ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 25 October 2016

Addressee: [redacted]

Decision number: TPE-D-2114346824-44-01/F
Substance name: Reaction mass of ethoxylated (≥ 3 moles) bisphenol A dimethacrylate and (1-methylethylidene)bis(4,1-phenyleneoxy-2,1-ethanediyl) bismethacrylate
EC number: 939-702-5
CAS number: n/a
Registration number: [redacted]
Submission number: [redacted]
Submission date: 04.02.2015
Registered tonnage band: 100-1000T

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA examined your testing proposal(s) and decided as follows.

Your testing proposal is accepted and you are requested to carry out:

1. **Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: Daphnia magna reproduction test, EU C.20./OECD TG 211) using the registered substance.**

While your originally proposed test for Sub-chronic toxicity study (90-day), oral route (EU B.26./OECD TG 408) in rats using the analogue substance Esterification products of 4,4'-isopropylidenediphenol, ethoxylated and prop-2-enoic acid, CAS No 64401-02-1 (EC No 613-584-2) is rejected, you are requested to perform:

2. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats using the registered substance; and**

While your originally proposed test for Pre-natal developmental toxicity study (EU B.31./OECD TG 414) in rats oral route using the analogue substance Esterification products of 4,4'-isopropylidenediphenol, ethoxylated and prop-2-enoic acid, CAS No 64401-02-1 (EC No 613-584-2) is rejected, you are requested to perform:

3. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rats or rabbits), oral route using the registered substance.**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective Annex, and an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by **1 November 2018**. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. Advice and further observations are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, shall be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under http://echa.europa.eu/regulations/appeals.

Authorised[1] by Hannu Braunschweiler, Head of Unit, Evaluation E1.

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

Appendix 1: Reasons

The decision of ECHA is based on the examination of the testing proposal(s) submitted by you.

0. Grouping of substances and read-across approach

Article 13(1) of the REACH Regulation requires information on intrinsic properties of substances on human toxicity to be generated whenever possible by means other than vertebrate animal tests, including from information from structurally related substances (grouping or read-across), "*provided that the conditions set out in Annex XI are met*".

The decision of ECHA is based on the examination of the testing proposals submitted by you for the registered substance Reaction mass of ethoxylated (≥ 3 moles) bisphenol A dimethacrylate and (1-methylethylidene)bis(4,1-phenyleneoxy-2,1-ethanediyl) bismethacrylate, EC No 939-702-5 (hereafter referred to as *'target (registered) substance'*).

You have proposed to cover the standard information requirements for:

- a sub-chronic toxicity study (90-days; Annex IX, Section 8.6.2.); and
- a pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

by performing the proposed tests with the analoge substance Esterification products of 4,4'-isopropylidenediphenol, ethoxylated and prop-2-enoic acid, CAS No 64401-02-1 (EC No 613-584-2); hereafter referred to as the *'source substance'*).

Annex XI, Section 1.5. requires a structural similarity among the substances within a group or category such that relevant properties of a substance within the group can be predicted from the data on reference substance(s) within the group by interpolation. The following analysis presents your justification for the proposed grouping approach and read-across hypothesis, together with ECHA's analysis concerning the justification in both a generic and property-specific context.

a. Description of the grouping and read-across approach proposed by you

You have provided the following hypothesis:

"*The read-across approach is based on the hypothesis that substances with a very close degree of ethoxylation and either acrylate or methacrylate functions at each end would show similar mechanisms of toxicity. It is also based on the hypothesis that substances with acrylate functions would be more toxic than substances with methacrylate functions. The read-across approach would be applied to the repeated toxicity and reproduction toxicity endpoints."*

In addition you state the following:

"*The read-across proposed between 2 moles Ethoxylated bisphenol A dimethacrylate (target substance) and Ethoxylated bisphenol A diacrylate (source substance) is considered to acceptable, because the worst case is chosen to fill data gaps in the 2 moles Ethoxylated bisphenol A dimethacrylate dossier.*

The source substance (diacrylate) seems to be more reactive and toxic than the target substance (dimethacrylate) in the repeated toxicity studies. That's why the 90-day repeated study and the developmental study on diacrylate could be used for the dimethacrylate dossier.".

b. Information/documentation submitted to support the grouping and read-across hypothesis

You have provided a read-across justification as a separate attachment in IUCLID section 13. This document outlines the read-across approach, the composition of the source and target substances, and provides a data matrix which allow comparison of available physico-chemical and toxicological information on the *'source substance'* and the *'target (registered) substance'*.

In addition, you provide the following infromation to support the read-across approach:

Studies conducted with the *'target (registered) substance'*:

- Acute oral toxicity (non-Guideline; Principles of the test: *"Test substance was administered undiluted in the highest tolerable amount of 30 ml/kg bw to groups of 10 males and 10 females."*); 1975; non-GLP; Rel. 2
- Acute dermal toxicity; (OECD TG 402); 2013; GLP; Rel. 1
- Skin irritation (non-Guideline; Principles of the test: *"Primary irritation to the skin is measured by a pacth-test technique on the abraded and intact skin albino rabbits."*); 1975; non-GLP; Rel. 2
- Eye irritation (non-Guideline; Principles of the test: *"2 moles Ethoxylated bisphenol A methacrylate was examined for eye irritating properties according to the techniques of tests published by the FDA of the US and Draize and Kelley."*); 1975; non-GLP; Rel. 2
- Skin sensitisation (non-Guideline; Principles of the test: *"The method employed in this study for the detection of delayed contact hypersensitivity was the guinea-pig maximization test described by B. Magnusson and A.M. Kligman (1970)."); 1978;* non-GLP; Rel. 2
- Bacterial reverse mutation assay (OECD TG 471); 2013; GLP; Rel. 1
- *In vitro* mammalian cell micronucleus *test* (OECD TG 487); 2013; Rel. 1
- *In vitro* mammalian cell gene mutation test (OECD TG 476); 2013; Rel. 1
- Combined repeated dose toxicity study with the reproduction / developmental toxicity screening test (OECD TG 422); 2013; GLP; Rel. 1

Studies conducted with the *'source substance'*:

- Repeated Dose 28-Day Oral Toxicity in Rodents (OECD TG 407); 2012; GLP; Rel. 1
- Reproduction / developmental toxicity screening test (OECD TG 422); 2013; GLP; Rel. 1

c. ECHA analysis of the grouping approach and read-across hypothesis in light of the requirements of Annex XI, 1.5.

ECHA understands that you base your read-across hypothesis upon the fact that two substances with *"very close degree of ethoxylation"* of bisphenol A will *"show similar mechanisms of toxicity"*; despite the fact that the *'target (registered) substance'* is a methacrylate and the *'source substance'* is an acrylate. Furthermore, you argue that the *'source substance'* is considered to be the worst case in terms of toxicity; because the acrylate- moeties present in *'source substance'* are assumed to have higher reactivity than the methacrylate- moeties present in the *'target (registered) substance'*.

Structural similarity and dissimilarity

You justify the structural similarity with the following statement: *"The 2 moles ethoxylated bisphenol A dimethacrylate (target substance) and the Ethoxylated bisphenol A diacrylate (source substance) showed numerous structural similarities like a [redacted]. Moreover, the average ethoxylation degree calculated according the proportions of the different constituents were also quite close between the target substance [redacted] and the source substance [redacted]. Also, both substances differ by their functionalities with methacrylate function for the target and acrylate function for the source substance."*

In addition, you have in the read-across justification document provided generic chemical structures, chemical name, chemical identifiers, and typical concentrations of the constituents for the *'target (registered) substance'* and the proposed *'source substance'*.

ECHA notes that the *'target (registered) substance'* is a multi-constituent substance with following constituents:

- [redacted] %; typically [redacted]
- [redacted] %; typically [redacted]

The *'target (registered) substance'* has the following impurities:

- [redacted] %; typically [redacted]
- [redacted] %; typically [redacted]

ECHA notes that the *'source substance'* is a substance of unknown or variable composition, complex reaction products or biological materials (UVCB) with the following constituents:

- [redacted] %; typically [redacted]
- [redacted] %; typically [redacted]
- [redacted] %; typically [redacted]
- [redacted] %; typically [redacted]
- [redacted] %; typically [redacted]
- [redacted] %; typically [redacted]
- [redacted] %; typically [redacted]
- [redacted] %; Typically [redacted]

ECHA understands that you base your read-across approach on the fact that both the *'target (registered) substance'* and *'source substance'* share a common stuctural core (*i.e.* [redacted]). Furthermore, ECHA understands that the substances differ in two aspects. Firstly, the substances differ in the degree of ethoxylation [redacted]. ECHA observes that the major constituents of the *'target (registered) substance'* are [redacted] (typically [redacted] (typically [redacted] In contrast, the *'source substance'* consists of [redacted] (typically [redacted] (typically [redacted] Furthermore, the amount of [redacted] are higher in the *'target (registered) substance'* ([redacted] % and [redacted]%, respectively) compared to the *'source substance'* ([redacted] % and [redacted]%, respectively).

Secondly, the *'target (registered) substance'* is an esterification product with 2-methylprop-2-enoic acid (*i.e.* a **methacrylate**) where as the *'source substance'* is an esterification *product with prop-2-enoic acid (i.e. an **acrylate**).*

ECHA concludes that you have provided information to demonstrate that both substances have a common structural core consisting of [redacted]. However, the degree of ethoxylation differs between the substances (the *'target (registered) substance'* is mostly [redacted] where as the *'source substance'* is mostly [redacted]. In addition, the substances differ in that the *'target (registered) substance'* is a methacrylate wheras the *'source substance'* is an acrylate. ECHA considers that the toxicological properties of the substances can not be predicted unless all identified stuctural and compositional differences between the *'target (registered) substance'* and the *'source substance'* are taken into account in the prediction.

Physico-chemical properties

You state that *"[...], for three of the major physical-chemical endpoints used to estimate the behaviour of the substances in humans and in the environment, 2 moles ethoxylated bisphenol A dimethacrylate and Ethoxylated bisphenol A diacrylate highlighted quite close values. These substances belong to a category of substances with the following physical-chemical properties: log Kow > 4, water solubility: 0.01 – 0.5 mg.L-1 (slightly soluble to insoluble) and vapour Pressure: <10-6 hPa (low volatilization)."*

ECHA observes that based on the data provided it can be concluded that the two substances have similar physico-chemical properties. However, ECHA observes that you have not explained as to why similarity in physico-chemical properties allow for prediction of toxicological properties.

ECHA considers that the fact that physico-chemical parameters are in the same range may be one element supporting a similar toxicokinetic and toxicity profile, but cannot be used alone to justify a prediction of properties related to human health.

Toxicological data (and Mode of Action)

You claim that two substances *"with a very close degree of ethoxylation"* of the common BPA core which differ in terms of *"either acrylate or methacrylate functions at each end"* will *"show similar mechanisms of toxicity".* Furthermore, you argue that because acrylates are generally more toxic than methacrylates testing the acrylate (*i.e.* the *'source substance'*) would be a worst case.

In addition, you have in the read-across justification document provided a data matrix to allow comparison of the toxicological profiles of the *'target (registered) substance'* and the proposed *'source substance'*.

To support the read-across hypothesis you bring forward the following:

- A data matrix in the read-across justification document to allow comparison of the toxicological profiles of the *'target (registered) substance'* and the proposed *'source substance'*.

  ECHA notes that for the *'source substance'* only the two studies listed above (under point b. above) are provided as endpoint study records in the technical dossier.

- Both the *'target (registered) substance'* and the *'source substance'* have similar oral and dermal acute toxicity, and none of the substances are irritating to skin or eyes, and none of the substances are skin sensitizers.

  ECHA notes that both substances have similar acute toxicity and similar local effects with regard to skin and eyes. However, ECHA considers that similarity in local effects

is not sufficient to demonstrate similarity also with regard to systemic toxicity effects.

- With regard to *in vitro* mutagenicity, the '*target (registered) substance*' has negative results in all three *in vitro* mutagenicity tests. In contrast, for the '*source substance*' one of the tests show positive results (*i.e.* the *In vitro* mammalian cell micronucleus test; OECD TG 487).

  ECHA notes that the results in the *In vitro* mammalian cell micronucleus test differ between the '*target (registered) substance*' and the '*source substance*'. ECHA consider that this is not in line with your claim of "*similar mechanisms of toxicity*".

- With regard to repeated dose toxicity, ECHA notes differences in NOAEL between the two substances. The '*target (registered) substance*' has been tested in a Combined repeated dose toxicity study with the reproduction / developmental toxicity screening test (OECD TG 422); and a NOAEL (P) for systemic toxicity has been established at 1000 mg/kg/day (based on no adverse effects observed). The proposed '*source substance*' has been tested in a Repeated Dose 28-Day Oral Toxicity study (OECD TG 407) and a NOAEL for systemic toxicity has been established at 300 mg/kg/day (based on increased blood cholesterol, increased liver weight and hepatocellular hypertrophy).

- You argue that the two substances will show "*similar mechanisms of toxicity*", and that the '*source substance*' is the "worst case" because the acrylate- functionalities are more reactive that methacrylate- functionalities.

  ECHA observes that the '*target (registered) substance*' showed no adverse effects at the limit dose in the available OECD TG 422 study. In contrast, the '*source substance*' showed increased blood cholesterol, increased liver weight and hepatocellular/centrilobular hypertrophy at 1000 mg/kg/day (NOAEL 250/300 mg/kg/day in the OECD TG 407 and OECD TG 421 study, respectively.
  Since the '*target (registered) substance*' did not cause adverse effects under the condition of the study, no conclusion can be made on the possible mechanism of its toxicity.

  It is also not possible to identify the '*source substance*' as worst case since it is not possible to compare the toxicity in terms of strength of effects due to the unknown effects of the target (registered) substance. Currently, it cannot be excluded that the '*target (registered) substance*' shows a different toxicity profile compared to the '*source substance*' in a 90-day repeated dose toxicity study.

  Furthermore ECHA notes that no specific mechanism of toxicity has been identified for the '*source substance*'. Therefore, the prediction lacks any mechanistic basis. A generic claim of "similar mechanism" is not providing a credible basis for a prediction.

- ECHA notes with regard to toxicity to reproduction that both the '*target (registered) substance*' and the '*source substance*' have been tested in the Reproduction / Developmental Toxicity Screening Test (OECD TG 422 and OECD TG 421, respectively), and that both substances the NOAELs for fertility (P) and developmental toxicity (F1) are 1000 mg/kg/day (based on no effects).

  ECHA does not consider absence of effects in the screening tests as supportive of "*similar mechanisms of toxicity*".

- To substantiate the claim that "*the acrylates are more toxic than methacrylates*" you provide a reference to a study which investigates *in vitro* hydrolysis rates of acrylate and methacrylate esters[2].

  ECHA notes that none of the substances investigated are the '*target (registered) substance*' nor the '*source substance*'. Furthermore, ECHA notes that you have provided no information to what extent the '*target (registered) substance*' or '*source substance*' hydrolyse. Moreover, you have not explained whether the toxicity of '*target (registered) substance*' and '*source substance*' is caused by the substances themselves (*i.e.* the parent substances) and/or their hydrolysis products. Finally you have not provided evidence to support that acrylates and methacrylates and/or their hydrolysis products are likely to cause the same type of toxicological effects with regard to sub-chronic toxicity (90-days).

- You also make reference to the category of chemicals with acrylates and methacrylates (SIDS of 2004[3]).

  ECHA notes that neither the '*target (registered) substance*' nor the '*source substance*' are members of any OECD SIDS category. ECHA therefore considers that the OECD categories are of limited value to the proposed prediction.

ECHA concludes that the toxicological information that you have provided does not support the assumption of "*similar toxicity*" between the '*target (registered) substance*' and the *'source substance*'. ECHA therefore considers that there is not an adequate basis for predicting the properties of the registered substance from the data obtained with the source substance.

Toxicokinetic properties

It is unclear to which substances the organism is exposed for the following reasons:

- No hydrolysis data, therefore it is not clear whether the acrylates or the methacrylates, respectively, are available as intact esters for systemic circulation or only hydrolysis products.
- It is also unclear which hydrolysis product is formed at which rate and which one is likely to drive the potential toxicity.
- No information on the toxicity of the [redacted] which are partly already present in the parent substances and further can be formed as hydrolysis products from the [redacted].
- No information on the fate and toxicity of the [redacted], if the [redacted] is indeed hydrolysed completely. Bisphenol A has a known toxicity profile and it is unclear what impact the ethoxylation has on this toxicity.
- It is not clear whether cleavage of the ethoxy groups is possible from the [redacted], if formed.
- It is not clear what impact the presence of [redacted] in the UVCB '*source substance*' has on the formation rates of potential toxic metabolites when compared to the formation rates of such metabolites from the '*target (registered) substance*'. It cannot be excluded that toxicokinetic interactions are only detectable

[2] TJ.McCarthy, G.Witz. Structure-activity relationships in the hydrolysis of acrylate and methacrylate esters by carboxylesterase in vitro. Toxicology 116 (1997), 153-158.
[3] Specialty Acrylates and Methacrylates Group, Multifunctional Acrylates Category. SIDS Test Plan and Data Review. Prepared for: American Chemistry Council, Specialty Acrylates and Methacrylates Panel. Prepared by: Toxicology/Regulatory Services, Inc. August 5, 2004

in a sub-chronic toxicity study (90-day) and/or a pre-natal developmental toxicity study, but not in the screening studies.

- No attempt has been made to assess the possible impact of the variability of the constituents of the source and target substance on the attempted prediction. E.g. which '*source substance*' composition will be tested and why and how would this composition be predictive for the range of possible constituent concentrations in the '*target (registered) substance*'. ECHA notes that depending on the rate of hydrolysis a significant amount of [redacted] may be formed; it is not explained how this impacts the prediction. Furthermore, the impact of such variation in the composition is not assessed under the conditions of repeated administration. In particular, it is not clear whether there is a preferential bioaccumulation potential for some constituents which would change the systemic exposure to these constituents at repeated administration over time in comparison to the constituent compositions in the parent substances.

You have proposed that the '*source substance*' has similar toxicity regarding sub-chronic and developmental toxicity and therefore the properties of the '*target (registered)substance*' can be predicted from data obtained from the '*source substance*'. ECHA concludes that the data provided does not provide sufficient evidence to conclude what constituents in the substances or which metabolic products drive the systemic toxicity.

Consequently, it is not possible to conclude on a mechanistic reasoning which could be considered to form the basis for the prediction. In addition, the differences in the toxicity profiles of the '*source substance*' and the '*target (registered) substance*' as explained in the previous section emphasises that the toxicokinetic issues pointed out above need to be addressed for a robust prediction.

ECHA therefore considers that there is not an adequate basis for predicting the properties of the '*target (registered) substance*' from the data obtained with the '*source substance*'.

Selection of the source substance

ECHA notes that you are proposing in a parallel registration to read-across from the same '*source substance*' to another analogue substance [redacted]. This means that the toxicity profiles of the '*source substance*' and the two target substances should all be similar to allow predictions.

However, this is not the case since the [redacted], show alpha-2u globulin nephropathy in males, increased urine volumen in males and females, and thymus atrophy effects which are not observed for the '*target (registered) substance*'. Furthermore, ECHA notes that you have not explained as to why the '*source substance*' and not [redacted], is the most appropriate source substance for the proposed predictions. Furthermore, since your prediction is based on a worst case approach, you have not provided sufficient evidence that the proposed '*source substance*' indeed is the worst case. Moreover, ECHA considers that all read-across approaches should be consistent and transparently reported in the concerned technical dossier; i.e. when a source substance is used to read-across to several target substances this should be reported in all concerned dossiers.

ECHA concludes that the information provided does not provide sufficient evidence to conclude that the '*target (registered) substance*' and/or its hydrolysis products does not

give rise to a different toxicological profile than that of the proposed '*source substance*' and/or its hydrolysis products. Furthermore, ECHA concludes that you have not demonstrated that the most appropriate analogue have been selected as a source substance for the read-across approach. ECHA therefore considers that there is not an adequate basis for predicting the properties of the registered substance from the data obtained with the source substance.

d. Conclusion on the read-across approach

Based on the data submitted by you, ECHA concludes that you have not provided adequate and reliable information to demonstrate that the read-across approach is plausible for the properties under consideration.

ECHA therefore concludes that the criteria of Annex XI, 1.5. are not met, and the read-across approach, as presented by you, cannot be considered plausible to meet the information requirements.

1. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.

"Long-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex IX, Section 9.1.5. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently, there is an information gap and it is necessary to provide information for this endpoint.
You have submitted a testing proposal for testing the registered substance for long-term toxicity testing on aquatic invertebrates (*Daphnia magna* reproduction test, EU C.20/OECD TG 211) with the following justification: "*No effects being observed at the water solubility limit and at the highest loading rate tested for all of the three trophic levels (fish, aquatic invertebrate and algae) in tests of Annex VII and VIII, no aquatic PNEC were derived. Therefore, a long-term toxicity test to aquatic invertebrates was proposed to be carried out according to OECD testing guideline 211.*" ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 9.1.5 of the REACH Regulation.

According to ECHA *Guidance on information requirements and chemical safety assessment* (version 3.0, February 2016), Chapter R7b (Section R.7.8.5 including Figure R.7.8-4), if based on acute aquatic toxicity data neither fish nor invertebrates are shown to be substantially more sensitive, long-term studies may be required on both. No effects were observed in short-term toxicity studies on aquatic species up to 100 mg/L loading rate, and therefore there were no indications in the dossier that fish would be substantially more sensitive than aquatic invertebrates.

In such case, according to the integrated testing strategy, the *Daphnia* study is to be conducted first. If based on the results of the long-term *Daphnia* study and the application of a relevant assessment factor no risks are observed (PEC/PNEC<1), no long-term fish testing may need to be conducted. However, if a risk is indicated, long-term fish testing may need to be conducted.

Note that with the current data in the dossier (acute aquatic toxicity studies), the most sensitive trophic level cannot be determined. This should be taken into account once the results of the long-term *Daphnia* study become available (e.g. when determining the appropriate assessment factor or in case no effects would be observed in the study).

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed test using the registered substance subject to the present decision: Long-term toxicity testing on aquatic invertebrates (test method: *Daphnia magna* reproduction test, EU C.20/OECD TG 211).

Notes for your consideration

Once results of the proposed test on long-term toxicity to aquatic invertebrates are available, you shall revise the chemical safety assessment as necessary according to Annex I of the REACH Regulation. If the revised chemical safety assessment indicates the need to investigate further the effects on aquatic organisms, you shall submit a testing proposal for a long-term toxicity test on fish in order to fulfil the standard information requirement of Annex IX, 9.1.6. If you come to the conclusion that no further investigation of effects on aquatic organisms is required, you shall update your technical dossier by clearly stating the reasons for adapting the standard information requirement of Annex IX, 9.1.6.

Due to the low solubility of the substance in water you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA Guidance, Chapter R7b, table R. 7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested long-term ecotoxicity test and for calculation and expression of the result of this test.

2. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.)

Pursuant to Article 40(3)(a) and (c) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test and to carry out additional tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.

A sub-chronic toxicity study (90 day) is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for a sub-chronic toxicity study (90 day) in rats by the oral route according to EU B.26./OECD TG 408 with the *'source substance'*. ECHA has evaluated your proposal to perform the test with the *'source substance'*. For the reasons explained above (see section 0), your proposed read-across approach has been rejected. Concequently, as there is an information gap the proposed test shall be perfomed with the *'target (registered) substance'*.

According to the test method EU B.26./OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat via oral administration.

Therefore, pursuant to Article 40(3)(a) and (c) of the REACH Regulation, you are requested to carry out the additional study with the 'target (registered) substance' subject to the present decision: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU

B.26./OECD TG 408); while your originally proposed test for *Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26./OECD TG 408) with the 'source substance'* is rejected according to Article 40(3)(d) of the REACH Regulation.

3. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

Pursuant to Article 40(3)(a) and (c) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test and to carry out additional tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.

A pre-natal developmental toxicity study for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for a pre-natal developmental toxicity study in rats according to EU B.31./OECD TG 414 by the oral with the *'source substance'*. ECHA has evaluated your proposal to perform the test with the *'source substance'*. For the reasons explained above (see section 0), your proposed read-across approach has been rejected. Concequently, as there is an information gap the proposed test shall be perfomed with the *'target (registered) substance'*.

According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed with the rat or rabbit as a first species. ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 40(3)(a) and (c) of the REACH Regulation, you are requested to carry out the additional study with the *'target (registered) substance'* subject to the present decision: Pre-natal developmental toxicity study in a first species (rats or rabbits), oral route (test method: EU B.31./OECD TG 414); while your originally proposed test for Pre-natal developmental toxicity study in a first species (rats or rabbits), oral route (test method: EU B.31./OECD TG 414) with the *'source substance'* is rejected according to Article 40(3)(d) of the REACH Regulation.

Notes for your consideration

For the selection of the appropriate species you are advised to consult ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015), Chapter R.7a, section R.7.6.2.3.2.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposal(s) for examination pursuant to Article 40(1) on 28 May 2013.

ECHA held a third party consultation for the testing proposal(s) from 12 December 2014 until 26 January 2015. ECHA did not receive information from third parties.

This decision does not take into account any updates after **8 August 2016**, 30 calendar days after the end of the commenting period.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

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

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

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) for amendment.

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided in your registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the registration at a later stage.

2. Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the Enforcement Authorities of the Member States.

3. In carrying out the test(s) required by the present decision it is important to ensure that the particular sample of substance tested is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported. If the registration of the substance covers different grades, the sample used for the new test(s) must be suitable to assess these. Furthermore, there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.