~~Confidential~~

Helsinki, 17 May 2023

Addressees
Registrant(s) of JS_110-88-3 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
27/09/2010

Registered substance subject to this decision ("the Substance")
Substance name: 1,3,5-trioxane
EC number: 203-812-5

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 ***22 February 2028***.

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) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102;

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 IX of REACH

4. Extended one-generation reproductive toxicity study also requested below (triggered by Annex IX, Section 8.7.3.);

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

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

7. Simulation testing on ultimate degradation in surface water (Annex IX, Section 9.2.1.2.; test method: EU C.25./OECD TG 309) at a temperature of 12°C. Non-extractable residues (NER) must be quantified and a scientific justification of the selected extraction procedures and solvents must be provided.;

8. Identification of degradation products (Annex IX, 9.2.3.; test method: using test method: EU C.25./OECD TG 309

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

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

10. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) by oral route, in rats, specified as follows:
    - Ten weeks premating exposure duration for the parental (P0) generation;
    - The highest dose level in P0 animals must be determined based on clear evidence of an adverse effect on sexual function and fertility without severe suffering or deaths in P0 animals as specified further in Appendix 1, or follow the limit dose concept. The reporting of the study must provide the justification for the setting of the dose levels;
    - Cohort 1A and 1B (Reproductive toxicity);
    - Cohorts 2A and 2B (Developmental neurotoxicity);and
    - Cohort 3 (Developmental immunotoxicity).

    You must report the study performed according to the above specifications. Any expansion of the study must be scientifically justified.

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.

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

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

How to comply with your information requirements

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

You must follow the general requirements for testing and reporting new tests under REACH, see Appendix 4.

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of

Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

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

Authorised[1] under the authority of Mike Rasenberg, Director of Hazard Assessment

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

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

Appendix 1: Reasons for the decision

Contents

0. Reasons common to several requests

0.1. Assessment of weight of evidence adaptations

1 You have adapted the following standard information requirements by applying weight of evidence (WoE) adaptation(s) under Annex XI, Section 1.2:

- In vitro gene mutation in bacteria, (Annex VII, Section 8.4.1.);
- Pre-natal developmental toxicity study (Annex X, Section 8.7.2.);
- Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.).

2 Your weight of evidence approaches have deficiencies that are common to all information requirements under consideration and also deficiencies that are specific for these information requirements individually. The common deficiencies are set out here, while the specific ones are set out under the information requirement concerned in the Sections below.

3 Annex XI, Section 1.2. requires a reasoned justification which explains why information from several independent sources together enable a conclusion on the information requirement. This justification must explain how the individual sources of information are weighted and how all the sources of information together enable a conclusion on each of the key parameters foreseen by the study normally required for the information requirement.

4 According to the Guidance on IRs and CSA, Section R.4, the weight given to the sources of information is influenced by the reliability of the data, consistency of results, nature and severity of effects, and relevance and coverage of the information for the given information requirement. The reliability of the data is strongly linked to the method used to generate the information.

5 Therefore, aspects such as exposure duration, dose-levels used, and the statistical power of the study affect the weight of the individual sources of information.

6 Subsequently, relevance, reliability, coverage, consistency and results of these sources of information must be integrated in order to decide whether they together provide sufficient weight to conclude whether the Substance has or has not the (dangerous) property investigated by each of the key parameters foreseen by the study normally required for the information requirement. As part of the overall conclusion, an assessment of the residual uncertainty is also required.

7 You have not weighted the individual sources of information nor provided a clear and transparent assessment of to which extent the sources of information cover each of the key parameters foreseen by the study normally required for the information requirement.

8 Additional issues related to weight of evidence are addressed under the corresponding information requirements.

Reasons related to the information under Annex VII of REACH

1. In vitro gene mutation study in bacteria

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

1.1. Information provided in your registration dossier

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

(i) *In vitro* gene mutation study in bacteria (1988) with the Substance;

(ii) *In vitro* gene mutation study in bacteria (1980) with the Substance;

(iii) *In vitro* gene mutation study in bacteria (1984) with the Substance.

11 You justify the adaptation as follows: "No bacteriotoxicity and no mutagenicity was observed in an Ames test with TA1535, 1537, 98, 100 ([…] 1988). This standard plate and preincubation test was performed according to the current OECD-guideline 471 with test concentrations up to 5000 µg/plate, lacking the E. coli or TA 102 strains (detection of oxidizing or cross-linking mutagens)" […] "No contradictory results were reported in further Ames assays (e.g. […] 1984; […] 1988) which were not performed according to current guidelines".

1.2. Assessment of the information provided in your registration dossier

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

13 As explained under section 0.1, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

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

- 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).

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

16 The studies (i) to (iii) are described as *in vitro* gene mutation studies on bacteria.

17 However, the following is not according to the specifications of OECD TG 471:

a) studies (i) to (iii) were all performed with the *S. typhimurium* strains TA1535, 1537, TA98, TA100.
However, one of the strains *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101) is missing.

18 Taken together, none of the sources of information provide infromation on the strain S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101).

19 Therefore, it is not possible to conclude, based on any source of information alone or together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 471 study.

20 Based on the above, your adaptation is rejected and the information requirement is not fulfilled.

1.3. Specification of the study design

21 To fulfil the information requirement for the Substance, the *in vitro* gene mutation study in bacteria (OECD TG 471, 2020) should be performed using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102.

1.4. Assessment of information provided with your comments to the draft decision

22 In your comments you bring forward an OECD TG 471 study with the Substance which include five strains (Salmonella strains TA100, TA1535, TA97, TA98, TA102) and thus also one of the strains missing from your submitted Weight-of-evidence adaptation. The study addresses the issues identified above.

23 However, the information is currently not available in your registration dossier, the data gap remains. You should submit this information in an updated registration dossier by the deadline set in this decision.

2. Short-term toxicity testing on aquatic invertebrates

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

2.1. Information provided in your registration dossier

25 You have provided the following studies with the Substance:

(i) A study on acute toxicity to aquatic invertebrates (1989) according to test guideline EG-Richtlinie 79/831/EWG, C.2;

(ii) A study on acute toxicity to aquatic invertebrates (1984) according to test guideline "ASTM draft".

2.2. Assessment of the information provided in your registration dossier

2.2.1. The provided studies do not meet the specifications of the test guideline(s)

26 To fulfil the information requirement, a study must comply with OECD TG 202 and the requirements of OECD GD 23 if the substance is difficult to test (Article 13(3) of REACH). The Substance is volatile for the reasons explained in Section 2,3 below, therefore it is difficult to test and the following specifications must be met:

27 Technical specifications impacting the sensitivity/reliability of the test

a) young daphnids, aged less than 24 hours at the start of the test, are used;

28 Characterisation of exposure

b) analytical monitoring must be conducted. A reliable analytical method for the quantification of the test material in the test solutions with reported specificity, recovery efficiency, precision, limits of determination (i.e. detection and quantification) and working range must be available;
c) the effect values can only be based on nominal or measured initial concentration if the concentration of the test material has been satisfactorily maintained within 20 % of the nominal or measured initial concentration throughout the test (see also Guidance on IRs and CSA, Section R.7.8.4.1).

29 Reporting of the methodology and results

d) the number of immobilised daphnids is determined at 24 and 48 hours. Data are summarised in tabular form, showing for each treatment group and control, the number of daphnids used, and immobilisation at each observation;
e) the dissolved oxygen measured at least at the beginning and end of the test is reported.

30 Validity criteria

f) The following criteria must be met:
- the percentage of immobilised daphnids is ≤ 10% at the end of the test in the controls (including the solvent control, if applicable);
- the dissolved oxygen concentration is ≥ 3 mg/L in all test vessels at the end of the test.

31 In studies (i, ii) described as short-term toxicity studies on daphnids:

32 Technical specifications impacting the sensitivity/reliability of the test

a) the age of the daphnids at the start of the test was above 24 hours (study ii).

33 Characterisation of exposure

b) no analytical monitoring of exposure was conducted (study i and ii);
c) the reported effect values are based on nominal concentrations (study i and ii).

34 Reporting of the methodology and results

d) tabulated data on the number of immobilised daphnids after 24 and 48 hours for each treatment group and control are not reported (study i and ii);
e) the dissolved oxygen measured at least at the beginning and end of the test is not reported (study ii).

35 Validity criteria

f) you have not indicated whether the validity criteria have been fulfilled (study i and ii) and you have not provided information on the validity criteria, specifically on the dissolved oxygen (study ii) and number of immobilised daphnids in the controls (studies i and ii).

36 Based on the above,

- there are critical methodological deficiencies resulting in the rejection of the study results. More specifically, in study ii the applied daphnids were older than 24 hours, which can affect the sensitivity of the test. Furthermore, no analytical monitoring was conducted. The Substance is difficult to test, thus difficulties in achieving and maintaining stable test concentrations can be expected. You have based effect levels on nominal values but in the absence of analytical monitoring you have not provided confirmation that exposures were within ± 20 % of the nominal concentration (studies i, ii);
- the reporting of the study is not sufficient to conduct an independent assessment

of its reliability, because you did not provide relevant information on the dissolved oxygen (study ii) or tabulated data (studies i and ii);
- it is not possible to conduct an independent assessment of the study validity, because you did not provide information on the validity criteria of the studies(i,ii).

37 Therefore, the requirements of OECD TG 202 are not met and the information requirement is not fulfilled.

2.3. Study design and test specifications

38 You report in various sections of the dossier that the Substance has high potential to volatilise from water (e.g. IUCLID Section 5.2). In addition, you provide two values for Henry's Law constant. One of the provided values (0.57 Pa m^3/mol) indicates that the Substance is volatile.

39 Based on the information you have provided, the Substance is difficult to test due to volatility. OECD TG 202 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance.

40 In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations.

41 Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results.

42 If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 202.

43 In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solution.

2.4. Assessment of information provided with your comments to the draft decision

44 In the comments to the draft decision, you agree with the study deficiencies identified for the information in your registration dossier. You indicate to adapt this information requirement by using Annex XI Section 1.3 ((Q)SAR).

45 You provide:

a. A prediction using QSAR Toolbox (trend analysis)

46 We have assessed this information and consider it appropriate to fulfil this information requirement.

47 However, as the information is currently not available in your registration dossier, the data gap remains.

3. Growth inhibition study aquatic plants

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

3.1. Information provided

49 You have provided the following studies with the Substance:

(i) A growth inhibition study on aquatic plants (1990) according to test guideline EG-guideline 88/302/EWG;

(ii) A growth inhibition study on aquatic plants (1980) according to US EPA AAP:BT guidelines.

3.2. Assessment of the information provided

3.2.1. The provided studies do not meet the specifications of the test guideline(s)

50 To fulfil the information requirement, a study must comply with OECD TG 201 and the requirements of OECD GD 23 if the substance is difficult to test (Article 13(3) of REACH). The Substance is volatile for the reasons explained in Request 2, therefore it is difficult to test. Therefore, the following specifications must be met:

51 Technical specifications impacting the sensitivity/reliability of the test

a) for *Desmodesmus subspicatus* the initial cell density is 2-5 x 10^3 cells/mL;

52 Characterisation of exposure

b) analytical monitoring must be conducted. Alternatively, a justification why the analytical monitoring of exposure concentrations is not technically feasible must be provided;
c) the results can be based on nominal or measured initial concentration only if the concentration of the test material has been maintained within ±20 % of the nominal or measured initial concentration throughout the test.

53 Reporting of the methodology and results

d) the test design is reported (*e.g.*, number of replicates, applied controls);
e) the test conditions are reported (*e.g.*, test temperature, pH);
f) the results of algal biomass determined in each flask at least daily during the test period are reported in a tabular form.

54 Validity criteria

g) the following validity criteria must be met:
- exponential growth in the control cultures is observed over the entire duration of the test;
- at least 16-fold increase in biomass is observed in the control cultures by the end of the test;
- the mean coefficient of variation for section-by-section specific growth rates (days 0-1, 1-2 and 2-3, for 72-hour tests) in the control cultures is ≤ 35%;
- the coefficient of variation of average specific growth rates during the whole test period in replicate control cultures is ≤ 7% in tests with *Pseudokirchneriella subcapitata* or *Desmodesmus subspicatus*.;

55 In studies (i, ii) described as growth inhibition study on aquatic plants/algae:

56 Technical specifications impacting the sensitivity/reliability of the test

a) study (i) was conducted on *Desmodesmus subspicatus* and the initial cell density was 10 000 cells/mL.

57 Characterisation of exposure

b) no analytical monitoring of exposure was conducted (study i and ii);
c) the reported effect values are based on nominal concentrations (study i and ii).

58 Reporting of the methodology and results

d) on the test design, you have not specified information on replicates or controls (study i);
e) on the test conditions, you have not specified information on pH (studies i, ii) or test temperature (study ii);
f) tabulated data on the algal biomass determined daily for each treatment group and control are not reported (studies i, ii).

59 Validity criteria

g) you have not provided information on the validity criteria (studies i and ii).

60 Based on the above,

- there are critical methodological deficiencies resulting in the rejection of the study results. More specifically, you did not apply the correct initial cell density affecting the sensitivity of the test (study (i). Furthermore, no analytical monitoring was conducted. The Substance is difficult to test, thus difficulties in achieving and maintaining stable test concentrations can be expected. You have based effect levels on nominal values but in the absence of analytical monitoring you have not provided confirmation that exposures were within ± 20 % of the nominal concentration (studies i, ii).
- the reporting of the study is not sufficient to conduct an independent assessment of its reliability, because you did not provide all relevant information on test design and test conditions or tabulated data.
- it is not possible to conduct an independent assessment of the study validity, because you did not provide information on the validity criteria of the studies.

61 Therefore, the requirements of OECD TG 201 are not met and the information requirement is not fulfilled.

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

3.3. Study design and test specifications

63 OECD TG 201 specifies that, for difficult to test substances, OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design and test specifications' under Request 2.

Reasons related to the information under Annex IX of REACH

4. Extended one-generation reproductive toxicity study

64 An extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is an information requirement under Annex IX, Section 8.7.3., if the available repeated dose toxicity studies indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity.

65 Furthermore, column 2 defines the conditions under which the study design needs to be expanded.

4.1. Triggering of the information requirement

66 You claim that the dominant lethal assays (oral, inhal.) with an extended protocol, the ovarian function assay and the oral 90-day study provide sufficient evidence, that no effects on female and male reproductive function were observed without systemic toxicity.

67 Your dossier indicate(s) adverse effects on reproductive organs or tissues:

- In the Sub-acute toxicity study (1990) with the Substance testicular atrophy was observed;
- In the Dominant lethal assay (1984) focal necrosis of seminiferous epithelium, alteration of spermatogenesis and bilateral testicular lesions were observed. You state that *"Due to lacking data no conclusions concerning severity and incedence of these effects are possible*".
- In a study of Ovarian function (1990) increased oestrus cycle length was observed.

68 In addition, your dossier indicates other concerns in relation with reproductive toxicity: the post-natal developmental toxicity study (1990) with the Substance shows adverse effects on post-natal survival of the pups and neuro/behavioural development.

69 You dismiss this these triggers based on (maternal) systemic toxicity. However, you do not elaborate on why these findings are to be regarded as secondary to (maternal) systemic toxicity.

70 According to the Guidance on IRs and CSA, Appendix R.7.6–5 triggers should be considered relevant even if observed at the same dose level than the (other) systemic toxicity findings if it cannot be justified why the triggers are secondary to (other) systemic toxicity.

71 Therefore, the information requirement is triggered.

4.2. Information provided

72 You have adapted this information requirement by using weight of evidence.

73 The assessment of your adaptation is addressed under Request 10.

74 In the comments on the draft decision, you did not comment on this request.

4.3. Specification of the study design

75 The specifications of the study design are addressed under Request 10.

5. Long-term toxicity testing on aquatic invertebrates

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

5.1. Information provided

77 You have adapted this information requirement by using Column 2 of Annex IX, Section 9.1. To support the adaptation, you have provided following justification: "*In Annex IX of Regulation (EC) No 1907/2006, it is laid down that long-term toxicity to aquatic invertebrates shall be proposed by the registrant if the chemical safety assessment indicates the need to investigate further the effects on aquatic invertebrates. According to Annex I of this regulation, the chemical safety assessment triggers further action when the substance or the preparation meets the criteria for classification as dangerous according to Directive 67/548/EEC or Directive 1999/45/EC or is assessed to be a PBT or vPvB. The hazard assessment of 1,3,5 trioxane reveals neither a need to classify the substance as dangerous to the environment, nor is it a PBT or vPvB substance, nor are there any further indications that the substance may be hazardous to the environment. Therefore, long-term toxicity test in aquatic invertebrates is not provided.*"

5.2. Assessment of the information provided

78 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).

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

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

5.3. Study design and test specifications

81 OECD TG 211 specifies that, for difficult to test substances, OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design and test specifications' under Request 2.

6. Long-term toxicity testing on fish

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

6.1. Information provided in your registration dossier

83 You have adapted this information requirement by using Column 2 of Annex IX, Section 9.1. To support the adaptation, you have provided following justification: "*In Annex IX of Regulation (EC) No 1907/2006, it is laid down that long-term toxicity to fish shall be proposed by the registrant if the chemical safety assessment indicates the need to investigate further the effects on fish. According to Annex I of this regulation, the chemical safety assessment triggers further action when the substance or the preparation meets the criteria for classification as dangerous according to Directive 67/548/EEC or Directive*

1999/45/EC or is assessed to be a PBT or vPvB. The hazard assessment of 1,3,5 trioxane reveals neither a need to classify the substance as dangerous to the environment, nor is it a PBT or vPvB substance, nor are there any further indications that the substance may be hazardous to the environment. Therefore, and for reasons of animal welfare, a long-term toxicity test in fish is not provided."

6.2. Assessment of the information provided in your registration dossier

84 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).

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

6.3. Study design and test specifications

86 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.).

87 The OECD TG 210 specifies that, for difficult to test substances, the OECD GD 23 must be followed. As already explained above, the Substance is difficult to test.

88 Therefore, you must fulfil the requirements described in 'Study design and test specifications' under Request 2.

6.4. Assessment of information provided with your comments to the draft decision

89 In the comments to the draft decision, you indicate your intention to adapt this information requirement by means of weight of evidence according to Annex XI, Section 1.2, of the REACH Regulation.

90 You indicate that study on long-term toxicity to fish may not be necessary because you consider that sufficient information can be gained from the other aquatic toxicity studies to conclude on absence of long-term toxicity to fish.

91 However, while you have described your intentions, you have not provided in your comments any new scientific information addressing the information requirement. Therefore, the data gap remains. Should you decide to pursue the strategy presented in your comments, ECHA will assess its compliance in the follow-up to the dossier evaluation.

7. Simulation testing on ultimate degradation in surface water

92 Simulation testing on ultimate degradation in surface water is an information requirement under Annex IX to REACH (Section 9.2.1.2.).

7.1. Information provided in your registration dossier

93 You have adapted this information requirement and provided the following justification: "*Based on the log Koc (-0.416) 1,3,5-trioxane has low adsorptive properties and is considered to be mobile in sediments. In addition, the substance is easily removed from water by stripping and inherently biodegradable. Therefore, simulation studies on biodegradation in surface water and sediment are not provided*."

7.2. Assessment of information provided in your registration dossier

94 A registrant may only adapt this information requirement based on the general rules set out in Annex XI or the specific rules set out in Annex IX, Section 9.2.1.2., Column 2.

95 Your justification to omit this information does not refer to any legal ground for adaptation under Annex XI to REACH or Annex IX, Section 9.2.1.2., Column 2.

96 Therefore, you have not demonstrated that this information can be omitted and the information requirement is not fulfilled.

7.3. Study design and test specifications

97 Simulation degradation studies must include two types of investigations (Guidance on IRs and CSA, Section R.7.9.4.1.):

1) a degradation pathway study where transformation/degradation products are quantified and, if relevant, are identified, and

2) a kinetic study where the degradation rate constants (and degradation half-lives) of the parent substance and of relevant transformation/degradation products are experimentally determined.

98 You must perform the test, by following the pelagic test option with natural surface water containing approximately 15 mg dw/L of suspended solids (acceptable concentration between 10 and 20 mg dw/L) (Guidance on IRs and CSA, Section R.11.4.1.1.3.).

99 The required test temperature is 12°C, which corresponds to the average environmental temperature for the EU (Guidance on IRs and CSA, Table R.16-8) and is in line with the applicable test conditions of the OECD TG 309.

100 As specified in Guidance on IRs and CSA, Section R.7.9.4.1., the organic carbon (OC) concentration in surface water simulation tests is typically 2 to 3 orders of magnitude higher than the test material concentration and the formation of non-extractable residues (NERs) may be significant in surface water tests.

101 Therefore, non-extractable residues (NER) must be quantified. The reporting of results must include a scientific justification of the used extraction procedures and solvents. By default, total NER is regarded as non-degraded Substance.

102 However, if reasonably justified and analytically demonstrated a certain part of NER may be differentiated and quantified as irreversibly bound or as degraded to biogenic NER, such fractions could be regarded as removed when calculating the degradation half-life(s) (Guidance on IRs and CSA, Section R.11.4.1.1.3.).

103 Further recommendations may be found in the background note on options to address non-extractable residues in regulatory persistence assessment available on the ECHA website.

104 Relevant transformation/degradation products are at least those detected at ≥ 10% of the applied dose at any sampling time or those that are continuously increasing during the study even if their concentrations do not exceed 10% of the applied dose, as this may indicate persistence (OECD TG 309; Guidance on IRs and CSA, Section R.11.4.1.).

7.4. Assessment of information provided with your comments to the draft decision

105 In your comments to the draft decision, you agree with ECHA's assessment of the information in your registration dossier.

106 Together with your comments to the draft decision you provide: a QSAR prediction conducted with CATALOGIC 301 (v. 12.17 – October 2021). We have assessed this information and found the following issues:

107 Under Section 1.3., first paragraph, third indent of Annex XI to REACH, a study may be omitted if QSAR results are adequate for the purpose of classification and labelling and/or risk assessment, including PBT assessment under Annex I, Sections 0.6.1 and 4 and Annex XIII.

108 According to ECHA Guidance R.6 on QSARs and grouping of chemicals, a (Q)SAR model is associated with a defined endpoint, that can be measured and therefore modelled. The intent of this principle is to ensure transparency in the endpoint being predicted by a given model, since a given endpoint could be determined by different experimental protocols and under different experimental conditions.

109 It follows for an adaptation for the information from a Simulation study under Annex IX, Section 9.2.1 of REACH that the model would need to be associated with information allowing assessment of P/vP properties as set out under Annex XIII, Section 3.2. As explained in ECHA Guidance on IR and CSA, Chapter R.11, in principle, degradation simulation studies (as described in OECD TGs 307, 308 and 309) performed in appropriate environmental media and at environmentally realistic conditions are the only tests that can provide a definitive degradation half-life that can be compared directly to the persistence criteria as defined in REACH Annex XIII. As further explained in ECHA Guidance R.11.4.1.1.4., the use of QSAR and SAR predictions for identifying substances for persistence (P and vP) might be used only at the screening level.

110 In the comments to the draft decision you reported primary and ultimate half-lives predicted by Catalogic 301C Model (v.12.17). The Catalogic 301C Model (v.12.17) predicts degradation under OECD 301C test conditions (Catalogic model manual), i.e. under conditions applied in standard ready biodegradability test.

111 The information from the Catalogic 301C Model (v.12.17) however can only be regarded as screening information on P/vP properties (Annex XIII, Section 3.1.).

112 Therefore, Catalogic 301C Model (v.12.17) cannot be considered a valid adaptation to predict half-lives which are estimated as outcome of analysis of the rate of (aerobic and/or anaerobic) transformation of the test material in natural surface water under conditions of OECD TG 309 required at Annex IX Section 9.2.1.

113 Therefore the data gap will remain, even if the information would be provided in your registration dossier.

8. Identification of degradation products

114 Identification of degradation products is an information requirement under Annex IX to REACH (Section 9.2.3.).

8.1. Information provided in your registration dossier

115 You have not submitted any information for this requirement.

8.2. Assessment of information provided in your registration dossier

116 Therefore, the information requirement is not fulfilled.

8.3. Study design and test specifications

117 To determine the degradation rate of the Substance, the requested study according to OECD TG 309 (Request 7) must be conducted at 12°C and at a test concentration < 100 µg/L. However, to overcome potential analytical limitations with the identification and quantification of major transformation/degradation products, you may consider running a parallel test at higher temperature (but within the frame provided by the test guideline, e.g. 20°C) and at higher application rate (i.e. > 100 µg/L).

8.4. Assessment of information provided with your comments to the draft decision

118 In your comments to the draft decision, you provide:

a. A QSAR prediction conducted with CATALOGIC 301 (v. 12.17 – October 2021)

119 We have assessed this information and consider it appropriate to fulfil this information requirement.

120 However, as the information is currently not available in your registration dossier, the data gap remains.

Reasons related to the information under Annex X of REACH

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

121 A pre-natal developmental toxicity (PNDT) study (OECD TG 414) in a second species is an information requirement under Annex IX, Section 8.7.2., Column 2, depending on the outcome of the first PNDT study and other relevant available data.

9.1. Information provided

122 ECHA understands that you have adapted this information requirement by using weight of evidence based on the following experimental data:

(i) Pre-natal developmental toxicity study (1990) in rats with the Substance;

(ii) Post-natal developmental toxicity study (1984) in rats with the Substance;

(iii) Publication: Teratogenicity, fetal and placental of toxicity of 1,3,5-Trioxane administered to pregnant female rats, Sitarek Ket al. 1988.

9.2. Assessment of the information provided

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

124 As explained under section 0.1, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the normally required study.

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

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

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

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

129 We have assessed the information provided.

130 All information on the pre-natal developmental toxicity is provided in rats. No information has been provided in a second species.

131 Therefore, it is not possible to conclude whether the Substance has or has not hazardous properties in relation to PNDT in the second species.

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

133 In the comments on the draft decision, you did not comment on this request.

9.3. Specification of the study design

134 A PNDT study according to the test method OECD TG 414 should be performed in rat or rabbit as preferred species. The study in the first species was carried out by using a rodent species (rat).

135 Therefore, a PNDT study in a second species must be performed in the rabbit as preferred non-rodent species.

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

137 Based on the above, the study must be conducted in rabbits with oral administration of the Substance.

10. Extended one-generation reproductive toxicity study

138 An extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is an information requirement under Annex X, Section 8.7.3.

10.1. Information provided

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

(i) Study of oestrus cycle in rats (1990) with the Substance;

(ii) Oral Dominant lethal assay and fertility study (1984) with the Substance;

(iii) Inhalation Dominant lethal assay and fertility study (1984) with the Substance;

(iv) Sub-chronic toxicity study (90-days) with the Substance.

140 You justify the adaptation as follows: "[…] In summary the dominant lethal assays (oral, inhal.) with an extended protocol, the ovarian function assay and the oral 90 -day study provide sufficient evidence, that no effects on female and male reproductive function were observed without systemic toxicity. It is well known, that oestrus cycle length is an indicator for more subtle impairments of fertility (e.g. reduced pup numbers). Histopathological findings in the testes are inconsistent and were only described in the dominant lethal test at dose levels with signs of general systemic toxicity but not in the 28- and 90-day studies. In rodents histopathological lesions in the testes have been shown to be a more sensible parameter of toxicity to fertility than male fertility indeces."

10.2. Assessment of the information provided

141 As explained under section 0.1, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of

information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

142 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.7.3 at Annex X includes similar information that is produced by the OECD TG 443 design as specified in this decisions. At general level, it includes information on 1) sexual function and fertility, 2) toxicity to offspring, 3) systemic toxicity, and 4) if column 2 triggers are met, also information on sexual function and fertility of the offspring, toxicity to F2 offspring, developmental neurotoxicity and/or developmental immunotoxicity.

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

10.2.1. Aspect 1) - Sexual function and fertility

144 Sexual function and fertility on both sexes must include information on mating, fertility, gestation (length), maintenance of pregnancy (abortions, total resorptions), parturition, lactation, organ weights and histopathology of reproductive organs and tissues, oestrous cyclicity, sperm count, sperm analysis, hormone levels, litter sizes, nursing performance and other potential aspects of sexual function and fertility.

145 The source of information (i) provides relevant information on the sexual function and fertility; however, the information is limited to the length of the oestrous cycles following exposure to the Substance.

146 The sources of information (ii) and (iii) provide relevant information on the sexual function and fertility; however, the information is limited to the histopathology of male reproductive organs and male functional fertility following exposure to the Substance because the exposed males were mated with non-exposed females.

147 The source of information (iv) provides relevant information on the sexual function and fertility; however, the information is limited to histopathology of male and female reproductive organs.

148 In summary, the sources of information provide relevant information with regard to histopathology of reproductive organs and tissues, length of the oestrous cycles and male functional fertility.

149 However, the sources of information do not provide any relevant information on the effects of the Substance for the other elements of this aspect, i.e. maternal effects and pre- and peri- or post-natal development of the offspring.

150 Therefore, the data set does not provide reliable information on all elements of aspect 1).

10.2.2. Aspect 2) - Toxicity to offspring

151 Toxicity to offspring must cover information on deaths before, during or after birth, growth, external malformations, clinical signs, sexual maturity, oestrous cyclicity, organ weights and histopathology of reproductive organs and tissues in adulthood and other potential aspects of toxicity to offspring.

152 As explained for aspect 1), none of the sources of information have investigated pre- and peri- or post-natal developmental toxicity in offspring with exposure starting in utero and continuing up to adulthood.

153 Consequently, the sources of information do not provide any relevant information with regard to aspect 2).

10.2.3. Aspect 3) - Systemic toxicity

154 Systemic toxicity must include information on clinical signs, survival, body weights, food consumption, haematology (full-scale), clinical chemistry (full-scale), organ weights and histopathology of non-reproductive organs and tissues (full-scale) and other potential aspects of systemic toxicity in the parental P and F1 generation up to adulthood.

155 The source of information (i) provides relevant information on the above-mentioned systemic toxicity in females; however, the information is limited to survival, body weights and clinical signs.

156 The sources of information (ii) and (iii) provide relevant information on the above-mentioned systemic toxicity in males; however, the information is limited to survival, body weights clinical signs, and relative organ weights for liver and kidney.

157 The source of information (iv) provides relevant information on the above-mentioned systemic toxicity; however, the information is limited to adult non-pregnant animals.

158 None of the sources of information evaluate systemic toxicity in offspring (F1 generation) with exposure starting in utero and continuing up to adulthood.

159 Consequently, the sources of information do not provide any relevant information with regard to aspect 3) for the F1 generation.

160 In summary, the sources of information provide relevant and reliable information with regard to systemic toxicity for adult non-pregnant animals following post-natal exposure.

161 However, no information is provided on systemic toxicity for the F1 generation following exposure starting in utero and continuing up to adulthood.

162 Therefore, the data set does not provide reliable information on all elements of aspect 3).

10.2.4. Aspect 4) - Information on triggered investigations

163 If column 2 triggers are met, information on sexual function and fertility of the offspring, developmental toxicity in F2 generation, developmental neurotoxicity and/or developmental immunotoxicity is relevant. Sexual function and fertility of the offspring includes the same key investigations than in P0 animals (above section "sexual function and fertility") and developmental toxicity in F2 generation includes investigations up to weaning similar to F1 generation. Developmental neurotoxicity includes assessment of neurotoxicity (auditory startle test, functional observation battery, motor activity), information on neurohistopathology and other potential aspects of developmental neurotoxicity. Developmental immunotoxicity includes splenic lymphocyte subpopulation analysis, T-cell dependant antibody response assay, assessment of immune organs and other potential aspects of developmental immunotoxicity.

164 The following key elements are not addressed:

165 Information on developmental neurotoxicity, the criteria for a particular concern relating to developmental neurotoxicity are met because signs of neurotoxicity are observed in the Post-natal developmental toxicity study (1990). The evidence meeting the criteria is explained under the specifications for the study design, "Cohorts 2A and 2B" requirement below.

166 Information on developmental immunotoxicity, the criteria for a particular concern relating to developmental immunotoxicity are met because signs of immunotoxicity are observed in the sub-acute and sub-chronic toxicity studies. The evidence meeting the criteria is explained under the specifications for the study design, "Cohort 3" requirement below.

10.3. Conclusion on the weight of evidence

167 Taken together, the sources of information provide relevant information only on some elements of aspect 1 (sexual function and fertility) and aspect 3 (systemic toxicity). However, none of the sources of information have investigated effects occurring during pregnancy in exposed females or pre-, peri- and post-natal developmental toxicity (aspect 2 and 4) as expected to be obtained from the OECD TG 443.

168 Therefore, it is not possible to conclude, based on any source of information alone or together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 443 study.

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

170 In the comments on the draft decision, you agreed with the request.

10.4. Specification of the study design

10.4.1. Species and route selection

171 A study according to the test method OECD TG 443 must be performed in rats with oral administration of the Substance (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

10.4.2. Pre-mating exposure duration

172 The length of pre-mating exposure period must be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

173 Ten weeks pre-mating exposure duration is required to obtain results adequate for classification and labelling and/or risk assessment. There is no substance specific information in the dossier supporting shorter premating exposure duration (Guidance on IRs and CSA, Section R.7.6.).

174 Therefore, the requested pre-mating exposure duration is ten weeks.

10.4.3. Dose-level setting

175 The aim of the requested test must be to demonstrate whether the classification criteria of the most severe hazard category for sexual function and fertility (Repr. 1B; H360F) and developmental toxicity (Repr. 1B; H360D) under the CLP Regulation apply for the Substance (OECD TG 443, paragraph 22; OECD GD 151, paragraph 28; Annex I Section 1.0.1. of REACH and Recital 7, Regulation 2015/282), and whether the Substance meets the criteria for a Substance of very high concern regarding endocrine disruption according to Art.57(f) of REACH as well as supporting the identification of appropriate risk management measures in the chemical safety assessment.

176 To investigate the properties of the Substance for these purposes, the highest dose level must be set on the basis of clear evidence of an adverse effect on sexual function and fertility, but no deaths (i.e., no more than 10% mortality; Section 3.7.2.4.4 of Annex I to the CLP Regulation) or severe suffering such as persistent pain and distress (OECD GD 19, paragraph 18) in the P0 animals.

177 In case there are no clear evidence of an adverse effect on sexual function and fertility, the limit dose of at least 1000 mg/kg bw/day or the highest possible dose level not causing severe suffering or deaths in P0 must be used as the highest dose level. A descending sequence of dose levels should be selected to demonstrate any dose-related effect and aiming to establish the lowest dose level as a NOAEL.

178 In summary: Unless limited by the physical/chemical nature of the Substance, the highest dose level in P0 animals must be as follows:

(1) in case of clear evidence of an adverse effect on sexual function and fertility without severe suffering or deaths in P0 animals, the highest dose level in P0 animals must be determined based on such clear evidence, or
(2) in the absence of such clear evidence, the highest dose level in P0 animals must be set to be the highest possible dose not causing severe suffering or death, or
(3) if there is such clear evidence but the highest dose level set on that basis would cause severe suffering or death, the highest dose level in P0 animals must be set to be the highest possible dose not causing severe suffering or death, or
(4) the highest dose level in P0 animals must follow the limit dose concept.

179 You have to provide a justification with your study results demonstrating that the dose level selection meets the conditions described above.

180 Numerical results (i.e. incidences and magnitudes) and description of the severity of effects at all dose levels from the dose range-finding study/ies must be reported to facilitate the assessment of the dose level section and interpretation of the results of the main study.

10.4.4. Cohorts 1A and 1B

181 Cohorts 1A and 1B belong to the basic study design and must be included.

10.4.4.1. Histopathological investigations in Cohorts 1A and 1B

182 In addition to histopathological investigations of cohorts 1A, organs and tissues of Cohort 1B animals processed to block stage, including those of identified target organs, must be subjected to histopathological investigations (according to OECD TG 443, paragraph 67 and 72) if:

- the results from Cohort 1A are equivocal,
- the test substance is a suspected reproductive toxicant or
- the test substance is a suspected endocrine toxicant.

10.4.4.2. Splenic lymphocyte subpopulation analysis

183 Splenic lymphocyte subpopulation analysis must be conducted in Cohort 1A (OECD TG 443, paragraph 66; OECD GD 151, Annex Table 1.3).

10.4.4.3. Investigations of sexual maturation

184 To improve the ability to detect rare or low-incidence effects, all F1 animals must be maintained until sexual maturation to ensure that sufficient animals (3/sex/litter/dose) are available for evaluation of balano-preputial separation or vaginal patency (OECD GD 151, paragraph 12 in conjunction with OECD TG 443, paragraph 47). For statistical analyses, data on sexual maturation from all evaluated animals/sex/dose must be combined to maximise the statistical power of the study.

10.4.5. Cohorts 2A and 2B

185 The developmental neurotoxicity Cohorts 2A and 2B must be conducted in case of a particular concern on (developmental) neurotoxicity.

186 Existing information on the Substance itself derived from the pre-natal developmental toxicity study (1990) show effects on neuro/behavioural development in the post-natal segment of the study. Statistically significant decrease in exploratory motor activity was reported for the female offspring of the mid dose group (8 and 14 weeks old; ca. 70% of control). Active avoidance acquisition also was statistically significantly decreased in this group (5-month old male and female offspring). These two findings suggest dysfunction of the central nervous system.

187 For the reasons stated above, the developmental neurotoxicity Cohorts 2A and 2B must be conducted.

10.4.6. Cohort 3

188 The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity.

189 Existing information on the Substance itself derived from the available sub-acute and sub-chronic toxicity studies show evidence of significantly reduced spleen weight in males (approx. -40%; in both studies) and a significant decrease in leukocyte count in both males and females (-40%; sub-acute study only). The effects on leukocytes occurred at doses not tested in the sub-chronic study.

190 According to ECHA Guidance on IRs and CSA, Appendix R.7.6–2, the combination of at least two (statistically significant and) biologically meaningful changes in haematology and/or organ weight associated with immunotoxicity, e.g. reduced leucocyte count in combination with reduced spleen weight, constitutes particular concern on (developmental) immunotoxicity.

191 For the reasons stated above, the developmental immunotoxicity Cohort 3 must be conducted.

10.5. Further expansion of the study design

192 The conditions to include the extension of Cohort 1B are currently not met. However, you may expand the study by including the extension of Cohort 1B if relevant information becomes available from other studies or during conduct of this study. Inclusion is justified if the available information meets the criteria and conditions which are described in Annex X, Section 8.7.3., Column 2. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in Guidance on IRs & CSA, Section R.7.6.

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 02 November 2021.

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

ECHA took into account your comments and did not amend the request(s).

In your comments on the draft decision, you requested an extension of the deadline to provide information from 42 to 54 months from the date of adoption of the decision.

ECHA considered your comments and extended the deadline to 54 months 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;
- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.

Appendix 4: Conducting and reporting new tests for REACH purposes

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

1.1. Test methods, GLP requirements and reporting

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

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

(3) Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[2].

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

1.2. Test material

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

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

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

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

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

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