EUROPEAN CHEMICALS AGENCY

Helsinki, 27 March 2018

Addressee: [redacted]

Decision number: CCH-D-2114394438-35-01/F
Substance name: 2-dimethylaminoethyl methacrylate
EC number: 220-688-8
CAS number: 2867-47-2
Registration number: [redacted]
Submission number: [redacted]
Submission date: 14/10/2015
Registered tonnage band: Over 1000

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

1. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a second species (rabbit), oral route with the registered substance;**

2. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral route with the registered substance 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;**
   - **Cohorts 2A and 2B (Developmental neurotoxicity).**

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 to the REACH Regulation. 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 adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by **5 October 2020**. You also have to 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 and advice and further observations are provided in Appendix 3.

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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, has to 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 Kevin Pollard, 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

TOXICOLOGICAL INFORMATION

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Your registration dossier contains for the endpoints pre-natal developmetal toxicity study (*Annex X, Section 8.7.2.)* in a second species (rabbit) and extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.) adaptation arguments in form of a grouping and read-across approach under Annex XI, Section 1.5. of the REACH Regulation. ECHA has considered first the scientific and regulatory validity of your read-across approach in general before assessing the individual endpoints (sections 1 and 2).

Grouping of substances and read-across approach

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. 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 (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological or ecotoxicological property is reliable and should be based on recognition of the structural similarities and differences between the source and registered substances[2]. This hypothesis explains why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration. Key physicochemical properties may determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests.

Similarly, biotic and abiotic degradation may alter the fate and bioavailability of compounds as well as be themselves hazardous, bioaccumulative and/or persistent. Thus, physicochemical and degradation properties influence the human health and environmental properties of a substance and should be considered in read-across assessments. However, the information on physicochemical and degradation properties is only a part of the read-

[2] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals.

across hypothesis, and it is necessary to provide additional justification which is specific to the endpoint or property under consideration.

The ECHA Read-across assessment framework foresees that there are two options which may form the basis of the read-across hypothesis[3]- (1) (Bio)transformation to common compound(s)- the read-across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed and (2) Different compounds have the same type of effect(s)- the read-across hypothesis is that the organism is exposed to different compounds which have similar (eco)toxicological and fate properties as a result of structural similarity (and not as a result of exposure to common compounds).

Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the quality of the studies which are to be read-across.

You consider to achieve compliance with the REACH information requirements for the registered substance 2-dimethylaminoethyl methacrylate (hereafter the 'target substance') using data of structurally similar substances methyl methacrylate (EC No 201-297-1) (hereafter the 'source substance').

However, there is no documentation for the read-across. Therefore, your dossier is lacking a basis for predicting relevant human health properties of the registered substance from data for the source substances.

Nevertheless, ECHA notes in section 13 of IUCLID you have provide the "*OECD SID assessment report*" for the target substance. This report states that the target substance "*belongs to esters of methacrylic acid. However,*" it "*is unique in the hydrophilic and alkaline nature and relatively low volatility (vapour pressure), that makes a substantial difference from other analogues in the toxicological properties. The most representative chemical among the analogues is*" the source substance.

ECHA's consideration and conclusion

ECHA has considered the statement included in the "*OECD SID assessment report*" for the target substance, and the information of the source substance disseminated on ECHA website[4] . Furthermore, these considerations are discussed below in three sections: "*structural difference*", "*physicochemical properties difference*", and "*uncertainty on toxicological similarity*" and ECHA's conclusion is presented below under the section "*conclusion*".

Structural difference

ECHA acknowledges that both the target and source substance "*belongs to esters of methacrylic acid"* and both have in common the methacrylate group. However, both differ in the additional alkyl side chain attached on the substances, *i.e.* the dimethylamino ethyl group for the target substance and the methyl group for the source substance. Hence, for the read across to be acceptable, it is necessary to justify the impact of such structural difference on the prediction of the toxicological property for the target substance from the source substance.

[3] Please see ECHA's Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across).
[4] https://echa.europa.eu/registration-dossier/-/registered-dossier/15528

Physicochemical properties difference

ECHA acknowledges the statement in the "*OECD SID assessment report*" that the target substance - among the methacrylates - has "*unique*" physicochemical properties due to its "*hydrophilic and alkaline nature and relatively low volatility (vapour pressure)*".

However, ECHA notes that the source substance, on the contrary, has higher volatility and no alkaline nature but a comparable partition coefficient in comparison to the target substance.

In addition, as indicated above, information on physicochemical properties are only a part of the read-across hypothesis, and for the read-across to be acceptable, it is necessary to provide additional information to justify the prediction of the toxicological property of the target substance from the source substance.

ECHA acknowledges the statement in the "*OECD SID assessment report*" that for the target substance, "*the most representative chemical among the analogues*" is the proposed source substance. However, no explanation was included in the report for such conclusion, hence again not allowing to verify the read-across hypothesis.

Uncertainty on toxicological similarity

On the one hand ECHA notes that in the OECD TG 422 study with the target substance there were dose dependent reduction in live birth index (%) at the mid (200 mg/kg bw/day) and high (1000 mg/kg bw/day) dose levels, and reduced pups body weight at the highest dose. The effects at the highest dose were observed in the presence of maternal toxicities. Based on these effects, you assign a NOAEL of 200 mg/kg bw/day for reproductive/developmental toxicity. However, you provide no justification for not considering the reduced birth index (%) from the mid dose group as adverse effect with respect to reproductive health. Therefore, ECHA considers that there is concern for reproductive toxicity for the target substance.

In contrast, ECHA also notes that no reproductive toxicity effect was reported in the provided two-generation study with the source substance. The highest dose (400 mg/kg bw/day) was assigned as a NOAEL. It is to be noted that, the highest dose tested for this study is considered as low. Because according to the conditions specified in the test guideline, "*the highest dose level should be chosen with the aim to induce toxicity but not death or severe suffering*" and the limit dose for testing is 1000 mg/kg bw/day.

Consequently, the potential effect of the source substance on reproductive toxicity might have been underestimated due to testing at low dose levels. Hence, the data from this study is considered as not reliable to provide information on the potential effect of the source substance on reproductive toxicity.

Therefore, ECHA considers that the information from the source substance is not reliable for the prediction of the toxicological property of the target substance with respect to reproductive toxicity.

Conclusion

As a conclusion, based on the above mentioned consideration (*structural difference*, *physichochemical properties difference*, *uncertainty on toxicological similarity*), ECHA

considers that information from the proposed source substance is unsuitable for prediction of the toxicological property – specifically on reproductive toxicity - for the target substance.

As described above, further elements are needed to establish a reliable prediction for a toxicological or ecotoxicological property, based on recognition of the structural similarities and differences between the source and registered substances. This could be achieved (if it is possible) by a well-founded hypothesis of (bio)transformation to a common compound(s), or that the registered and source substance(s) have the same type of effect(s), together with sufficient supporting information to allow a prediction of human health properties , and specifically to reproductive toxicity.

In your comments to the draft decision according to Article 50(1) of the REACH Regulation, you agreed with the decision and recognised that the data requirements for fulfilling Annex X, Section 8.7.2. and Annex X, Section 8.7.3. of the REACH Regulation were not met. However, you showed your intention to improve the read-across adaptation according to Annex XI, Section 1.5. of the REACH Regulation. ECHA understands that the basis of the read-across proposed by you is the assumption that the registered substance will undergo a rapid hydrolysis to methacrylic acid and 2-dimethylaminoethanol. As a consequence, since methyl methacrylate hydrolyses quickly (half-life for enzymatic hydrolysis is 0.29 min) into methacrylic acid and methanol you consider that data from methyl methacrylate and 2-dimethylaminoethanol could be used to reliably predict properties of the registered substance.

ECHA notes that the read-across justification and the data you are referring to are not available in the current submission of the registration dossier. As also mentioned in the Appendix 2 to this decision, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation. Thus, ECHA will examine this information after the deadline set in the adopted decision has passed and in case you will follow this approach and update your dossier accordingly.

Nevertheless, ECHA has considered the information provided by you in the formal comments and has the following considerations:

ECHA notes that, although the read-across adaptation explained by you seems plausible, you need to prove that indeed the rate of metabolic transformation (hydrolysis) of the registered substance is fast enough so there will be no systemic exposure to the parent substance.

Further ECHA notes that the read-across would become more robust by comparing toxicological effects between source- and target-substances from other relevant endpoints. If type and potency of effects are comparable, successful predictions are possible.

In addition, ECHA also notes that the source data must be valid and adequate to fulfil the information requested in the draft decision, *i.e.* the source studies need to address the same concern as for the target substance in order to allow reliable predictions of properties. For instance, the same test design for a source study as requested for the target would be ideal. This includes the test design and the route of administration. Any deviation must be adequately justified.

1. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species**

Pre-natal developmental toxicity studies (test method EU B.31./OECD TG 414) on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

The technical dossier contains information on a pre-natal developmental toxicity study in rats by the oral route using the registered substance as test material.

However, there is no information provided for a pre-natal developmental toxicity study in a second species with the registered substance.

Instead, you have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a "*developmental toxicity*" (OECD TG 414) with the analogue substance methyl methacrylate (EC no 201-297-1). However, as explained above in section "*Grouping of substances and read-across approach*", your adaptation of the information requirement is rejected.

In addition, you have sought to adapt this information according to Annex XI, Section 1.2., weight of evidence. You provided the following justification for the adaptation*: "As an outcome of the studies recently performed (OECD 414 and OECD 408), there is no indication of toxicity to reproduction. Therefore, testing with a second species is not considered as necessary for the sake of animal welfare".*

An adaptation pursuant to Annex XI, Section 1.2. requires sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property with respect to the information requirement in question including an adequate and reliable documentation while the information from each single source alone is regarded insufficient to support this notion.

Your weight of evidence adaptation needs to address the specific dangerous (hazardous) properties of the registered substance with respect to pre-natal developmental toxicity study in a second species as requested in this decision. ECHA considers that this study provides relevant information on pre-natal developmental toxicity in a second species including growth, survival, external, skeletal and visceral alterations, and maternal toxicity. Thus, together the results from two species provide information on species differences related to prenatal developmental toxicity.

However, the available pre-natal developmetal toxicity study with the registered substance covers only the information requirement of pre-natal developmental toxicity study in the first species and does not address the species differences. In addition, the available repeated dose 90-day oral toxicity study performed according to OECD TG 408 does not provide information on pre-natal developmental toxicity. The OECD TG 408 provides information on possible health hazards from repeated exposure over prolonged time covering post-weaning maturation and growth into adulthood, while the pre-natal developmental toxicity study provides information on the possible effects on pregnant animals and developing organism due to prenatal exposure (e.g, maternal toxicity, structural abnormalities or altered growth in foetus).

Hence, the individual sources of information you provided, together with your justification

for the adaptation, do not allow to assume/conclude that the substance does not have a particular dangerous (hazardous) property with respect to the information requirement for Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species, thus addressing the species differences for pre-natal developmental toxicity.

Therefore, the general rules for adaptation laid down in Annex XI, Section 1.2. of the REACH Regulation are not met and your adaptation of the information requirement is rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

The test in the first species was carried out by using a rodent species (rat). According to the test method EU B.31./OECD 414, the rabbit is the preferred non-rodent species. On the basis of this default assumption, ECHA considers that the test should be performed with rabbit as a second 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 6.0, July 2017) Chapter R.7a, Section 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 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a second species (rabbit) by the oral route.

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

The basic test design of an extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443 with 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 X. If the conditions described in column 2 of Annex X 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 the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

The information provided

You have provided the following sources of information in IUCLID section 8.7.1:

- End-point study record 1:- Key study**:** screening for reproductive / developmental toxicity, rat, oral (OECD TG 422; GLP) with registered substance, Ministry of Health and Welfare Japan, 1998 (summary report), 2003 (publication), rel 2.

- End-point study record 2:- key study: two-generation reproductive toxicity, rat, oral

(OECD TG 416; GLP) with the analogue substance (methyl methacrylate, EC no 201-297-1), [redacted], 2009 (study report), rel 1.

- End-point study record 3:- "*justification: as an outcome of the studies recently performed (OECD 414 and OECD 408), there is no indication of toxicity to reproduction. Therefore, testing with a second species is not considered as necessary for the sake of animal welfare*". To support your justification, you have provided the study record for the OECD TG 408 and OECD TG 414 in IUCID section 7.5.1 and IUCID section 7.8.2, respectively.

While you have not explicitly claimed an adaptation, the provided information for the end-point study records could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.2 (weight of evidence); and Annex XI, Section 1.5 (read across), respectively. ECHA has first evaluated the information you provided on read-across and then the information you provided on weight of evidence.

Read-across

Evaluation approach and conclusion

ECHA has evaluated the information you provided on read-across according to the provision of REACH Annex XI, Section 1.5. ECHA has considered whether the information you have provided with the source substances methyl methacrylate is sufficient to predict the properties of the registered substance with respect to reproductive toxicity. However, as explained above in section "*Grouping of substances and read-across approach*" of this decision, your adaptation of the information requirement according to Annex XI, Section 1.5., is rejected. Furthermore, the results of this study are not reliable because the dose level tested are considered as low for the reason already mentioned above.

Therefore, ECHA has not considered the information from the two-generation reproductive toxicity study with source substances ([redacted], 2009) in the weight of evidence evaluation.

Weight of evidence

Furthermore, ECHA has evaluated your weight of evidence adaptation proposal according to REACH Annex XI, Section 1.2., and assessed whether you have provided "*sufficient weight of evidence from several independent sources of information leading to the assumption/ conclusion that the substance has or has not a particular dangerous property*" with respect to the information requirement of Annex X, Section 8.7.3. for the registered substance.

Evaluation approach/criteria on the weight of evidence

Your weight of evidence adaptation needs to address the specific dangerous (hazardous) properties of the registered substance with respect to an extended one-generation reproductive toxicity study (EU B.56./OECD TG 443) as requested in this decision. ECHA considers that this study provides, in addition to information to general toxicity, information in particular on two aspects, namely on sexual function and fertility in P0 and F1 generations (further referred to as 'sexual function and fertility') and on development and toxicity of the offspring from birth until adulthood due to pre- and postnatal and adult exposure in the F1 generation (further referred to as 'effects on offspring').

Relevant elements for 'sexual function and fertility' are in particular functional fertility (oestrous cycle, sperm parameters, mating behaviour, conception, pregnancy, parturition, and lactation) in the P0 parental generation after sufficient pre-mating exposure duration and histopathological examinations of reproductive organs in both P0 and F1 generations. Relevant elements for 'effects on offspring' are in particular peri- and post-natal investigations of the F1 generation up to adulthood including investigations to detect certain endocrine modes of action, sexual development, and investigations on developmental neurotoxicity. Also the sensitivity and depth of investigations to detect effects on 'sexual function and fertility' and 'effects on offspring' needs to be considered.

Furthermore, as indicated in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.4., Section 4.4 (version 1.1, December 2011), ECHA has evaluated individually your provided sources of information with respect to relevance and reliability and has evaluated the overall provided information for consistency and coverage of the relevant elements as specified above.

Based on the criteria above, ECHA considers the following:

Sexual function and fertility

With respect to the aspect of sexual function and fertility of P and F1 generation, you have provided information on histopathological changes in major reproductive organs (OECD TG 408 study and OECD TG 422 screening study).

You have also provided information on male and female reproductive performance such as gonadal function, mating behaviour, conception, development of the conceptus and parturition (OECD TG 422 screening study). However, ECHA notes that the statistical power of OECD TG 422 screening study is lower than that of the extended one-generation reproductive toxicity study, and certain investigations are not included, such as functional fertility after 10 weeks premating exposure to cover spermatogenesis and folliculogenesis before mating, histopathology of the reproductive organs in F1 animals in adulthood, sexual maturation, oestrous cycle measurements in F1 animals, and investigations related to hormonal modes of action.

Thus, the information you provided does not adequately address all relevant elements with respect to sexual function and fertility.

Effects on offspring

ECHA notes that your adaptation justification does not address the effects on offspring. The provided information does not cover the key elements of offspring toxicity observable postnatally (survival, growth and sexual maturation) which need to be investigated in this regard. More specifically, the OECD TG 422 screening study with the registered substance investigates development and offspring toxicity only until postnatal day 4. In addition, the study according to OECD TG 414 in the rat provides information only on effects observable pre-natally and not effects on offspring observable and/or due to postnatal exposure. Furthermore, the information provided does not address the concern for developmental neurotoxicity.

Thus, the information you provided does not adequately address all relevant elements with respect to effects on offspring.

ECHA notes that in your conclusion to weight of evidence justification, you have stated that *"Therefore, testing with a second species is not considered as necessary for the sake of animal welfare"*. However, ECHA has already addressed the need for testing in a second species above in section 1.

Conclusion on weight of evidence

Hence, the sources of information you provided, together with your justification for the adaptation, do not allow to assume/conclude that the substance does not have a particular dangerous (hazardous) property with respect to the information requirement for Annex X, Section 8.7.3.

Therefore, the general rules for adaptation laid down in Annex XI, Section 1.2 of the REACH Regulation are not met and your adaptation of the information requirement is rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint. Thus, an extended one-generation reproductive toxicity study according Annex X, Section 8.7.3. is required.

The following refers to the specifications of this required study:

a) *The specifications for the study design*

Premating exposure duration and dose-level setting

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* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

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 conducted 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.
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 X. When there are triggers for developmental neurotoxicity, both the Cohorts 2A and 2B are to be conducted as they provide complementary information. These triggers include existing information on effects caused by substances structurally analogous to the registered substance, suggesting such effects or mechanisms/modes of action.

ECHA notes that existing information on the substance itself derived from OECD TG 422 study (Ministry of Health and Welfare Japan, 1998 and 2003) show evidence of adverse effect in the nervous system. More specifically, clinical effects and histopathological changes (twitching and chronic convulsion; degeneration of nerve fibers in the brain and spinal cord) were shown at 1000 mg/kg bw/day in both sexes. These effects were observed in the presence of general toxicity (mortality (3/10), reduction of body weight gain, decreased food consumption, histopathological changes in forestomach, slight anemic changes and atrophy in thymus).

Similar effects were not observed in the 90-day study with the registered substance but the highest dose tested was lower, 500 mg/kg bw/day, which was also a NOAEL ([redacted], 2014). Hence, the adverse effects on the adult nervous system were observed in the OECD TG 422 study but not in the 90-day study. The inconsistency in the findings between the studies regarding to the neurotoxicity may be due to lower dose level in the 90-day study. The neurological findings in the OECD TG 422 study were observed at lethal dose level. However, the findings, in particular the degeneration of nerve fibres and convulsions, are severe and likely indications of direct neurotoxicity and, thus, relevant for a concern for developmental neurotoxicity. Therefore, the inclusion of Cohorts 2A and 2B are justified.

Consequently, ECHA concludes that the developmental neurotoxicity Cohorts 2A and 2B need to be conducted because there is a particular concern on (developmental) neurotoxicity based on the results from the above-identified *in vivo* study on the registered substance itself.

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 assumption, 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 6.0, July 2017) Chapter R.7a, Section 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.

b) Outcome

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443), in rats, oral route, 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;
- Cohorts 2A and 2B (Developmental neurotoxicity)

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohort 3 (developmental immunotoxicity) was identified. However, you may expand the study by including the extension of Cohort 1B, 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 X and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

You 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.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 12 May 2017.

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 requests.

ECHA notified the draft decision to the competent authorities of the Member States for proposals 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 compliance check decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage.

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests 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 by each registrant.

If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.