EUROPEAN CHEMICALS AGENCY

Helsinki, 23 March 2017

Decision number: TPE-D-2114354032-63-01/F

DECISION ON TESTING PROPOSAL(S) SET OUT IN A REGISTRATION PURSUANT TO ARTICLE 40(3) OF REGULATION (EC) NO 1907/2006

For m-(2,3-epoxypropoxy)-N,N-bis(2,3-epoxypropyl)aniline, EC No 275-662-9 (CAS No 71604-74-5), registration number: [redacted]

Addressee: [redacted]

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

I. Procedure

Pursuant to Article 40(1) of the REACH Regulation, ECHA has examined the following testing proposals submitted as part of the registration dossier in accordance with Articles 10(a)(ix) and 12(1)(d) thereof for m-(2,3-epoxypropoxy)-N,N-bis(2,3-epoxypropyl)aniline, EC No 275-662-9 (CAS No 71604-74-5), submitted by [redacted] (Registrant).

- Developmental toxicity / teratogenicity study (OECD 414) in rats, using the analogue substance p-(2,3-epoxypropoxy)-N,N-bis(2,3-epoxypropyl)aniline (CAS No 5026-74-4; EC No 225-716-2).

- Two-generation reproduction toxicity study (OECD 416), in rats, using the analogue substance p-(2,3-epoxypropoxy)-N,N-bis(2,3-epoxypropyl)aniline (CAS No 5026-74-4; EC No 225-716-2).

This decision is based on the registration as submitted with submission number [redacted], for the tonnage band of 100 to 1000 tonnes per year.

This decision does not take into account any updates after 7 September 2015, i.e. 30 calendar days after the end of the commenting period.

This decision does not imply that the information provided by the Registrant in his 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.

ECHA received the registration dossier containing the above-mentioned testing proposals for further examination pursuant to Article 40(1) on 14 February 2013.

ECHA held a third party consultation for the testing proposals from 15 July 2014 until 29 August 2014. ECHA received information from third parties (see section III below).

On 30 June 2015 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision. That draft decision was based on submission number [redacted].

On 5 August 2015 ECHA received comments from the Registrant on the draft decision.

On 3 September 2015 the Registrant updated his registration dossier (submission number [redacted]).

The ECHA Secretariat considered the Registrant's comments and update.
On basis of this information, Section II was amended. The Statement of Reasons (Section III) was changed accordingly.

On 21 July 2016 ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals for amendment of the draft decision within 30 days of the receipt of the notification.

Subsequently, proposal(s) for amendment to the draft decision were submitted.

On 26 August 2016 ECHA notified the Registrant of the proposal(s) for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on the proposal(s) for amendment within 30 days of the receipt of the notification.

The ECHA Secretariat reviewed the proposal(s) for amendment received and amended the draft decision.

On 5 September 2016 ECHA referred the draft decision to the Member State Committee.

By 26 September 2016, in accordance to Article 51(5), the Registrant provided comments on the proposals for amendment. In addition, the Registrant provided comments on the draft decision. The Member State Committee took the comments on the proposals for amendment of the Registrant into account. The Member State Committee did not take into account the Registrant's comments on the draft decision as they were not related to the proposals for amendment made and are therefore considered outside the scope of Article 51(5).

After discussion in the Member State Committee meeting on 25–27 October 2016, a unanimous agreement of the Member State Committee on the draft decision was reached on 27 October 2016.

ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Testing required

Tests required pursuant to Article 40(3) of the REACH Regulation

The Registrant shall carry out the following proposed tests pursuant to Article 40(3)(c) and 13(4) of the REACH Regulation using the indicated test methods and the registered substance subject to the present decision:

1. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31/OECD 414) in rats or rabbits, oral route;
2. Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral route by diet, specified as follows:
   - Ten weeks premating exposure duration for the parental (P0) generation;
   - Dose level setting shall aim to induce some toxicity at the highest dose level;
   - Cohort 1A (Reproductive toxicity);

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

while the proposed tests for a pre-natal developmental toxicity study (OECD TG 414) and a two-generation reproduction toxicity study (OECD 416) carried out using the the analogue substance p-(2,3-epoxypropoxy) -N, N-bis(2,3-epoxypropyl) aniline (CAS No 5026-74-4; EC No 225-716-2) are rejected pursuant to Article 40(3)(d) of the REACH Regulation.

Note for consideration by the Registrant:

The Registrant 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 to and conforming with the appropriate rules in the respective Annex, and an adequate and reliable documentation.

Failure to comply with the requests in this decision, or to fulfil otherwise the information requirements with a valid and documented adaptation, will result in a notification to the Enforcement Authorities of the Member States.

Deadline for submitting the required information

Pursuant to Articles 40(4) and 22(2) of the REACH Regulation, the Registrant shall submit to ECHA by **30 September 2019** an update of the registration dossier containing the information required by this decision, including, where relevant, an update of the Chemical Safety Report. The timeline has been set to allow for sequential testing as appropriate.

III. Statement of reasons

The decision of ECHA is based on the examination of the testing proposals submitted by the Registrant for the registered substance. ECHA has considered first the scientific validity of the proposed read-across and grouping approach (Section III.0. below), before assessing the testing proposed (Sections III.1. to III.2.).

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally related substances (grouping of substances and read-across), *"provided that the conditions set out in Annex XI are met."*

Annex XI, 1.5. has the following provision: *"Substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group or 'category' of substances. Application of the group concepts requires that physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s) with this group by interpolation to other substances in the group (read-across approach)."*

The Board of Appeal stated in the summary of its decision A-006-2012 of 13 February 2014: *"that for a read-across adaptation to be assessed and potentially accepted by the Agency, registrants have to show with clear reasoning and supporting data, set out in the appropriate section of the registration dossier, that the substances involved in the read-across are structurally similar and are likely to have similar properties (or follow a similar pattern). Registrants should also explain how and why the similarity of properties is the result of the structural similarity.*

The Board of Appeal explained that inclusion of the above information in the dossier is essential to allow the Agency to carry out its role of evaluating whether the read-across proposal complies with the relevant provisions of the REACH Regulation."

0. Grouping of substances and read-across approach

a. Introduction of the grouping approach and read-across hypothesis proposed by the Registrant

The Registrant has proposed to cover the standard information requirements for pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) and extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.) for the registered substance with tests that are being performed on the analogue substance p-(2,3-epoxypropoxy)-N,N-bis(2,3-epoxypropyl)aniline, EC No 225-716-2 (CAS No 5026-74-4).

The Registrant has provided the following hypothesis/justification:

"p-(2_3-epoxypropoxy)-N_N-bis(2_3-epoxypropyl)anilineis a a monoconstituent substance under REACH with a purity of typically 80 % (range: 70-100%). The impurities are mainly isomers of the impurities of those present in m-(2_3-epoxypropoxy)-N_N-bis(2_3-epoxypropyl)aniline. The hypothesis will be to read-across data on phys/chem., environmental fate, ecotoxicity and toxicity from the p-(2_3-epoxypropoxy)-N_N-bis(2_3-epoxypropyl)aniline to the isomer m-(2_3-epoxypropoxy)-N_N-bis(2_3-epoxypropyl)aniline",

"Based on available experimental data (see Table on Read-Across), including basic physico-chemical properties, the read-across is justified. There are no functional groups not common to source. Both substances are structural isomers and therefore share all substituents, have the same mol weight and are similar in lipophilicity and molecular size. The critical functional group determining the toxicity of both isomers are the three glycidyl ethers, which are reactive and are responsible for the main effect of toxicity, DNA- and/or protein-binding. This function is equally present in both substances and its effect on adduct formation is not depending on the isomer position of the side groups.",

"It is concluded that p-(2_3-epoxypropoxy)-N_N-bis(2_3-epoxypropyl)aniline and m-(2_3-epoxypropoxy)-N_N-bis(2_3-epoxypropyl)aniline are likely very similar with respect to all physico-chemical properties, environmental fate, environmental toxicity and human health effects. This will cause that C&L, PBT/vPvB properties and dose descriptors are identical. No differences are expected for all endpoints of REACH and no adaptations are necessary.", and

"It is considered that the isomers show an identical toxicity profile because they do not differ in mol wt, composition or functional groups. From the chemical structure, it is evident that the glycidyl ethers (which are reactive, DNA- and protein-binding functional groups) of the isomers react identically with DNA and/or protein as the reactivity of the functional group is not altered by the isomerisation. It is evident from all available toxicity data, including additional substances, that the toxicological profile of glycidyl ethers is determined by the functional group and to a much lesser (insignificant) amount by the backbone molecule...".

b. Information submitted by the Registrant to support the grouping and read-across hypothesis

In order to support the testing proposals, the Registrant has provided a read-across justification document "[redacted]" which contains a tabular comparison of the physico-chemical data, the environmental fate and pathway, the environmental toxicity and the mammalian toxicity data, and a document "[redacted]", which is the summary of the read across rationale, containing the hypothesis, identification of the source and target substance, a high level comparison of the impurity profiles, a short justification to apply analogue approach and a conclusion.

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

Based on the information provided, ECHA understands that the read-across hypothesis proposed by the Registrant is based on the substances being structural isomers with the same functional groups, molecular weight, and similar lipophilicity and molecular size. In addition, they share the same mechanism of action, i.e. toxicity is caused by three reactive glycidyl ethers responsible for DNA- and/or protein binding, which effect is not depending on the isomer position of the groups.

Impact of different isomers

ECHA notes that indeed since the substances are isomers, they do have the same functional groups, same molecular weight, similar lipophilicity and molecular weight, and glycidyl ether groups.

i. The Registrant states that the m- and p- positional isomerism has no influence on the toxicity profile of the substances because they "*do not differ in molecular weight, composition or functional groups*", and "*as the reactivity of the functional groups is not altered by the isomerisation*". However, the Registrant has not provided any mechanistic/kinetic/other data or explanation to support his claim that the m- and p- positional isomerism has no influence on the toxicity profile of the substances.

   ECHA notes that different isomers do not necessarily have similar reactivity, toxicokinetic properties and toxicological profiles, and a statement about similar molecular weight, composition and functional groups does not provide sufficient evidence to support similar behaviour of the two isomers.

ii. The Registrant further states that "*From the chemical structure, it is evident that the glycidyl ethers (which are reactive, DNA- and protein-binding functional groups) of the isomers react identically with DNA and/or protein as the reactivity of the functional group is not altered by the isomerisation. It is evident from all available toxicity data, including additional substances, that the toxicological profile of glycidyl ethers is determined by the functional group and to a much lesser (insignificant) amount by the backbone molecule.*"

   ECHA notes that with regards to the reactive glycidyl ether structure in the substances the read-across approach appears to be justifiable for mutagenicity. However, as the Registrant has not provided any explanation/data to support the similar behaviour of the isomers, a common mechanism of action alone is not considered sufficient to justify the read-across approach. ECHA further notes that no data has been provided to support the toxicological behaviour of the glycidyl ethers and the impact of the backbone molecule on toxicity.

iii. Regarding the toxicokinetics the Registrant states that *"Glycidyl ethers are detoxified in vivo by hydrolysis. This is done by epoxyde hydrolases which are present in the skin, liver, plasma and most tissues. The efficiency of the detoxification is considered to depend on the rate of absorption (which is dependent on mol wt, charge, lipophilicity) and the three-dimensional structure of the backbone molecule. Because the differences between the substance as described in Section 1 and its e p-isomer (data donor) is restricted to the three-dimensional structure of the backbone molecule it is reasonably assumed that the toxicities of both isomers is identical."*

ECHA notes that the Registrant refers to the metabolism of glycidyl ethers in general but has not provided data on the metabolism of the registered and analogue substances. In addition, as stated in sections i-ii above, no data has been provided to explain the expected similar behaviour of the isomers.

Human health data

The Registrant states that *"Based on available experimental data, including basic physico-chemical properties, the read-across is justifiedand 1:1 read-across (of test results and derived classification) is considered justified for all endpoints"*. For the genotoxicity endpoint, the Registrant has provided an additional explanation: *"As the glycidyl ether sidechains are the possible mutagenic and clastogenic moieties, it is considered that the result of the study is valid for both the substance described in section 1.2 and the test substance"*.

ECHA understands that the proposed prediction is based on the hypothesis that two different substances, p-(2,3-epoxypropoxy)-N,N-bis(2,3-epoxypropyl)aniline (registered substance) and m-(2,3-epoxypropoxy) -N, N-bis(2,3-epoxypropyl) aniline (CAS no 71604-74-5, EC no 275-662-9), (analogue substance) are assumed to cause the same effects due to identified structural similarities. Furthermore, ECHA notes that the Registrant has clearly identified the structural (dis)similarities between the source and the target substance and that there are certain physicochemical properties that appear to be similar. Moreover, ECHA notes that the Registrant assumes this read-across hypothesis apply to all toxicological properties.

ECHA notes that experimental data is available only for some physico-chemical and environmental endpoints. Based on the data provided it can be concluded that the substances have similar physico-chemical properties (e.g. melting/freezing point, Log Pow and water solubility).

However, ECHA notes that based on the short term fish and daphnia studies, the registered substance seems to be more toxic than the analogue substance. In addition, no experimental human health toxicity data has been provided for the analogue substance.

ECHA considers that data on physico-chemical properties and short term ecotoxicity is not sufficient to support the Registrant's claim "read-across is justified for all endpoints"

ECHA notes that the read-across in its current form cannot be considered plausible due to uncertainties explained above, i.e. the explanation as to why the different isomers would have similar reactivity, toxicokinetic and toxicological behaviour, and the lack of human health toxicity data for the analogue substance. Therefore, the prediction of properties from the results conducted with the analogue substance to the registered substance may lead to underestimation of the hazard.

iv. Conclusion on the read-across approach

ECHA observes that no supporting data has been provided on how and why the similarity of properties is the result of the structural similarity. In addition, no human health toxicity data has been provided for the analogue substance.

ECHA concludes that the proposed analogue substance and the registered substances are structurally similar. Structural similarity alone however is not sufficient for predicting toxicological properties. It has to be explained why such prediction is possible in view of the structural differences and the provided evidence has to support such explanation.
ECHA concludes that the Registrant has failed to meet the provisions in Annex XI, Section 1.5. by failing to demonstrate that the toxicological properties of the substances '*are likely to be similar or follow a regular pattern'*. ECHA concludes that it is not possible to predict the toxicological properties of the target substance from the studies conducted with the source substance.

1. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

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

The Registrant has submitted a testing proposal for a pre-natal developmental toxicity study in rats according to EU B.31/OECD 414 to be performed with the analogue substance p-(2,3-epoxypropoxy)-N,N-bis(2,3-epoxypropyl)aniline (EC No 225-716-2) with the following justification: "*In response to the test rules "Testing of Certain High Production Volume Chemicals; Third Group of Chemical" (76 FR 65385, October 21, 2011), the US-EPA authorities has request from* [redacted] *to perform a Pre-natal developmental toxicity study on the on the analogue substance, p-(2,3-epoxypropoxy)-N,N-bis(2,3-epoxypropyl)aniline. It is proposed to read-across the results to the registered substance based on the read-across statement attached under section 13*".

ECHA has evaluated the proposal to perform the test with the analogue substance p-(2,3-epoxypropoxy)-N,N-bis(2,3-epoxypropyl)aniline (EC No 225-716-2). However, as explained above in section III, 0 of this decision, the adaptation of the information requirement is rejected. As the data on the analogue substance is not yet available, it is irrelevant whether or not the data may be generated following regulatory needs of other countries as the Registrant explains in his comments.

ECHA considers that the proposed study performed with the registered substance is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

The Registrant proposed testing in rats. He did not specify the route for testing. According to the test method EU B.31/OECD 414, the rat is the preferred rodent species, the rabbit the preferred non-rodent species and the test substance is usually administered orally. ECHA considers these default parameters appropriate and testing should be performed by the oral route with the rat or the rabbit as a first species to be used.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, the Registrant is requested to carry out the following study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in rats or rabbits, oral route (test method: EU B.31/OECD 414) while the proposed tests for a pre-natal developmental toxicity study (OECD TG 414), proposed to be carried out using the the analogue substance p-(2,3-epoxypropoxy) -N, N-bis(2,3-epoxypropyl) aniline (CAS No 5026-74-4; EC No 225-716-2) is rejected pursuant to Article 40(3)(d) of the REACH Regulation.

Notes for your consideration

ECHA notes that, apparently, in the 28-d oral gavage study available in the registration dossier, severe irritant, if not corrosive, effects were observed in the gastro-intestinal tract at and above the lowest dose level of 50 mg/kg bw. In certain OECD test guidelines, e.g. OECD 408, advice has been given that for irritating or corrosive substances, the concentration may be adjusted to avoid these effects. The registrant is advised to examine this possiblity, keeping in mind the effect of the volume of the test substance administered. ECHA recognises that in this case none of the ways to administer the substance is without potential technical complications in the test design, and therefore, the registrant is expected to use all information available to him in order to, on one hand to maximise the systemic uptake of the test substance, and on the other hand to minimise any unwanted effects, which may compromise the value of the test result.

One possibility to avoid adverse effects in the gastro-intestinal tract may be to expose the animals via diet. However, the aim of a pre-natal developmental study is to get high systemic exposure, and you need to ensure that the choice of dosing methodology (gavage or diet) leads to the highest bioavailability. As the default exposure route according to the OECD test guideline 414 is gavage; dietary exposure can be applied but needs to be justified.

2. Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.)

a) Examination of the testing proposal

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

The basic test design of an extended one-generation reproductive toxicity study (Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex IX of the REACH Regulation if the available repeated dose toxicity studies (e.g. 28-day or 90-day studies, OECD TGs 421 or 422 screening studies) indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity. If the conditions described in column 2 of Annex IX are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in in ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015).

ECHA considers that adverse effects on reproductive organs or tissues and/or other concerns in relation with reproductive toxicity are observed in the provided 28 day study according to OECD TG 407 (study report, 2013). More specifically, changes in the reproductive organs were observed in the mid and high-dose groups (150 mg/kg bw/day and/or 450 mg/kg bw/day).

These include: atrophy in the uterus, cervix and vagina; a reduced size and/or weight of uterus, ovaries, prostate and seminal vesicles; a small prostate gland (with normal histology); and reduced contents of the seminal vesicles and coagulating glands. Furthermore, pale discolouration and vacuolation zona fasciculate in adrenal glands was observed at the highest dose level. As the condition of Annex IX, Section 8.7.3. is fulfilled, an extended one-generation reproductive toxicity study is an information requirement for the registered substance pursuant to Annex IX, Section 8.7.3.

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.

The Registrant has submitted a testing proposal for a two-generation reproductive toxicity study according to EU B.35/OECD 416 to be performed with the analogue substance p-(2,3-epoxypropoxy)-N,N-bis(2,3-epoxypropyl)aniline (EC No 225-716-2) with the following justification: *"Due to requests within other regulatory jurisdictions (US-EPA) for provision of additional data (1), in response to the test rules "Testing of Certain High Production Volume Chemicals; Third Group of Chemical" (76 FR 65385, October 21, 2011), and its preference of a 2-generation reproductive study, a test is currently contracted to a testing laboratory and underway with the analogue p-(2,3-epoxypropoxy)-N,N-bis(2,3-epoxypropyl)aniline. It is proposed to read-across the results to the registered substance based on the read-across statement attached under section 13".*

A two-generation reproductive toxicity study is no longer an information requirement of the REACH Regulation. According to Annex IX, Section 8.7.3., as amended by Commission Regulation (EU) 2015/282 (entered into force on 13 March 2015), an extended one-generation reproductive toxicity study is an information requirement if adverse effects on reproductive organs or tissues have been observed in the available repeated dose toxicity studies (e.g. a 28-day or 90-day repeated dose toxicity study, OECD 421 or 422 screening studies) or if they reveal other concerns in relation to reproductive toxicity. However, a two-generation reproductive toxicity study (EU B.35/OECD TG 416) that was initiated before 13 March 2015 shall be considered appropriate to address this information requirement according to Annex IX, Section 8.7.3., column 2.

ECHA has evaluated the proposal to perform the test with the analogue substance p-(2,3-epoxypropoxy)-N,N-bis(2,3-epoxypropyl)aniline (EC No 225-716-2). As explained above in section III, 0 of this decision, the adaptation of the information requirement is rejected. As the data on the analogue substance is not yet available, it is irrelevant whether or not the data may be generated following regulatory needs of other countries as the Registrant explains in its comments. The proposed experimental study (EU B.35/OECD 416) conducted on an analogue substance can at this stage not considered appropriate to meet the information requirements under REACH with the adapatation argument presented being dismissed.

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement. Thus, an extended one-generation reproductive toxicity study according to column 1 of 8.7.3., Annex IX performed with the registered substance is required. The following refers to the specifications of this required study.

Premating exposure duration and dose-level setting

ECHA consideres that to ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to ECHA Guidance, the starting point for deciding on the length of premating exposure period should 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 because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015).
The highest dose level shall aim to induce some toxicity to allow comparison of effect levels and effects of reproductive toxicity with those of systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

If there is no existing relevant data to be used for dose level setting, it is recommended that results from a range-finding study (or range finding studies) are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

Extension of Cohort 1B

If the column 2 conditions of 8.7.3., Annex IX are met, Cohort 1B must be extended, which means that the F2 generation is produced by mating the Cohort 1B animals. This extension provides information also on the sexual function and fertility of the F1 animals.

ECHA considers that the criteria to extend the Cohort 1B are not met and concludes that Cohort 1B must not be extended to include mating of the animals and production of the F2 generation.

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Cohorts 2A and 2B

The developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity as described in column 2 of 8.7.3., Annex IX . When there are triggers for developmental neurotoxicity, both the Cohorts 2A and 2B are to be conducted as they provide complementary information.

ECHA considers that the criteria to include Cohorts 2A and 2B are not met and concludes that the developmental neurotoxicity Cohorts 2A and 2B need not to be conducted.

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Cohort 3

The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity as described in column 2 of 8.7.3., Annex IX.

ECHA considers that the criteria to include Cohort 3 are not met and concludes that the developmental immunotoxicity Cohort 3 needs not to be conducted.

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Species and route selection

According to the test method EU B.56./OECD TG 443, the rat is the preferred species. On the basis of this default consideration, ECHA considers that testing should be performed in rats.

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.

ECHA notes that, apparently, in the 28-d oral gavage study available in the registration dossier, severe irritant, if not corrosive, effects were observed in the gastro-intestinal tract at and above the lowest dose level of 50 mg/kg bw. Possibly the registered substance used as test substance in this study, and which itself has been tested negative in skin and eye irritation/corrosion tests in vivo, is hydrolysed to a much more irritant/corrosive chemical species upon contact with acidic gastric fluid. Using gavage administration with lower, non-corrosive concentrations would bear the risk of missing significant reproductive/developmental toxicity at higher doses (e.g. in the 28-d test, atrophy of reproductive organs was not reported at the lowest, but only at higher doses). Performing a feeding study instead should allow for achieving higher dose levels while at the same time avoiding strong irritant or corrosive effects and, hence, unnecessary suffering of the animals.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation.

A third party has indicated that the tonnage level of the registered substance only requires the conduct of a reproduction toxicity study if the 28-day or 90-day study indicates adverse effects on reproductive organs or tissues.

As already stated under section III.3.a above, ECHA notes that according to Annex IX, Section 8.7.3., an extended one-generation reproductive toxicity study is an information requirement if adverse effects on reproductive organs or tissues have been observed in the available repeated dose toxicity studies (e.g. a 28-day or 90-day repeated dose toxicity study, OECD 421 or 422 screening studies) or if they reveal other concerns in relation with reproductive toxicity. For the substance subject to the present decision there is a repeated dose toxicity study available in the registration dossier that triggers a reproductive toxicity study.

c) Outcome

Therefore, pursuant to Article 40(3)(d) of the REACH Regulation, the Registrant is requested to carry out the following study with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method: EU B.56/OECD 443) in rats, oral route by diet, according to the following study-design specifications:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce some toxicity at the highest dose level;

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

while the proposed test for a two-generation reproduction toxicity study (OECD 416), proposed to be carried out using the the analogue substance p-(2,3-epoxypropoxy) -N, N-bis(2,3-epoxypropyl) aniline (CAS No 5026-74-4; EC No 225-716-2) is rejected pursuant to Article 40(3)(d) of the REACH Regulation.

Note for consideration by the Registrant:

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 Cohort 3 (developmental immunotoxicity) were identified. However, the Registrant may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the new information shows triggers which are described in column 2 of Section 8.7.3., Annex IX and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment* R.7.a, chapter R.7.6 (version 4.1, October 2015). The Registrant may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented. The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

IV. Adequate identification of the composition of the tested material

The process of examination of testing proposals set out in Article 40 of the REACH Regulation aims at ensuring that the new studies meet real information needs. Within this context, the Registrant's dossier was sufficient to confirm the identity of the substance to the extent necessary for examination of the testing proposal. The Registrant must note, however, that this information has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation.

It is important to ensure that the particular sample of substance tested in the new studies 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. If the registration of the substance covers different grades, the sample used for the new studies must be suitable to assess these.

Finally, there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the studies to be assessed.

V. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Article 51(8) of the REACH Regulation. Such appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on the ECHA's internet page at http://www.echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

Authorised[2] by Claudio Carlon, Head of Unit, Evaluation E2

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