

Helsinki, 12 October 2023

**Addressees**

Registrant(s) of 271-235-6 Joint Subm. EM Lead as listed in Appendix 3 of this decision

**Date of submission of the dossier subject to this decision**

18/03/2022

**Registered substance subject to this decision ("the Substance")**

Substance name: Alcohols, C11-14-iso-, C13-rich

EC/List number: 271-235-6

**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 **19 July 2027**.

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

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

1. Justification for an adaptation of a Screening for reproductive/developmental toxicity based on the results of the Extended one-generation reproductive toxicity study requested below (Annex VIII, Section 8.7.1.)

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

2. 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)
3. Extended one-generation reproductive toxicity study also requested below (triggered by Annex IX, Section 8.7.3., column 1)

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

4. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: OECD TG 414) by oral route, in a second species (rabbit or rat)
5. 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 pre-mating 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 (Reproductive toxicity);
  - Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation which shall be followed to

- weaning;  
– Cohorts 2A and 2B (Developmental neurotoxicity).

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<sup>1</sup> under the authority of Mike Rasenberg, Director of Hazard Assessment

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<sup>1</sup> 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

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## 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:
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
  - In addition, you have supported other adaptations with data from substances other than the Substance for these standard information requirements: Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
  - Pre-natal developmental toxicity study in a second species (Annex X, Section 8.7.2.)
  - Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)
- 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).

#### 0.1.1. Predictions for toxicological properties

- 5 You provide a read-across justification document in IUCLID Section 13.
- 6 You predict the properties of the Substance from information obtained from the following source substance(s):
- Isoundecan-1-ol / Branched alcohols, C10-12, C11 rich EC 271-360-6, CAS 68551-08-6
- 7 You provide the following reasoning for the prediction of toxicological properties: "similar chemical structure, manufacturing process, physicochemical properties and the same type of biological effects or trends among each of these substances".
- 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:

##### 0.1.1.1. Missing supporting information to compare properties of the substances

- 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 Supporting information must include bridging studies to compare properties of the Substance and source substances.
- 12 As indicated above, your read-across hypothesis is based on the assumption that the structurally similar substances cause the same type of effect(s) or trend. 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 or trend. Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and of the source substance(s).
- 13 For the source substances, you provide in your dossier the studies used in the prediction in the registration dossier which have deficiencies as identified in sections 1, 2, 3 and 5 below. With your comments, you provide two sub-chronic toxicity studies (2018, 2020) with the source substance Exxal 11 and the Substance. Apart from those studies, your read-across justification or the registration dossier does not include
- any robust study summaries or descriptions of data for the Substance,
  - that would confirm that it causes the same type of effects as the source substances, for information requirements (endpoints) that you adapt via grouping and read-across, in particular those for toxicity to reproduction and development.
- 14 You have not indicated an intention to generate further supporting information that would be relevant to the adapted information requirement, e.g. OECD TG 421/422 studies.
- 15 In the absence of such information, you have not established that the Substance and the source substance(s) are likely to have similar properties. Therefore you have not provided sufficient supporting information to scientifically justify the read-across.

*0.1.2. Comments to the draft decision*

- 16 In your comments to the draft decision you propose that your updated read-across hypothesis (attachment 2 to your comments) is valid based on data generated since 2018; specifically, that biotransformation to a common set of substances occurs, with predictable qualitative and quantitative trends in toxicological outcomes.
- 17 As data is still being generated for members of the category you explain that you maintain the analogue-based read-across hypothesis between isoundecanol and isotridecanol, and have provided additional information to clarify the specific points made in the draft compliance check letter. You have provided the following information:
- Basic toxicokinetics, Ex Vivo (2019), liver microsomal activities on Exxal 13 / isotridecanol.
  - Basic toxicokinetics, Ex Vivo (2019), liver microsomal activities on Exxal 11 / isoundecanol.
  - Repeated dose toxicity: oral (2018). 90 day study on Exxal 13 / isotridecanol.
  - Repeated dose toxicity: oral (2020). 90 day study on Exxal 11 / isoundecanol (read across source).
- 18 In addition attachment 8 of your comments contains an explanation on how this new information contributes to validate your read-across approach.

- 19 ECHA agrees that the provided information can be used as bridging information for repeated dose toxicity. However, there is still no information available with the Substance to compare with the source substance/s important reproductive properties such as reproductive performance and pre- or postnatal development. In the absence of such information, you have not established that the Substance and the source substance(s) are likely to have similar properties for the endpoints relevant to this decision. Therefore you have not provided sufficient supporting information to scientifically justify the read-across, and you remain responsible for complying with this decision by the set deadline.

*0.1.3. Conclusion on the read-across approach*

- 20 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 approach under Annex XI, Section 1.5. is rejected.

**Reasons related to the information under Annex VIII of REACH****1. Justification for an adaptation of a Screening for reproductive/developmental toxicity based on the results of the Extended one-generation reproductive toxicity study**

21 A screening for reproductive/developmental toxicity (OECD 421 or OECD 422) is an information requirement under Annex VIII, Section 8.7.1. This information may take the form of a study record or a valid adaptation in accordance with either a specific adaptation rule under Annex VIII, Section 8.7.1., Column 2 or a general adaptation rule under Annex XI, Section 8.7.1., Column 2.

**1.1. Information provided**

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

(i) sub-chronic toxicity study (OECD TG 408) 2018 with the Substance

(ii) pre-natal developmental toxicity study in rats (OECD TG 414) 2020 with the source substance Branched alcohols C10-12, C11 rich (EC 271-360-6)

23 To support your adaptation, you have also provided the following statements:

(iii) *"At this time it is expected that isotridecanol will not be a reproductive toxicant. A one-generation study in rats (██████, 1992) was performed with the analog substance 1-dodecanol (CAS RN 112-53-8) using the Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test protocol. Male and female rats were administered 1-dodecanol orally via the feed at doses of 100, 500 and 2000 mg/kg/day for a period of 14 days. No effects were seen on reproductive or developmental parameters up to doses of 2000 mg/kg/day. 1-Dodecanol at the dose administered had no influence on body weight, weight gain, food consumption and reproductive efficiency in the parental generation. Pregnancy rates were not statistically altered and there were no differences in the lengths of the gestation periods. No organ toxicity was observed in the females, and there was no effect on the number of pups per litter, weight, sex ratio, or mortality rate from Days 1 to 5 after birth.*

(iv) *Data collected from analogue substances used for read-across in subchronic 90- day studies (Isooctanol, 68526-83-0;*

(v) *Isotridecanol, 68526-86-3) provide evidence of lack of effects on spermatogenesis parameters, and provide no indication of neurotoxicity or immunotoxicity based on clinical chemistry parameters and organ weights. If the decision is made to run an EOGRTS study, this data would allow justification for a shortened pre-mating dosing period (shortened from standard 10-week window to a 2-week dosing period) as well as a lack of justification for including cohorts 2A and 2B.*

(vi) *We will also be evaluating PNDR information to inform justification for this endpoint. Further test data that will be collected as part of the integrated*



*testing strategy as agreed upon by ECHA (decision number CCH-D-2114342397-45-01/F) are outlined in the assessment reports and will be used to inform the justification for this endpoint."*

- 24 You have provided several pieces of information, of which the experimental studies were provided in a IUCLID section other than for the information requirement.

*1.2. Assessment of the information provided*

- 25 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.
- 26 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.
- 27 According to ECHA Guidance R.4, a weight of evidence adaptation involves an assessment of the relative values/weights of the different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance and coverage of the information for the given regulatory information requirement. Subsequently, relevance, reliability, coverage, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude on the corresponding information requirement.
- 28 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.
- 29 You have not included a justification for your weight of evidence adaptation, 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.
- 30 In addition, Annex XI, Section 1.2 requires studies used as sources of information to be provided in the form of robust study summaries.
- 31 The information provided in statements iii. and iv. cannot be taken into account in the assessment of your weight of evidence adaptation because the studies they refer to are not actual sources of information in the form of a robust study summary, as required under Article 10(a)(vi) and (vii). Instead they are limited to a short description of the results.
- 32 Further, future data such as in statement vi., cannot be taken into account.
- 33 In spite of these critical deficiencies, 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.
- 34 Relevant information that can be used to support weight of evidence adaptation for the information requirement of Annex VIII, Section 8.7.1 includes similar information that is produced by the OECD TG 421/422 with a design as specified in this decision. OECD TG 421/422 requires the study to investigate the following key elements: A) sexual function and fertility, B) toxicity to offspring, and C) systemic toxicity.

*A) Sexual function and fertility*

- 35 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, litter sizes, nursing performance and other potential aspects of sexual function and fertility.
- 36 The studies i. and ii. you submitted provide limited information on sexual function and fertility. More specifically, they provide information only on oestrous cyclicity and sperm parameters and they do not inform on mating performance and gestation length of pre-exposed animals, parturition, lactation, litter sizes, nursing performance and other potential aspects of sexual function and fertility. The study ii. gives information on maintenance of pregnancy (abortions, total resorptions) limited to not pre-exposed parental animals. Statement iii. gives information on these parameters. Statements iv. and v. do not provide any such information.
- 37 The reliability of study ii. and statement iii. is significantly affected by the deficiencies identified and explained in the Section on Reasons common to several requests, and cannot contribute to the conclusion on this key element.

*B) Toxicity to offspring*

- 38 Information on pre- and perinatal developmental toxicity is reflected by litter sizes, postimplantation loss (resorptions and dead fetuses), stillborns, and external malformations; postnatal developmental toxicity is reflected by survival, clinical signs and body weights of the pups (or litters), and other potential aspects related to pre-, peri- and postnatal developmental toxicity observed up to postnatal day 13.
- 39 Study ii. provides information on pre-natal developmental toxicity to offspring. None of the studies (i-ii) provide information on developmental toxicity observed up to postnatal day 13. Statement iii. provides information on the requirement up to postnatal day 5. Statements iv. and v. do not provide such information.
- 40 The reliability of study ii. and statement iii. is significantly affected by the deficiencies identified and explained in the Section on Reasons common to several requests, and cannot contribute to the conclusion on this key element.

*C) Systemic toxicity*

- 41 Information on systemic toxicity include clinical signs, survival, body weights, food consumption, haematology, clinical chemistry, organ weights and histopathology of non-reproductive organs and other potential aspects of systemic toxicity in the parental generation up to postnatal day 13.
- 42 Study i. provides relevant information on systemic toxicity, whereas study ii. provides only limited information on systemic toxicity. Statement iii. provides limited information and does not detail clinical signs and functional observations, organ toxicity in males, gross- and histopathology, and organ weights. Statements iv. and v. do provide such information.
- 43 The reliability of study ii. and statements iii. and v. is significantly affected by the deficiencies identified and explained in the Section on Reasons common to several requests. There is no robust study summary available for the study referred to in statement iv. and ECHA cannot independently assess the reliability of this information. Therefore, these pieces of information cannot contribute to the conclusion on this key element.
- 44 Your claim of no relevance of the thyroid toxicity is addressed in section 3.1.

*1.3. Comments on the draft decision*

- 45 In your comments to the draft decision you do not agree to perform the requested study. Instead, you propose to adapt the information requirement for this endpoint according to

Annex VIII, Section 8.7.1, Column 2, specifying that the Substance (isotridecanol) is assessed by read-across to a PNDT (completed) on a source substance (isoundecanol).

- 46 As your proposed strategy relies on a read-across approach that has not yet been fully described and justified, as well as on data which is yet to be generated (including bridging information), no conclusion on the compliance of the proposed adaptation can be made. You remain responsible for complying with this decision by the set deadline.

*1.4. Conclusion*

- 47 Taken together, the sources of information, as indicated above, provide information on reproductive and systemic toxicity, but essential parts of information of the hazardous property is lacking, including information on: mating, gestation (length), maintenance of pregnancy (abortions, total resorptions), parturition, lactation, litter sizes, nursing performance and other potential aspects of sexual function and fertility; and toxicity to offspring. Furthermore, the reliability of all pieces of information and statements except one is significantly reduced.
- 48 Therefore, it is not possible to conclude based on any source of information alone or considered together, whether your Substance has the particular (hazardous) properties.
- 49 On this basis, the information requirement is not fulfilled.

*1.5. Specification of the study design*

- 50 The present decision requests the registrants concerned to generate and submit a reliable extended one-generation toxicity study (see request 3). According to Annex VIII, Section 8.7.1., Column 2 and to prevent unnecessary animal testing, a screening for reproductive-developmental toxicity study does not therefore need to be conducted.
- 51 Because you still must comply with the information requirement in Annex VIII, Section 8.7.1., you are requested to submit a justification for the adaptation provided in Column 2 of that provision.

**Reasons related to the information under Annex IX of REACH****2. Pre-natal developmental toxicity study in one species**

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

*2.1. Information provided*

53 You have adapted this information requirement by using Annex XI, Section 1.5 grouping and read-across. To support the adaptation, you have provided following information:

- i. Developmental toxicity study (OECD TG 414), 2020, with the source substance Exxal 11 / Isoundecan-1-ol / Branched alcohols, C10-12, C11 rich (EC 271-360-6)

*2.2. Assessment of the information provided*

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

55 As explained in Section 0.1., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected.

*2.3. Comments on the draft decision*

56 In your comments to the draft decision you do not agree to perform the requested study. Instead, you request ECHA to reconsider the rejection of the read-across hypothesis based on clarifications provided with your comments that in your views demonstrate toxicological similarity between isotridecanol (Substance) and isoundecanol (source). ECHA has addressed this comment in Section 0.

57 As your proposed strategy relies on a read-across approach that has not yet been fully described and justified, as well as on data which is yet to be generated (including bridging information), no conclusion on the compliance of the proposed adaptation can be made. You remain responsible for complying with this decision by the set deadline.

*2.4. Specification of the study design*

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

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

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

**3. Extended one-generation reproductive toxicity study**

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

### 3.1. Triggering of the information requirement

62 Your dossier contains a sub-chronic toxicity study with the Substance (OECD TG 408, 2018), which indicates concerns in relation with reproductive toxicity. Specifically, the study shows toxicity to thyroid:

- higher thyroid/parathyroid gland weights were observed in all treated groups.

63 Higher thyroid/parathyroid gland weights correlated histologically with follicular cell hypertrophy/hyperplasia in the thyroid gland in a dose-dependent manner. Furthermore, you have provided a document in Section 13 of the technical dossier where you also present thyroid hormone (T3, T4, TSH) values for the Substance, measured after 90 days of exposure for one dose level (1000 mg/kg bw/day). The results show

- decreased T3 in females,
- decreased T4 in both sexes, and
- increased TSH in both sexes.

64 According to OECD GD 150<sup>2</sup>, the above-mentioned effects are indicative of thyroid disruption.

65 You also provide justification documents in Sections 7.8.1 and 13 of the technical dossier:

- I) Human relevance thyroid subchronic
- II) Analogue-based read-across approach Oxo alcohols

66 In the study report you consider these thyroid-related changes to be non-adverse, representing an adaptive change secondary to test substance-related hepatic enzyme induction. In both justification documents I and II, you also question the human relevance of these findings, based on '*quantitative differences in thyroid homeostasis and function between rats and humans*'. We have identified the following shortcomings in your reasoning:

#### 3.1.1. Not substance specific data as required by guidance

67 According to the ECHA/EFSA Guidance for the identification of endocrine disruptors<sup>3</sup>, 'In the absence of substance-specific data which provide proof of the contrary, humans and rodents are considered to be equally sensitive to thyroid-disruption (including cases where liver enzyme induction is responsible for increased TH clearance).'

68 You have not provided substance-specific data which would provide proof that the observed thyroid-related effects would not be relevant to humans. At present, information from analogue substances is rejected due to the reasons explained in Section 0.1.

69 Therefore your claim that the observed effects would not be relevant to humans is unsubstantiated.

#### 3.1.2. Relevance of carcinogenic MoA covers some but not all aspects of the ED MoA

70 In justification document I, you argue that the thyroid effects are to be considered secondary to the liver enzyme induction. You postulate a mode of action (MoA) which starts with hepatocellular hypertrophy, which through increased clearance of thyroid hormones

<sup>2</sup> <https://www.oecd-ilibrary.org/docserver/9789264304741-en.pdf?expires=1590588065&id=id&accname=guest&checksum=E35A4458AB8BAC1C4A0145EFCCDE304B>

<sup>3</sup> <https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5311>

(TH) by the liver results in lower T3/T4, leading to increased production of TSH and eventually to follicular cell hypertrophy/hyperplasia and increased thyroid weights. You refer to literature<sup>4,5,6,7</sup> comparing hepatic clearance of T3 and T4, half-life of T4, and TSH levels between rats and humans. To further support the MoA, you refer to measurements of liver enzymes for the Substance ('Exxal 13') and the analogue substance Exxal 11 (EC No. 271-360-6; tabular data provided in justification document II/IUCLID section 13), concluding that the the results of liver enzyme induction between Exxal 11 and Exxal 13 are highly concordant.

- 71 Based on the above, you argue that the thyroid-related changes indicate a non-adverse adaptive set of changes that are not human relevant, but rather a reflection of quantitative differences in thyroid homeostasis and function between rats and humans.
- 72 Firstly, ECHA notes that the effects on the thyroid outlined in your proposed MoA are adverse in the rat; they ultimately result in thyroid cancer<sup>5</sup>.
- 73 Secondly, the non-human relevance argumentation applies to the ultimate adverse outcome, i.e. carcinogenicity<sup>5</sup>. Following sustained substance-induced reduced TH levels (irrespective of cause), and a compensatory increase in THS levels, rats ultimately develop thyroid cancer. However, this adverse effect can be considered not relevant to humans if it can be demonstrated that it is caused by liver enzyme induction due to quantitative differences in thyroid homeostasis and function between rats and humans<sup>5</sup>.
- 74 ECHA wants to emphasise that the hypothalamic–pituitary–thyroid (HPT) axis is highly conserved across evolution in vertebrates. The regulation of serum THs levels and of TH action in various tissues involves a complex interplay of physiological processes. The thyroid function depends on iodine uptake, TH synthesis and storage in the thyroid gland, stimulated release of hormone into and transport through the circulation, hypothalamic and pituitary control of TH synthesis, cellular TH transport, tissue-specific TH de-iodination and degradation of THs by catabolic hepatic enzymes. Interference in any of these processes can adversely affect the thyroid function, resulting in reduced TH levels and adverse outcomes. Which adverse outcome(s) are expected depends on the lifestage exposed.
- 75 You argue that the observed effects on the thyroid should be considered non-relevant to humans. However, such a conclusion is currently not supported by the data that you have provided. The assumption that thyroid effects observed in rat are not human relevant must be substantiated using, for instance, evidence of species specific differences in metabolic capacity, and based on weight of evidence<sup>8</sup>. To investigate whether liver enzyme induction is responsible for the effects seen on TH levels and thyroid histopathology, as well as whether the effect is or not likely to be human relevant, the following three pieces of information are needed (see Appendix A of the ECHA/EFSA Guidance<sup>9</sup>, for details):
1. Results of analysis of serum/plasma samples for TSH, T3 and T4 in the existing repeated dose toxicity studies.
  2. Comparative studies of enzyme activity induced by the test substance in liver *in vitro* systems should be measured in both the relevant test species (i.e. rats) and humans.

<sup>4</sup> Dohler et al. (1979). The rat as a model for the study of drug effects on thyroid function: Consideration of methodological problems. *Pharmacol. Ther.* 5:305-318

<sup>5</sup> Meek ME et al (2003). A framework for human relevance analysis of information on carcinogenic modes of action. *Crit Rev Toxicol.* 33(6):591-653

<sup>6</sup> McClain RM et al (1992). Thyroid gland neoplasia: Non-genotoxic mechanisms. *Toxicol. Lett.* 64/65:397-408.

<sup>7</sup> Liu et al (1995). Alteration of thyroid hormone homeostasis by UDP-glucuronosyltransferase inducers in rats: A dose-response study. *J. Pharmacol. Exp. Ther.* 273:977-985.

<sup>8</sup> Boobis AR et al. (2008) IPCS framework for analyzing the relevance of a noncancer mode of action for humans. *Crit Rev Toxicol* 38(2):87-96.

<sup>9</sup> <https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5311>



3. The presence of other possible thyroid-disrupting modes of action such as interference with TH synthesis should also be excluded, e.g. by evaluating *in vitro* the potential for inhibition of the sodium–iodide symporter and thyroid peroxidase.

76 ECHA emphasises that even though the ECHA/EFSA Guidance<sup>4</sup> was developed for hazard identification for endocrine-disrupting properties for other regulatory purposes, the same scientific principles are also relevant under the REACH Regulation.

77 Regarding point 1., ECHA notes that the existing studies have investigated TSH, T3 and T4 levels in rats.

78 Regarding point 2., the data indicate liver enzyme induction in the rat from the Substance and the source substance Exxal 11. In order to assess relevance to humans, a qualitative and quantitative comparison of liver enzyme induction between rats and humans must be provided.

79 Regarding point 3., you have not ruled out any of the other possible MoA(s). To support non-relevance it must be demonstrated that the liver enzyme induction is the primary MoA causing the effects on the thyroid.

80 Based on the above, you have not demonstrated that the thyroid effects would not be relevant to humans, and they do not dismiss the indications of one or more modes of action related to endocrine disruption, i.e. thyroid disruption. Furthermore, the EOGRTS is designed to investigate potential reproductive and developmental (neurotoxicological) effects that may occur as a result of pre- and postnatal chemical exposure. There is no basis to dismiss potential adverse effects as non-human relevant before such effects have been identified. This is because any conclusion on non-human relevance must consider the nature and the severity of the effects as well as the life-stage of the organism exposed.

81 In conclusion, the findings observed in rats are relevant to the model (test system) and thus require further investigation for identifying potential hazards to reproduction.

82 Therefore, the concern for reproductive toxicity must be further investigated.

### 3.2. Information provided

83 You have adapted the following standard information requirements by applying weight of evidence (WoE) adaptation in accordance with Annex XI, section 1.2. You have provided the same information as for request 1, above.

### 3.3. Assessment of the information provided

84 Relevant information that can be used to support weight of evidence adaptation for the information requirement of Annex IX, Section 8.7.3 includes similar information that is produced by the OECD TG 443 with a design as specified in this decision. OECD TG 443 requires the study to investigate the following key elements: A) sexual function and fertility, B) toxicity to offspring, and C) systemic toxicity.

85 The studies provide only limited information on these key elements and one of these studies is not reliable for the same reasons already addressed under Section 1.

86 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.

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

### 3.4. Comments on the draft decision

88 Comments related to this request are addressed in request 5 of this decision.

*3.5. Specification of the study design*

89 The study design is specified in request 5 of this decision.



**Reasons related to the information under Annex X of REACH****4. Pre-natal developmental toxicity study in a second species**

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

*4.1. Information provided*

91 You have adapted this information requirement by using substance-tailored exposure-driven testing under Section 3.2(a) of Annex XI to the REACH Regulation. To support the adaptation, you have provided the following information:

- (i) "The Registrant determined that an exposure-driven approach may substitute for a PNDT study in a second species because there is sufficient developmental toxicity test data to conclude that the registered substance is not a developmental toxicant and importantly risk management measures and operational conditions are sufficient to demonstrate that there is no significant exposure during manufacturing and in all identified uses. The results of the exposure assessment throughout the lifecycle stage demonstrated that exposures were well below the DNELs (RCR range [REDACTED]) for the registered conditions of use (i.e. for industrial populations)", and for the RCR derivation:
- (ii) a pre-natal developmental toxicity study in a first species (OECD TG 414) 2020, with the source substance Branched alcohols, C10-12, C11 rich (EC 271-360-6),
- (iii) QSAR prediction of NOAEL for RCR derivation.

*4.2. Assessment of the provided information**4.2.1. Assessment of the exposure-based adaptation*

92 As stated in Annex XI, Section 3, testing in accordance with Sections 8.6 and 8.7 of Annex VIII and in accordance with Annexes IX and X may be omitted based on the exposure scenario(s) developed in the CSR, by providing an adequate and scientifically-supported justification based on a thorough and rigorous exposure assessment in accordance with Section 5 of Annex I and by communicating the specific conditions of use through the supply chain. Any one of the following criteria 3.2.(a), (b) or (c) shall be met. In particular for 3.2.(a), the manufacturer or importer demonstrates and documents that the following condition is fulfilled:

a suitable DNEL or a PNEC can be derived from results of available test data for the Substance taking full account of the increased uncertainty resulting from the omission of the information requirement, and that DNEL or PNEC is relevant and appropriate both to the information requirement to be omitted and for risk assessment purposes.

*4.2.1.1. Assessment of the DNEL derivation as basis for calculating RCR*

93 Instead of a PNDT study (in a first species) with the Substance, you have provided

- ii. a PNDT in a first species with a source substance (ii); and
- iii. a QSAR prediction to derive a NOAEL (iii); both for the derivation of the DNEL in order to calculate RCRs.

- 94 We have assessed this information according to the requirements of Annex XI, Section 3 of the REACH Regulation and identified the following issue:
- 95 You have not accounted for interspecies differences and intra-species differences and remaining uncertainties due to data waiving for toxicity to pre-natal development through the use of appropriate assessment factors according to ECHA Guidance R.8, version 2.1, 2012.
- 96 You have not derived a suitable DNEL, because you do not have reliable results from a (first species) PNDT study as a starting point to derive a DNEL that would be suitable for waiving the requirement for a second species PNDT.
- 97 As explained in Section 0.1, your read-across adaptation is rejected.
- 98 Furthermore, the QSAR prediction fails due to the shortcomings identified in sections 4.2.1.1.1 - 4.2.1.1.3. below.

*4.2.1.1.1. Assessment of the QSAR-derived DNEL derivation as basis for calculating RCR*

- 99 Under ECHA Guidance R.6.1.3., a (Q)SAR model must fulfil the principles described in the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) to be considered scientifically valid. The first OECD principle requires the endpoint of a (Q)SAR model to be well defined. ECHA Guidance R.6.5.1.2 specifies that for a well-defined endpoint:
- the training set must be obtained from experimental data generated with homogeneous experimental protocols, and
  - the effect modelled being predicted by the (Q)SAR must be the same as the effect measured by a defined test protocol relevant to the information requirement, which in this case includes skeletal and visceral malformations and deviations in a second species as basis for deriving the NOAEL for developmental toxicity; as well as NOAELs for fetotoxicity and maternal toxicity (OECD TG 414).
- 100 You claim that "This model was developed with the assumption that rat developmental dNOAEL is available to be used to derive a rabbit rdNOAEL5. However, the model may also be adapted to be applied in reverse, starting with the rabbit dNOAEL to derive an rdNOAELrat."
- 101 You have provided a (Q)SAR model which is based on data generated using the following methodology: the model is an inter-species correlation based on a linear regression between rat and rabbit NOELs. The model deviates from the structure-activity-relationship (SAR) in that it does not use the chemical structure or structural-related properties of the substance to predict an endpoint.
- 102 The provided information indicates that also test protocols other than OECD TG 414 were used. Therefore, the integrity of the training set may be compromised since non-homogeneous test protocols were used.
- 103 It is not clear and it cannot be excluded that the endpoint predicted by the (Q)SAR is not the same as the endpoint measured by the relevant test protocol (OECD TG 414), because effects that are missing include the type and strength of visceral or skeletal malformation or deviations. Also missing are the discrimination between developmental toxicity and fetotoxicity; and maternal toxicity; as basis of NOAELs in a second species.
- 104 The endpoint is not well defined since both species rat and rabbit could be derived with the same model. In addition it is not mentioned in the documentation which effects from the

PNDT study have been covered by the prediction. Therefore it is not possible to assess the scientific validity of the model.

105 Therefore, the endpoint of the model is not well defined and you have not established that the use of this model is a scientifically valid approach to meet this information requirement.

*4.2.1.1.2. The substance is outside the applicability domain of the model*

106 Under ECHA Guidance R.6.1.5.3., a prediction is within the applicability domain of the model, when, among others, the substance and the structures selected for the prediction falls within descriptor, structural, mechanistic and metabolic domain.

107 You claim in your registration dossier that *"The model is populated with most known compounds for which data exists comparing rat and rabbit developmental NOAEL. The applicability domain is limited to Cramer Class I compounds, which exhibit a closer relationship between rat and rabbit developmental NOAEL."* You did not consider chemical structures or structural-related properties of the main constituents of the UVCB.

108 ECHA's guidance on QSARs lists the elements that define applicability domain in terms of descriptor, structural fragment and mechanistic and metabolic domains. You did not relate the applicability domain to the intrinsic properties of the substances but rather to their toxicological class, Cramer class I in this case, which is derived from the threshold of toxicological concern (TTC) concept for data-poor substances. In response to your comment on the draft decision that the model is valid, ECHA notes that you did not consider chemical structures or structural-related properties of the main constituents of the UVCB.

109 In addition to Cramer class, you make reference to *"LogP, Water solubility, functional groups"*. However you did not use these parameters to derive the model, and not to define the applicability domain, but instead claim that *"These parameters were evaluated to determine if a relationship could be gleaned as to how they contribute to differences in developmental toxicity between the rat and the rabbit."*

110 Therefore, it is not possible to confirm that the Substance as well as the source substances fall within the applicability of the model for the Substance.

*4.2.1.1.3. Selection of the representative structure(s)*

111 Under ECHA Guidance R.6.1.7.3. a prediction is adequate for the purpose of classification and labelling and/or risk assessment if the following cumulative conditions are met:

- the composition of the substance is clearly defined, and
- representative structure(s) for the assessment are selected.

112 Your registration dossier provides the following information:

- In Section 1.1 of your technical dossier, you define the Substance as UVCB substance
- In Section 1.2, you indicate the following constituents in the composition of your Substance:
  - 3,5,7-Trimethyl-decanol
  - Isododecan-1-ol
  - Isotetradecan-1-ol
  - Isoundecan-1-ol

- For the assessment, you have not provided a structure to be used as input for the proposed model.

113 You have not considered any substance as representative structure(s).

114 Therefore, you have not demonstrated that the prediction is adequate for the purpose of classification and labelling and/or risk assessment.

#### 4.2.2. Conclusion on the exposure based adaptation

115 Therefore, the information you provided in the dossier does not meet the general rules for adaptation of Annex XI, Section 3, as not all of the cumulative aspects of criterion 3.2.(a) are currently fulfilled.

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

#### 4.3. Comments on the draft decision

117 In your comments to the draft decision you do not agree to perform the requested study. Instead, you request ECHA to reconsider the rejection of the read-across hypothesis based on clarifications provided that in your views demonstrate toxicological similarity between isotridecanol (Substance) and isoundecanol (source). ECHA has addressed this comment in Section 0 and rejects your read-across. Therefore there is at present no study from which a NOAEL could be used to derive a DNEL for this endpoint. Your adaptation according to Annex XI, Section 3.2(a) is therefore still rejected.

118 You also question ECHA's conclusion on your use of assessment factors in your DNEL derivation. ECHA agrees that the assessment factors you used are correct.

119 You further provided in your comments comprehensive information on the "QSAR" approach that is used to predict NOAELs for developmental toxicity in rabbits. ECHA concludes that the information provided with the comments does not alter ECHA's conclusion. This is because the proposed model does not fulfil the definition of "structure-activity relationship" (SAR). The reasons are explained above in section 4.2.1.1.

120 As your proposed strategy for adapting this endpoint relies on a read-across approach that has not yet been fully described and justified, as well as on data which is yet to be generated (including bridging information), no conclusion on the compliance of the proposed adaptation can be made. You remain responsible for complying with this decision by the set deadline.

#### 4.4. Specification of the study design

121 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).

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

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

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

### 5. Extended one-generation reproductive toxicity study

125 An extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is an information requirement under Annex X, Section 8.7.3. Furthermore column 2 defines the conditions under which the study design needs to be expanded.

5.1. *Information provided*

126 You have adapted the following standard information requirements by applying weight of evidence (WoE) adaptation in accordance with Annex XI, section 1.2. You have provided the same information as for requests 1 and 3, above.

5.2. *Assessment of the information provided*

127 The provided information does not satisfy the requirements of an OECD TG 443 as assessed in Section 3.

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

5.3. *Specification of the study design*

5.3.1. *Species and route selection*

129 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.).

5.3.2. *Pre-mating exposure duration*

130 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.

131 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 pre-mating exposure duration (Guidance on IRs and CSA, Section R.7.6.).

132 In this specific case, ten weeks exposure duration is supported by the lipophilicity of the Substance ( $\log K_{ow} = >4.5$ ) to ensure that the steady state in parental animals has been reached before mating.

133 Therefore, the requested pre-mating exposure duration for the P0 animals is ten weeks.

5.3.3. *Dose-level setting*

134 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.

135 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.

- 136 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.
- 137 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.
- 138 You have to provide a justification with your study results demonstrating that the dose level selection meets the conditions described above.
- 139 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.

#### 5.3.4. Cohorts 1A and 1B

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

##### 5.3.4.1. Splenic lymphocyte subpopulation analysis

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

##### 5.3.4.2. Investigations of sexual maturation

- 142 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.

#### 5.3.5. Extension of Cohort 1B

- 143 The use of the Substance reported in the joint submission is leading to significant exposure of professionals and consumers, because the Substance is used by professionals in coatings, metal working fluids, indoor and outdoor use as processing aid, and in oil/gas field drilling/production operations (PROCs 8a, 10, 11, 19, 28). Consumer uses include adhesives and sealants, anti-freeze products, biocides (e.g. disinfectants, pest control products), coating products, fillers, putties, plasters, modelling clay, non-metal-surface treatment products, inks and toners, leather treatment products, lubricants and greases, polishes and waxes and textile treatment products and dyes.
- 144 In addition, there are indications that the internal dose for the Substance and/or any of its metabolites will reach a steady state in the test animals only after an extended exposure.



Specifically, the logKow for the substance (4.9) is above 4.5, which indicates a potential for accumulation.

- 145 Finally, there are indications of one or more modes of action related to endocrine disruption because changes in organs/parameters sensitive to endocrine activity are observed. Specifically, in a sub-chronic toxicity study with the Substance, higher thyroid/parathyroid gland weights were observed in all treated groups. Higher thyroid/parathyroid gland weights correlated histologically with minimal follicular cell hypertrophy/hyperplasia in the thyroid gland in a dose-dependent manner. Furthermore, you have provided information on thyroid hormone levels after 90 days of repeated exposure, showing decreased T3 and T4 levels as well as increased TSH levels. Reasons why ECHA considers these effects in thyroid gland relevant for humans are explained above in section 3.1. Furthermore, also other endocrine organs were affected by the test item, as increased adrenal gland weights were reported in females.
- 146 For the reasons stated above, Cohort 1B must be extended.
- 147 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) because there is a concern for reproductive toxicity/endocrine activity indicated by the toxicity-triggers to extend the Cohort 1B.
- 148 The F2 generation must be followed to weaning allowing assessment of nursing and lactation of the F1 parents and postnatal development of F2 offspring. Investigations for F2 pups must be similar to those requested for F1 pups in OECD TG 443 and described in OECD GD 151.

#### 5.3.6. Cohorts 2A and 2B

- 149 The developmental neurotoxicity Cohorts 2A and 2B must be conducted in case of a particular concern on (developmental) neurotoxicity.
- 150 As explained under section 3.1 above, existing information on the Substance itself derived from the available sub-chronic toxicity study (OECD TG 408 (2018)), shows evidence of thyroid toxicity indicating changes of thyroid hormone levels. This is considered a specific mechanism/mode of action with an association to developmental neurotoxicity (OECD GD 150).
- 151 For the reasons stated above, the developmental neurotoxicity Cohorts 2A and 2B must be conducted.

#### 5.4. Comments on the draft decision

- 152 In your comments to the draft decision you do not agree to perform the requested study. Instead, you request ECHA to reconsider the rejection of the read-across hypothesis based on clarifications provided that in your views demonstrate toxicological similarity between isotridecanol (Substance) and isoundecanol (source), request a reconsideration of the EOGRTS testing request, until the EOGRTS on isoundecanol is completed.
- 153 ECHA has addressed the comments related to read-across in Section 0.
- 154 As regards a reconsideration of the EOGRTS testing request until the EOGRTS on isoundecanol is completed, ECHA cannot modify the deadline as your registration dossier is currently non-compliant for the present information requirement. Issues related to extension of the deadline are addressed in Annex 2.
- 155 You furthermore inform that the EOGRTS study with isoundecanol will address the concern for thyroid related effects, as both isoundecanol and isotridecanol similarly impact the thyroid in the 90-day studies. You also describe your ongoing mechanistic investigations to

comparatively assess the weight of evidence for a range of thyroid-disruptive modes of action, with particular focus on the potential for developmental (neurotoxicological) effects, consistent with the ECHA/EFSA guidance on how to assess the potential for thyroid disruption of human health. ECHA acknowledges this information.

- 156 Furthermore, as your proposed strategy for adapting this endpoint relies on a read-across approach that has not yet been fully described and justified, as well as on data which is yet to be generated (including bridging information), no conclusion on the compliance of the proposed adaptation can be made. You remain responsible for complying with this decision by the set deadline.

*5.5. Further expansion of the study design*

- 157 No triggers for the inclusion of Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including Cohort 3 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 IX/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 07 February 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 request(s) but extended the deadline.

In your comments, you requested an extension of the deadline. The deadline of the draft decision was set based on standard practice for carrying out OECD TG tests. It has been exceptionally extended by 12 months from the standard deadline granted by ECHA to take into account currently longer lead times in contract research organisations and aligning with the category members.

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.

Following the Board of Appeal's decision in cases A-002-2022 and A-003-2022 ECHA removed the request to perform additional investigations on learning and memory function as part of the information requirement of the second column of Annex IX/X, section 8.7.3.

**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.

<b>Registrant Name</b>	<b>Registration number</b>	<b>Highest REACH Annex applicable to you</b>
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

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

## Appendix 4: Conducting and reporting new tests for REACH purposes

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

#### 1.1. Test methods, GLP requirements and reporting

- (1) Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.
- (2) Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.
- (3) Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries<sup>10</sup>.
- (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.

##### *Selection of the Test material(s)*

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

- a) the variation in compositions reported by all members of the joint submission,
- b) the boundary composition(s) of the Substance,
- c) 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.

##### *Information on the Test Material needed in the updated dossier*

- a) 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.
- b) The reported composition must include the careful identification and description of the characteristics of the Tests Materials in accordance with OECD GLP (ENV/MC/CHEM(98)16) and EU Test Methods Regulation (EU) 440/2008 (Note,

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<sup>10</sup> <https://echa.europa.eu/practical-guides>

Annex) and Annex XI Section 1.5 of REACH; namely all the constituents must be identified as far as possible as well as their concentration and the variability in these concentrations. Also any constituents that have harmonised classification and labelling according to the CLP Regulation must be identified and quantified using the appropriate analytical methods,

With that detailed information, ECHA can confirm whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers (<https://echa.europa.eu/manuals>).