~~Confidential~~

Helsinki, 02 November 2023

**Addressees**
Registrant(s) of JS_OTB_202-268-6 as listed in Appendix 3 of this decision

**Date of submission of the dossier subject to this decision**
21/03/2022

**Registered substance subject to this decision ("the Substance")**
Substance name: 1-o-tolylbiguanide
EC/List number: 202-268-6

**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 ***9 February 2027***.

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

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

1. Skin sensitisation (Annex VII, Section 8.3.)
   i. *In vitro/in chemico* skin sensitisation information on molecular interactions with skin proteins (OECD TG 442C), inflammatory response in keratinocytes (OECD TG 442D) and activation of dendritic cells (EU B.71/OECD TG 442E)(Annex VII, Section 8.3.1.); and
   ii. Only if the *in vitro/in chemico* test methods specified under point 1.i.) above are not applicable for the Substance or the results obtained are not adequate for classification and risk assessment, *in vivo* skin sensitisation (Annex VII, Section 8.3.2.; test method: EU B.42./OECD TG 429);

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

2. Short-term repeated dose toxicity (28 days; Annex VIII, Section 8.6.1.) to be combined with the Screening for reproductive/developmental toxicity below

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

4. Simulation testing on ultimate degradation in surface water (triggered by Annex VIII, Section 9.2.; test method: EU C.25./OECD TG 309) at a temperature of 12°C.

5. Identification of degradation products (triggered by Annex VIII, Section 9.2; test method: test method: EU C.13./OECD TG 309

6. Bioaccumulation in aquatic species (triggered by Annex VIII, sections 9.3; test method: EU C.13./OECD TG 305)

The reasons for the decision(s) are explained in Appendix 1.

**Information required depends on your tonnage band**

You must provide the information listed above for all REACH Annexes applicable to you in accordance with Articles 10(a) and 12(1) of REACH. The addressees of the decision and their corresponding information requirements based on registered tonnage band are listed in Appendix 3.

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

**How to comply with your information requirements**

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

You must follow the general requirements for testing and reporting new tests under REACH, see Appendix 4. In addition, the studies relating to biodegradation and bioaccumulation are necessary for the PBT assessment. However, to determine the testing needed to reach the conclusion on the persistency and bioaccumulation of the Substance you should consider the sequence in which these tests are performed and other conditions described in this Appendix.

**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

**Reasons related to the information under Annex VII of REACH**

## 1. Skin sensitisation

1 Skin sensitisation is an information requirement under Annex VII, Section 8.3. Under Section 8.3., Column 1, the registrants must submit information allowing (1) a conclusion whether the substance is a skin sensitiser and (2) whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A).

### *1.1. Information provided*

2 You have provided:

i. a survey from plant operators, (1996) with the Substance

3 In the comments to the draft decision you have provided the original documentation on the survey listed above. Furthermore you state: *"As 8 out of a total of 19 workers assessed produced symptoms, we propose that this is sufficient evidence to classify OTB as a category 1A skin sensitiser".*

### *1.2. Assessment of the information provided*

#### *1.2.1. Assessment whether the Substance causes skin sensitisation*

##### *1.2.1.1. Adequacy of the provided study i. for hazard identification*

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

5 You have provided a human test survey conducted on the operators that have worked in the plant. Based on the survey results you consider that the Substance may be a skin sensitiser rather than simply an irritant, although equivocal results have been reported.

6 A survey done with workers with very limited details provided i.e. no information about exposure conditions and reporting of results, is not considered as adequate to investigate the intrinsic properties of the Substance as required for the purpose of hazard identification. Therefore, the survey with very limited details does not allow to make a conclusion whether the Substance causes skin sensitisation.

7 Therefore, the study is rejected and does not allow to make a conclusion whether the Substance causes skin sensitisation.

#### *1.2.2. No assessment of potency*

8 To be considered compliant and enable a conclusion in cases where the substance is considered to cause skin sensitisation, the information provided must also allow a conclusion whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A).

9 As the currently available data does not allow to conclude whether the Substance causes skin sensitisation (see section 1.2.1 above), this condition cannot be assessed.

10 ECHA acknowledges your intentions to add further details on human exposure and skin sensitisation to the dossier and to re-classify the substance as Skin Sens 1A. ECHA considers this approach plausible.

11 However, as the additional information and the classification as Skin Sens 1A 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 the decision.

*1.3. Specification of the study design*

12 To fulfil the information requirement for the Substance, information on molecular interaction with skin proteins and inflammatory response in keratinocytes and activation of dendritic cells (OECD TG 442C and OECD TG 442D and EU B.71/OECD TG 442E) must be provided. Furthermore an appropriate risk assessment is required if a classification of the Substance as a skin sensitiser (Cat 1A or 1B) is warranted.

13 In case no conclusion on the skin sensitisation potency can be made for the Substance based on the existing data or newly generated in vitro/in chemico data, in vivo skin sensitisation study must be performed and the murine local lymph node assay (EU Method B.42/OECD TG 429) is considered as the appropriate study for the potency estimation.

**Reasons related to the information under Annex VIII of REACH**

## 2. Short-term repeated dose toxicity (28 days)

14 A short-term repeated dose toxicity study (28 days) is an information requirement under Annex VIII, Section 8.6.1. This information may take the form of a study record or a valid adaptation in accordance with either a specific adaptation rule under Column 2 of Annex VIII or a general adaptation rule under Annex XI.

### *2.1. Information provided*

15 You have provided:

i. a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD TG 422, 2017) with the Substance.

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

ii. a QSAR Prediction of Reproductive toxicity for 2-tolylbiguanide, 2015, QSAR Toolbox 3.3.0.132 TPRF v.3.3.1.33005, Database version: 3.7.9/3.1.2

### *2.2. Assessment of the information provided with the Substance (study i)*

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

18 For the reasons explained in Section 3.2, the study (i) does not cover all key parameters required by the OECD TG 407 and therefore is not reliable.

19 In the comments to the draft decision you have provided an explanation for the dose selection and the full study report for the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test.

20 The assessment of the explanation you have provided in your comments is assessed under section 3.2.

### *2.3. Assessment of the information from QSAR toolbox (study ii)*

21 In your registration dossier you have provided information derived from experimental data from a group of substances/analogues a group of 27 substances using the OECD QSAR Toolbox and flagged the information as QSAR.

22 As the group of substances are used as source substances to predict the property of the Substance, we understand that you have adapted the standard information requirements under Annex XI, Section 1.5 of REACH (grouping and read-across).

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

#### *2.3.1. Read-across adaptation*

24 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.

25 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).

*2.3.1.1. Absence of read-across documentation*

26 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 include a an explanation why the properties of the Substance may be predicted from information on the source substance(s).

27 You have provided QSAR Toolbox prediction based on read-across which is based on results of studies that were conducted with other substances than the Substance in order to comply with the REACH information requirements. However, you have not provided documentation as to why this information is relevant for the Substance and thus why the properties of the Substance may be predicted from information on the source substance(s).

28 In the absence of such documentation, the properties of the Substance cannot be reliably predicted from the data on the source substances.

*2.3.1.2. Missing supporting information*

29 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.).

30 Supporting information must include bridging studies to compare properties of the Substance and source substances.

31 As indicated above, your read-across hypothesis is based on the assumption that the structurally similar substances cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the Substance and of the source substance(s) is necessary to confirm that both substances cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and of the source substance(s).

32 You have provided a TG 422 study with the Substance, study (i), which, if reliable, could allow to compare the properties of the Substance with data on the source substances.

33 As explained below (section 3.2) the study (i) performed with the Substance is not reliable. Furthermore, for the source substances, robust study summaries are missing as explained below. Thus the data set reported in the technical dossier does not include relevant, reliable and adequate information for the Substance and of the source substances to support your read-across hypothesis.

34 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.

*2.3.1.3. Missing robust study summaries*

35 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 include robust study summary for each source study used in the adaptation.

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

37 In your QSAR toolbox document you have indicated that no alert was found regarding DNA and protein binding based on alerts from the five closest neighbours in your category. The report lists the predictions of 10 chemicals in more detail, the remaining category members are listed in a table with basic information. Besides that, you have not included robust study summaries for any of these above mentioned source substances.

38 Therefore, you have not provided detailed information on the methods, results and conclusions, allowing for an independent assessment of the reliability of the studies as required by Annex XI, Section 1.5.

39 As explained above, you have not established that relevant properties of the Substance can be predicted from data on the source substances. Therefore, your read-across approach under Annex XI, Section 1.5. is rejected.

40 In the comments to the draft decision you state that ”the QSAR Prediction of Reproductive toxicity for 2-tolylbiguanide will be removed”. ECHA acknowledges your decision to remove the attachment ”QSAR Prediction of Reproductive toxicity for 2-tolylbiguanide”.

41 The information provided in your comments does not change the assessment.

42 Therefore, the information requirement is not fulfilled.

### *2.4. Specification of the study design*

43 When there is no information available neither for the 28-day repeated dose toxicity (EU B.7, OECD TG 407), nor for the screening study for reproductive/developmental toxicity (OECD TG 421 or TG 422), the conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) is preferred to ensure that unnecessary animal testing is avoided. Such an approach offers the possibility to avoid carrying out a 28-day study according to OECD TG 407, because the OECD TG 422 can at the same time fulfil the information requirement of REACH Annex VIII, Section 8.6.1 and that of REACH Annex VIII, Section 8.7.1. (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

44 For information on the study design see request for OECD TG 422 below.

## 3. Screening for reproductive/developmental toxicity

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

### *3.1. Information provided*

46 You have provided:

i. a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD TG 422, 2017)

with the Substance

*3.2. Assessment of the information provided*

47 To fulfil the information requirement, a study must comply with EU B.63/OECD TG 421 or EU B.64/OECD TG 422 (Article 13(3) of REACH). Therefore, the following specifications must be met:

a) the highest dose level aims to induce toxicity or aims to reach the limit dose.

48 The study (i) is described as a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test

49 The study does not cover the key parameters of EU B.63/OECD TG 421 or EU B.64/OECD TG 422:

a) the highest dose levels tested was 50 mg/kg bw/day (i.e., below the limit dose of the OECD TG 421/422) and no adverse effects were observed and the justification for the dose setting provided is not acceptable. *"After reducing the dose to 50 mg/kg bw/day, the mean body weights were apparently (-2.6% to -6.7%) lower and net body weight gains were significantly lower during treatment period in males, when compared to concurrent vehicle control. However, in females, the mean body weights and net body weight gains were comparable to concurrent vehicle control group".* ECHA considers, that in females the 50 mg/kg bw/day was clearly not high enough as no effects were observed. The same applies for males since the reduction in body weight (-2.6-6.7%) is not considered as adverse.

50 In the comments to the draft decision you have provided an explanation for the dose selection and the full study report for the combined repeated dose toxicity study with the reproduction/developmental screening test.

51 You explain, that the initially chosen high dose of 300 mg/kg bw/d was reduced to 50 mg/kg bw/d. In the attached report it is described that it was reduced because of slight salivation, piloerection, dehydration and emaciation observed 30 minutes after dosing. At the new high dose (50 mg/kg bw/d) the animals *"showed salviation for the duration of the study"* and*"there was a slightly reduced weight gain in the top dose".* Furthermore, you conclude that the increase in body weight gain observed after treatment in the recovery group *"was a good indication that 50 mg/kg/day can be considered a maximum tolerated dose in terms of parental toxicity*". However, according to the study report, the change in bodyweight at 50 mg/kg bw/d on day 3 was below 10 % and below 5% in the mid-dose group, and hence based on the available information, there was no aim for toxicity at 50 mg/kg bw/d. Furthermore, it is important to see if there is toxicity above 50 mg/kg bw/d for correct NOAEL setting. Regarding dose selection ECHA refers to the Guidance on information requirements and chemical safety assessment (Chapter 7a, R.7.6) and the Advice on dose-level selection for the conduct of reproductive toxicity studies (OECD TGs 414, 421/422 and 443) under REACH [2]: […*" the highest dose level should be chosen with the aim [...]*

i. (OECD TG 414) to induce some developmental and/or maternal toxicity (clinical signs of a decrease in body weight)

ii. (OECD TG 421/422) of inducing toxic effects

iii. (OECD TG 443) to induce some systemic toxicity

[2] Advice on dose-level selection for the conduct of reproductive toxicity studies (OECD TGs 414, 421/422 and 443) under REACH; https://www.echa.europa.eu/documents/10162/17220/211221_echa_advice_dose__repro_en.pdf/27159fb1-c31c-78a2-bdef-8f423f2b6568?t=1640082455275

52 *but not death or severe suffering"…].*

53 In your comments you also state *"A study according to test method EU B.64/OECD TG 422 is included in the dossier. Repeating this study would contravene the EU policy of reducing animal testing. However, it is accepted that the dossier itself did not make it apparent that the highest dose level used was only just tolerated suggesting this was a highest tolerated dose. Further clarification is needed regarding the choice of dose level and it is accepted that this may result in re-classification as STOT RE2."*

54 As, based on your current data, you have not self- classified yet, the data gap for short term repeated dose toxicity remains. As explained in Annex 1 Section 3.9.2.9.5 of CLP the guidance values (see table 3.9.2 and 3.9.3 of CLP) can be extrapolated if a 28-day study is used for classification. See also Guidance on information requirements and chemical safety assessment (Guidance on IRs & CSA) Chapter R.7a Endpoint specific guidance, Section R.7.5.6.3.1.

55 Furthermore, minimisation of vertebrate animal testing is not on its own a legal ground for adaptation under Column 2 nor under the general rules of Annex XI.

56 Based on the above, the information you provided does not fulfil the information requirement.

### *3.3. Specification of the study design*

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

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

59 Therefore, the study must be conducted in rats with oral administration of the Substance.

## 4. Simulation testing on ultimate degradation in surface water

60 Further degradation testing must be considered if the chemical safety assessment (CSA) according to Annex I indicates the need to investigate further the degradation of the substance (Annex VIII, Section 9.2., Column 2).

61 This information requirement is triggered in case the chemical safety assessment (CSA) indicates the need for further degradation investigation (Annex I, Section 4; Annex XIII, Section 2.1), such as if the substance is a potential PBT/vPvB substance (Guidance on IRs and CSA, Section R.11.4.). This is the case if the Substance itself or any of its constituent or impurity present in concentration ≥ 0.1% (w/w) or relevant transformation/degradation product meets the following criteria:

- it is potentially persistent or very persistent (P/vP) as:
  - it is not readily biodegradable, *i.e.* <60% degradation in an OECD TG 301D, and
  - it shows <70% degradation within 7 days in an inherent biodegradation test OECD 302B and/or lag phase > 3 days;
- it is potentially bioaccumulative or very bioaccumulative (B/vB) as:
  - for some groups of substances (e.g. organometals, ionisable substances, surfactants) other partitioning mechanisms may drive bioaccumulation (e.g. binding to protein/cell membranes) and high potential for bioaccumulation cannot be excluded solely based on its potential to partition to lipid.

### *4.1. Information provided*

62 Your registration dossier provides the following:

- the Substance is not readily biodegradable (app. 20% degradation after 28 days in OECD TG 301D)
- the Substance is not inherently biodegradable (0% degradation after 28 days in OECD TG 302B)
- based on the pKa value of 11 provided in the dossier the Substance is ionisable substance (i.e. present in ionised form(s) at environmentally relevant pHs) and therefore high potential for bioaccumulation cannot be excluded based on available information.

*4.2. Assessment of the information provided*

63 Under section 5.3.1 of your IUCLID dossier you provide bioaccumulation factor (BCF) value of 3.62 l/kg predicted by BCFBAF v3.01 model.

64 However, non-testing data, such as (Q)SAR predictions, can be used in a weight of evidence approach for B and vB assessment (ECHA Guidance R.11). This implies that such non-testing data cannot be used as standalone information to conclude on bioaccumulation potential.

65 In addition to the above, the BCFBAF model estimates BCF of an organic substance using the substance's octanol-water partition coefficient (Kow). As explained in Annex IX, Section 9.3.2., column 2 of REACH and ECHA Guidance R.11 (p.83), Kow can be used to predict bioaccumulation potential if bioaccumulation of the substance is solely driven by lipophilicity and is not a valid descriptor for assessing the bioaccumulation potential of ionisable substances. Therefore, predicted BCF of the Substance is not reliable and cannot be used for the B/vB assessment.

66 Based on the above, the available information on the Substance indicates that it is a potential PBT/vPvB substance. Further, the additional information on BCF of the Substance is not adequate to conclude on the B/vB (PBT/vPvB) properties of the Substance.

67 Therefore, the chemical safety assessment (CSA) indicates the need for further degradation investigation.

68 In your comments to the draft decision you agree that further testing is necessary as this substance is potentially persistent. You further agree that it is important to understand the potential degradation products and you suggest the following tiered approach to be able to conclude on the presence or absence of persistent and accumulative degradation products and metabolites:

> 1) Scoping tests to establish potential degradation pathways 2) Perform a theoretical assessment ('paper-exercise') of possible metabolic pathways in soil and water 3) Consider nitrogen-cycle degradation processes that may be found in soil bacteria, but not necessarily in non-adapted sewage sludge 4) Based on the outcomes considering soil and water studies with 'adapted' sludge.

69 ECHA considers this suggested approach valid and you should submit this information in an updated registration dossier by the deadline set in the decision.

*4.3. Study design and test specifications*

70 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.

71 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.).

72 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.

73 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. Paragraph 52 of the OECD TG 309 provides that the "*total recovery (mass balance) at the end of the experiment should be between 90% and 110% for radiolabelled substances, whereas the initial recovery at the beginning of the experiment should be between 70% and 110% for non-labelled substances*". NERs contribute towards the total recovery. Therefore, the quantity of the (total) NERs must be accounted for the total recovery (mass balance), when relevant, to achieve the objectives of the OECD TG 309 to derive degradation rate and half-life. The reporting of results must include a scientific justification of the used extraction procedures and solvents.

74 For the persistence assessment by default, total NERs is regarded as non-degraded Substance. However, if reasonably justified and analytically demonstrated a certain part of NERs may be differentiated and quantified as irreversibly bound or as degraded to biogenic NERs, 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.). 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 (NER - summary 2019 (europa.eu)).

75 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.).

## 5. Identification of degradation products

76 Further degradation testing must be considered if the chemical safety assessment (CSA) according to Annex I indicates the need to investigate further the degradation of the substance (Annex VIII, Section 9.2., Column 2).

77 This information requirement is triggered in case the chemical safety assessment (CSA) indicates the need for further degradation investigation (Annex I, Section 4; Annex XIII, Section 2.1), such as if the substance is a potential PBT/vPvB substance (Guidance on IRs and CSA, Section R.11.4.).

78 As already explained in Request 4 above, the Substance is a potential PBT/vPvB substance.

79 Therefore, the chemical safety assessment (CSA) indicates the need for further degradation investigation.

80 In your comments to the draft decision you agree that further testing is necessary as this substance is potentially persistent. You further agree that it is important to understand the

potential degradation products and in your suggested tiered approach (see above section 4.2) you list as one point to examine the degradation products. You provide results from a preliminary study performed in May 2022 on hydrolysis (at a concentration of 100 mg/L) in synthetic gastric fluid (pH 1) for 3 days at 40°C (biological and under accelerated conditions of 80°C. The aim of this study was to start investigating potential degradation of the substanc and the results provided information on two metabolites suggesting acid hydrolysis with removal of the terminal nitrogen. This is supported by a literature reference from Lewis & Wolfenden (2014) (The Nonenzymatic Decomposition of Guanidines and Amidines. J. Am.Chem.Soc. 136, 130-136) analysing decomposition of guanidines. This scoping work does not give information on the degradation pathway but forms the basis for your further studies. However, results from a hydrolysis study at pH 1 and elevated temperatures (40°C and 80°C) are not considered relevant for environmental degradation pathways. Simulation studies are normally carried out at 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. Therefore degradation products have to be identified from the simulation studies for environmental relevance.

81 ECHA acknowledges your efforts to already gain insights into the degradation behaviour of the substance but does not consider it relevant for environmental degradation as explained above. You should submit information on identified degradation products from simulation studies in an updated registration dossier by the deadline set in the decision.

*5.1. Study design and test specifications*

82 Identity, stability, behaviour, and molar quantity of the degradation/transformation products relative to the Substance must be evaluated and reported. In addition, identified transformation/degradation products must be considered in the CSA including PBT assessment. You must obtain this information from the degradation study requested in request 4.

83 To determine the degradation rate of the Substance, the requested study according to OECD TG 309 (request 4) 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).

## 6. Bioaccumulation in aquatic species

a) Under Annex VIII, Section 9.3., Column 2, further information on bioaccumulation or further testing as described in Annex IX must be generated if the chemical safety assessment (CSA) in accordance with Annex I indicates the need to investigate further the bioaccumulation properties of the substance.

84 Therefore, this information requirement is triggered in case if for example additional information on bioaccumulation as set out in Annex XIII, point 3.2.2, is required to assess PBT or vPvB properties of the substance in accordance with subsection 2.1 of that Annex.

85 As already explained in Request 4, the Substance is a potential PBT/vPvB substance.

86 Therefore, the chemical safety assessment (CSA) indicates the need for further investigation on bioaccumulation in aquatic species.

87 In your comments to the draft decision you do not agree to the request for a bioaccumulation study in aquatic species with the argument of a high water solubility of 2.75 g/L water @30°C and a low log Know of 0.71 indicating a low potential for bioaccumulation. However you do not take into account that the Substance is present in its ionized form at environmentally relevant pHs (pka 11, section 4.21 of your IUCLID dossier). If a substance is ionizable, other partitioning mechanisms may drive bioaccumulation (e.g. binding to protein/cell membranes) and a high potential for bioaccumulation cannot be excluded solely based on its potential to partition to lipids (see also section 4). As described in section 4.2 you provide a bioaccumulation factor (BCF) value of 3.62 l/kg predicted by BCFBAF v3.01 model. However, non-testing data, such as (Q)SAR predictions, can be used in a weight of evidence approach for B and vB assessment (ECHA Guidance R.11). This implies that such non-testing data cannot be used as standalone information to conclude on bioaccumulation potential.

88 In addition to the above, the BCFBAF model estimates BCF of an organic substance using the substance's octanol-water partition coefficient (Kow). As explained in Annex IX, Section 9.3.2., column 2 of REACH and ECHA Guidance R.11 (p.83), Kow can be used to predict bioaccumulation potential if bioaccumulation of the substance is solely driven by lipophilicity and is not a valid descriptor for assessing the bioaccumulation potential of ionisable substances. Therefore, predicted BCF of the Substance is not reliable and cannot be used for the B/vB assessment.

89 Based on the above, the available information on the Substance indicates that it is a potential PBT/vPvB substance. Further, the additional information on BCF of the Substance is not adequate to conclude on the B/vB (PBT/vPvB) properties of the Substance.

90 The information provided in your comments does not change the assessment.

### *6.1. Study design and test specification*

91 Bioaccumulation in fish: aqueous and dietary exposure (Method EU C.13 / OECD TG 305) is the preferred test to investigate bioaccumulation (Guidance on IRs and CSA, Section R.7.10.3.1.). Exposure via the aqueous route (OECD TG 305-I) must be conducted unless it can be demonstrated that:

- a stable and fully dissolved concentration of the test material in water cannot be maintained within ± 20% of the mean measured value, and/or
- the highest achievable concentration is less than an order of magnitude above the limit of quantification (LoQ) of a sensitive analytical method.

92 This test set-up is preferred as it allows for a direct comparison with the B and vB criteria of Annex XIII of REACH.

93 You may only conduct the study using the dietary exposure route (OECD 305-III) if you justify and document that testing through aquatic exposure is not technically possible as indicated above. You must then estimate the corresponding BCF value from the dietary test data according to Annex 8 of the OECD 305 TG and OECD Guidance Document on Aspects of OECD TG 305 on Fish Bioaccumulation (ENV/JM/MONO(2017)16).

## 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 16 November 2021.

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

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

The deadline of the decision is set based on standard practice for carrying out OECD TG tests. It has been exceptionally extended by 12 months from the standard deadline granted by ECHA to take into account currently longer lead times in contract research organisations.

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 case A-001-2022 ECHA revised the study design specifications for meeting the information requirement for simulation testing on ultimate degradation in surface water (Annex VIII, column 2, section 9.2 and/or Annex IX, first column, section 9.2.1.2).

**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] |

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

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

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

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

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

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

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

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

### 1.2. Test material

(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.

Technical instructions on how to report the above is available in the manual on How to

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

prepare registration and PPORD dossiers[4].

## 2. General recommendations for conducting and reporting new tests

### 2.1. Strategy for the PBT/vPvB assessment

Under Annex XIII, the information must be based on data obtained under conditions relevant for the PBT/vPvB assessment. You must assess the PBT properties of each relevant constituent of the Substance present in concentrations at or above 0.1% (w/w) and of all relevant transformation/degradation products. Alternatively, you would have to justify why you consider these not relevant for the PBT/vPvB assessment.

You are advised to consult Guidance on IRs & CSA, Sections R.7.9, R.7.10 and R.11 on PBT assessment to determine the sequence of the tests needed to reach the conclusion on PBT/vPvB. The guidance provides advice on 1) integrated testing strategies (ITS) for the P, B and T assessments and 2) the interpretation of results in concluding whether the Substance fulfils the PBT/vPvB criteria of Annex XIII.

In particular, you are advised to first conclude whether the Substance fulfils the Annex XIII criteria for P and vP, and then continue with the assessment for bioaccumulation. When determining the sequence of simulation degradation testing you are advised to consider the intrinsic properties of the Substance, its identified uses and release patterns as these could significantly influence the environmental fate of the Substance. You must revise your PBT assessment when the new information is available.

[4] https://echa.europa.eu/manuals