~~Confidential~~

Helsinki, 15 November 2021

**Addressees**
Registrant(s) of Trimellitic Anhydride-PMC as listed in the last Appendix of this decision

**Date of submission of the dossier subject to this decision**
17/03/2017

**Registered substance subject to this decision ("the Substance")**
Substance name: Benzene-1,2,4-tricarboxylic acid 1,2-anhydride
EC number: 209-008-0
CAS number: 552-30-7

**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 ***20 August 2024***.

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

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

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

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

1. 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);

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

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

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

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

2. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) by oral route, in rats, specified as follows:

   - Ten weeks pre-mating exposure duration for the parental (P0) generation;
   - Dose level setting shall aim to induce systemic toxicity at the highest dose level;
   - Cohort 1A (Reproductive toxicity); and

- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.

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 X of REACH respectively.

**Information required depends on your tonnage band**

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

- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;
- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

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

**How to comply with your information requirements**

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

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

**Appeal**

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

**Failure to comply**

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

Authorised[1] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

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

**Appendix on Reasons common to several requests**

1. **Assessment of your weight of evidence adaptation under 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:

- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Pre-natal developmental toxicity study in a second species (Annex X, Section 8.7.2.)
- Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)
- Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)
- Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

Your weight of evidence adaptation raises the same decifiencies irrespective of the information requirement for which it is invoked. Accordingly, ECHA addressed these deficiencies in the present Appendix, before assessing issues specific to the individual information requirements in the following 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.

You have not included a justification for your weight of evidence adaptation for each of the relevant information requirements, 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, ECHA has nevertheless assessed the validity of your adaptation. Your weight of evidence approach has deficiencies that are common to all information requirements under consideration and also deficiencies that are specific for these information requirements individually. The common deficiencies are set out below, while the specific ones are set out under the information requirement concerned in the Appendices.

These issue(s) identified below are essential for all the information requirements in which you invoked a weight of evidence.

**Reliability of the information on analogue substances**

ECHA understands that you intend to predict the (eco)toxicological properties of the Substance for the listed above endpoints, from data obtained with source substances in a read-across approach as part of your weight of evidence adaptation.

Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (addressed under 'Assessment of prediction(s)').

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance R.6. and related documents[2,3].

**Predictions for (eco)toxicological properties**

You have provided a read-across justification document in IUCLID Section 13 named "[redacted]"

For (eco)toxicological properties you read-across between the following substances as source substances and the Substance as target substance:

- TMLA trimellitic acid (EC No. 208-432-3);
- 4-MHHPA hexahydro-4-methylphthalic anhydride (EC No. 243-072-0);
- MTHPA tetrahydromethylphthalic anhydride (EC No. 234-290-7);
- HHPA hexahydrophthalic anhydride (EC No. 201-604-9);
- THPA tetrahydrophthalic anhydride (EC No. 201-605-4);
- PA phthalic anhydride (EC No. 201-607-5);
- MA maleic anhydride (EC No. 203-571-6);
- PHA phthalic acid (EC No. 201-873-2).

To support your read-across approach you refer to the Cyclic anhydrides category defined by US EPA HPV challenge program[4] and WHO group of cyclic anhydrides, described in Concise International Chemical Assessment Document 75[5]

You have provided the following reasoning for the prediction of (eco)toxicological properties: *"Overall, the defined group is made up of substances consisting of a (bi)cyclic ring structure with the carboxylic acid anhydride group as the single reactive and functional moiety responsible for both the irritant and sensitising properties of the group. Structural differences such as the level of saturation in the ring structure, presence or different location of substituted functional group are expected to have no or only negligible influence with regard to eco- and systemic toxicity."*

ECHA understands that you predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects. The properties of your Substance are predicted to be quantitatively equal to those of the source substance(s).

ECHA notes the following shortcomings with regards to predictions of (eco)toxicological properties.

[2] Read-across assessment framework (RAAF, March 2017)
[3] RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)
[4] ECHA assumes you mean https://hpvchemicals.oecd.org/UI/handler.axd?id=beb213b6-aa5b-40e2-a716-12a001dd8197
[5] http://www.inchem.org/documents/cicads/cicads/cicad75.pdf

## *I.1* Predictions for toxicological properties

ECHA notes that there are issue(s) that are common to all toxicological information requirements under consideration and also issue(s) that are specific for these information requirements individually. Altogether they result in a failure to meet the requirement of Annex XI, 1.5. The common issue(s) are set out below, while the issues specific to the individual endpoints are set out in the following Appendices under the information requirement(s) concerned (in particular Appendix B, Section B.1. and Appendix C, Section C.1. below).

*I.1.1. Read-across hypothesis contradicted by existing data*

Annex XI, Section 1.5. provides that "*substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances*". The ECHA Guidance[6] indicates that "*it is important to provide supporting information to strengthen the rationale for the read-across*". The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substances.

The observation of differences in the toxicological properties between the source substance(s) and the Substance would contradict the hypothesis that the properties of the Substance can be predicted from the data on the source substance(s). An explanation why such differences do not affect the read-across hypothesis needs to be provided and supported by scientific evidence.

As indicated above, your read-across hypothesis is based on the assumption that the structurally similar target and source substances cause the same type of effect(s).

To support your hypothesis, you have provided a data matrix in your Justification document with information from experimental studies as follows:

- Results of studies on reproductive toxicity with:
  - TMLA; NOAEL of 450 mg/kg bw/day
  - 4-MHHPA; NOAEL 450 mg/kg bw/day
  - MTHPA; NOAEL 300 mg/kg bw/day
  - HHPA; NOAEL 1000 mg/kg bw/day
  - THPA; NOAEL 250 mg/kg bw/day
  - MA; NOAEL 55 mg/kg bw/day

- Results of studies on developmental toxicity with:
  - PA; NOAEL ca 1700 mg/kg bw/day
  - MA; NOAEL 140 mg/kg bw/day

You conclude that *"The available mammalian studies may be considered sufficiently rigorous to serve in demonstrating similarities with the registered substance."*

The information provided is not adequate to assess whether or not there is similarity in the toxicity patterns between the source substances and the Substance. According to the information provided in your dossier, the results of the Pre-natal developmental toxicity (PNDT) studies and of the reproductive toxicity studies obtained with the Substance and the source substances vary. You have not provided any explanation to justify how and why these differences are not affecting the predictions. In addition, several reproductive toxicity studies with the source substances are not provided in the dossier, hence their reliability cannot be assessed.

[6] ECHA Guidance R.6, Section R.6.2.2.1.f

The available set of data on the source substances indicates differences in the toxicological properties of the substances. This contradicts your read-across hypothesis whereby the structurally similar target and source substances cause qualitative and quantitively similar effects. Therefore you have not demonstrated and justified that the properties of the source substance(s) and of the Substance are likely to be similar despite the observation of these differences.

In the comments to the draft decision, you argue that the differences in No Effect Levels (NOELs) are a reflection of dose levels tested rather than differing toxicity.

Firstly, ECHA notes that the values listed in the above are No Adverse Effect Levels (NOAELs) not NOELs. Secondly, the differences between the NOAELs vary 18- and 12-fold for reproductive toxicity and developmental toxicity, respectively. The magnitude of this variation is well beyond what can be explained by differences in the selection of test doses: dose levels are usually varying in increments of 2-4 fold. Finally, the severity of adverse effects differs between the substances in the group e.g. for PA (EC 201-607-5, [redacted]) no effects were found at the highest dose of 1000 mg/kg bw; in contrast for MA (EC 203-571-6, two-generation reproductive toxicity study, oral gavage) severe toxicity in parental animals was found, resulting in the termination of [redacted] This is in contradiction to your read-across hypothesis.

### *I.2* Predictions for ecotoxicological properties

ECHA notes that there are issue(s) that are common to all ecotoxicological information requirements under consideration and also issue(s) that are specific for these information requirements individually. Altogether they result in a failure to meet the requirement of Annex XI, 1.5. The common issue(s) are set out below, while the issues specific to the individual endpoints are set out under the information requirement(s) concerned (Appendix B. section B.2) below.

*I.2.1. Read-across hypothesis contradicted by existing data*

Annex XI, Section 1.5. provides that "*substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances*". The ECHA Guidance[7] indicates that "*it is important to provide supporting information to strengthen the rationale for the read-across*". The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substances. The observation of differences in the (eco)toxicological properties between the source substance(s) and the Substance would contradict the hypothesis that the properties of the Substance can be predicted from the data on the source substances. An explanation why such differences do not affect the read-across hypothesis needs to be provided and supported by scientific evidence.

As indicated above, your read-across hypothesis is based on the assumption that the structurally similar target and source substances cause the same type of effect(s).

In order to support your hypothesis, you have provided a data matrix with information from experimental studies as follows:

- Results of studies on algae growth inhibition, short-term toxicity to aquatic invertebrates and to fish with the Substance and with source substances 4-MHHPA, MTHPA, HHPA,

[7] ECHA Guidance R.6, Section R.6.2.2.1.f

THPA, PA and MA.
- Results of long-term toxicity to aquatic invertebrates studies with source substances MTHPA, PA and MA.
- Results of long-term toxicity to fish studies with source substances MTHPA and PA.

You conclude that "*The data available indicate that all the bicyclic anhydrides exhibit similar aquatic toxicity*".

The results of the algae growth inhibition and of the short-term aquatic toxicity studies obtained with the Substance and the source substances vary. You have not provided any explanation to justify how and why these differences are not affecting the predictions. In addition, the algae growth inhibition and the short-term aquatic toxicity studies with the source substances are not provided in the dossier, hence their reliability cannot be assessed.

Furthermore, for long-term toxicity to aquatic invertebrates the available source studies for PA and MA are not reliable data based on OECD TG 211 requirements (as explained in Appendix B.2 below), while for long-term toxicity to fish all available source studies are not reliable based on OECD TG 210 requirements (as explained in Appendix B.3 below). Therefore, it is not possible to make a comparison of chronic aquatic toxicity.

The available set of data on the target and source substances indicates differences in the ecotoxicological properties of the substances. This contradicts your read-across hypothesis whereby the structurally similar target and source substances cause the same type of effect(s). Therefore you have not demonstrated and justified that the properties of the source substance(s) and of the Substance are likely to be similar despite the observation of these differences.

**I.3. Your general comments to the draft decision regarding read-across**

In the comments to the draft decision, you challenge the rejection of your read-across approach. You consider that the read-across is justified based on the following information on source and target substances:

- common functional group determining a common (eco)toxicological profile;
- similar physico-chemical properties with the exception of melting temperature;
- similarities in the results of the available mammalian studies;
- common metabolic pathway "*where the cyclic anhydride is metabolised to the corresponding di-carboxylic acid and excreted in urine*";
- rapid hydrolysis in contact with water and "*it is the dicarboxylic acid degradation product that is of concern with respect to effects in the environment*";
- similar aquatic toxicity based on the data available.

You conclude that this information "*is regarded as sufficiently robust to justify the use of read-across to generate a weight of evidence adequate to define the properties of the registered substance".*

ECHA notes that the arguments brought forward in the comments are the same as in your registration dossier, and this information is incompliant for the reasons set out above. You also recognise in your comments that the documentation to support the adaptations is not adequate when compared to existing Guidance (RAAF, 2017 and RAAF UVCB, 2017).

You have not provided any new scientific information addressing these issues. Your further intentions to use information being generated with the source substance PA has been noted by ECHA, but no new adaptation was provided with your comments on the draft decision.

Therefore, the information provided in your comments does not change the assessment outcome.

### I.4 Conclusion for predictions for toxicological and ecotoxicological properties

Based on the above, the information from the source substances submitted under your weight of evidence adaptation is not considered reliable. Additional issues related to weight of evidence are addressed under the corresponding endpoints.

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

### 1. Justification for an adaptation of the screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

A Screening for reproductive/developmental toxicity study (test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) is a standard information requirement under Annex VIII to REACH, if there is no evidence from analogue substances, QSAR or *in vitro* methods that the Substance may be a developmental toxicant.

You have provided the following adaptation: *"a screening study for reproductive/developmental toxicity does not need to be conducted because there is evidence from available information on structurally related substances, from (Q)SAR estimates or from in vitro methods that the substance may be a developmental toxicant. The critical effect of trimellitic anhydride is respiratory sensitisation. […] The sensitising properties of the substance are such that only relatively low exposure concentrations can be used in repeated inhalation studies. Repeated dose oral toxicity studies performed with trimellitic anhydride and the read-across substance (hydrolysis product) show very low toxicity, with no evidence of systemic toxicity at dose levels of up to and including 1000 mg/kg bw/d and findings limited to local effects on the caecum. The substance is therefore clearly of very low systemic toxicity, whereas local effects are seen following inhalation exposure to very low concentrations"*

In addition, you have provided an adaptation under Section 1.2, Annex XI to REACH (weight of evidence).

In support of your adaptation, you have provided:

i. [redacted] 2010 - reproduction/developmental toxicity screening test with the source substance 4-MHHPA, EC No. 243-072-0;
ii. [redacted] 1997 - combined repeated dose toxicity study with the reproduction/developmental toxicity screening test study with the source substance MTHPA, EC No. 234-290-7;
iii. Short 1986 - two-generation reproduction toxicity study with the source substance MA, EC No. 203-571-6;
iv. [redacted] 1970 - non-guideline testes toxicity study with the source substance PA, EC No. 201-607-5.

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

A. Waiving argument

A Screening for reproductive/developmental toxicity study (test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) is a standard information requirement under Annex VIII to REACH, if there is no evidence from analogue substances, QSAR or *in vitro* methods that the Substance may be a developmental toxicant.

There is no information available in your dossier indicating that your Substance may be a developmental toxicant.

Regarding the exposure considerations, the route of administration in reproductive toxicity studies is oral unless the substance is a gas or a highly volatile liquid. Your Substance is a solid. Therefore, reproductive toxicity must be conducted via the oral route in order to maximise systemic exposure. The sensitising properties of the Substance do not limit testing via the oral route.

B. Adaptation according to Annex XI, Section 1.2 (weight of evidence)

As explained under Appendix on Reasons common to several requests, the weight of evidence must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

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 EU B.63/OECD TG 421 or EU B.64/OECD TG 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 and histopathology of reproductive organs and tissues, litter sizes, nursing performance and other potential aspects of 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.

*3. Systemic toxicity*
Information on systemic toxicity include clinical signs, survival, body weights, food consumption, clinical biochemistry, and other potential aspects of systemic toxicity in the parental generation up to postnatal day 13.

*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.

<u>Concerning 4) Specific investigations for hormonal activity</u>
None of the sources of information provide relevant information on this key investigation.

In your comments you remind ECHA that the available studies performed under the test guideline in place back in the past should be acceptable. You have adapted this information requirement using a weight of evidence approach. For the purpose of compliance, weight of evidence adaptations are assessed against the version of the corresponding test method into force at the time of the compliance check. The current version of the OECD TG 421/422 includes specific investigations for hormonal activity. Therefore, while the information obtained from the sources of information is in line with the requirements of the corresponding test guideline into force when this information was generated, it does not address/include relevant investigations on hormonal activity as expected from the current version of the corresponding test guideline.

<u>Concerning key investigations 1) Sexual function and fertility, 2) Toxicity to offspring and 3) Systemic toxicity</u>, the sources of information i., ii. and iii. provide relevant information.

However, these are sources of information on structural analogue substances. As explained

above in the Appendix on Reasons common to several requests, you have not demonstrated that this information on the analogue substances can reliably contribute to a weight of evidence approach intended to identify the properties of the Substance.

Conclusion
Accordingly, 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 and OECD TG 422 study. Therefore, your adaptation is rejected.

In addition, in your comments you state that ECHA has misinterpreted your waiving statement based on sensitising properties. You argue that "*the sensitizing properties of the registered substance are of the greatest concern with respect to hazards to human health and this property is manifest at low concentration. As a result, risk management measures are in place to mitigate against exposure and an exposure based waiving of the endpoint is justifiable*".

However, hazard identification is endpoint specific. Risk management measures applied for controlling some hazards such as sensitising properties do not constitute arguments for waiving other information requirements. The information requirements can be adapted according to the specific rules for adaptation in Column 2 of the Annexes on the information requirements or according to the general rules for adaptation listed in Annex XI. Section 3 of Annex XI in particular specifies the use of Substance-tailored exposure-driven testing. While you refer to exposure based waiving in your comments, you have not provided any adequately justified and documented exposure-based adaptation.

On this basis, the information requirement is not fulfilled.

The present decision requests the registrants concerned to generate and submit an extended one-generation reproductive toxicity study (EOGRTS) (see Section D.2). Once an EOGRTS is available, according to Column 2 of Annex VIII, Section 8.7.1. and in order to prevent unnecessary animal testing, a screening for reproductive/developmental toxicity does not therefore need to be conducted. While you still have to comply with the information requirement in Annex VIII, Section 8.7.1., you are requested to submit a justification for the adaptation based on Column 2 of that provision.

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

### 1. 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 this information requirement under Section 1.2, Annex XI to REACH (weight of evidence). In support of your adaptation, you have provided:

i. [redacted] 1988 – non-guideline PNDT study with Substance in rats and guinea pigs via inhalation route, investigating neonatal respiratory sensitization;
ii. Ema 1997 – non-guideline PNDT study with source substance PHA, EC No. 201-873-2;
iii. Short 1986 – PNDT study with the source substance MA, EC No. 203-571-6;
iv. [redacted] – non-guideline intraperitioneal teratogenicity study in mice with the source substance PA, EC No. 201-607-5.

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

A. Adaptation according to Annex XI, Section 1.2 (weight of evidence)

As explained under Appendix on Reasons common to several requests, the weight of evidence must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

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, 3) maintenance of pregnancy and 4) Specific investigations for hormonal activity.

*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).

*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.

*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.

*4) Specific investigations for hormonal activity*
Specific investigations for hormonal activity in rats includes information on anogenital distance, T4, T3 and TSH levels in dams.

<u>First species covered by the weight of evidence</u>
According to the OECD TG 414, testing should be done in species and strains which are commonly used in prenatal developmental toxicity testing. The preferred rodent species is the rat and the preferred non-rodent species is the rabbit. Justification should be provided if

another species is used. In your dossier the majority of data is on rats, therefore ECHA considers rats to be the first species.

Concerning 4) Specific investigations for hormonal activity
None of the sources of information provide relevant infromation on investigations for hormonal activity.

In your comments you remind ECHA that the available studies performed under the test guideline in place back in the past should be acceptable. But as already explained above, you have adapted this information requirement using a weight of evidence approach. For the purpose of compliance, weight of evidence adaptations are assessed against the version of the corresponding test method into force at the time of the compliance check. The current version of the OECD TG 414 includes specific investigations for hormonal activity. Therefore, while the information obtained from the sources of information is in line with the requirements of the corresponding test guideline into force when this information was generated, it does not address/include relevant investigations on hormonal activity as expected from the current version of the corresponding test guideline.

Concerning key investigations 1) Pre-natal developmental toxicity, 2) Maternal toxicity and 3) Maintenance of pregnancy
The sources of information i., ii. and iii. provide relevant information on the key investigation 1) to 3).

However, the sources of information ii. and iii. relate to information on structural analogue substances. Also with a view to your comments on the draft decision concerning the contribution of this data to weight of evidence, as explained above in the Appendix on Reasons common to several requests, you have not demonstrated that this information on the analogue substances can reliably contribute to a weight of evidence approach intended to identify the properties of the Substance.

The reliability of the source of information ii. is also affected by the following issues:
The study has low statistical power. It uses 11 pregnant rats compared to the 20 pregnant rats required by the OECD TG 414. The unconventional method of administration and low statistical power significantly affect the reliability of the information obtained from study in the context of this weight of evidence approach.

In the comments to the draft decision you agree that the reduced numbers of animals used does reduce the statistical power of the study.

The reliability of the source of information i. is also affected by the following issues:
Firstly, this study has been conducted via the inhalation route. The default route of administration in reproductive toxicity studies is oral unless the substance is a gas or a highly volatile liquid. Your substance is a solid. The Substance is an anhydride which hydrolyses in contact with water and is a respiratory sensitizer. Due to this the maximal attainable dose via inhalation is much lower than what can be attained via the oral route. You have not established that the systemic exposure after inhalation exposure to the Substance is likely to be equivalent to the systemic exposure which would occur after exposure via the default route of administration, i.e. the oral route.

Secondly, although the rat study had the correct number of dams (27), because only half of the dams were sacrificed one day prior to parturition, the statistical power of this study concerning pups teratogenicity examinations is lower than requested by the OECD TG 414.
Thirdly, the following key investigations are not addressed: data on embryonic/foetal survival (number of live foetuses; post-implantation loss).

Finally, the study was conducted at a single dose level which failed to identify a NOAEC.

The issues identified above significantly affect the reliability of the information obtained from this study in the context of this weight of evidence approach.

In the comments to the draft decision you agree that the reliability of the study is impaired by the issues highlighted above.

The reliability of the source of information iv. is also affected by the following issues:
You have assigned a reliability score of 4 (not assignable) to the study by [redacted]; ECHA agrees with your assessment of the reliability of this information and the study has not been assessed further. Therefore, this study does not contribute to the weight of evidence.

Contribution of sources i. and ii. to a weight of evidence:
In your comments to the draft decision, you generally express the opinion that the information may still contribute to a weight of evidence when multiple sources of information are assessed. As already explained in the appendix on reasons common to several requests, 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. You did not demonstrate how the several independent sources of information can lead to the conclusion that the Substance has or has not the properties investigated in a study according to OECD TG 414. Most crucially, you did not include a justification of the particular value and weight of the individual sources of information, taking into account the limitations of each source of information and the reliability of their contribution to the adaptation, for a conclusion on all the relevant properties.

Conclusion

Taken together, sources of information as indicated above provide information on prenatal developmental toxicity, maternal toxicity and maintenance of pregnancy but parts of information of the dangerous property is lacking (specific investigations for hormonal activity).

Furthermore, the sources of information ii., iii. and iv. are obtained from structural analogue substances, and you have not demonstrated that this information on the analogue substances can reliably contribute to a weight of evidence approach intended to identify the properties of the Substance.

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 414 study. Therefore, your adaptation is rejected.
On this basis, the information requirement is not fulfilled.

*Specification of the study design*

A PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit as preferred species with oral[1] administration of the Substance.

## 2. Long-term toxicity testing on aquatic invertebrates

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

You have provided the following information in the registration dossier:

A. A justification to omit the study which you consider to be based on Annex IX, Section 9.1., Column 2. In support of your adaptation, your justification provides the following arguments: the Substance is safe to use based on the Chemical Safety Assessment, exposure to the aquatic compartment is not expected, and the Substance is readily biodegradable.

B. You have adapted this information requirement under Section 1.2, Annex XI to REACH (weight of evidence). In support of your adaptation, you have provided the following study records with source substances:
   i. OECD TG 211 study with MTHPA (EC No. 234-290-7), [redacted] 2010;
   ii. OECD TG 211 study with MTHPA (EC No. 234-290-7), [redacted] 1997;
   iii. OECD TG 211 study with PA (EC No. 201-607-5), [redacted] 2003;
   iv. Prolonged toxicity test study according to a proposal of the German Federal Environmental Agency (1984) with MA (EC No. 203-571-6), [redacted] 1988.

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

A. Adaptation according to Annex IX, Section 9.1., Column 2

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

In the comments to the draft decision, you state further that you "*acknowledge that this requirement acts as a trigger for the need to provide further information but contends that the requirements have not been met to trigger such need and, as such, the adaptation is valid.*" However, as explained above, Column 2 of Section 9.1. of Annex IX requires registrants to submit information on a *further* study than the one listed in Column 1 of Section 9.1.5. of Annex IX, if the chemical safety assessment indicates that it is necessary to investigate the effects of a substance on aquatic organisms beyond what that study would do. The Column 1 information requirement cannot be adapted based on this Column 2 provision referring to the Chemical Safety Assessment.

Your adaptation is therefore rejected.

B. Adaptation according to Annex XI, Section 1.2 (weight of evidence)

As explained under Appendix on Reasons common to several requests, the weight of evidence must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 9.1.5 at Annex IX includes similar information that is produced by the OECD TG 211. This includes:

1. the reproductive output of *Daphnia sp.*, and
2. the survival of the parent animals during the test, and
3. the time to production of the first brood.

<u>1. Concerning key investigation (1) *the reproductive output of Daphnia sp.*</u>

The sources of information (i), (ii), (iii) and (iv) provide relevant information on this key investigation, but have the following deficiencies affecting their reliability.

a) Reliability on the information on analogue substances

The reliability on sources of information (i), (ii), (iii) and (iv) is significantly affected by the deficiency identified and explained above in the Appendix on Reasons common to several requests.

In addition, ECHA has also identified the following endpoint specific issue with the reliability of the information on analogue substances.

*Bias for the prediction of Long-term toxicity testing on aquatic invertebrates*

When a grouping and read-across approach is used, the results must be adequate for the purpose of classification and labelling and risk assessment. In this respect, where more than one study addressing the same effect are available, the one giving rise to the highest concern must be used as a source study to draw a hazard conclusion, unless justified (Section 3.1.5, Annex I of REACH).

For the endpoint Long-term toxicity testing on aquatic invertebrates, you have provided studies with source substances as listed above.

You predict the properties of the Substance from study (i) with source substance MTHPA, since you use the results of this study (NOEC = 20 mg/L based on reproduction of *Daphnia magna*) to derive the NOEC value for the Substance (Endpoint Summary in IUCLID Section 6.1.4).

You have also provided study (ii) with source substance MTHPA (NOEC = 0.94 mg/L based on reproduction of *Daphnia magna*) investigating the same effects. You have disregarded this study and assigned a reliability score of 4 (not assignable) with the following justification (rationale for reliability): "*The Daphnia magna Reproduction Test is not assignable due to several reasons: (1) The study report is available only in Japanese language and does not give enough experimental details. Therefore, evaluation of the complete study and especially raw data is not possible or can just be accomplished with major doubts. (2) In this study the analytical measurement of MTHPA does not represent the state of the art and does not allow final conclusions of the concentration tested. Several relevant measurements were conducted in concentration ranges that are more than 50 times below the lowest standard used for calibration and validation of the results.*"

Study (ii) is the study of highest concern, but you have assigned a reliability score of 4 and you have not used it to conclude on the endpoint. Concerning the reliability of study (ii) and the justification provided to disregard this study, ECHA notes the following:

Based on ECHA Guidance R.4, a Klimisch score 4 (not assignable) may be assigned, for example, for studies or data "*which do not give sufficient experimental details and which are only listed in short abstracts or secondary literature (books, reviews, etc.).*"

ECHA considers that your justification for disregarding study (ii) is not acceptable since the data source for study (ii) is a study report and sufficient details are provided to verify that the requirements of OECD TG 211 (listed under point (b) below) have been fulfilled, more specifically:

- *Characterisation of the exposure:* For study (ii), you provide information on the

analytical method used to characterise the exposure (HPLC-UV, detection limit (LOQ or LOD) of 0.2 mg/L). While you do not provide the calibration curve, you have identified the LOD/LOQ as 0.2 mg/L, which is below the measured concentrations (lowest is 0.85 mg/L). Hence, ECHA considers that the analytical method used is sufficiently sensitive.

- *Validity criteria:* For study (ii), you report tabulated data on living offspring and number of deaths among the parent animals, which allow to verify that the validity criteria of OECD TG 211 have been met, i.e. mortality of the parent animals at the end of the test is below 20% in the controls (4/40) and mean number of living offspring per parent animal surviving at the end of the test is > 60 in the controls (73.4).

Therefore, the requirements of Annex I, section 3.1.5 are not fulfilled since you have not provided an acceptable justification for disregarding the study of highest concern to conclude on the endpoint.

In conclusion, there is an available study that gives rise to a greater concern than the source study (i) you use to to predict the properties of the Substance for the endpoint. Therefore, your predictions may underestimate the hazards of the Substance and the results are not adequate for the purpose of classification and labelling and risk assessment.

In your comments to the draft decision you acknowledge that a re-assessment of the information for study (ii) is needed "*regarding a conclusion on classification, labelling and risk assessment*".

b) The reliability of sources of information (iii) and (iv) is also affected by the following issue:

Testing in accordance with the OECD TG 211 requires that the following specifications/conditions must be met:

*Characterisation of the exposure:*

- during the test, the concentrations of the test material are analysed at regular intervals by using a reliable analytical method (with reported specificity and limits of determination);
- the results can be based on nominal or measured initial concentration only if there is evidence that the concentration of the test material has been 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);

*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.

In your dossier you have provided the following information:

*Characterisation of the exposure:*

- you have not specified if analytical monitoring of exposure was conducted for studies (iii) and (iv);
- you have not provided evidence of stability of the test subtances in the test media for any of the studies and for study (iii) the results are reported based on nominal concentrations while for study (iv) you have not specified if results are based on nominal or measured concentrations.

*Validity criteria:*

- for studies (iii) and (iv), you have not reported if validity criteria were met and you have not provided the mortality of parent animals and the mean number of living offspring per survived parent animal at the end of the test.

Based on the above, there are critical deficiencies resulting in the rejection of the study results for studies (iii) and (iv). More specifically:

- *Characterisation of the exposure:* in the absence of information on analytical monitoring, you have not demonstrated that the concentration of the test material was maintained within 20 % of the nominal or measured initial concentration throughout the test for both studies.
- *Validity criteria:* in the absence of information on living offspring and number of deaths among the parent animals, you have not demonstrated whether the validity criteria were met for both studies.

Lacking the above information, sources (iii) and (iv) cannot be considered as reliable/or have low reliability.

Altogether, the provided sources of information as indicated above cannot be considered a reliable source of information that could contribute to the conclusion on this key investigation.

2. Concerning key investigation (2) *survival of parent animal during the test*.

The sources of information (i) and (ii) provide relevant information on this key investigation. However, as explained under point "1.a)" above, the reliability of these sources of information is significantly affected. Therefore, these sources of information cannot contribute to the conclusion on this key investigation.

3. Concerning key investigation (3) *the time to produce the first brood*.

The source of information (i) provides relevant information on this key investigation. However, as explained under point "1.a)" above, the reliability of this source of information is significantly affected. Therefore, this source of information cannot contribute to the conclusion on this key investigation.

Taken together, the sources of information as indicated above provide relevant information on reproductive output of *Daphnia sp.*, survival of parental animals and time of production of first brood. However, the information provided on these key investigations is not reliable.

Conclusion

Accordingly, 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.

In the comments to the draft decision, you indicate that you "*contend that the information requirements of the endpoint have been fulfilled in accordance with the requirements of OECD TG 211.*" ECHA agrees that sources (i) and (ii) are conducted according to the requirements of OECD TG 211, as indicated under point "1.a)" above. However, as already explained in the Appendix on reasons common to several requests (cross-reference is already made under "1.a)" above), these sources of information are obtained from analogue substances and you have not demonstrated that this information on the analogue substance can reliably contribute to a weight of evidence approach intended to identify the properties of the Substance.

Therefore, your adaptation is rejected.

On this basis, the information requirement is not fulfilled.

### 3. Long-term toxicity testing on fish

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

You have provided the following information:

A. A justification to omit the study which you consider to be based on Annex IX, Section 9.1., Column 2.

B. You have adapted this information requirement under Section 1.2, Annex XI to REACH (weight of evidence). In support of your adaptation, you have provided the following study records with source substances:

   i. OECD TG 204 study with MTHPA (EC No. 234-290-7), [redacted] 1997;

   ii. OECD TG 210 (draft) study with PA (EC No. 201-607-5), [redacted] 1990;

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

A. Adaptation according to Annex IX, Section 9.1., Column 2

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

A registrant may only adapt this information requirement based on the general rules set out in Annex XI.

You have adapted this information requirement under Annex XI, Section 9.1., Column 2. In support of your adaptation, your justification provides the following arguments: the Substance is safe to use based on the Chemical Safety Assessment, exposure to the aquatic compartment is not expected, and the Substance is readily biodegradable.

Furthermore, you consider that "*the expenditure of vertebrate test organisms is not ethically justified.*"

As explained above, this information cannot be omitted based under Annex XI, Section 9.1., Column 2.

Furthermore, minimisation of vertebrate animal testing is not on its own a legal ground for adaptation under the general rules of Annex XI.

In the comments to the draft decision, you state further that you "*acknowledge that this requirement acts as a trigger for the need to provide further information but contends that the requirements have not been met to trigger such need and, as such, the adaptation is valid.*" However, as explained above, Column 2 of Section 9.1. of Annex IX requires registrants to submit information on a *further* study than one of the three listed in Column 1 of Section 9.1.6. of Annex IX, if the chemical safety assessment indicates that it is necessary to investigate the effects of a substance on aquatic organisms beyond what any one of those three studies would do. The Column 1 information requirement cannot be adapted based on this Column 2 provision referring to the Chemical Safety Assessment.

Your adaptation is therefore rejected.

B. Adaptation according to Annex XI, Section 1.2 (weight of evidence)

As explained under Appendix on Reasons common to several requests, the weight of evidence must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 9.1.6 at Annex IX includes similar information that is produced by the OECD TG 210. This includes:

1. the stage of embryonic development at the start of the test, and
2. hatching of fertilized eggs and survival of embryos, larvae and juvenile fish, and
3. the appearance and behaviour of larvae and juvenile fish, and
4. the weight and length of fish at the end of the test.

1. Concerning key investigations (1) *the stage of embryonic development at the start of the test* and (4) *the weight and length of fish at the end of the test*.

The source of information (ii) provides relevant information on these key investigations, but has the following deficiencies affecting its reliability.

a) The reliability of source of information (ii) is significantly affected by the deficiency identified and explained under Appendix on Reasons common to several requests.

b) The reliability of source of information (ii) is also affected by the following issue:

Testing in accordance with the OECD TG 210 requires that the following specifications/conditions must be met:

*Validity criteria (among others):*

- the analytical measure of the test concentrations is conducted.

In your dossier you have provided the following information for study (ii):

*Validity criteria:*
[redacted]
Based on the above, the validity criteria of the OECD TG 210 are not met.

Due to the above, source (ii) cannot be considered as reliable/or has low reliability.

Altogether, even though the source of information (ii) as indicated above may provide relevant information on these key investigations, its reliability is affected significantly, therefore, it cannot contribute to the conclusion on these key investigations.

2. Concerning key investigation (2) *hatching of fertilized eggs and survival of embryos, larvae and juvenile fish*.

The source of information (ii) provides relevant information on this key investigation. However, as explained under point (1) above, the reliability of source of information (ii) is significantly affected.

The source of information (i) provides partial information on this key investigation as only survival of juvenile fish is reported, while it does not inform on hatching of fertilized eggs and survival of embryos and larvae as required in OECD TG 210. Furthermore, source of information (i) has the following deficiencies affecting its reliability.

a) The reliability of source of information (i) is significantly affected by the deficiency identified and explained under Appendix on Reasons common to several requests.

b) In addition, the reliability of source of information (i) is also affected by the following issue:

The conditions of exposure in the OECD TG 210 specifies that the test must start as soon as possible after the eggs have been fertilised and continue until species-specific time period that is necessary for the control fish to reach a juvenile life-stage (30-d post-hatch is recommended for *Oryzias latipes*, according to Annex 2 of OECD TG 210).

Study (i) is perfomed with developed fish (*Oryzias latipes*, length 2.0-2.2 cm at study initiation) and has a duration of 14 days. You did not report that the test started after the eggs have been fertilised and covered a species-specific time period that is necessary for the control fish to reach a juvenile life-stage.

Therefore, the study duration is shorter than indicated in the OECD TG 210. This condition of exposure is essential because the effects observed in a long-term study might be considerably more pronounced than over a shorter study duration.

Due to the above, source (i) cannot be considered as reliable/or has low reliability.

In the comments to the draft decision you agree that study (i) does not provide the same information as a study conducted according to OECD TG 210. You indicate that this study provides partial information "*that has possible use in predicting the properties of the registered substance*." However, as already explained in the Appendix on reasons common to several requests (cross-reference is already made under "1.a)" above), this source of information is obtained from an analogue substance and you have not demonstrated that this information on the analogue substance can reliably contribute to a weight of evidence approach intended to identify the properties of the Substance.

Altogether, the provided sources of information as indicated above cannot be considered a reliable source of information that could contribute to the conclusion on this key investigation.

3. Concerning key investigation (3) *the appearance and behaviour of larvae and juvenile fish*

Sources of information (i) and (ii) do not provide any information covering this key investigation. Therefore, they do not provide information that would contribute to the conclusion on this key investigation.

Taken together, sources of information as indicated above provide information on long-term toxicity to fish but essential parts of information of the dangerous property is lacking (appearance and behaviour of larvae and juvenile fish). Furthermore, the information provided on these key investigations is not reliable.

Conclusion
Accordingly, 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 210 study. In the comments to the draft decision, you acknowledge the deficiencies identified by ECHA.

Therefore, your adaptation is rejected.

On this basis, the information requirement is not fulfilled.

*Study design*

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

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

### 1. Pre-natal developmental toxicity study in a second species

Pre-natal developmental toxicity (PNDT) studies (OECD TG 414) in two species is a standard information requirement under Annex X to REACH.

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

i. [redacted] 1988 - non-guideline PNDT study with Substance in rats and guinea pigs via inhalation route, investigating neonatal respiratory sensitizarion;
ii. Ema 1997 - non-guideline PNDT study with source substance PHA, (EC No. 201-873-2)
iii. Short 1986 – PNDT studywith the source substance MA, (EC No. 203-571-6)
iv. [redacted] - non-guideline intraperitioneal teratogenicity study in mice with the source substance PA (EC 201-607-5)

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

A. Adaptation according to Annex XI, Section 1.2 (weight of evidence)

As explained under Appendix on Reasons common to several requests, the weight of evidence must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

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

*1) Prenatal developmental toxicity*

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

*2) Maternal toxicity*

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

*3) Maintenance of pregnancy*

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

<u>Concerning key investigations 1) Prenatal developmental toxicity, 2) Maternal toxicity and 3) Maintenance of pregnancy</u>

The sources of information i., ii. and iii. provide relevant information on the key investigation 1) to 3) , but have the following deficiencies affecting their reliability.

The sources of information ii. and iii. are obtained from structural analogue substances. As explained under Appendix on Reasons common to several requests, you have not demonstrated that this information on the analogue substances can reliably contribute to a weight of evidence approach intended to identify the properties of the Substance.

The reliability of the source of information iv. is also affected by the following issues:
You have assigned a reliability score of 4 (not assignable) to the study by [redacted] ECHA agrees with your assessment of the reliability of this information and the study has not been assessed further. Therefore, this study does not contribute to the weight of evidence.

As explained in Appendix C, Section 2, the information provided is not sufficient to conclude on whether the Substance is or is not a developmental toxicant in the first species (rat).

According to the OECD TG 414, testing should be done in species and strains which are commonly used in prenatal developmental toxicity testing. The preferred rodent species is the rat and the preferred non-rodent species is the rabbit.

The study i. with the Substance was also performed in the rat and in the guinea pig, which are both rodents. You have not submitted a PNDT study with non-rodent species. No source of information provide information regarding potential for developmental toxicity in a second species.

Taken together, the sources of information as indicated above provide relevant information on prenatal developmental toxicity, maternal toxicity and maintenance of pregnancy. However, the information provided on these key investigations is not reliable.

Conclusion
Accordingly, 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 414 study. Therefore, your adaptation is rejected.

On this basis, the information requirement is not fulfilled.

In the comments to the draft decision, you agree that the OECD TG 414 in second species has not been submitted. In addition, you state that a sequential testing approach needs to be adopted to address a particular endpoint dependent on the outcome of other studies. For example, the need to investigate pre-natal development toxicity in a second species is dependent on the outcome of studies in the first, typically rodent, species.

The results of the pre-natal development toxicity in a first species needs to be considered before initiating testing in the second species. The deadline set in the initial draft decision already considers the need for such consideration and for sequential testing where appropriate.

*Specification of the study design*

A PNDT study according to the OECD TG 414 study should be performed in the rabbit or rat as the preferred second species, depending on the species tested in the first PNDT study , depending on the species tested in the first PNDT study (request B.1 in this decision). The study shall be performed with oral[8] administration of the Substance.

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

## 2. Extended one-generation reproductive toxicity study

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

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

i. [redacted] 2010 - reproduction/developmental toxicity screening test with the source substance 4-MHHPA, EC No. 243-072-0;
ii. [redacted] 1997 - combined repeated dose toxicity study with the reproduction/developmental toxicity screening test study with the source substance MTHPA, EC No. 234-290-7;
iii. [redacted] 1979; Kluwe 1986; Kluwe 1984 - non-guideline carcinogenicity studies in rats and mice with the source substance PA, EC No. 201-607-5;
iv. Short 1986 - two-generation reproduction toxicity study with the source substance MA, EC No. 203-571-6;
v. [redacted] 1970 - non-guideline testes toxicity study with the source substance PA, EC No. 201-607-5.

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

A. Adaptation according to Annex XI, Section 1.2 (weight of evidence)

As explained under Appendix on Reasons common to several requests, the weight of evidence must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

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

*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 and histopathology of reproductive organs and tissues, oestrous cyclicity, sperm count, sperm analysis, hormone levels, litter sizes, nursing performance and other potential aspects of sexual function and fertility.

*2) Toxicity to the offspring*

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

*3) Systemic toxicity*

Systemic toxicity must include information on clinical signs, survival, body weights, food consumption, haematology (full-scale), clinical chemistry (full-scale), organ weights and

histopathology of non-reproductive organs and tissues (full-scale) and other potential aspects of systemic toxicity in the parental P and F1 generation up to adulthood.

Concerning key investigations 1) Sexual function and fertility, 2) Toxicity to the offspring and 3) Systemic toxicity
The sources of information i., ii., iii. and iv. provide relevant information on the key investigations 1) to 3), but they have the following deficiencies affecting their reliability.

The sources of information i., ii., iii. and iv. are obtained from structural analogue substances.
As explained under Appendix on Reasons common to several requests, you have not demonstrated, neither in your dossier nor in your comments to the draft decision, that this information on the analogue substances can reliably contribute to a weight of evidence approach intended to identify the properties of the Substance.

The reliability of the sources of information i. and ii. is further affected by the following issues:
Firstly, these studies do not cover all relevant life stages required in OECD TG 443, as the extensive post-natal investigations of the fully exposed F1 generation up to the adulthood are not included.

Secondly, the statistical power of the information provided is not sufficient, because it does not fulfil the criterion of 20 pregnant females for each test group as required OECD TG 443.

In the comments to the draft decision, you agree that above mentioned parameters were not investigated in study i and ii.

The reliability of the source of information iii. is also affected by the following issue:
The study by [redacted] 1979 does not meet the requirement of OECD TG 443 as effects on mating, fertility, pregnancy, lactation and postnatal development of the fully exposed F1 generation up to the adulthood are not investigated.

In the comments to the draft decision, you agree that above mentioned parameters were not investigated in study iii.

The reliability of the source of information iv. is also affected by the following issue:
This study does not meet the requirement of OECD TG 443 as sperm parameters and oestrus cyclicity have not been analysed in P0 and F1.

In your comments you remind ECHA that an OECD TG 416 was the valid REACH information requirement at the time when the study was conducted and the time your dossier was submitted. You have adapted this information requirement using a weight of evidence approach. For the purpose of compliance, weight of evidence adaptations are assessed against the version of the corresponding test method into force at the time of the compliance check. The current information requirement is the OECD TG 443, which includes sperm parameters and oestrus cyclicity.

The reliability of the source of information v. is finally affected by the following issue:
You have assigned a reliability score of 4 (not assignable) to the study by Protsenko 1970; ECHA agrees with your assessment of the reliability of this information and the study has not been assessed further. Therefore, this study does not contribute to the weight of evidence.

Contribution of sources i., ii. and iii. to a weight of evidence
In your comments to the draft decision, you generally express the opinion that the information may still contribute to a weight of evidence when multiple sources of information are assessed. As already explained in the appendix on reasons common to several requests, 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. You did not demonstrate how the several independent sources of information can lead to the conclusion that the Substance has or has not the properties investigated in a study according to OECD TG 443. Most crucially, you did not include a justification of the particular value and weight of the individual sources of information, taking into account the limitations of each source of information and the reliability of their contribution to the adaptation, for a conclusion on all the relevant properties.

Conclusion

Taken together, the sources of information as indicated above provide relevant information on sexual function and fertility, toxicity to the offspring and systemic toxicity. However, The issues identified above significantly affect the reliability of the information obtained from these studies in the context of this weight of evidence approach.

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

On this basis, the information requirement is not fulfilled.

The specifications for the study design

*Species and route selection*

The study must be performed in rats with oral[9] administration.

*Premating exposure duration and dose-level setting*

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

Ten weeks premating exposure duration is required to obtain results adequate for classification and labelling and /or risk assessment. There is no substance specific information in the dossier supporting shorter premating exposure duration[10].

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

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

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

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

[9] ECHA Guidance R.7a, Section R.7.6.2.3.2.
[10] ECHA Guidance R.7a, Section R.7.6.

*Cohorts 1A and 1B*

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

*Further expansion of the study design*

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and/or Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if relevant information becomes available from other studies or during the conduct of this study. Inclusion is justified if the available information meets the criteria and conditions which are described in Column 2, Section 8.7.3., Annex X. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in ECHA Guidance[11].

## 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[12].

### 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[13].

[12] https://echa.europa.eu/practical-guides
[13] 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 08 October 2020.

ECHA notified you of the draft decision and invited you to provide comments within 30 days of the notification.

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

In your general comments on the draft decision you also expressed your intention to possibly fulfil certain information requirements by alternative methods. More specifically you refer to providing an adaptation relying partly on information yet to be generated on the source substance PA. You request "to postpone the final decision till this new data will be available".

ECHA points out that it is its mandate under Article 41 of REACH to check the compliance of the dossiers that were submitted by the registrants. This examination includes the compliance check of the adaptations submitted in the dossier submission subjected to this compliance check. It is not the task of ECHA to consider future development or improvements of adaptations submitted to provide the information required under REACH. The timeline set in this decision allows for generation of the information required under REACH, the incompliance of which was identified in this decision.

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[14] 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)[15]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[16]

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[17]

[14] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[15] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[16] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316
[17] 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 their corresponding information requirements

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

| Registrant name | Registration number | (Highest) data requirements to be fulfilled |
|---|---|---|
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |

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