~~Confidential~~

Helsinki, 16 March 2021

Addressees
Registrant(s) of JS_78-96-6_MIPA as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
22/07/2019

Registered substance subject to this decision ("the Substance")
Substance name: 1-aminopropan-2-ol
EC number: 201-162-7
CAS number: 78-96-6

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 ***24 June 2024***.

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

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

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

2. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: OECD TG 210)

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

1. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route, specified as follows:
   - Ten weeks premating exposure duration for the parental (P0) generation;
   - Dose level setting shall aim to induce systemic toxicity at the highest dose level;
   - Cohort 1A (Reproductive toxicity);
   - Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation which shall be followed to weaning;

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

Reasons for the request(s) are explained in the following appendix

- Appendix entitled "Reasons to request information required under Annexes IX to X of REACH", respectively.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

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 testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

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 Christel Schilliger-Musset, Director of Hazard Assessment

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

Appendix A: Reasons to request information required under Annex IX of REACH

1. Long-term toxicity testing on aquatic invertebrates

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

You have provided the following information:

i. a justification to omit the study which you consider to be based on Annex IX, Section 9.1., Column 2,
ii. a justification to omit the study based on Annex XI, Section 3 (Substance-tailored exposure-driven testing) arguing that risk characterisation ratios (RCR) are "*below 1 for all compartments*",
iii. a justification to omit the study based on Annex XI, Section 1.2 (Weight of evidence).

In support of your weight of evidence approach, you have provided the following information:

a) a QSAR prediction using model ECOSAR v1.11 with ECOSAR SAR: "Aliphatic Amines, Daphnia ChV"
b) predictions based on acute-to-chronic ratio (ACR) approaches as presented in ECETOC Technical Report No. 91 (ECETOC, 2003)[2]

We have assessed this information and identified the following issues:

i. Justification based on Annex IX, Section 9.1., Column 2

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

ii. Justification based on Annex XI, Section 3 (Substance-tailored exposure-driven testing)

Under Annex XI, Section 3, testing may be omitted based on the exposure scenario(s) developed in the Chemical Safety Report (CSR). The justification must be based on a rigorous exposure assessment in accordance with Annex I, Section 5. Under Section 3.2(a), the justification must demonstrate among others that:

a) for all identified uses and throughout the whole life cycle of the Substance (including manufacture and waste management) that exposure is absent or not significant; and
b) exposures are always well below the PNEC.

a) Absence or no significant exposure is not demonstrated

In Section 3.5 of your registration dossier you report consumer uses and widespread uses by professional workers for the Substance.

These uses are, by definition, considered to be widespread (ECHA Guidance R.12) and indicate a potential for release (ECHA Guidance R.16). Therefore, you have not demonstrated that environmental exposure throughout the life-cycle, including waste stage, of the Substance is absent or not significant.

b) RCR are not well below 1

In your CSR you have reported RCRs below 1, but for some exposure scenarios RCRs are above [redacted].

[2] ECETOC, 2003. Aquatic Hazard Assessment II, Technical Report No. 91, ISSN-0773-8072-91, Brussels, November 2003

The results of the exposure assessment must show that exposures are always well below the PNEC, i.e. RCRs must always be well below 1. This means that the risks must always be controlled, under every plausible condition of the uses of the Substance. Therefore, every RCR must be low enough to ensure that the risks are always controlled considering the possible sources of variability and uncertainty in the assessment of exposure. ECHA Guidance R.19 on uncertainty analysis provides a framework for carrying out a stepwise, tiered approach to uncertainty analysis: either qualitative, deterministic, or probabilistic. The data in your dossier are insufficient to perform a probabilistic or a deterministic analysis, and only a qualitative analysis is possible. For most of the exposure scenarios, you have not based your exposure assessment on the generic assumptions recommended in ECHA Guidance R.16 but have used less conservative input parameters (in particular for the release factors). You have not demonstrated that your exposure assessment is always conservative enough and the RCRs always low enough to cover the possible sources of variability and uncertainty. Therefore, exposures cannot be regarded as being always well below the PNEC.

iii. Justification based on Annex XI, Section 1.2 (Weight of evidence)

Annex XI, Section 1.2 states that there may be sufficient weight of evidence from several independent sources of information leading to assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

According to ECHA Guidance R.4.4, a weight of evidence adaptation involves an assessment of the relative values/weights of different pieces 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 of the information for the given regulatory information requirement. Subsequently, relevance, reliability, consistency and results of these pieces of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the properties investigated by the required study.

To fulfil the information requirement, normally a study performed according to OECD TG 211 must be provided. OECD TG 211 requires the study to investigate the concentrations of the test material leading to no observed effect (NOECs).

Pieces of information a) and b) provide information on NOECs for long-term toxicity to aquatic invertebrates. However, the reliability of these pieces of information is significantly affected by the following deficiencies:

a) QSAR prediction

Annex XI, Section 1.3. states that results obtained from valid QSAR models may be used instead of testing when, among others, the results are adequate for classification and labelling and/or risk assessment. Under ECHA Guidance R.6.1.3.4 a prediction is adequate for the purpose of classification and labelling and/or risk assessment when the model is applicable to the chemical of interest with the necessary level of reliability.

You have estimated the long-term toxicity to *Daphnia* using model ECOSAR v1.11 with ECOSAR SAR: "Aliphatic Amines, Daphnia ChV". This model predicts a chronic toxicity value of 8.53 mg/L for the Substance.

Based on the data used for the training set, reported in the help-file of the model, the 95% prediction interval can be calculated as: 2.19E-03 mg/L - 3.27E+04 mg/L. Therefore, this prediction is highly uncertain and is as such not reliable for assessing the long-term toxicity of the Substance to aquatic invertebrates.

b) Acute-to-Chronic (ACR) approach

For this approach, you refer to ECETOC Technical Report No. 91 (ECETOC, 2003)[3]. Acute to chronic ratios (ACR) are calculated as the ratios of acute EC50 values to chronic/sub chronic values. The ECETOC report presents different ACR values, depending on the data set used to calculate them, e.g.: with all species combined, based on individual species, based on invertebrates only, based on substances with the same mode of action.

You have estimated the long-term toxicity to aquatic invertebrates by multiplying the EC50 value for short term toxicity to *Daphnia* (EC50 (48 h) mg/L: > 100 mg/L) by the different ACR values presented in the ECETOC report.

The approach described in the ECETOC report is not substance-specific. The Substance is an alkanolamine. However, the data used in the report to derive the ACR values do not cover substances with this moiety. Therefore, the Substance is outside the applicability domain of this approach and there is no evidence to rule out that a higher ACR value applies to the Substance. Therefore, this approach is not reliable for assessing the long-term toxicity of the Substance to aquatic invertebrates.

c) Conclusion on the weight-of-evidence

Taken together, even though the pieces of information a) and b) as indicated above may provide relevant information, their reliability is affected significantly. Therefore, they cannot contribute to the conclusion on the key investigation for this information requirement.

Accordingly, it is not possible to conclude, based on any piece of information alone or considered together, whether the Substance has or has not the properties foreseen to be investigated in an OECD TG 211 study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

iv. Conclusion on your adaptations

Therefore, your adaptations are rejected.

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

On this basis, the information requirement is not fulfilled.

2. Long-term toxicity testing on fish

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

You have provided the following information:

i. a justification to omit the study which you consider to be based on Annex IX, Section 9.1., Column 2,
ii. a justification to omit the study based on Annex XI, Section 3 (Substance-tailored exposure-driven testing) arguing that risk characterisation ratios (RCR) are "*below 1 for all compartments*",
iii. a justification to omit the study invoking animal welfare,
iv. a justification to omit the study based on Annex XI, Section 1.2 (Weight of evidence).

In support of your weight of evidence approach, you have provided the following information:

- a QSAR prediction using model ECOSAR v1.11 with ECOSAR SAR: "Aliphatic Amines,

[3] ECETOC, 2003. Aquatic Hazard Assessment II, Technical Report No. 91, ISSN-0773-8072-91, Brussels, November 2003

Fish ChV"
- predictions based on acute-to-chronic ratio (ACR) approaches as presented in ECETOC Technical Report No. 91 (ECETOC, 2003)[4]

We have assessed this information and identified the following issues:

i. Justification based on Annex IX, Section 9.1., Column 2

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

ii. Justification based on Annex XI, Section 3 (Substance-tailored exposure-driven testing)

Under Annex XI, Section 3, testing may be omitted based on the exposure scenario(s) developed in the Chemical Safety Report (CSR). The justification must be based on a rigorous exposure assessment in accordance with Annex I, Section 5. Under Section 3.2(a), the justification must demonstrate among others that:

a) for all identified uses and throughout the whole life cycle of the Substance (including manufacture and waste management) that exposure is absent or not significant; and
b) exposures are always well below the PNEC.

a) Absence or no significant exposure is not demonstrated

In Section 3.5 of your registration dossier you report consumer uses and widespread uses by professional workers for the Substance.

These uses are, by definition, considered to be widespread (ECHA Guidance R.12) and indicate a potential for release (ECHA Guidance R.16). Therefore, you have not demonstrated that environmental exposure throughout the life-cycle, including waste stage, of the Substance is absent or not significant.

b) RCR are not well below 1

In your CSR you have reported RCRs below 1, but for some exposure scenarios RCRs are above [redacted].

The results of the exposure assessment must show that exposures are always well below the PNEC, i.e. RCRs must always be well below 1. This means that the risks must always be controlled, under every plausible condition of the uses of the Substance. Therefore, every RCR must be low enough to ensure that the risks are always controlled considering the possible sources of variability and uncertainty in the assessment of exposure. ECHA Guidance R.19 on uncertainty analysis provides a framework for carrying out a stepwise, tiered approach to uncertainty analysis: either qualitative, deterministic, or probabilistic. The data in your dossier are insufficient to perform a probabilistic or a deterministic analysis, and only a qualitative analysis is possible. For most of the exposure scenarios, you have not based your exposure assessment on the generic assumptions recommended in ECHA Guidance R.16 but have used less conservative input parameters (in particular for the release factors). You have not demonstrated that your exposure assessment is always conservative enough and the RCRs always low enough to cover the possible sources of variability and uncertainty. Therefore, exposures cannot be regarded as being always well below the PNEC.

iii. Justification invoking animal welfare

[4] ECETOC, 2003. Aquatic Hazard Assessment II, Technical Report No. 91, ISSN-0773-8072-91, Brussels, November 2003

Animal welfare does not constitute as such a valid justification to omit the standard information requirements of Annexes VII – X or a valid adaptation to these information requirements.

iv. Justification based on Annex XI, Section 1.2 (Weight of evidence)

Annex XI, Section 1.2 states that there may be sufficient weight of evidence from several independent sources of information leading to assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

According to ECHA Guidance R.4.4, a weight of evidence adaptation involves an assessment of the relative values/weights of different pieces 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 of the information for the given regulatory information requirement. Subsequently, relevance, reliability, consistency and results of these pieces of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the properties investigated by the required study.

To fulfil the information requirement, normally a study performed according to OECD TG 210 must be provided. OECD TG 210 requires the study to investigate the concentrations of the test material leading to no observed effect (NOECs) on the survival and development of fish in early life stages.

a) QSAR prediction

Annex XI, Section 1.3. states that results obtained from valid QSAR models may be used instead of testing when, among others, the results are adequate for classification and labelling and/or risk assessment. Under ECHA Guidance R.6.1.3.4 a prediction is adequate for the purpose of classification and labelling and/or risk assessment when the model is applicable to the chemical of interest with the necessary level of reliability.

You have estimated the long-term toxicity to fish using model ECOSAR v1.11 with ECOSAR SAR: "Aliphatic Amines, Fish ChV". This model predicts a chronic toxicity value of 327 mg/L for the Substance.

Based on the data used for the training set, reported in the help-file of the model, the 95% prediction interval can be calculated as: 6.74E-02 mg/L - 1.56E+06 mg/L. Therefore, this prediction is highly uncertain and is as such not reliable for assessing the long-term toxicity of the Substance to fish.

b) Acute-to-Chronic (ACR) approach

For this approach, you refer to ECETOC Technical Report No. 91 (ECETOC, 2003)[5]. Acute to chronic ratios (ACR) are calculated as the ratios of acute EC50 values to chronic/sub chronic values. The ECETOC report presents different ACR values, depending on the data set used to calculate them, e.g.: with all species combined, based on individual species, based on selected fish species only, based on substances with the same mode of action.

You have estimated the long-term toxicity to fish by multiplying the LC50 value for short term toxicity to fish (LC50 (96 h) mg/L: > 100 mg/L) by the different ACR values presented in the ECETOC report.

The approach described in the ECETOC report is not substance-specific. The Substance is an alkanolamine. However, the data used in the report to derive the ACR values do not cover

[5] ECETOC, 2003. Aquatic Hazard Assessment II, Technical Report No. 91, ISSN-0773-8072-91, Brussels, November 2003

substances with this moiety. Therefore, the Substance is outside the applicability domain of this approach and there is no evidence to rule out that a higher ACR value applies to the Substance. Therefore, this approach is not reliable for assessing the long-term toxicity of the Substance to fish.

c) Conclusion on the weight-of-evidence

Taken together, even though the pieces of information a) and b) as indicated above may provide relevant information, their reliability is affected significantly. Therefore, they cannot contribute to the conclusion on the key investigation for this information requirement.

Accordingly, it is not possible to conclude, based on any piece of information alone or considered together, whether the Substance has or has not the properties foreseen to be investigated in an OECD TG 210 study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

v. Conclusion on your adaptations

Therefore, your adaptations are rejected.

In your comments to the draft decision, you acknowledge the rejection of the adaptation of the information requirement based on the Decision of the Board of Appeal in case A-011-2018. However, you have indicated that you do not intend to perform a long-term toxicity to fish, but to use another weight of evidence approach as a new adaptation for this information requirement. In support of this new weight of evidence approach, you have provided the following justifications:

a) The substance is fully characterised and is readily biodegradable. It will be easily removed from the aquatic environment. Exposure of the aquatic environment will be reduced. Furthermore, degradation products do not need to be considered;
b) No structural alert for protein binding was found and, based on MOA by OASIS, the mode of action of the substance is assumed to be only by narcosis;
c) Fish is not the most sensitive trophic level in the available short-term toxicity test results for the Substance;
d) Long-term toxicity testing on fish is not necessary for the PBT assessment of the Substance;
e) Unnecessary animal testing should be avoided;
f) Long-term toxicity to fish could be derived using an acute-to-chronic ratio (ACR) approach.

ECHA acknowledges these different justifications but notes that:

a) Even though exposure of the aquatic environment will be reduced as the Substance is readily biodegradable, exposure still occurs and RCR are not well below 1 as explained in point A.2. ii above;
b) There is conflicting information in the way the mode of action of the Substance is characterised. For example, model ECOSAR v1.11 (see point A.2. iv, a) above) characterises the Substance preferably as "Aliphatic Amines" instead of only by a narcotic mode of action;
c) For registrations at more than 100 tpa, REACH does not foresee that information on long-term toxicity to fish could be extrapolated from information on short-term toxicity or from information on other trophic levels;
d) Long-term toxicity testing on fish is not necessary for the PBT assessment of the Substance but is a standard information requirement of Annex XI Section 9.1.6.;
e) Animal welfare does not constitute as such a valid justification to omit the information requirement or a valid adaptation to this information requirement (see point A.2. iii above);
f) The ACR approach is not reliable (see point A.2. iv, b) above). Besides, for registrations

at more than 100 tpa, REACH does not foresee that information on long-term aquatic toxicity could be extrapolated from information on short-term aquatic toxicity.

On this basis, the information requirement is not fulfilled.

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

Appendix B: Reasons to request information required under Annex X of REACH

1. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)**

The basic test design of an Extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is a standard information requirement under Annex X to REACH. Furthermore Column 2 of Section 8.7.3. defines when the study design needs to be expanded.

You have provided a weight of evidence adaptation using the following studies:

1. TG 422 study, rel 1, made in 2007, under GLP, read-across proposed, source substance is 1-aminopropan-2-ol hydrochloride EC No 231-948-5 (HCl-MIPA). The doses are 100, 300, 1000 mg/kg. At 1000 mg/kg body weight/day: F0 parental animals: statistically significantly reduced hemoglobin and hematocrit values (i.e. indications of a mild anemic process) in the F0 males

2. "One-generation study" with a read-across substance EC No 204-528-4, 1,1',1''-nitrilotripropan-2-ol (TIPA), entitled [redacted] rel 1, according to the FDA guideline, under GLP, made in 1988. The doses were 43.7,182, and 700 mg/kg bw/day. The no-observable-effect level (NOEL) for this study was 7,500 ppm since no effects were observed at any dietary concentration in parental rats or in offspring rats prior to or after weaning.

In support of your adaptation, you have provided the source studies referred to above.

Based on the presented sources of information, you argue that
"*The OECD 422 study in rats with MIPA HCl salt showed no fertility effects up to the highest dose tested. In the oral one-generation study with TIPA in rats according to FDA guidelines, the NOAEL for the parental generation as well as the off-spring was reported to be the highest dose tested. Although the premating exposure period was five instead of 10 weeks, the endpoint fertility is considered to be covered, because adverse effects were detected neither in the parental generation nor in the offspring (exposed for 90 days after weaning; prior to weaning, in utero, by maternal milk and in any diet consumed prior to weaning). Thus, an EOGRTS (basic test design: cohorts 1A and 1B without F2 generation) is scientifically not justified. In line with REACH Annex X, 8.7.3, column 2, further testing with respect to cohort C1b (F2 generation), cohorts 2A/2B (developmental neurotoxicity) or cohort 3 (developmental neurotoxicity) is also considered not to be justified, as no adverse findings or alerts concerning these endpoints were described for MIPA or structural similar substances, e.g. DIPA and TIPA.*"

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

Annex XI, Section 1.2 states that there may be sufficient weight of evidence from several independent sources of information leading to assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

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 endpoint. 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 that the Substance has or has not the (dangerous) property investigated by the required study.

Annex XI, section 1.2 requires that adequate and reliable documentation is provided to describe your weight of evidence approach.

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

Sexual function and fertility

Sexual function and fertility on both sexes includes information on mating, fertility, gestation, parturition, lactation, organ weights and histopathology of reproductive organs and tissues, oestrous cyclicity, sperm count, sperm analysis, hormone levels, litter sizes, nursing performance and other potential aspects of sexual function and fertility.

Information on sexual function and fertility (functional fertility and histopathology of reproductive organs and tissues) must be investigated in parental P0 animals as indicated in OECD TG 443 after at least ten weeks premating exposure duration if extension of Cohort 1B is not included[6] to ensure the exposure of full spermatogenesis and folliculogenesis before mating.

In the case of your Substance, the conditions to include the extension of Cohort 1B are currently not met. The source of information (i.) investigates sexual function and fertility with the premating exposure duration of two weeks for the parental P0 animals. The other source study (ii.) investigates sexual function and fertility with the premating exposure duration of five weeks for the parental P0 animals.

Neither sources of information investigate the sexual function and fertility in the P0 generation with sufficient premating exposure duration to ensure the coverage of full spermatogenesis and folliculogenesis before mating.

In the absence of information on the sexual function and fertility after exposure to the Substance over a pre-mating period of 10 weeks, no conclusion can be drawn on sexual function and fertility as required by the information requirement.

Toxicity to the offspring

Toxicity to offspring includes information on deaths before, during or after birth, growth, sexual maturity, oestrous cyclicity, histopathology of reproductive organs in adulthood and other potential aspects of toxicity to offspring.

Information provided on toxicity to offspring is limited and does not cover all relevant and essential aspects as defined above. Neither the sources of information (i.) nor (ii.) inform on sexual maturity, oestrous cyclicity. Therefore, no conclusion can be drawn on toxicity to the offspring as required by the information requirement.

Taken together, the relevant sources of information as indicated above provide information on

- sexual function and fertility on parental P0 generation but its reliability is affected by

[6] ECHA Guidance R.7a, Section R.7.6

no sufficient premating exposure
- toxicity to offspring, but not covering sexual maturity, oestrous cyclicity.

Therefore, a significant amount of essential information is limited or totally lacking that would inform on sexual function and fertility, and toxicity to offspring in order to conclude on these aspects.

It is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 443 study with a design described in this decision. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

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

The specifications for the study design

Premating exposure duration and dose-level setting

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

Ten weeks premating exposure duration is required to obtain results adequate for classification and labelling and /or risk assessment. There is no substance specific information in the dossier supporting shorter premating exposure duration.[1]

Therefore, the requested premating exposure duration is at least ten weeks.

In order to be compliant and not to be rejected due to too low dose levels, the highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects. A descending sequence of dose levels should be selected in order to demonstrate any dose-related effect and to establish NOAELs.

If there is no relevant data to be used for dose level setting, it is recommended that range-finding results are reported with the main study.

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

In your comments to the draft decision, you suggest "the usual premating period of two weeks". You quote the ECHA Guidance R.7a, which specifies that "based on substance specific justifications the premating exposure duration may be shorter than ten weeks but should not be shorter than two weeks". Furthermore, you argue that no testicular toxicity has been observed in the available studies with the registered substances or with two analogues.

To adequately assess the fertility endpoint, ten weeks premating exposure period is needed as it covers the full spermatogenesis, sperm maturation and folliculogenesis before the mating allowing a meaningful assessment with the full spectrum of the effects after the same exposure history. Furthermore, two weeks premating exposure period may not be adequately long enough for detecting toxicity in hypothalamus-pituitary-gonad axis.

As set out in ECHA Guidance, acceptable substance-specific scientific justification for shorter than ten weeks premating exposure duration could be that effects on fertility are already adequately addressed. Furthermore, very low general toxicity, fast elimination, no distribution to sex organs, accessory sex organs and brain, and no concern on germ cell toxicity/mutagenicity would provide elements to support the substance-specific justification.

You have not provided substance specific justifications that would meet these prerequisites of a shorter duration of exposure. Therefore, the required duration of premating exposure is not revised in this decision.

In addition, in your comments you request a deadline extension. ECHA has addressed this comment in the procedural Appendix D, below.

Species and route selection

The study must be performed in rats with oral[7] administration.

[7] ECHA Guidance R.7a, Section R.7.6.2.3.2.

Appendix C: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. 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[8].

B. Test material

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

1. Selection of the Test material(s)

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

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

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

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[9].

[8] https://echa.europa.eu/practical-guides
[9] https://echa.europa.eu/manuals

Appendix D: 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 10 February 2020.

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

ECHA took into account your comments and amended the deadline.

Deadline to submit the requested information in this decision

The timeline indicated in the initial draft decision to provide the information requested was 24 months from the date of adoption of the decision.

In your comments on the draft decision, you requested an extension of the timeline to 36 months due to the EOGRTS study. You justified your request with the following arguments, which ECHA has evaluated in turn further below:

The Registrant does not agree with the requested time frame for submitting the information listed in the draft decision within 24 months from the date of the decision. Taking into account the complexity of the requested EOGRTS and based on the Registrant's experience, a time period of at least 36 months from the date of the final decision is appropriate. The Registrant wants to highlight that conducting such an EOGRTS requires a time-consuming protocol for the main study and additional work arising from potential high-dose findings and discussions of results and reporting. Furthermore, the results of the proposed pre-natal developmental toxicity study (ECHA's draft decision on a testing proposal, 27. July 2020: TPE-D-2114518193-55-01/D) should be available before even commencing the EOGRTS. Finally, the laboratories which are able to perform such complex studies, are nearly at their capacity limits; among other things particularly due to the many EOGRTSs, that need to be conducted under the REACH regulation. Hence, the Registrant kindly requests a time extension for submitting the requested information of 36 months from the date of the decision.

In relation to your arguments underpinning your request for an extension of the imposed timeline, ECHA notes the following:

- *The Registrant wants to highlight that conducting such an EOGRTS requires a time-consuming protocol for the main study and additional work arising from potential high-dose findings and discussions of results and reporting.*

There is planning time included for these purposes in the EOGRTS deadline. ECHA considers that you have not provided any justification to extend the deadline based on the exceptional specificities of the Substance or the specific circumstances of your case.

- *"Finally, the laboratories which are able to perform such complex studies, are nearly at their capacity limits; among other things particularly due to the many EOGRTS, that need to be conducted under the REACH regulation."*

  ECHA requested the registrant to substantiate the above laboratory over capacity claim. You have provided a justification to extend the deadline based on the over capacity of the laboratory.

- *"Furthermore, the results of the proposed pre-natal developmental toxicity study (ECHA's draft decision on a testing proposal, 27. July 2020: TPE-D-2114518193-55-01/D) should be available before even commencing the EOGRTS."*

The testing proposal draft decision has been notified to the Member States at the same time with the present decision. ECHA understands that the test design of the EOGRTS study is only dependent on the result of the 90-day study. ECHA has considered the 90-day toxicity results for the present draft decision. In addition, you have provided no justification to extend the deadline based on the specificities of the Substance.

ECHA has considered your arguments and has partially granted the request based on the indication that the testing facilities are heavily booked and set the deadline to 36 months.

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

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

Appendix E: List of references - ECHA Guidance[10] and other supporting documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)[11]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[11]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents[12]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

[10] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[11] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[12] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

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

You must provide the information requested in this decision for all REACH Annexes applicable to you.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[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.