~~Confidential~~

Helsinki, 19 January 2021

**Addressees**
Registrants of 62-56-6_Thiourea as listed in the last Appendix of this decision

**Date of submission of the dossier subject to this decision**
01/03/2016

**Registered substance subject to this decision ("the Substance")**
Substance name: thiourea; thiocarbamide
EC number: 200-543-5
CAS number: 62-56-6

**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 ***26 April 2023***.

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

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

1. Skin sensitisation (Annex VII, Section 8.3.) with the Substance

   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 i.) 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)

2. *In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14./OECD TG 471), using one of the following strains: *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102

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

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

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

1. In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2.; test method: OECD TG 473) or In vitro micronucleus study (Annex VIII, Section 8.4.2.; test method: OECD TG 487)

2. Only if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. is obtained, In vitro gene mutation study in mammalian cells;

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

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

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

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

Reasons for the request(s) are explained in the following appendices:

- Appendix entitled "Reasons common to several requests";
- Appendices entitled "Reasons to request information required under Annexes VII to IX 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 Annex VII to REACH, for registration at 1-10 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.

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". In addition, you should follow the general recommendations provided under the Appendix entitled "General recommendations 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 on Reasons common to several requests**

**1. Assessment of the weight of evidence adaptations under the requirements of Annex XI, section 1.2**

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

- In vitro gene mutation study in bacteria
- Short-term toxicity testing on aquatic invertebrates
- Growth inhibition study aquatic plants
- In vitro cytogenicity study in mammalian cells or In vitro micronucleus study
- In vitro gene mutation study in mammalian cells
- Screening for reproductive/developmental toxicity
- Extended one-generation reproductive toxicity study
- Pre-natal developmental toxicity study
- Long-term toxicity testing on aquatic invertebrates

Your weight of evidence adaptation has a decifiency that is common to all of the information requirements for which it is used. Accordingly, ECHA has addressed this common deficiency in the present Appendix, before assessing specific issues with your weight of evidence adaptations under the corresponding standard information requirements in the other appendices.

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 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 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.

However, you have not included a justification for your weight of evidence adaptations for each of the relevant information requirement, which would include an adequate and reliable (concise) documentation as to why the sources of information provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

In spite of this critical deficiency, which in itself could lead to rejection of the adaptation, ECHA has nevertheless assessed the validity of your adaptations in the Appendices below.

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

### 1. Skin sensitisation

Skin sensitisation is an information requirement under Annex VII (Section 8.3.).

You have provided the following information in your dossier, based on which you conclude that the Substance is not a skin sensitiser:

i. An *in vivo* OECD TG 406 from 1981, with negative results.

To fulfil the information requirement, as specified in the Annex VII, Section 8.3., Column 1 to the REACH Regulation, the following aspects must be covered:
A) whether the Substance causes skin sensitisation, and
B) whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A), in case, the Substance is considered to be a skin sensitiser.

**A) Assessment of whether the Substance causes skin sensitisation**
You have provided an OECD TG 406 study according to the Guinea Pig Maximization test method.

We have assessed this information and identified the following issue:

To be considered compliant and enable concluding whether the Substance causes skin sensitisation, a study has to meet the requirements of the OECD TG 406. The following key parameter(s) of this test guideline include:

a) The concentration used for induction should be the highest to cause mild-to-moderate skin irritation and the concentration used for challenge should be the highest non-irritant concentration.

   In your dossier, it is unclear what concentration was used and whether intradermal induction caused irritation. Your comments on the draft decision are based on an assumption that the study followed the provisions of OECD 406. Your assumption is based on the fact that the study used a dose leading to irritation after intradermal application or that the concentrations used in the percutaneous induction phase and the challenge phase are sufficient. However, you do not submit with your comments any factual evidence allowing your assumption to be verified. Therefore, your comments do not clarify what concentration was used and whether intradermal induction caused irritation.

b) If the substance is not a skin irritant, sodium lauryl sulphate (SLS) in vaseline should be used in order to create a local irritation.

   As the substance is not irritating to the skin, SLS should have been used but this is not reported in your dossier. In your comments on the draft decision, you argue that the use of SLS seems to be dispensable, because during the intradermal induction period, the test material is applied with FCA to create local inflammation and consequently enhance the immune response. Furthermore, you argue that SLS might induce hyperirritability of the skin which can lead to false-positive skin reactions after treatment with the test material. However, due to the lack of reporting on whether the topical application of the substance during induction caused irritation without SLS, it is not possible to assess whether the topical induction dose was high enough.

c) An adequate number of exposures as scheduled in OECD 406 is used;

However, in your dossier the number of exposures used is not clear. In your comments on the draft decision you provided further information on exposures and doses used showing that the topical induction and challenge concentrations were the same. However, the same concentration cannot be the dose causing mild to moderate irritation and the highest non-irritating concentration. In addition, it is not clear at which point during the study the different exposures were given. OECD 406 specifies the following schedule: Intradermal induction on day 0 / Topical induction on day 5 to 7 / Challenge day: 20-22. The information in the dossier shows that intradermal induction was on day 0 but the challenge is on day 7 and the comments do not provide further information on this aspect. Therefore, your comments do not clarify the number of exposures used nor the schedule.

d) Details on negative and positive controls must be provided;

However, no negative control data are provided in your dossier. In your comments on the draft decision you challenge the need of a negative control for this study. Nevertheless, the reporting of control animals is an explicit specification in the test guideline.

e) Readings should be performed at appropriate times, namely at 48h and 72h from the start of the challenge.

However, only the results from the 3rd reading were provided in your dossier (72h after challenge). In your comments on the draft decision you state that "*According to the original study report, skin reactions were assessed after 24 h and 48 h, following the challenge experiment.*" However, you do not provide the results from these other readings. Therefore, contrary to the specification in the test guideline, it is still not clear how many and when the readings were done.

Therefore the study does not fulfil the key parameters set in the EU method B.6/OECD TG 406 and does not allow to make a conclusion whether the Substance causes skin sensitisation.

**B) Assessment of whether the Substance can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A).**

As the currently available data does not allow to conclude whether the Substance causes skin sensitisation, this condition cannot be assessed.

In your comments on the draft decision you refer to several human studies provided in IUCLID in section 7.10.4. (Sensitisation data in humans). However, in the dossier all of the human data have been flagged as unreliable (reliability 4). Nevertheless, they still raise a concern, as indications of skin sensitisation has been seen. You also commented that "*MAK commission recognized the occurrence of sensitisation reactions to thiourea by designating thiourea to substances where there is a danger of sensitisation of the skin and photocontact sensitisation, this is not sufficient for classification according to the CLP criteria (The MAK collection for occupational health and safety; Occupational Toxicants, Vol. 14 (2000))*.". However, it is noted that MAK report (2000) also concluded that there is a danger for skin sensitisation, and did not conclude that "*this is not sufficient for classification according to the CLP criteria*" i.e. the Classification, Labelling and Packaging (CLP) Regulation (EC) nº 1272/2008 was not in force at that point of time and this statement was not there. Moreover, there are no statements related to the Dangerous Substance Directive 67/548/EC in the MAK report, just a conclusion that "*In view of the usually grave consequences for those affected, contact or photocontact allergy to thiourea, in particular with the development of a persistent reaction*

*to light, thiourea has nevertheless been designated with "Sh" and "SP" (for substances where there is a danger of sensitization of the skin and of photocontact sensitization). There is no evidence that the substance has potential to cause sensitization of the airways.".* According to the classification criteria of the CLP Regulation, some of the positive incidence level indicate high frequencies, e.g. in study by [redacted] (2005) (not referred to in your comments but provided in the dossier) 2.4% showed positive reactions. For all these reasons, the potential of the substance to produce significant sensitisation in humans cannot be assessed based on the information currently available.

Therefore, the information requirement is not fulfilled.

To fulfil the information requirement for the Substance for skin sensitisation, *in vitro/in chemico* studies (OECD TG 442C, 442D and 442E) are considered suitable. In case *in vitro/in chemico* methods are not suitable for the Substance or the results cannot be used for classification and risk assessment an *in vivo* skin sensitisation study must be performed and the murine local lymph node assay (LLNA) (OEDC TG 429) is considered as the appropriate study.

**2. In vitro gene mutation study in bacteria**

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

You have adapted the standard information requirement under Annex XI, Section 1.2. of REACH (weight of evidence). In support of your adaptation, you have provided the following sources of information with the Substance:

1) Determination of cytotoxicity, mutagenicity and micronucleus induction in V79 cells and hepatocytes of the rat, [redacted]. 1989.
2) Genetic toxicity *in vitro* study in mammalian cells, [redacted] 1998.
3) *In vitro* gene mutation study in mammalian cells, Wangenheim et al. 1988.
4) *In vitro* gene mutation study in mammalian cells, Caspary et al. 1988.
5) *In vitro* DNA damage and repair assay, unscheduled DNA synthesis in mammalian cells, Fautz et al. 1991.
6) Mammalian cell cytogenetics assay, [redacted] 1978 (equivalent or similar to OECD 479 (*In Vitro* Sister Chromatid Exchange Assay in Mammalian Cells)
7) *In vitro* mammalian cell micronucleus test, Fritzenschaf et al. 1993.
8) DNA repair assay (gene mutation), Korte and Greim 1981 (equivalent or similar to OECD Guideline 482 (Genetic Toxicology: DNA Damage and Repair, Unscheduled DNA Synthesis in Mammalian Cells *In Vitro*)
9) Genetic toxicity *in vitro* study in *aspergillus*, Crebelli et al. 1986.
10) DNA repair test using derivatives of *E. coli* K-12 343/113, Hellmer and Bolcsfoldi, 1992.
11) Microsome test and SOS chromotest in bacteria, Brams et al. 1987.
12) *In vitro* gene mutation study in mammalian cells, Morita et al. 1989.
13) Genetic toxicity *in vitro* study in *Saccharomyces cerevisiae*, Zuoshu et al. 1989.
14) *In vitro* gene mutation study in mammalian cells, Schiesti et al., 1989.
15) *In vitro* DNA damage and/or repair study in *S. typhimurium* TA 1535 pSK1002, Nakamura et al. 1987.
16) *In vitro* gene mutation study in bacteria, Zeiger et al. 1988.
17) *In vitro* gene mutation study in bacteria, [redacted] 1977 (equivalent or similar to OECD Guideline 471).
18) *In vitro* gene mutation study in bacteria, Korte and Greim 1981 (equivalent or similar to OECD Guideline 471).

19) In the endpoint summary, you stated that "*to emphasise the amount of available, ambiguous data*" you provided a table (Table 1) with results only from the studies in the dossier as well as from secondary literature studies "*referred to in IPCS 2003, Health Canada 2008, IARC 2001, or MAK 1990*". From the secondary literature, 7 additional studies in bacterial cells were reported.

To fulfil the information requirement, normally a study performed according to the OECD TG 471 (1997) must be provided. The OECD TG 471 investigates gene mutations in bacteria using 5 different bacterial strains.

The sources of information 1 to 15 do not investigate gene mutations in bacterial strains as required by OECD TG 471. Therefore, these sources of information do not provide relevant information that would contribute to the information investigated by OECD TG 471.

The sources of information 16 to 19 provide relevant information on *in vitro* gene mutations in bacteria. Korte and Greim 1981, investigated gene mutation in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and 1538 and [redacted] (1977) investigated gene mutation in *S. typhimurium* TA 1535, TA 1537, TA 1538, TA 98 and TA 100 and E. coli uvrA-.

However, the reliability of these sources of information is significantly affected by the following deficiencies:

a) Some of the specifications/conditions of OECD TG 471 (1997) include that:
   - the test must be performed with 5 strains: four strains of *S. typhimurium* (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101);
   - the maximum dose tested must induce a reduction in the number of revertant colonies per plate compared to the negative control;
   - one positive control must be included in the study.

   However, the reported data for source of information 18 does not include results for the required fifth strain, *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101). The reported data for source of information 17 indicates that the highest concentration was too low to induce a reduction in the number of revertant colonies per plate compared to the negative control. Also this study 17 had no information on the positive control.

   Therefore, source of information 18 does not investigate the specificity of the fifth strain which may detect certain oxidising mutagens, cross-linking agents and hydrazines, that the other four strains cannot detect. Moreover, while source of information 17 investigates the five required strains, because of the issues indicated above the study is affected by significant deficiencies and cannot contribute to providing the information investigated by OECD TG 471.

b) Pursuant to Article 10(a)(vii) of the REACH Regulation, the information set out in Annex VII to XI must be provided in the form of a robust study summary. Article 3(28) defines a robust study summary as 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 minimising the need to consult the full study report.

   However, for sources of information 16 and 19 you have not provided adequate and reliable documentation in the form of a robust study summary, as required by Article 10(a)(vii) and Article 3(28). Source of information 16 does not have a robust study

summary and the 7 additional studies referred to in source of information 19, whose results are mentioned in the endpoint summary, were not included in the IUCLID dossier.

Taken together, the sources of information 16 to 19 provide information on gene mutations in bacteria, but their reliability is affected so significantly that they cannot be taken into consideration in a weight of evidence approach.

On the basis of the information provided in the Appendix on Reasons common to several requests and on the above 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 property foreseen to be investigated in an OECD TG 471. Therefore, your adaptation is rejected and the information requirement is not fulfilled. In your comments on the draft decision you indicated your agreement to perform the requested study.

*Information on the study design*

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

### 3. Short-term toxicity testing on aquatic invertebrates

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

You have adapted this standard information requirement under Annex XI, Section 1.2. of REACH (weight of evidence). In support of your adaptation, in your registration dossier you have provided the following sources of information:

i. Study from NAPM, 1974 (non Guideline study);
ii. Study from Broecker *et al.*, 1984 (non Guideline study);
iii. Study from Schmidt-Bleek *et al.*, 1982 (non Guideline study);
iv. Study from [redacted], 1992 (DIN 38412 Part 11 - modified),
v. Study from [redacted] 1984 ((non Guideline study).

Furthermore, in your comments on the draft decision, you acknowledge that the reported results for the studies listed above vary widely (from 4000-6000 mg/L to 5.6 mg/L) and that there are remaining uncertainties with your weight of evidence adaptation. You proposed to further strengthen the weight of evidence by providing the following additional information:

vi. an additional OECD TG 202 study on the Substance from the Japanese Ministry of the Environment;
vii. a QSAR prediction using T.E.S.T. by US EPA (IC50 predicted to be 7.48 mg/L using the Consensus method);
viii. a QSAR prediction using ECOSAR (IC50 predicted to be 6.84 mg/L).

To fulfil the information requirement, normally a study performed according to OECD TG 202 must be provided. OECD TG 202 requires the study to investigate the following key parameter:

- the concentration of the test material leading to the immobilisation of 50% of daphnids at the end of the test.

The sources of information (i.) to (viii.) provide relevant information on the concentration of the Substance leading to the immobilisation of 50% of daphnids at the end of the exposure period.

However, the reliability of these sources of information included in your registration dossier or provided as part of your comments on the draft decision is significantly affected by the following deficiencies:

A. *The experimental evidence from your registration dossier and your comments on the draft decision are not reliable:*

For a study conducted according to OECD TG 202, the following specifications must be met:

*Validity criteria*
- the percentage of immobilised daphnids is ≤ 10% at the end of the test in the controls (including the solvent control, if applicable);

*Technical specifications impacting the sensitivity/reliability of the test*
- the test duration is 48 hours or longer;
- young daphnids, aged less than 24 hours at the start of the test, are used;
- test animals are not fed during the test;
- at least 20 animals are used at each test concentration and for the controls;
- the concentrations of the test material are measured at least at the highest and lowest test concentration, at the beginning and end of the test;
- the effect values can only be based on nominal or measured initial concentration if the concentration of the test material has been satisfactorily maintained within 20 % of the nominal or measured initial concentration throughout the test (see also ECHA Guidance R.7b, Section R.7.8.4.1);

*Reporting of the methodology and results*
- the test design is reported (*e.g.* test concentrations, number of replicates)
- the test procedure is reported (*e.g.* composition of the test medium, loading in number of *Daphnia* per test vessel);
- the number of immobilised daphnids determined at 24 hours intervals are summarised in tabular form for each treatment group and control.

However, on source of information i., your dossier provides the following information:
- the test was conducted on "*two week old young daphnia*";
- you report that 10 to 20 animals were used per test vessel and you did not indicate that replicate test vessels were prepared at each test concentration and in the control;
- on the test design and procedure, you have not specified at what test material concentrations the test was conducted, the composition of the test medium and if the test animals were fed during the test;
- information on the analytical verification of exposure concentrations is not provided;
- the number of immobilised daphnids determined at 24 hours intervals for each treatment group and control is not provided.

On source of information ii., your dossier provides the following information:
- you specify that the information reported originate from secondary literature and that the original reference is not available;
- the test guideline used is not specified and key information is missing on the test design and procedure (e.g. number of replicate, number of test animals, age of test animals, composition of the test medium);
- the test duration was 24 hours;
- information on the analytical verification of exposure concentrations is not

provided;
- the number of immobilised daphnids determined at 24 hours intervals for each treatment group and control is not provided.

On source of information iii., your dossier provides the following information:
- you specify that the information reported originate from secondary literature;
- the test guideline used is not specified and key information is missing on the test design and procedure (e.g. number of replicate, number of test animals, age of test animals, composition of the test medium);
- you specify that "*Test duration was not reported*";
- information on the analytical verification of exposure concentrations is not provided;
- the number of immobilised daphnids determined at 24 hours intervals for each treatment group and control is not provided.

On source of information iv., your dossier provides the following information:
- you specify that the "*documentation* [is] *insufficient for assessment*";
- key information is missing on the test design and procedure (e.g. age of test animals, composition of the test medium);
- you specify that no monitoring of exposure concentrations was conducted;
- the number of immobilised daphnids determined at 24 hours intervals for each treatment group and control is not provided.

On source of information v., your dossier provides the following information:
- you specify that the information reported originate from secondary;
- the test guideline used is not specified and key information is missing on the test design and procedure (e.g. number of replicate, number of test animals, age of test animals, composition of the test medium);
- the test duration was 24 hours;
- information on the analytical verification of exposure concentrations is not provided;
- the number of immobilised daphnids determined at 24 hours intervals for each treatment group and control is not provided.

On source of information vi. provided in your comments on the draft decision, you have provided no information on how the effect value was obtained apart from stating the the study was conducted according to OECD TG 202. However, based on the information reported in the Japan CHEmical Collaborative Knowledge database (J-CHECK), we note the following:
- it is specified that dechlorinated tap water was used as dilution water. However, the composition of the test medium is not reported;
- the life-stage of the test organisms is not reported;
- it is specified that the analytical monitoring of exposure concentrations was conducted using HPLC-MS. However, no information is provided on the performance parameters of the analytical method or the determination of exposure concentrations during the test;
- the number of immobilised daphnids determined at 24 hours intervals for each treatment group and control is not provided.

Based on the above there are major deficiencies impacting all sources of evidence provided in support of your weight-of-evidence adaptation, including the following:
- *Missing information on study design and procedure:* none of the robust study summaries included in your dossier or the additional study referred to in your comments on the draft decision provides adequate information to verify if the

test design and test conditions were consistent with the requirements of OECD TG 202 (e.g. in terms of test medium composition, pH, dissolved oxygen concentration, absence of feeding during the test). This leads to significant uncertainty with regard to the reliability of these studies;

- *Exposure duration*: the exposure duration was shorter (i.e. 24 hours) for study ii. and v. or unknown for study iii and iv. Shorter test duration reduces the sensitivity of the test and leads to an underestimation of the intrinsic toxicity of the substance tested. Therefore, these studies do not provide a reliable estimate of the % immobilisation of daphnids after 48 hours;
- *Verification of exposure*: no analytical verification of exposure was conducted in any of the studies included in your registration dossier. Therefore, you have not demonstrated that effect values can reliably be based on nominal test material concentrations. For study vi., an analytical verficiation of exposure concentration is claimed to have been conducted. However, key information are missing to verify the validity of the analytical method and of the effect values that is reported.
- *Life stage of the test organisms*: study i. was not conducted on neonates and the life stage of Daphnia is not specified in any of the other studies. Testing non-neonates test organisms will negatively impact the sensitivity of the test and therefore the reported results are not reliable;
- *Number of test organisms*: the number of test organisms per test concentrations was < 20 in study i. and this information is not specified for study ii., iii. and v. A lower number of test organisms leads to a lower statistical power to detect differences compared to control therefore impacting the reliability of the reported effect values;
- *Available information on the study results*: as you have not provided the number of immobilised daphnids determined at 24 hours intervals for each treatment group and control for any of the reported studies, it is not possible to verify the number of immobilised Daphnia in the controls at the end of the test or if the reported effect values are consistent with the test results.

Due to these significant deficiencies, the sources of information i. to vi. do not provide adequate and reliable coverage of the key parameter addressed in OECD TG 202. Therefore, the reliability of such information in support of your weight of evidence adaptation under Annex XI, Section 1.2 is considered low.

B. *Inadequate documentation of the T.E.S.T model (QMRF) (source of information vii.provided in your comments on the draft decision)*

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

- the predicted endpoint, including information on experimental protocol and data quality for the data used to develop the model.

However, the documentation available on the model does not include information on the experimental protocols and data quality for the data used to develop the model.

In the absence of such information, ECHA cannot establish that the model can be used to meet this information requirement. Therefore, the reliability of such information in support of your weight of evidence adaptation under Annex XI, Section 1.2 is considered low.

C. *Robustness of the ECOSAR model (source of information viii. provided in your comments on the draft decision)*

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. For that purpose, the fourth OECD principle requires that appropriate measures of the internal performance (i.e. goodness-of-fit and robustness using the learning data set) and predictivity (using a test data set) of the model are available.

Furthermore, to have appropriate robustness, a model must be built from a training set which includes a sufficient number of observations (i.e. data). The minimum number of observations depends on the number of variables or descriptors included in the model. The ratio between the number of observations and the number of variables or descriptors must be at least 5.

The ECOSAR model includes the substance in the training set and the prediction does not represent an external prediction. Therefore, this model does not provide any appropriate measure of predictivity. Futhermore, the training set is based on a single measured value for the Substance. Therefore, independent of the lack of appropriate measure of predictivity this model does not have appropriate robustness as the ratio between the number of observations and the number of variables or descriptors is too low.
On this basis, the validity of this model to predict the properties of the Substance is not established. Therefore, the reliability of such information in support of your weight of evidence adaptation under Annex XI, Section 1.2 is considered low.

As explained above, there are a number of major deficiencies impacting the reliability the individual sources of information included in your weight-of-evidence. In your comments on the draft decision, you agreed with the deficiencies and missing information identified in the studies listed in your registration dossier. Concerning the additional QSAR predictions provided in your comments on the draft decision (sources of information vii. and viii. listed above), you acknowledge that "*both predictions are based on a small sample size of available studies and therefore the explanatory power is limited*" and, as explained above, we agree that the scientific validity of these models to predict the properties of the Substance is not demonstrated. On the additonnal experimental study referred to in your comments on the draft decision (source of information vi. listed above), the available information does not allow conducting an independent assessment of its reliability. Therefore, the additional information referred to in your comments on the draft decision does not provide significant additional weight to your weight of evidence adaptation.
Considering the severity of the deficiencies listed above, it cannot be concluded with sufficient confidence what is the concentration of the Substance leading to the immobilisation of 50% of daphnids at the end of a 48 hours exposure period.

On the basis of the information provided in the Appendix on Reasons common to several requests and on the above, 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 202 study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

## 4. Growth inhibition study aquatic plants

Growth inhibition study aquatic plants is an information requirement under Annex VII to

REACH (Section 9.1.2).

You have adapted this standard information requirement under Annex XI, Section 1.2. of REACH (weight of evidence). In support of your adaptation, you have provided the following sources of information:

i. Study from Geyer *et al.*, 1985 (non Guideline study);
ii. Study from [redacted] 1984 (non Guideline study).

To fulfil the information requirement, normally a study performed according to OECD TG 201 must be provided. OECD TG 201 requires the study to investigate the following key parameters:

- the concentrations of the test material leading to a 50 % and 0% (or 10%) inhibition of growth at the end of the test. Growth must be expressed as the logarithmic increase in biomass (average specific growth rate) during the exposure period.

Source of information (ii.) only provides information on inhibition of yield (i.e. cell number) rather than inhibition of growth and is therefore not relevant for this information requirement.

In your comments on the draft decision, you specify that "*in the study report the inhibition of the growth based on the measurement of the optical density is given, in IUCLID the wrong "basis for effect" was used*". We note that your comment does not clarify whether or not the reported effect values refers to an inhibition of growth, where growth is expressed as the logarithmic increase in biomass (average specific growth rate) during the exposure period. However, while the relevance of this information remains unclear, we have nevertheless further assessed the overall reliability of the reported information below.

Source of information (i.) provides relevant information on the concentrations of the Substance leading to a 50 % and 0% (or 10%) inhibition of growth (based on specific growth rate) at the end of the test.

However, the reliability of source of information (i. and ii.) is significantly affected by the following deficiency:

For a study conducted according to OECD TG 201, the following requirements must be met:

*Validity criteria*

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

*Technical specifications impacting the sensitivity/reliability of the test*

- the concentrations of the test material are measured at least at the beginning and end of the test:
  1) at the highest, and
  2) at the lowest test concentration, and
  3) at a concentration around the expected $EC_{50}$.

- the effect values can only be based on nominal or measured initial concentration if the concentration of the test material has been satisfactorily maintained within 20 % of the nominal or measured initial concentration throughout the test (see also ECHA Guidance R.7b, Section R.7.8.4.1);

*Reporting of the methodology and results*

- the results of algal biomass determined in each flask must at least daily during the test period are reported in a tabular form;
- Algal biomass is determined based on dry weight per volume, or alternatively as cell counts or biovolume using microscopy or an electric particle counter. If an alternative method is used (*e.g.* flow cytometry, *in vitro* or *in vivo* fluorescence, or optical density), a satisfactory correlation with biomass must be demonstrated over the range of biomass occurring in the test.

However, source of information i. and ii. provides the following information:

- biomass was determined based on optical density. You have not provided information to support that the method allows a satisfactorily correlation with biomass over the range of biomass occurring in the test;
- you have not provided any information on the analytical verification of exposure concentrations;
- you have not provide the results of algal biomass determinations in each flask at least daily during the test period.

Based on the above, as you have not provided the results of algal biomass determinations in each flask at least daily during the test period, it is not possible to verify that the validity criteria applicable to OECD TG 201 were met in any of these studies. Then, you have not demonstrated that the method used to determine algal biomass was adequate to monitor inhibition of growth. Finally, as no analytical verification of exposure was conducted in any of these studies, you have not demonstrated that effect values can be based on nominal test material concentrations. Considering the severity of these deficiencies, it cannot be concluded with sufficient confidence what are the concentrations of the Substance leading to a 50 % and 0% (or 10%) inhibition of growth (based on specific growth rate) at the end of the test.

In your comments on the draft decision, you acknowledge that the missing information listed above is not available for any of the reported studies.

Due to these significant deficiencies, the sources of information i. and ii. do not provide an adequate and reliable coverage of the key parameter addressed in OECD TG 201. Therefore, the reliability of such information in support of your weight of evidence adaptation under Annex XI, Section 1.2 is considered low.

Considering the severity of the deficiencies listed above, it cannot be concluded with sufficient confidence what is the concentration of the Substance leading to a 50 % and 0% (or 10%) inhibition of growth at the end of the test.

In your comments on the draft decision, you further state that "*currently no classification for acute toxicity is triggered as the EC50 values of all species are above 1 mg/L.* [...] *Consequently, a change in the classification and labelling (i.e.aquatic acute toxicity) is not anticipated*". However, for the reasons explained in the appendix as well as in appendix A.4., the information requirements for short-term toxicity on aquatic invertebrates and growth inhibition on aquatic plants are not met. In the absence of reliable information to cover these information requirements, it cannot be anticipated whether or not the Substance would meet the classification criteria for acute toxicity. We also emphasize that the absence of (or low)

toxicity observed for a given trophic level is not a compelling evidence to demonstrate the absence of (or low) toxicity for other trophic levels.

Finally, you consider that the prolonged exposure (96 hours) in study ii. above, in combination with the reported effect values being above 1 mg/L, indicates that conducting a new growth inhibition study in algae would not lead to a change of classification for acute aquatic toxicity. However, for the reasons already explained above this source of information is not reliable. Furthermore, the exposure duration is on its own not sufficient to demonstrate that a study provides conservative estimates of the toxicity of a substance. Many other considerations have to be taken into account including among others the test design and procedure, the analytical verification of exposure concentrations as well as the results of the monitoring of algal growth during the test.

Therefore, none of these additonnal considerations included in your comments on the draft decision provide any additional weight to your weight of evidence adaptation.

On the basis of the information provided in the Appendix on Reasons common to several requests and on the above, 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 201 study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

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

### 1. In vitro cytogenicity study in mammalian cells or In vitro micronucleus study

An *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study is an information requirement under Annex VIII (Section 8.4.2.).

You have adapted the standard information requirement according to Annex XI, Section 1.2.) of REACH (weight of evidence).

In support of your adaptation, you have provided the following sources of information with the Substance:

You provided the same sources of information 1) to 19) as listed under section A.2 above.

To fulfil the information requirement, normally a study performed according to OECD TG 473/487 must be provided. OECD TG 473/487 requires the study to investigate the following key parameters:

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

Sources of information 1) to 6) and 8) to 18), do not investigate structural or numerical chromosomal aberrations in cultured mammalian cells. Specifically, these are studies addressing genetic toxicity in microorganisms 9) to 18) or gene mutation in mammalian cells 1) to 5) and 8). The information provided in source of information 6) and 8) provides an indication of induced damage to DNA (but not direct evidence of mutation) via the detection of reciprocal exchanges of DNA between two sister chromatids of a duplicating chromosome. Therefore, these studies are not relevant as they do not address chromosomal aberration in mammalian cells.

Sources of information 7) and 19) provide relevant information on structural or numerical chromosomal aberrations in cultured mammalian cells. However, the reliability of these sources of information is significantly affected by the following deficiency:

- Pursuant to Article 10(a)(vii) of the REACH Regulation, the information set out in Annex VII to XI must be provided in the form of a robust study summary. Article 3(28) defines a robust study summary as 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 minimising the need to consult the full study report.

  However, source of information 7) has no robust study summary and the 5 additional studies referred to in source of information 19), whose results are mentioned in the endpoint summary, were not included in the IUCLID dossier in the form of a robust study summary, as required by Article 10(a)(vii) and Article 3(28).

In your comments to draft decision you commited to substantiate the weight-of-evidence approach by providing appropriate robust study summaries for the sources of information used in this approach. However, this information is not currently available and assessed only during in the stage of follow-up.

In your comment, you refered to an available *in vivo* micronucleus test and which does not show any evidence for structural or numerical chromosomal aberrations. ECHA assumes you

refer to the study of [redacted] 1979, considered equivalent or similar to OECD Guideline 474 (Mammalian Erythrocyte Micronucleus Test), no GLP. However, the following deficiencies were noted with this study:

- The test samples were administered twice with an interval of 24 h. Six hours after the last treatment, the animals were killed. OECD 474 states that "*If 2 daily treatments are used (e.g. two treatments at 24 hour intervals), samples should be collected once between 18 and 24 hours following the final treatment for the bone marrow*". However, in this study the samples were collected 6h following the last treatment. The described harvest times in the testing guideline are a consequence of the kinetics of appearance and disappearance of the micronuclei in the tissue compartment and an earlier sampling may lead to false negative results.
- Only one dose of 350 mg/kg bw was used instead of 3 doses as per OECD 474 which states that "single treatments can be administered, if scientifically justified (e.g. test chemicals known to block cell cycle)." Nevertheless, no justification for single dose was provided in this case.

Due to the above mentioned important deficiencies the study cannot be considered reliable. Therefore, the information requirements is not fulfilled.

Taken together, even if the sources of information provide information on structural or numerical chromosomal aberrations in cultured mammalian cells, their reliability is affected so significantly that they cannot be taken into consideration in a weight of evidence approach.

Consequently for this endpoint, on the basis of the information provided in the Appendix on Reasons common to several requests and on the above, 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 473 or OECD TG 487 study. Therefore, your adaptation is rejected and the information requirements is not fulfilled.

In your comments to draft decision you commited to substantiate the weight-of-evidence approach by providing appropriate robust study summaries for the sources if information used in this approach. However, this information is not currently available and cannot be taken into account in the assessment of compliance of the dossier with the information requirement.

*Study design*

To fulfil the information requirement for the Substance, either *in vitro* cytogenicity study in mammalian cells (OECD TG 473) or *in vitro* micronucleus study (OECD TG 487) are considered suitable.

**2. Only if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. is obtained, In vitro gene mutation study in mammalian cells**

An *in vitro* gene mutation study in mammalian cells is a standard information requirement in Annex VIII to REACH in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test.

*Triggering of the study*

Your dossier contains an adaptation (weight of evidence) for an *in vitro* gene mutation study in bacteria, and an adaptation (weight of evidence) for an in vitro cytogenicity study in mammalian cells or *in vitro* micronucleus study.

The information for the *in vitro* gene mutation study in bacteria and for the *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study provided in the dossier are rejected for the reasons provided in sections A.2 and B1 of this draft decision.

The result of the requests for information in A.2 and B.1 of this decision will determine whether the present requirement for an *in vitro* mammalian cell gene mutation study in accordance with Annex VIII, Section 8.4.3 is triggered.

*Assessment of the information provided*

You have adapted the standard information requirement according to Annex XI, Section 1.2. Weight of evidence of REACH.

In support of your adaptation you have provided the following sources of information with the Substance:

You provided the same sources of information 1) to 19) as listed under section A.2 above.

To fulfil the information requirement, normally a study performed according to OECD TG 476/490 must be provided. OECD TG 476/490 requires the study to investigate the following: detection and quantification of gene mutations (point mutations, frame-shift mutations, small deletions, etc.) in cultured mammalian cells including data on the frequency of mutant colonies.

The sources of information 6) to 18) do not provide information on *in vitro* gene mutations in cultured mammalian cells that would contribute to the conclusion on the information investigated by OECD TG 476/490. They investigate in vitro cytogencity or gene mutation in bacterial cells.

Regarding the sources of information provided under 1) to 5) and 19), these studies provide relevant information on gene mutation in mammalian cells. However, the reliability of these sources of information is significantly affected by the following deficiency:

> Pursuant to Article 10(a)(vii) of the REACH Regulation, the information set out in Annex VII to XI must be provided in the form of a robust study summary. Article 3(28) defines a robust study summary as 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 minimising the need to consult the full study report.
>
> However, you have not provided adequate and reliable documentation in a form of robust study summaries, as required by Article 10(a)(vii) and Article 3(28). The 5 additional studies covered by source of information (19), whose results are mentioned in the endpoint summary, were not included in the IUCLID dossier.

Consequently, the studies 1) to 5) and 19) cannot be taken into consideration in a weight of evidence approach.

On the basis of the information provided in the Appendix on Reasons common to several requests and on the above, 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 476 or OECD TG 490 study. Therefore, your adaptation is rejected and the information requirements is not fulfilled.

In your comment to draft decision you indicate your intention to update the dossier with robust studies summaries for the studies provided on this endpoint. However, this information is not currently available and cannot be taken into account in the assessment of compliance with the information requirement.

*Study design*

To fulfil the information requirement for the Substance, either the *in vitro* mammalian cell gene mutation tests using the hprt and xprt genes (OECD TG 476) or the thymidine kinase gene (OECD TG 490) are considered suitable.

## 3. Screening for reproductive/developmental toxicity

A screening for reproductive/developmental toxcity study is a standard information requirement in Annex VIII to REACH.

You have adapted the standard information requirement according to Annex XI, Section 1.2. of REACH (weight of evidence).

You have provided the following information:

i. Alavi Shoushrari 1993, sub-chronic study.
ii. Sokkar et al. 2000, sub-chronic study.
iii. Fitzhugh and Nelson 1948, chronic study.
iv. Reddy et al. 1998, equivalent or similar to OECD Guideline 415 [One-Generation Reproduction Toxicity Study (before 9 October 2017)].

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.7.3 at Annex VIII includes similar information that is produced by the OECD TG 421/422. At general level, it includes information on the following key elements: 1) sexual function and fertility, 2) toxicity to offspring, 3) systemic toxicity and 4) Specific investigations for hormonal activity.

*1) Sexual function and fertility*

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
- histopathology of reproductive organs and tissues,
- litter sizes,
- nursing performance and other potential aspects of sexual function and fertility.

The pieces of evidence (i.) to (iii.) are subchronic studies that can provide partially relevant information, i.e. information on organ weights and histopathology of reproductive organs. However, they are missing essential key investigations required for sexual functions and fertility such as: mating, gestation, maintenance of pregnancy, parturition, lactation and postnatal development of pups.

The information provided in the source of information (iv) is a One-Generation Reproduction Toxicity Study and it is relevant for the sexual function and fertility. However, the reliability of this study is significantly affected by the following critical issue:

- To fulfil the information requirement, normally an OECD TG 421/422 is required which include the following key parameter(s):

a) Testing of at least three dose levels and a concurrent control,
b) The test substance is administered orally.
c) The test substance is administered to males and females.
d) For statistical power at least 10 male and 12-13 female animals for each test and control group.

However, in the study (iv):
a) Only two doses tested in the same treatment group (100 mg/kg bw/day for the first 15 days of treatment and 66.6 mg/kg bw/day for the subsequent 15 days of treatment).
b) Exposure via subcutaneous injection instead or oral route.
c) Exposure to the test substance only of the males but not of the females.
d) Only 5 males were used in the one test group. Therefore, the study has no sufficient statistical power.

Therefore, no conclusion can be drawn on sexual function and fertility.

2) *Toxicity to offspring*

Information on pre- and perinatal developmental toxicity reflected by litter sizes, postimplantation loss (resorptions and dead foetuses), stillborns, and external malformations, postnatal developmental toxicity 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.

Sources of information (i-iii) are not relevant as these studies do not investigate toxicity to offspring. Source of information (iv), while relevant for the toxicity of offspring, has severe reliability issues, for the reasons mentioned above under "Sexual function and fertility".

Therefore, no conclusion can be drawn on toxicity to offspring.

3) *Systemic toxicity*

For both OECD TG 421/422 the systemic toxicity must include information on clinical signs, survival, body weights, food consumption, clinical chemistry, and other potential aspects of systemic toxicity in the parental generation up to postnatal day 13. For OECD TG 422 it should also include information on haematology, organ weights and histopathology of non-reproductive organs.

Sources of information (i) to (iii) are subchronic studies that can provide partially relevant information on the organ weights and histopathology of organs, body weights, food/water consumption, clinical signs, clinical chemistry, haematology, and urinalysis. However, this information is derived from non-pregnant animals.

Therefore, while some conclusions can be drawn on systemic toxicity, the duration does not cover from parental generation up to postnatal day 13 (i.e. from animals going through the pregnancy and 13 days of lactation). Consequently, the information provided by the sources of information (i) to (iii) is not sufficient to conclude on systemic toxicity.

4) *Specific investigations for hormonal activity*

Specific investigations for hormonal activity includes information on anogenital distance, nipple retention in male pups, and thyroid toxicity and T4 (and TSH) levels in males and day 13 pups and conditionally in dams and day 4 pups.

Sources of information (i) to (iii) did not investigate the specified hormonal activity parameters and thus they are not relevant for this key element.

Source of information (iv) reports on lower plasma T3, T4 in the male exposed goats but the study has severe reliability issues as explained above under "Sexual function and fertility".

Therefore, no conclusion can be drawn on the specific investigations for hormonal activity.

From the studies provided only very limited information is available on sexual function and fertility (organ weights and histopathology of reproductive organs) and systemic toxicity (organ weights and histopathology of organs, body weights, food/water consumption, clinical signs, clinical chemistry, haematology, and urinalysis) in non-pregnant animals. No reliable information is available on toxicity to offspring nor on the specific investigations for hormonal activity.

On the basis of the information provided in the Appendix on Reasons common to several requests and on the above, 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 421 or OECD TG 422 study. Therefore, your adaptation is rejected and the information requirements is not fulfilled.

In your comments to draft decision you argue that this endpoint can be waived on the basis of an available prenatal developmental toxicity study according to OECD 414. However, as already demonstrated in section C.2 of this decision, the information provided in the dossier on prenatal developmental toxicity is not compliant.As long as a compliant PNDT study is not submitted an adaption of the requirement for a screening for reproductive/developmental toxcity study on that ground cannot be accepted.

You also commented that "*in the draft decision a OECD 422 is required. This study design includes a 28 days repeated dose toxicity study, which is available and not questioned.*" ECHA observes that while an OECD 422 includes a 28d study as part of its design, a 28d study (i.e. OECD 407) does not address reproduction and offspring. Therefore a 28 days study does not cover all the parameters required in an OECD 422.

A study according to the test method EU B.63/OECD TG 421 or EU B.64/OECD TG 422 must be performed in rats with oral[2] administration of the Substance.

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

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

### 1. Sub-chronic toxicity study (90-day)

A Sub-chronic toxicity study (90 day) is a standard information requirement in Annex IX to REACH.

You have provided the following in your dossier:

i. An OECD 408 key study ([redacted] 1987),
ii. 11 supporting studies:
    1. Hartzell, A. 1942,
    2. [redacted] 1984,
    3. Korte, F. and Greim, H. 1981, OECD 407,
    4. MacKenzie, C.G. and MacKenzie, J.B. 1943,
    5. Nasseri and Prasad, 1987a
    6. [redacted] 1979, 28-day dose range finding study,
    7. Astwood, E.B. 1945,
    8. Astwood, E.B. 1943,
    9. Hartzell, A. 1942,
    10. Hartzell A. 1945,
    11. Jones, 1946,

We have assessed this information and identified the following issue:

To be considered compliant and enable concluding whether the Substance has dangerous properties and supports the determination of the No-Observed Adverse Effect Level (NOAEL), a study has to meet the requirements of OECD TG 408. The following specifications of this test guideline include, among others:

1. Testing of at least three dose levels and a concurrent control

   However, the studies (ii.3), (ii.4), (ii.5), (ii.8) and (ii.11) were conducted with less than three dose levels.

2. Highest dose level should aim to induce some systemic toxicity, but not death or severe suffering

   However, the highest dose level in the key study (i) did not induce any systemic toxicity. Therefore, the dose level selection was too low.

   In your comments to draft decision you argue that the key study (i) ([redacted] 1987) "*was performed according to GLP*" and you consider that "*this high-quality study should be taken into account for the sub-chronic toxicity endpoint because it is fully compliant with the requirements of the OECD guideline 408*". However, your comment is a generic consideration that does not address the deficiency specified in the draft decision concerning the selection of the dose levels. This explicit requirement in the OECD 408 test guideline specifies that " *the highest dose level should aim to induce some systemic toxicity, but not death or severe suffering*" allowing the derivation of "*any dosage related response and a NOAEL at the lowest dose level.*" However, neither your dossier or your comment provide any documentation on how the dose selection was made. You have provided one supporting 28-d study in the dossier ([redacted] 1979) with thiourea in diet, which mentions under the Rationale for reliability including deficiencies "*28-day*

*dose range finding study (preceding the 90-day drinking water study)*". However, if this is the dose range finding study used for key study (i) ([redacted], 1987), the selection of the doses is still not justified; [redacted], 1979 found a LOAEL equivalent to 30 mg/kg bw/d. Interestingly, a chronic drinking study with thiourea, also preceding the 90d study, found a NOAEL of 6.88 mg/kg (Hartzell 1945). Neither the study of [redacted] 1979 nor of Hartzell, A. (1945) justifies the choice of the dose levels in the 90d study.

In your comment, you explain that the use of the NOAELs from the study of [redacted], 1987 would lead to a conservative DNEL one order of magnitude below the daily oral dose of 10–15 mg (corresponding to 0.14–0.21 mg/kg bw/d for a 70 kg individual) and that this dose was reported insufficient to depress thyroid activity in humans (secondary source in IUCLID 7.10.3. from MAK 1990, data from [redacted] 1948 and [redacted] 1947). However, in the above mentioned study thiourea was administered together with iodine solution in hyperthyroid subjects and while providing useful mechanistic insights it does not give a direct effect level for thiourea in humans in general and does not clarify the hazard.

As explained in Chapter R.7a: Endpoint specific guidance (Version 6.0–July 2017, p. 416), among others, the objectives of assessing repeated dose toxicity are to evaluate the hazard of a substance and to establish the basis for risk characterisation and classification and labelling (C&L) of substances for repeated dose toxicity. A study employing unjustified low doses which do not allow to derive a dose response cannot be used to fulfill these objectives.

Finally, the DNEL calculation in Section 5.11. of the CSR in your dossier does not employ the NOAELs from key study (i) ([redacted], 1987) but a NOAEL of 6.88 mg/kg bw/day from the above mentioned chronic rat study in drinking water, Hartzell, A. (1945). The following justification was made for the endpoint selection: "*Study meets generally accepted scientific standards, provides a dose response relationship and the NOAEL/LOAEL is supported by several other repeat dose studies*". Therefore, the comments you provided on the draft decision do not remove the incompliance of key study (i).

3. At least 10 female and 10 male animals should be used at each dose level (including control group)

   However, the studies (ii.2, ii.3, ii.6, ii.11) were conducted with less than 10 animals per sex per test dose group and for (ii.2.) and (ii.9) the studies used only females. The statistical power of the information provided is not sufficient because it does not fulfil the criterion of 20 animals (10 males + 10 females) for each test group set in OECD TG 408.

4. Dosing of the Substance daily for a period of 90 days until the scheduled termination of the study

   However, the studies (ii.2), (ii.3), (ii.7), (ii.8) and (ii.11) indicate an exposure duration of 10-28 days and study (ii.6) indicates an exposure duration up to 8 weeks. Therefore, these studies do not have the required exposure duration of 90 days.

5. The study must report various information, including hematology, clinical biochemistry, and subsequent histopathology

   However, in the studies (ii. 1), (ii.9) and (ii.10), the following specifications are missing: clinical chemistry, haematology and histopathology.

Based on the above, none of the studies you have provided meet the specifications set out in OECD TG 408. Therefore, the information requirement is not fulfilled.

*Information on the design of the study to be performed (route/ species/ strain)*

Referring to the criteria provided in Annex IX, Section 8.6.2, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity, because The substance is a water soluble solid with low vapour pressure.

Therefore the sub-chronic toxicity study must be performed according to the OECD TG 408, in rats and with oral administration of the Substance

**2. Pre-natal developmental toxicity study in one species**

A Pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is a standard information requirement under Annex IX to REACH.
You have adapted the standard information requirement according to Annex XI, Section 1.2. weight of evidence of REACH.

In support of your adaptation, you have provided the following sources of information:

i. Nasseri and Prasad 1987b,
ii. Kern et al. 1980, no data on maternal tox, growth retard and malformation (ext and visceral)
iii. Ruddick 1976, -abstract, not maternaly and dev toxic
iv. Teramoto 1981. Abstract, maternaly toxic and embritotoxic

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.7.2 at Annex IX includes similar information that is produced by the OECD TG 414 on one species. The following aspects are covered: 1) prenatal developmental toxicity, 2) maternal toxicity, and 3) maintenance of pregnancy.

1) *Prenatal developmental toxicity*

Prenatal developmental toxicity includes information after prenatal exposure on embryonic/foetal survivial (number of live foetuses; number of resorptions and dead foetuses, postimplantation loss), growth (body weights and size) and structural malformations and variations (external, visceral and skeletal).

Sources of information (i) provides information on some of the elements of developmental toxicity, such as growth of pups and external malformation in growing lambs. However, it does not inform on litter sizes, postnatal survival, structural visceral and skeletal malformations and variations as foreseen to be investigated in OECD TG 414. Therefore, it only provides limited information on this key element in general.

Sources of information (ii. to iv.) may cover relevant aspects of prenatal developmental toxicity.

However, the reliability of these sources of information is significantly affected by the following deficiencies:

- Concerning source of information i.

  To fulfil the information requirement, normally a study performed according to OECD TG 414 which requires the study to investigate the following key parameters:

1. 20 female animals with implantation sites for each test and control group to allow statistical significance
2. At least three dose levels and a concurrent control should be used.
3. Dosing of the substance daily from implantation to the day prior to scheduled caesarean section.
4. Individual animal data should be provided. Additionally, all data should be summarised in tabular form.
5. Adequate statistical analysis of the study findings, including sufficient information on the method

However, the source of information i. suffers from crititcal deviations from the OECD TG 414 protocol such as:

1. The number of animals is too low (9 pregnant and 3 control ewes) to allow statistical significance.
2. Only one dose was used instead of three as required for a dose-response.
3. The dose administration schedule and the gestation time covered is unclear (i.). This is particularly important to understand one of the conclusions of this study saying that "*the severity of changes was dependent upon the stage of gestation when hypothyroidism was induced*".
4. No individual data provided in tabular form to allow the interpretation of the data.
5. No adequate statistical analysis of the study findings, including sufficient information on the method to allow to conclude on the reliability of the findings.

- Concerning sources of information ii. to iv.

  Pursuant to Article 10(a)(vii) of the REACH Regulation, the information set out in Annex VII to XI must be provided in the form of a robust study summary. Article 3(28) defines a robust study summary as 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 minimising the need to consult the full study report.

  However, you have not provided adequate and reliable documentation in a form of robust study summaries, as required by Article 10(a)(vii) and Article 3(28).

2) *Maternal toxicity*

Maternal toxicity includes information after gestational exposure on maternal survival, body weight and clinical signs and other potential aspects of maternal toxicity in dams.

Only sources of information i., iii. and iv. provide information on maternal toxicity. However, the reliability of the sources of information is significantly affected by the deficiencies identified and explained above in the section on "Prenatal developmental toxicity". Therefore, they cannot contribute to the conclusion on this key element.

3) *Maintenance of pregnancy*

Maintenance of pregnancy includes information on abortions and/or early delivery as a consequence of gestational exposure and other potential aspects of maintenance of pregnancy.

All sources of information provide relevant information on maintenance of pregnancy. However, the reliability of all these sources of information is significantly affected by the

deficiencies identified and explained above in the section on "Prenatal developmental toxicity". Therefore, they cannot contribute to the conclusion on this key element.

Taken together, the sources of information as indicated above provide information on maternal toxicity and maintenance of pregnancy, but only limited information on the key elements of (prenatal) developmental toxicity. Specifically, no information is provided on structural malformations and variations (visceral and skeletal) as sources of information i. does not investigate these. In any case all the sources of information provided are affected by significant deficiencies.

On the basis of the information provided in the Appendix on Reasons common to several requests and on the above, 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 OECD TG 414, prenatal developmental toxicity study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

In your comments to draft decision you acknowledged that "*the study design of the two studies used for the weight-of-evidence approach (Nasseri and Prasad, 1987; Kern et al., 1980) is not fully compliant with the OECD 414 guideline. In addition,* we *recognize that some of the information provided from the supporting studies is limited in order to assess adverse developmental effects.*". Nevertheless, you argued that "*thiourea is known to induce hypothyroidism as a result of peroxidase inhibition (MAK, 1988; IARC, 2001) and studies with 35S-thiourea in rats and mice showed that the substance crosses the placenta and is potentially stored in the thyroid gland where it affects iodine metabolism ([redacted], 1963).*

The Guidance on the Application of the CLP CriteriaVersion 5.0 –July 2017, (p. 402) provides that even in cases where a causal relationship is established between reproductive and parental toxicity and the effects on the offspring can be proved to be secondary to maternal toxicity, the effects may still be relevant for developmental classification, dependent on the severity of the effects.

You conclude that *"therefore, thiourea is considered to affect reproduction as a result of hypothyroidism. This is supported by the observation that the severity of effects on reproduction in the study from Nasseri & Prasad (1987) was dependent upon the stage of gestation when hypothyroidism was induced. As a consequence, effects on reproduction are expected to be absent at dose levels that do not impair thyroid function. The dose levels relevant for adverse effects on thyroid metabolism and therefore potential developmental effects are expected to be extrapolated from the repeated dose toxicity studies available for this endpoint."*

The thyroids effects can indeed affect the developmental toxicity. However, in the studies provided on this endpoint severe effects were observed such as: infantile and stunted external genitalia in growing lambs, no aestrus in growing lambs and retarded mammary development, birth of weak/low-weight lambs (Nasseri and Prasas 1987b), growth retardation and malformations of the nervous system and skeleton (Kern et al. 1980), embryotoxicity (Teramoto 1981). No conclusion on the above effects can be infered from the repeated dose studies. Therefore, a PNDT study according to OECD 414 is still needed to clarify the hazard for this endpoint.

In your comments you also commited to provide in a further update adequate and reliable documentation of the sources of information in the form of robust study summaries. However, this information is not currently available and cannot be taken into account in the assessment of compliance with the information requirement.

A PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit as preferred species with oral[3] administration of the Substance.

### 3. 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 adapted this standard information requirement under Annex XI, Section 1.2. of REACH (weight of evidence). In support of your adaptation, you have provided the following sources of information:

i. EEC-Directive 79/831: Prolonged Toxicity for Daphnia magna Rev. 1, [redacted] 1984;
ii. EEC-Directive 79/831: Prolonged Toxicity for Daphnia magna Rev. 1, Boje & Rudolph, 1985;
iii. EU Method C.20, [redacted] 1984.

Furthermore, in your comments on the draft decision, you refer to the following additional source of information that you intend to use to further strengthen your weight of evidence adaptation:

iv. an additional OECD TG 211 study on the Substance from the Japanese Ministry of the Environment.

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 following key parameters:

- the concentrations of the test material leading to no observed effect (NOECs) on the following parameters:
  1) the reproductive output of *Daphnia* sp. expressed as the total number of living offspring produced at the end of the test, and
  2) the survival of the parent animals during the test, and
  3) the time to production of the first brood.

1. *Concerning key parameters (1) the reproductive output of Daphnia sp. expressed as the total number of living offspring produced at the end of the test and (2) the survival of the parent animals during the test*

   All the reported source of information (i.e. studies i., ii. and iii. above) provide relevant information on these key parameters. For study iv., the information from the J-CHECK database is unclear whether or not the key parameter (1) is covered by the study. With regard to key parmaters (2), the following statement is reported: "*Median lethal concentration of parental Daphnia (21d-LC50): LC50 was not calculated because reversal of mortality rate was observed*". On this basis we understand that the relevance of this study is unclear. However, we have nevertheless further assessed the reliability of this source of information.

   We note that the reliability of all the sources of information provided to support your weight of evidence is significantly affected by the following deficiency:

   For a study conducted according to OECD TG 201, the following specifications must normally be met:

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

*Validity criteria*

- the percentage of mortality of the parent animals (female *Daphnia*) is ≤ 20% at the end of the test;
- the mean number of living offspring produced per parent animal surviving is ≥ 60 at the end of the test;

*Technical specifications impacting the sensitivity/reliability of the test*

- for semi-static tests, test animals are individually held;
- the concentrations of the test material are measured at least at the highest and lowest test concentration, at the beginning and end of the test;
- the effect values can only be based on nominal or measured initial concentration if the concentration of the test material has been satisfactorily maintained within 20 % of the nominal or measured initial concentration throughout the test (see also ECHA Guidance R.7b, Section R.7.8.4.1);

*Reporting of the methodology and results*

- the test design is reported (*e.g.* test concentrations, number of replicates)
- the test procedure is reported (*e.g.* composition of the test medium, loading in number of *Daphnia* per test vessel);
- the full record of the daily production of living offspring during the test by each parent animal is provided;
- the number of deaths among the parent animals (if any) and the day on which they occurred is reported;
- the coefficient of variation for control reproductive output is reported

On study i., your dossier provides the following information:

- you specify that the "*documentation* [is] *insufficient for assessment (purity of the test substance is not reported; no details on test conditions and results)*";
- you specify that the test was conducted under semi-static test conditions and that 5 animals were held per test vessel;
- you have not provided any information on the analytical verification of exposure concentrations;
- the full record of the daily production of living offspring during the test by each parent animal is not provided;
- the number of deaths among the parent animals (if any) and the day on which they occurred is not reported;
- the coefficient of variation for control reproductive output is not reported.

On study ii. and iii., your dossier provides the following information:

- you specify for study ii. that the information originates from secondary literature and for study iii. that "*documentation* [is] *insufficient for assessment*";
- key information is missing on the test design and procedure (e.g. number of test animal, number of test vessels, composition of the test medium);
- specifically for study iii., you specify that the validity criteria were not met as the "number of offspring in control is too low";
- the full record of the daily production of living offspring during the test by each parent animal is not provided;
- the number of deaths among the parent animals (if any) and the day on which they occurred is not reported;
- the coefficient of variation for control reproductive output is not reported.

On source of information iv., you have provided no information on how the effect value was obtained apart from stating the the study was conducted according to OECD TG 211. However, based on the information reported in the Japan CHEmical Collaborative

Knowledge database (J-CHECK), we note the following:

- it is specified that dechlorinated tap water was used as dilution water. However, the composition of the test medium is not reported;
- it is specified that the analytical monitoring of exposure concentrations was conducted using HPLC-MS. However, no information is provided on the performance parameters of the analytical method or the determination of exposure concentrations during the test;
- the full record of the daily production of living offspring during the test by each parent animal is not provided;
- the number of deaths among the parent animals (if any) and the day on which they occurred is not reported;
- the coefficient of variation for control reproductive output is not reported.

Based on the above there are major deficiencies impacting all sources of evidence provided in support of your weight-of-evidence adaptation for this key parameter, including the following:

- *Missing information on study design or inadequate design:* for study ii. and iii., it is unclear if the test design allows to determine the reproductive output per parental animals as normally required by OECD TG 211 for semi-static tests. For study i., animals were not held individually and therefore it can already be concluded that this information is not available from this study. As no information is provided on the number of deaths among the parent animals, it cannot be verified whether or not mortality of parental animals may have biased the results;
- *Missing information to verify the validity of the tests:* none of the robust study summaries included in your dossier provides adequate information on the test results to verify if the validity criteria normally expected to be fulfilled in a long-term toxicity to aquatic invertebrates were met. For study iii., you specify that the reproductive output in the control was too low and therefore, the results of this study are considered unreliable due to low statistical power. For study iv., it is specified in the J-CHECK website that *"reversal of mortality rate was observed"* which further questions the reliability of this study;
- *Verification of exposure*: no analytical verification of exposure was conducted in any of the studies included in your registration dossier.. Therefore, you have not demonstrated that effect values can reliably be based on nominal test material concentrations. For study iv., an analytical verficiation of exposure concentration is claimed to have been conducted. However, key information are missing to verify the validity of the analytical method and of the effect values that is reported.

As explained above, there are a number of major deficiencies impacting the reliability of each individual studies including in your weight-of-evidence. Considering the severity of these deficiencies, it cannot be concluded with sufficient confidence what is the survival of parental animals at the end of the test and what is the reproductive output of parental animals and that effect values for the Substance can be reliably estimated based on nominal concentrations.

2. *Concerning key parameter (3) the time to production of the first brood*

Only the source of information i. provides information on the time to production of the first brood.

However, reliability of this source on information is significantly affected by the deficiencies explained above.

On the basis of the deficiencies listed above, the sources of information i. to iv. do not provide an adequate and reliable coverage of the key parameter addressed in OECD TG 211. Therefore, the reliability of such information in support of your weight of evidence adaptation under Annex XI, Section 1.2 is considered low.

In your comments on the draft decision, you emphasize that, as specified in ECHA's practical guide on How to use alternatives to animal testing to fulfil your information requirements, a weight of evidence adaptation involves "*using evidence from several sources, where the information from each of the sources individually may be regarded as not sufficient*". You further consider that "*although each of the cited studies suffers from specific shortcomings, a robust conclusion associated with an acceptable level of uncertainty can be drawn by holistically evaluating the information from the reported studies*".

We acknowledge that, in the context of a weight of evidence adaptation, full compliance with the requirement of the test method referred to in Article 13(3) to REACH is not required on the whole body of evidence available. However, to be considered valid, the set of sources information must provide a comprehensive coverage of the key parameters generated by the study normally requested for that information requirement.

Regarding this information requirement, OECD TG 211 aims at investigating specific key parameters. The results of these investigations are necessary to conclude that a substance has or has not the property concerned by the information requirement. Therefore, the sources of information must provide either individually or collectively the results normally expected from a OECD TG 211 study. Moreover, these results must be sufficiently reliable.

In the present case, the time to production of the first brood is normally provided by any OECD TG 211 study. The result of this investigation is therefore necessary to conclude that a substance has or has not the property investigated. However, as already explained above, the sources of information submitted in your dossier or in your comments on the draft decision do not provide any information on the time to production of the first brood, neither individually nor collectively. Therefore, these sources of information do not enable to conclude on the property investigated by a OECD TG 211 study.

Furthermore, individual sources of information submitted in your dossier may provide results on key parameters normally investigated by OECD TG 211 (e.g. reproductive output of Daphnia sp. expressed as the total number of living offspring produced at the end of the test and survival of the parent animals during the test). However, as explained above, all the sources of information submitted are affected by deficiencies that are so significant that they are individually or collectively not sufficiently reliable to enable reaching a conclusion that the substance has or has not the property investigated.

Therefore, on the basis of the information provided in the Appendix on Reasons common to several requests and on the above, 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 211 study. Therefore, your adaptation is rejected and the information requirements is not fulfilled.

## Appendix D: 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[4].

### 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[5].

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

**Appendix E: 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 13 February 2020.

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

ECHA took into account your comments and did not amend the requests.

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 F: List of references - ECHA Guidance[6] 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)[7]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[8]

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[9]

[6] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[7] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[8] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316
[9] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

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

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 G: Addressees of this decision and the corresponding information requirements applicable to them

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] |
| [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.