, the Substance and source substance ATBC also form non-common hydrolysis products. The non-common hydrolysis products are, amongst others, ethanol for the

Substance and butanol for ATBC, which differ structurally, in analogy to the substances. Further non-common hydrolysis products for the analogue substance ATBC include acetyl citrate and acetic acid.

22 You have not provided information characterising the exposure to the non-common compounds resulting from exposure to the Substance and to the source substance. No experimental data or other adequate and reliable information addressing the impact of exposure to these non-common compounds is included in the documentation of your read-across approach.

23 Moreover, you indicate in your justification document that the metabolism rate in human serum for the Substance to be >4 hours, and for the analogue substance ATBC 7 hours.

24 Therefore, exposure to the parent compounds cannot be disregarded and their contribution to the toxicological properties of the substances has also to be taken into account. You have not provided adequate supporting information on the impact of exposure to the parent compounds on the prediction.

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

26 In the absence of such information, you have not established that the Substance and the source substance are likely to have similar properties.

27 Based on the above, you have not provided sufficient supporting information to strengthen the rationale for the read-across.

0.1.2. Adequacy and reliability of source studies

28 According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across must:

- be adequate for the purpose of classification and labelling and/or risk assessment;
- have adequate and reliable coverage of the key parameters addressed in the corresponding study that shall normally be performed for a particular information requirement.

29 Specific reasons why the study on the source substance does not meet these criteria are explained further below under the applicable information requirement section 9. Therefore, no reliable predictions can be made for this information requirement .

0.1.3. Conclusion on the read-across approach

30 For the reasons above, you have not established that relevant properties of the Substance can be predicted from data on the source substance(s). Your read-across approaches under Annex XI, Section 1.5. is rejected.

0.2. Assessment of weight of evidence adaptations

31 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* cytogenicity study in mammalian cells or *in vitro* micronucleus study (Annex VIII, Section 8.4.2.);
- *In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.);
- Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2).

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

33 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.

34 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.

35 According to Guidance on IRs and CSA 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.

36 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.

37 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.

38 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.

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

0.2.1. Missing robust study summaries

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

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

42 For the endpoints of mutagenicity, you list additional studies in the Chemical Safety Report that are not included in IUCLID, to be considered in a weight of evidence to conclude on genotoxicity.

43 You only provide the type of study performed, the test substance and the result, such as “not mutagenic” or “not clastogenic”. However, you do not provide detailed information on the methods, results and conclusions, allowing for an independent assessment of each source of information and contributing to the overall weight of evidence for the information requirement under consideration.

44 Consequently, sources of information with missing robust study summaries cannot be considered as contributing to the overall weight of evidence for the information requirement under consideration.

0.2.2. Reliability of the information provided from analogue substances

45 ECHA understands that you use data obtained with the following analogue substances 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 to predict *in vitro* mammalian chromosome aberration and *in vitro* mammalian cell gene mutation
- citric acid, EC 201-069-1 to predict *in vitro* mammalian chromosome aberration.

46 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.

47 As explained in Section 0.1 of the Reasons common to several requests, two conditions must be fulfilled whenever a read-across approach is used.

48 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.

49 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.

50 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).

51 You provide a read-across justification in separate endpoint study records under section 7.6.1 in IUCLID and in the respective section of your Chemical Safety Report.

52 You provide the following reasoning for the prediction of toxicological properties: *"The analogue approach is based on common breakdown products via physical and biological processes, and similar functional groups"*, adding that *"for each of these endpoints, filling of data by read-across is supported by the established common route of metabolism"*.

53 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.

Information provided from analogue substance ATBC

54 Section 0.1.1. of the Reasons common to several requests identifies shortcomings of the grouping and read-across approach with the analogue substance ATBC used in your dossier. These findings apply equally to the sources of information relating to the analogue substance ATBC submitted under your weight of evidence adaptations.

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

0.3. Assessment of (Q)SAR information

56 You have adapted the following standard information requirements by applying (a) (Q)SAR approach(es) in accordance with Annex XI, Section 1.3:

- Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)
- Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)

57 ECHA has considered the scientific and regulatory validity of your (Q)SAR adaptation(s) in general before assessing the specific standard information requirements in the following appendices.

58 Under Annex XI, Section 1.3., the following conditions must be fulfilled whenever a (Q)SAR approach is used:

(1) the prediction needs to be derived from a scientifically valid model,
(2) the substance must fall within the applicability domain of the model,
(3) results need to be adequate for the purpose of risk assessment or classification and labelling, and
(4) adequate and reliable documentation of the method must be provided.

59 With regard to these conditions, we have identified the following issue(s):

0.3.1. (Q)SAR for ecotoxicological properties

0.3.1.1. Inadequate documentation of the model (QMRF)

60 Under Appendix C of the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) and Guidance on IRs and CSA Section R.6.1.6.3., adequate and reliable documentation must include a (Q)SAR Model Reporting Format document (QMRF) which reports, among others, the following information:

- an unambiguous definition of the algorithm, the descriptor(s) of the model and its applicability domain.

61 The documentation available on the model does not include specification of the version number of the software and the ECOSAR class considered.

62 In absence of such information, ECHA cannot identify the algorithm used for the prediction and therefore establish that the model can be used to meet this information requirement.

0.3.1.2. Lack of or inadequate documentation of the prediction (QPRF)

63 Guidance on IRs and CSA Section R.6.1.6.3 states that the information specified in or equivalent to the (Q)SAR Prediction Reporting Format document (QPRF) must be provided to have adequate and reliable documentation of the applied method. For a QPRF this includes, among others:

- a precise identification of the substance modelled,
- the identities of close analogues, including considerations on how predicted and experimental data for analogues support the prediction.

64 You have not provided information regarding the precise identification of the substance modelled and the identities of close analogues.

65 In absence of such information, ECHA cannot establish that the prediction can be used to meet this information requirement.

66 Based on the above, you have not provided adequate and reliable documentation of the applied method and your adaptations are rejected.

Reasons related to the information under Annex VII of REACH

1. In vitro gene mutation study in bacteria

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

1.1. Information provided

68 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* mammalian chromosome aberration test (2004) with the analogue substance tributyl 2-acetoxypropane-1,2,3-tricarboxylate (ATBC), EC 201-067-0;

(iii) *in vitro* mammalian chromosome aberration test (1984) with the analogue substance citric acid, EC 201-069-1;

(iv) *in vitro* mammalian cell gene mutation test (1991) with the analogue substance ATBC, EC 201-067-0;

(v) *in vitro* mammalian cell gene mutation test (2004) with the analogue substance ATBC.

69 You justify the weight of evidence as follows in the Chemical Safety Report: "*In bacterial and mammalian in vitro mutation assays, triethyl citrate (TEC) and an analogue substance, acetyl tributyl citrate (ATBC) were nonmutagenic. Another analogue, citric acid, was not clastogenic in a guideline chromosomal aberrations assay. Taken together in a weight of evidence approach, triethyl citrate can be considered non-mutagenic and non-clastogenic*."

70 In the Chemical Safety Report, you list 12 additional studies to be considered in a weight of evidence, stating that "*the highly-weighted studies consistently show a lack of genotoxicity*":

(vi) bacterial reverse mutation assay (1976) with the Substance;

(vii) bacterial reverse mutation assay (1988) with the analogue substance citric acid, EC 201-069-1;

(viii) bacterial reverse mutation assay (no year indicated) with the analogue substance citric acid, EC 201-069-1;

(ix) chromosomal aberrations assay (no year indicated) with the analogue substance citric acid, EC 201-069-1;

(x) chromosomal aberrations assay (WI-38) (no year indicated) with the analogue substance citric acid, EC 201-069-1;

(xi) *in vivo* rat cytogenetics assay (no year indicated) with the analogue substance citric acid, EC 201-069-1;

(xii) *in vivo* mouse host-mediated cytogenetics assay (no year indicated) with the analogue substance citric acid, EC 201-069-1;

(xiii) bacterial reverse mutation assay (2004a) with the analogue substance

ATBC, EC 201-067-0;

(xiv) bacterial reverse mutation assay (2004b) with the analogue substance ATBC, EC 201-067-0;

(xv) in vitro HPRT mammalian mutagenicity assay assay (2004) with the analogue substance ATBC, EC 201-067-0;

(xvi) Mouse lymphoma (L5178Y TK+/- locus) mammalian mutagenicity assay (2004) with the analogue substance ATBC, EC 201-067-0;

(xvii) *in vitro* chromosomal aberrations assay (2004) with the analogue substance ATBC, EC 201-067-0.

1.2. Assessment of the information provided

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

72 As explained under Section 0.2. 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 requirements under consideration.

73 As explained in Section 0.2. 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.

74 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).

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

76 For the reasons explained in the section 0.2.1. of the Reasons common to several requests, the sources of information (vi) to (xvii) that are lacking robust study summaries cannot be considered as contributing for these aspects with any relevant and reliable information.

77 Sources of information (ii) to (v) do not provide relevant information on the detection and quantification of gene mutations (base pairs, substitution or frame shift) in cultured bacteria. More specifically, studies (ii) and (iii) provide information on the detection and quantification of structural or numerical chromosomal aberrations in cultured mammalian cells and studies (iv) and (v) provide 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.

78 The source of information (i) provides relevant information on detection and quantification of gene mutations in bacteria. However, the test was performed with the strains S. typhimurium TA 1535, TA 1537, TA 1538, Saccharomyces cerevisiae strain D4, i.e., the strains S. typhimurium TA98; TA100 and one strain which is either S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101) are missing. Consequently, the source of information (i) only provides partially relevant information on gene mutation in bacteria.

79 In addition, the reliability of the source of information (i) is significantly affected by the following deficiencies:

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

80 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.

81 Study (i) was conducted following the OECD TG 471. This test guideline requires that:

- at least 5 doses are evaluated, in each test condition;
- one positive control is included in the study and the positive control substance produces a statistically significant increase in the number of revertant colonies per plate compared with the concurrent negative control;
- the number of revertant colonies per plate for the concurrent negative control is inside the historical control range of the laboratory;
- the mean number of revertant colonies per plate is reported for the treated doses and the controls.

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

- it is not clear how many test doses were evaluated in absence and in presence of metabolic activation (i.e., whether 5 doses were evaluated);
- positive and negative controls were not specified;
- the mean number of revertant colonies per plate for the treated doses and the controls was not reported.

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

1.3. Conclusion on the weight of evidence

84 Taken together, only one source of information (study (i)) provides partially relevant information on gene mutation in bacteria. Information on the strains S. typhimurium TA98, TA100 and on the 5th strain, which is either S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101), is missing.

85 Furthermore, the reliability of this source of information is hampered by limitations of the study design and/or reporting listed above affecting directly the reliability of the results and their contribution to the weight of evidence adaptation, since they introduce uncertainty in the results.

86 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

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

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

2. Short-term toxicity testing on aquatic invertebrates

89 Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII to REACH (Section 9.1.1.).

2.1. Information provided

90 You have adapted this information requirement by using Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs). To support the adaptation, you have provided the following information:

(i) ECOSAR prediction from 2004.

2.2. Assessment of the information provided

91 We have assessed this information and identified the following issue:

2.2.1. Assessment of your (Q)SAR adaptation

92 As explained in Section 0.3. of the Reasons common to several requests, your adaptation is rejected.

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

2.3. Information regarding data sharing

94 The jointly submitted registration for the Substance contains a Daphnia sp. Acute Immobilisation Test (2010) which is adequate for this information requirement. In accordance with Title III of the REACH Regulation, you may request it from the other registrants and then make every effort to reach an agreement on the sharing of data and costs (Guidance on data-sharing).

95 In the comments to the draft decision you indicate your intention to use data sharing (by requesting data from the Lead Registrant to the joint submission) to fulfil this information requirement.

3. Growth inhibition study aquatic plants

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

3.1. Information provided

97 You have adapted this information requirement by using Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs). To support the adaptation, you have provided following information:

(i) ECOSAR prediction from 2004.

3.2. Assessment of the information provided

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

3.2.1. Assessment of your (Q)SAR adaptation

99 As explained in Section 0.3. of the Reasons common to several requests, your adaptation is rejected.

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

3.3. Information regarding data sharing

101 The jointly submitted registration for the Substance contains a Algae, Growth Inhibition Test (2010) which is adequate for this information requirement. In accordance with Title III of the REACH Regulation, you may request it from the other registrants and then make every effort to reach an agreement on the sharing of data and costs (Guidance on data-sharing).

102 In the comments to the draft decision you indicate your intention to use data sharing (by requesting data from the Lead Registrant to the joint submission) to fulfil this information requirement.

Reasons related to the information under Annex VIII of REACH

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

103 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.

4.1. Information provided

104 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* mammalian chromosome aberration test (2004) with the analogue substance tributyl 2-acetoxypropane-1,2,3-tricarboxylate (ATBC), EC 201-067-0;

(iii) *in vitro* mammalian chromosome aberration test (1984) with the analogue substance citric acid, EC 201-069-1;

(iv) *in vitro* mammalian cell gene mutation test (1991) with the analogue substance ATBC, EC 201-067-0;

(v) *in vitro* mammalian cell gene mutation test (2004) with the analogue substance ATBC.

105 You justify the weight of evidence as follows in the Chemical Safety Report: "*In bacterial and mammalian in vitro mutation assays, triethyl citrate (TEC) and an analogue substance, acetyl tributyl citrate (ATBC) were nonmutagenic. Another analogue, citric acid, was not clastogenic in a guideline chromosomal aberrations assay. Taken together in a weight of evidence approach, triethyl citrate can be considered non-mutagenic and non-clastogenic*."

106 In the Chemical Safety Report, you list another 12 studies to be considered in a weight of evidence, stating that "the highly-weighted studies consistently show a lack of genotoxicity":

(vi) bacterial reverse mutation assay (1976) with the Substance;

(vii) bacterial reverse mutation assay (1988) with the analogue substance citric acid, EC 201-069-1;

(viii) bacterial reverse mutation assay (no year indicated) with the analogue substance citric acid, EC 201-069-1;

(ix) chromosomal aberrations assay (no year indicated) with the analogue substance citric acid, EC 201-069-1;

(x) chromosomal aberrations assay (WI-38) (no year indicated) with the analogue substance citric acid, EC 201-069-1;

(xi) *in vivo* rat cytogenetics assay (no year indicated) with the analogue substance citric acid, EC 201-069-1;

(xii) *in vivo* mouse host-mediated cytogenetics assay (no year indicated) with the analogue substance citric acid, EC 201-069-1;

(xiii) bacterial reverse mutation assay (2004a) with the analogue substance ATBC, EC 201-067-0;

(xiv) bacterial reverse mutation assay (2004b) with the analogue substance ATBC, EC 201-067-0;

(xv) in vitro HPRT mammalian mutagenicity assay assay (2004) with the analogue substance ATBC, EC 201-067-0;

(xvi) Mouse lymphoma (L5178Y TK+/- locus) mammalian mutagenicity assay (2004) with the analogue substance ATBC, EC 201-067-0;

(xvii) *in vitro* chromosomal aberrations assay (2004) with the analogue substance ATBC, EC 201-067-0.

4.2. Assessment of the information provided

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

108 As explained under Section 0.2. 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 requirements under consideration.

109 As explained in Section 0.2. 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.

110 Relevant information that can be used to support weight of evidence adaptation for the information requirement of Annex VIII, Section 8.4.2 includes similar information that is produced by the OECD TG 473 or OECD TG 487. The following aspects are covered:

- Detection and quantification of structural or numerical chromosomal aberrations in cultured mammalian cells including data on the cytotoxicity and the frequency of cells with chromosomal aberrations or micronuclei.

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

112 For the reasons explained in the section 0.2.1. of the Reasons common to several requests, the sources of information (vi) to (xvii) that are lacking robust study summaries cannot be considered as contributing for these aspects with any relevant and reliable information.

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

114 The sources of information (ii) and (iii) provide relevant information on detection and quantification of structural or numerical chromosomal aberrations in cultured mammalian cells, since the studies are stated to follow a guideline equivalent to OECD TG 473. However, data on the cytotoxicity and/or the frequency of cells with structural chromosomal aberrations for the treated and control cultures are not reported. Consequently, the sources of information (ii) and (iii) only provide partially relevant information for this information requirement.

115 In addition, the reliability of the sources of information (ii) and (iii) is significantly affected by the following deficiencies:

4.2.1. Reliability of the contribution of the information on the analogue substance (study (ii))

116 For the reasons explained in the section 0.2.2. 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.

4.2.2. Reliability of the contribution of the studies (ii) and (iii)

117 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.

118 The studies (ii) and (iii) were conducted following the OECD TG 473. This test guideline requires that:

- the maximum concentration tested induces 55+5% 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;
- at least 3 concentrations are evaluated, in absence and in presence of metabolic activation;
- at least 300 well-spread metaphases are scored per concentration
- one positive control is included in the study.

119 In the source of information (ii), the following investigation/specification is not to the requirements of OECD TG 473:

- A justification for the highest concentrations used (lower than 2000 µg/mL) is not reported
- The number of scored metaphases is not reported.

120 In the source of information (iii), the following investigations/specifications are not to the requirements of OECD TG 473:

- The different concentrations (number of concentrations used) are not reported.
- The number of well-spread metaphases observed is indicated as 100, i.e. lower than 300 metaphases
- You indicate that a positive control has been used and that valid results were obtained. However, no information on the identity of the substance used as positive control is provided. In the absence of this information, the adequacy of the substance used as positive control cannot be assessed.

121 Based on the above, the reliability of the contribution of the results obtained from the studies (ii) and (iii) 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.

4.3. Conclusion on the weight of evidence

122 Taken together, only the sources of information (ii) and (iii) provide partially relevant information on detection and quantification of structural or numerical chromosomal aberrations in cultured mammalian cells.

123 However, the reliability of the contribution of the information from studies (ii) and (iii) is hampered by:

- the deficiency identified related to the use of information on the analogue substance (study (ii))

- limitations of the study design and/or reporting listed above affecting directly the reliability of the results of studies (ii) and (iii) and their contribution to the weight of evidence adaptation, since they introduce uncertainty in the results.

124 Therefore, it is not possible to conclude, based on any source of information alone or considered together, on the information requirement for an in vitro cytogenicity study in mammalian cells or in vitro micronucleus study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

4.4. Specification of the study design

125 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.

126 In the comments to the draft decision, you agree to perform the requested study (OECD TG 487).

5. In vitro gene mutation study in mammalian cells

127 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.

5.1. Triggering of the information requirement

128 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.

129 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 4.

130 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.

131 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.

5.2. Information provided

132 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* mammalian chromosome aberration test (2004) with the analogue substance tributyl 2-acetoxypropane-1,2,3-tricarboxylate (ATBC), EC 201-067-0;

(iii) *in vitro* mammalian chromosome aberration test (1984) with the analogue substance citric acid, EC 201-069-1;

(iv) *in vitro* mammalian cell gene mutation test (1991) with the analogue substance ATBC, EC 201-067-0;

(v) *in vitro* mammalian cell gene mutation test (2004) with the analogue substance ATBC.

133 You justify the weight of evidence as follows in the Chemical Safety Report: "*In bacterial and mammalian in vitro mutation assays, triethyl citrate (TEC) and an analogue substance, acetyl tributyl citrate (ATBC) were nonmutagenic. Another analogue, citric acid, was not clastogenic in a guideline chromosomal aberrations assay. Taken together in a weight of evidence approach, triethyl citrate can be considered non-mutagenic and non-clastogenic*."

134 In the Chemical Safety Report, you list another 12 studies to be considered in a weight of evidence, stating that "*the highly-weighted studies consistently show a lack of genotoxicity*":

(vi) bacterial reverse mutation assay (1976) with the Substance;

(vii) bacterial reverse mutation assay (1988) with the analogue substance citric acid, EC 201-069-1;

(viii) bacterial reverse mutation assay (no year indicated) with the analogue substance citric acid, EC 201-069-1;

(ix) chromosomal aberrations assay (no year indicated) with the analogue substance citric acid, EC 201-069-1;

(x) chromosomal aberrations assay (WI-38) (no year indicated) with the analogue substance citric acid, EC 201-069-1;

(xi) *in vivo* rat cytogenetics assay (no year indicated) with the analogue substance citric acid, EC 201-069-1;

(xii) *in vivo* mouse host-mediated cytogenetics assay (no year indicated) with the analogue substance citric acid, EC 201-069-1;

(xiii) bacterial reverse mutation assay (2004a) with the analogue substance ATBC, EC 201-067-0;

(xiv) bacterial reverse mutation assay (2004b) with the analogue substance ATBC, EC 201-067-0;

(xv) in vitro HPRT mammalian mutagenicity assay assay (2004) with the analogue substance ATBC, EC 201-067-0;

(xvi) Mouse lymphoma (L5178Y TK+/- locus) mammalian mutagenicity assay (2004) with the analogue substance ATBC, EC 201-067-0;

(xvii) *in vitro* chromosomal aberrations assay (2004) with the analogue substance ATBC, EC 201-067-0.

5.3. Assessment of the information provided

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

136 As explained under Section 0.2. 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 requirements under consideration.

137 As explained in Section 0.2. 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.

138 Relevant information that can be used to support weight of evidence adaptation for the information requirement of Annex VIII, Section 8.4.3 includes similar information that is produced by the OECD TG 476/490 and OECD TG 488. The following aspects are covered:

- 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*).

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

140 For the reasons explained in the section 0.2.1. of the Reasons common to several requests, the sources of information (vi) to (xvii) that are lacking robust study summaries cannot be considered as contributing for these aspects with any relevant and reliable information.

141 Sources of information (i) to (iii) do not provide relevant information on the detection and quantification of gene mutations in cultured mammalian cells. More specifically, study (i) provides information on the detection and quantification of gene mutations (base pairs, substitution or frame shift) in cultured bacteria and studies (ii) and (iii) provide 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.

142 The sources of information (iv) and (v) provide relevant information on detection and quantification of gene mutations in cultured mammalian cells, since the studies are stated to follow a guideline equivalemnt to OECD TG 476. However, data on the the frequency of mutant colonies in cultured mammalian cells are not reported for study (v). Consequently, the source of information (v) only provides partially relevant information on gene mutation in mammalian cells.

143 In addition, the reliability of the sources of information (iv) and (v) is significantly affected by the following deficiencies:

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

144 For the reasons explained in the section 0.2.2. of the Reasons common to several requests above, you have not established that the information from studies (iv) and (v) can reliably contribute to your weight of evidence adaptation.

5.3.2. Reliability of the contribution of the study (v)

145 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.

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

- a positive control is included in the study.

147 In the source of information (v), the following investigations/specifications are not to the requirements of OECD TG 476:

- You indicate that a positive control has been used and that valid results were obtained. However, no information on the identity of the substance used as

positive control is provided. In the absence of this information, the adequacy of the substance used as positive control cannot be assessed.

148 Based on the above, the reliability of the contribution of the results obtained from the studies (iv) and (v) 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.

5.4. Conclusion on the weight of evidence

149 Taken together, only the sources of information (iv) and (v) provide relevant information on detection and quantification of gene mutations in cultured mammalian cells.

150 However, the reliability of the contribution of the information from studies (iv) and (v) is hampered by:

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

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

5.5. Specification of the study design

152 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.

153 In the comments to the draft decision, you agree to assess the need for this study based on the results obtained for the requested OECD TG 471 and OECD TG 487 studies.

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

6. Screening for reproductive/developmental toxicity

155 A screening for reproductive/developmental toxicity study (OECD 421 or OECD 422) is an information requirement under Annex VIII, Section 8.7.1., if there is no evidence from analogue substances, QSAR or in vitro methods that the substance may be a developmental toxicant.

6.1. Information provided

156 You have adapted this information requirement by using a Grouping of substances and read-across approach based on the following experimental data:

(i) a modified 90-day repeated dose study with an *in utero* exposure (2002) with the analogue substance tributyl 2-acetoxypropane-1,2,3-tricarboxylate (ATBC), EC 201-067-0.

6.2. Assessment of the information provided

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

6.2.1. Read-across adaptation rejected

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

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

6.3. Specification of the study design

160 A study according to the test method EU B.63/OECD TG 421 or EU B.64/OECD TG 422 must be performed in rats.

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

162 In the comments to the draft decision, you state that conducting a study according to "*OECD 421/422 is not required under REACH Annex VIII if the data endpoint for Annex IX, pre-natal developmental toxicity, is satisfied*" and that "*you will include a waiver in the dossier*". ECHA understands that you have the intention to adapt the information requirement according to Annex VIII 8.7.1, Col. 2, first paragraph, fourth indent.

163 However, ECHA notes that at present there is no valid study or adaptation included in your dossier to fulfil the information requirement of a pre-natal developmental toxicity study (Annex IX, 8.7.2). Therefore no conclusion on the compliance of a potential future adaptation can currently be made.

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

7. Short-term toxicity testing on fish

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

7.1. Information provided

166 You have adapted this information requirement by using Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs). To support the adaptation, you have provided the following information:

(i) ECOSAR prediction from 2004.

167 In addition, you have provided the following supporting information:

(ii) a *Preliminary assessment study of fish toxicity* (1974), with the Substance.

168 Regarding study (ii), ECHA understands that you intend to rely on an adaptation according to Annex XI, Section 1.1.2 regarding data from experiments generated prior to the 1st of June 2008 and not carried out according to GLP or the test guideline normally required for this information requirement.

7.2. Assessment of the information provided

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

7.2.1. Assessment of your (Q)SAR adaptation

170 As explained in Section 0.3. of the Reasons common to several requests, your adaptation is rejected.

7.2.2. Assessment of your adaptation under Annex XI, Section 1.1.2

171 Under Annex XI, Section 1.1.2., data from experiments generated prior to the 1st of June 2008 and not carried out according to GLP or the test guideline normally required for the information requirement must be considered equivalent to data generated from the test method if the following condition(s) are met:

1) adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3).

172 For this information requirement, the data from the experiment must have adequate and reliable coverage of the key parameters of the OECD TG 203. Therefore, the following specifications must be met:

a. Testing of at least five concentrations of test material with at least one control group, unless a limit test is performed (at 100 mg/L or at the limit of solubility in the test medium)

b. At least 7 juvenile fish (before reaching sexual maturity) are tested for each test concentration and control group

c. Where a fish species not recommended in the test guideline is tested, a rationale for the selection of is reported together with any adaptations to the test guideline's recommendations

d. Evidence confirming stability of the test substance in the test solutions is provided (if the concentrations cannot be maintained stable, the results should be calculated using the measured concentrations of the test chemical)

e. Test medium fulfils the following condition(s): particulate matter ≤ 5 mg/L, total organic carbon (TOC) ≤ 2 mg/L or carbon oxygen demand (COD) ≤ 5 mg/L, pH between 6 and 8.5, dissolved oxygen concentration ≤60%)

f. The suitability of the test conditions and procedure is demonstrated by ≤ 10% mortality at the end of the test in the control(s)

g. Observations and recording is performed at least at 24, 48, 72 and 96 hours.

173 Your registration dossier provides study (ii) showing the following:

a. You have not specified the tested concentrations nor if you have used control group(s)

b. You have not specified how many fish were used in the study. Furthermore, you indicate that the fish were acconditioned for 1 month however, you do not indicate their life stage at the beginning of the study

c. You have used *Fundalus heteroclitus*, which is not a fish species recommended in the test guideline, and you do not provide a rationale for the selection of this species

d. You claim that analytical monitoring (gas chromatography) was performed however you have not provided evidence of the test substance stability nor reported if the results where calculated using the measured concentrations

e. You have not reported the particulate matter, total organic carbon (TOC) or carbon oxygen demand (COD), pH and dissolved oxygen concentration of the test medium

f. You have not reported the mortality at the end of the test in the control(s)

g. You have not reported any observations and recording during the test.

174 Therefore, the data provided does not have adequate and reliable coverage of the key parameters of the OECD TG 203.

175 Based on the above, the adaptation is rejected.

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

7.3. Possibility for data sharing:

177 The other registrants of the joint submission relied on an adaptation to meet this information requirement. You may consider sharing this information[2].

178 In the comments to the draft decision you indicate your intention to use data sharing (by requesting data from the Lead Registrant to the joint submission) to fulfil this information requirement. Alternatively, you consider the possibility to "*review and adjust*" your own adaptation. However, in the absence of further details ECHA is not yet in position to assess your adaptation and hence, you remain bound to this request.

[2] https://echa.europa.eu/regulations/reach/registration/data-sharing

Reasons related to the information under Annex IX of REACH

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

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

8.1. Information provided

180 You have provided:

(i) a combined repeated dose and carcinogenicity study in rats via diet (1954) with the Substance;

(ii) a 6-8 week-study in rats via diet (1959) with the Substance;

(iii) a 6-month-study in beagle dogs via diet (1956) with the Substance;

(iv) a 6-8-week oral study in cats (1959) with the Substance;

(v) a 62-day inhalation study in rats (1998) with the Substance;

(vi) not specified study extracting the analogues substance tributyl 2-acetoxypropane-1,2,3-tricarboxylate (ATBC), EC 201-067-0 from plastic toys (1999).

181 In your dossier, you do not explicitly refer to a specific or general adaptation rule under the REACH provisions. ECHA understands that you are adapting the information requirement according to Annex XI, Section 1.2. of REACH (weight of evidence) and has assessed the information provided accordingly.

8.2. Assessment of the information provided

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

183 As explained under Section 0.2. 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 requirements under consideration.

184 As explained in Section 0.2. 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.

185 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.

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

8.2.1. Studies (iii) and (iv) not conducted on appropriate species

187 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.

188 The sources of information (iii) and (iv) provide information on other species than rodent, more specifically dog and cat.

189 Therefore, the sources of information (iii) and (iv) do not provide relevant information.

8.2.2. Study (v) not conducted by the most appropriate route

190 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.

191 The Substance is a liquid of very low vapour pressure (0.00025 Pa at 25°C).

192 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.

193 The study (v) has been conducted with inhalation route of exposure, which does not correspond to the most appropriate route. You do not provide any information on the relative bioavailability for the substance after inhalation exposure compared to oral exposure.

194 Furthermore, no details on the examinations conducted as part of this study is provided in the endpoint study record included in the technical dossier. In the absence of this information, you have not established that the study (v) as currently reported provides relevant information that can be used to support any of the aspects of the weight of evidence adaptation for the information requirement of Annex IX, Section 8.6.2.

8.2.3. Adequacy of the provided study (vi) for hazard identification

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

196 According to the information provided in your dossier, the study (vi) has been designed for the purpose of risk assessment. The study provides a quantification of the release of the substance investigated in the context of a specific use, i.e. estimation of the levels of the Substance extracted from plastic toys chewed/mouthed by a child, and does not investigate the intrinsic properties of the Substance as required for the purpose of hazard identification.

197 Therefore, the study does not inform on the intrinsic hazard of the Substance and does not allow to make a conclusion whether the Substance has a hazard of repeated dose toxicity.

198 In conclusion, the source of information (vi) does not provide relevant information that can be used to support any of the aspects of the weight of evidence adaptation for the information requirement of Annex IX, Section 8.6.2.

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

8.2.4. Aspect 1) in-life observations

200 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).

201 For the reasons explained under 8.2.1., 8.2.2. and 8.2.3., the sources of information (iii) to (vi) are not considered to provide relevant information on this aspect.

202 The sources of information (i) and (ii) 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 (ii) does not inform on survival and clinical signs.

203 Consequently, the sources of information (i) and (ii) only provide partially relevant information on aspect 1).

204 In addition, the source of information (ii) has deficiencies affecting its reliability:

8.2.4.1. Reliability of the contribution of the study (ii)

205 For a sub-chronic toxicity study, 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.

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

- an exposure duration of only 6-8 weeks
- it is not clear how many animals were used per group.

207 Therefore, the actual exposure period in study (ii) 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.

208 Furthermore, it is not clear whether study (ii) has 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.

209 Therefore, the the reliability of the contribution of the results obtained from the study (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.

8.2.5. Aspect 2) blood chemistry

210 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).

211 For the reasons explained under 8.2.1., 8.2.2. and 8.2.3., the sources of information (iii) to (vi) are not considered to provide relevant information on this aspect.

212 The sources of information (i) and (ii) 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.

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

214 In addition, the source of information (ii) has deficiencies affecting its reliability:

8.2.5.1. Reliability of the contribution of the study (ii)

215 The reliability issues identified in section 8.2.4.1. above, related to exposure duration and statistical power, equally apply to the aspect 2).

216 As a result, the reliability of the contribution of the results obtained from the study (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.

8.2.6. Aspect 3) organ and tissue toxicity

217 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).

218 For the reasons explained under 8.2.1., 8.2.2. and 8.2.3., the sources of information (iii) to (vi) are not considered to provide relevant information on this aspect.

219 The source of information (i) and (ii) 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.

220 Specifically, in source study (i) the following organs and tissues were not investigated: brain, spinal cord, pituitary, gland, thyroid, thymus, cervix vagina, epididymides, prostate, coagulation glands, mammary glands, urinary bladder, lymph nodes, peripheral nerves, skeletal muscle, bone, bone marrow.

221 The source study (ii), based on the information provided in the study record, does not investigate the following organs and tissues: 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.

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

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

224 In addition, the source of information (ii) has deficiencies affecting its reliability:

8.2.6.1. Reliability of the contribution of the study (ii)

225 The reliability issues identified in section 8.2.4.1. above, related to exposure duration and statistical power, equally apply to the aspect 2).

226 As a result, the reliability of the contribution of the results obtained from the study (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.

8.2.7. Conclusion on the weight of evidence

227 Taken together, only the sources of information (i) and (ii) 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 408 for all aspects 1) to 3), as described above.

228 Furthermore, any robust conclusion on any of the 3 aspects is hampered by reliability issues related to how the results were obtained in the studies which increases the uncertainty of the conclusion for the Substance (study (ii)).

229 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.

8.3. Specification of the study design

230 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.

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

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

233 In the comment to the draft decision, you disagree to perform the requested study. You acknowledge that the provided studies were performed "*prior to today's OECD testing guidelines*", but you state that "*this does not mean the studies are without merit*". You re-iterate that the information provided is sufficient to fulfil the information requirement, also referring to the fact that "*several worldwide expert groups have reviewed the existing body of data for Triethyl Citrate and have used it to determine safe levels for use in food, feed, pharma and cosmetic applications*", claiming that this "*indicates that Triethyl Citrate already has sufficient data available to make robust risk determinations*" and that the Substance "*has been approved for use in these applications for nearly 50 years, without a history of safety concerns*". You state that further studies using the current OECD guideline will not provide "*any relevant new information regarding hazard and risk for this substance*" and that "*requiring vertebrate animal testing for this endpoint would negatively impact animal welfare*".

234 ECHA notes that the conclusions on safe levels of use and for specific applications, by the different authorities and Committees you are referring to, do not indicate that an overall analysis of the intrinsic properties of the substance has taken place as required under Annexes VII-X of the REACH Regulation. ECHA further notes that the minimisation of vertebrate animal testing is not on its own a legal ground for adaptation under the general rules of Annex XI.

235 You have not provided in your comments any new information to address the deficiencies of your adaptation/fulfil the information requirement for sub-chronic toxicity (90-day) as explained above. Therefore, the information provided in your comments does not change the assessment outcome.

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

9. Pre-natal developmental toxicity study in one species

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

9.1. Information provided

238 You have adapted this information requirement by using a Grouping of substances and read-across approach based on the following experimental data:

(i) a modified 90 day repeated dose study with an in utero exposure (2002) with the analogue substance tributyl 2-acetoxypropane-1,2,3-tricarboxylate (ATBC), EC 201-067-0.

9.2. Assessment of the information provided

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

9.2.1. Read-across adaptation rejected

240 As explained in Section 0.1. of the Reasons common to several request, your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected. In addition, ECHA identified endpoint specific issue(s) addressed below.

9.2.2. Source study not adequate for the information requirement

241 As explained in Section 0.1 of the Reasons common to several requests, the results to be read across must have an adequate and reliable coverage of the key parameters addressed in the test guideline for the corresponding study that shall normally be performed for a particular information requirement, in this case the OECD TG 414. Therefore, the following specifications must be met:

- caesarean section
- the foetuses are examined for body weight, number and percent of live and dead foetuses and resorptions, sex ratio, external, skeletal and soft tissue alterations (variations and malformations), measurement of anogenital distance in all live rodent foetuses.

242 The study (i) is described as a modified 13 week dietary repeated dose study in rats with an added *in utero* exposure phase. It investigates post-natal effects on the offspring after natural delivery instead of caesarean section. The study is not a conclusive developmental toxicity study.

243 That study does not cover key parameters of the OECD TG 414:

- no caesarean section but natural birth
- no foetuses examined for skeletal and soft tissue alterations (variations and malformations).

244 Based on the above, the study does not provide an adequate and reliable coverage of the key parameter(s) addressed by the OECD TG 414 and this study is not an adequate basis for your read-across predictions.

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

9.3. Specification of the study design

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

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

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

249 In the comments to the draft decision, you refer to your comments on request 8, i.e. the Sub-chronic toxicity study (90-day), which ECHA summarised and addressed above (see request 8). However, you have not provided in your comments any new information to address the deficiencies/fulfil the information requirement for pre-natal developmental toxicity as explained above.

250 Therefore, you remain responsible for complying with this decision by the set deadline.

10. Long-term toxicity testing on aquatic invertebrates

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

10.1. Information provided

252 You have adapted this information requirement by using Column 2 of Annex IX, Section 9.1. To support the adaptation, you have provided the following justification:

(i) *"According to Regulation (EC) No.1907/2006, Annexes VIII and IX, Column 2, long-term aquatic toxicity testing shall be conducted if the substance is poorly soluble in water, or if the chemical safety assessment indicates the need to investigate further the effects on aquatic organisms. The substance is soluble in water. However, aquatic exposures do not require further investigation, based on the low predicted short-term toxicity of the substance to daphnia, the rapid biodegradability of the substance, and the low potential for bioaccumulation. Therefore, long-term toxicity testing in aquatic organisms, including aquatic invertebrates, is not indicated."*

10.2. Assessment of the information provided

253 We have assessed this information and identified the following issue:

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

254 Annex IX, Section 9.1., Column 2 does not allow omitting the need to submit information on long-term toxicity to aquatic invertebrates under Column 1. It must be understood as a trigger for providing further information on aquatic invertebrates if the chemical safety assessment according to Annex I indicates the need (Decision of the Board of Appeal in case A-011-2018).

255 Your adaptation is therefore rejected.

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

257 In the comments to the draft decision ECHA understands you agree with the request.

11. Long-term toxicity testing on fish

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

11.1. Information provided

259 You have adapted this information requirement by using Column 2 of Annex IX, Section 9.1. To support the adaptation, you have provided the following justification:

(i) "*According to Regulation (EC) No.1907/2006, Annexes VIII and IX, Column 2, long-term aquatic toxicity testing shall be conducted if the substance is poorly soluble in water, or if the chemical safety assessment indicates the need to investigate further the effects on aquatic organisms. The substance is soluble in water. However, aquatic exposures do not require further investigation, based on the low predicted short-term toxicity of the substance to fish, the rapid biodegradability of the substance, and the low potential for bioaccumulation. Therefore, long-term toxicity testing in aquatic organisms, including fish, is not indicated.*"

11.2. Assessment of the information provided

260 We have assessed this information and identified the following issue:

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

261 Annex IX, Section 9.1., Column 2 does not allow omitting the need to submit information on long-term toxicity to fish under Column 1. It must be understood as a trigger for providing further information on long-term toxicity to fish if the chemical safety assessment according to Annex I indicates the need (Decision of the Board of Appeal in case A-011-2018).

262 Your adaptation is therefore rejected.

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

264 In the comments to the draft decision you disagree with the request.

265 You consider that long-term toxicity on fish does not need to be investigated if no toxicity is observed in the requested long-term toxicity study on Daphnia (Request 10 of this decision). We understand that you are referring to column 2 of Annex IX, Section 9.1.

266 However, as explained above, Annex IX, Section 9.1., Column 2 is not a valid basis to omit the study.

267 You further claim that "*vertebrate testing is expressly forbidden for cosmetic ingredients under EU Regulation 1223/2009/EC*".

268 However, the EU Regulation 1223/2009/EC ('Cosmetics Regulation') does not restrict testing under REACH, if:

- this testing is required for environmental endpoints; or
- the substance is also registered for non-cosmetic uses.

269 First, the Cosmetics Regulation does not restrict testing under REACH, if the testing is required for environmental endpoints. ECHA notes that recital 5 of the Cosmetics Regulation explains that "*the environmental concerns that substances used in cosmetic products may raise are considered through the application of [the REACH Regulation], which enables the assessment of environmental safety in a cross-sectoral manner*". As indicated above, an OECD TG 210 study is required to fulfil the REACH standard information requirement for the long-term toxicity on fish.

270 Second, in your dossier, you report formulation and re-packaging uses as flavors and fragrances and cosmetics and personal care, the last one including also use as laboratory reagent. You also report industrial uses as pharmaceutical excepient and plasticiser. You further report consumer uses as flavor, fragrance, cosmetic consumer.

271 In summary, you do not report that the substances is exclusively used in cosmetics (i.e. product category (PC) 39 - Cosmetics, personal care products).

272 For all these reasons, the Cosmetics Regulation does not restrict the long-term toxicity test on fish for the Substance.

11.3. Study design and test specifications

273 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.).

References

The following documents may have been cited in the decision.

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

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

Guidance on data-sharing; ECHA (2017).

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

Read-across assessment framework (RAAF)

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

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

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

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

Appendix 2: Procedure

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

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

The compliance check was initiated on 20 January 2022.

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 deadline.

In the comments to the draft decision you have requested that the deadline allows for sequential performance of the *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study and the *in vitro* gene mutation study in mammalian cells. However, ECHA notes that the initially set deadline already takes into account the foreseen sequential testing.

Irrespectively, the deadline has been exceptionally extended by 12 months from the standard deadline granted by ECHA to take into account currently longer lead times in contract research organisations.

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

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

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

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

- the information specified in 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;

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

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

Appendix 4: Conducting and reporting new tests for REACH purposes

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

1.1. Test methods, GLP requirements and reporting

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

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

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

(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

Selection of the Test material(s)

The Test Material used to generate the new data must be selected taking into account the following:

- 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.

(1) Information on the Test Material needed in the updated dossier

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

This information is needed to assess whether the Test Material is relevant for the Substance.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[4].

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