Helsinki, 21 December 2018

Addressee: [redacted]

Decision number: TPE-D-2114456461-51-01/F
Substance name: Reaction mass of 2-(1,1-dimethylpropyl)anthraquinone and 2-(1,2-dimethylpropyl)anthraquinone
List number: 915-623-1
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 26/07/2017
Registered tonnage band: Over 1000

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation ((EC) No 1907/2006) (the REACH Regulation), ECHA has taken the following decision.

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

1. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: OECD TG 414) in a second species (rabbit), oral route using the registered substance.**
2. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; 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 systemic 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;**
3. **Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method: Fish, early-life stage (FELS) toxicity test, OECD TG 210) 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 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 an adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by **28 June 2021**. You also have to update the chemical safety report, where relevant.

The reasons for 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.

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 Claudio Carlon, Head of Unit, Evaluation

[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 proposals submitted by you and scientific information submitted by third parties.

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

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

Examination of the testing proposal

Pre-natal developmental toxicity studies on two species are part of the standard information requirements for 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 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 a second species rabbit according to OECD TG by the oral route with the registered substance. You provided the following justification:
"The developmental toxicity study with a second species has been identified as a standard requirement for reproductive toxicity according to Annex IX and X. Since 2-amylanthraquinone has been registered at a volume of >1000 tonnes/year and a data gap has been identified, the developmental toxicity study for a second species (rabbit) is proposed."

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (pre-natal developmental toxicity). ECHA notes that you provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

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

You proposed testing with the rabbit as a second species. According to the test method 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 rabbit or the rat as a second species, depending on the species tested in the first pre-natal developmental toxicity study.

You did not specify the route for testing. 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.

Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are thus requested to carry out the proposed study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in a second species (rabbit), oral route (test method: OECD TG 414).

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 6.0, July 2017), Chapter R.7a, Section R.7.6.2.3.2.

ECHA notes that a revised version of OECD TG 414 was adopted this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. You should test in accordance with the revised version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788).

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

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

Examination of the testing proposal

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 X of the REACH Regulation. 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 in ECHA *Guidance on information requirements and chemical safety assessment,* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

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 an extended one-generation reproductive toxicity study according to OECD TG 443 by the oral with the following justification and specification of the study design:

"*The extended one generation study has been identified as standard requirement for reproductive toxicity according to Annex IX and X. Since 2-amylanthraquinone has been registered at a volume of >1000 tonnes/year and a data gap has been identified for reproductive toxicity, the EOGRTS is proposed.*

Considerations that the general adaptation possibilities of Annex XI of the REACH Regulation were not adequate to generate the necessary information:

• *Available GLP studies*
No GLP studies are available on the test substance for the endpoint 'reproductive toxicity'. A developmental toxicity / teratogenicity study according to OECD 414 has been conducted with 2-amylanthraquinone and rats. However, this study did not provide sufficient data on reproductive parameters.

• *Available non-GLP studies*
Non-GLP studies are not available for the endpoint 'reproductive toxicity'.

• *Historical human data*
No human data are available for this substance.

• *(Q)SAR*
No validated (Q)SAR's exist for the endpoint 'reproductive toxicity' in organic substances. There is no known mode of action for 2-amylanthraquinone causing reprotoxic effects.

• *In-vitro methods*
With regards to in vitro studies for reproductive toxicity, the regulatory acceptance of these studies and approaches to replace the animal testing for reproductive toxicity has not been achieved as they do not provide equivalent information and thus, cannot be used alone for classification and labelling and/or risk assessment.

• *Weight of evidence*
No data are available to complete the IUCLID requirements as a weight of evidence approach.

• *Grouping and read-across*
The registrant has not been able to identify relevant information on structural analogues. An EOGRTS is not available for 2-ethylanthraquinone.

• *Substance-tailored exposure driven testing*
Not applicable since the results of the exposure assessment covering all relevant exposures throughout the life cycle of the substance do not demonstrate the absence of or no significant exposure in all scenarios of the manufacture and all identified uses.

• *Approaches in addition to above*
Not applicable

Considerations that the specific adaptation possibilities of Annexes VI to X (and column 2 thereof) were not applicable. Adaptation options as defined in Annexes VI to X are not applicable for this substance and this endpoint."

"The study will be performed in rats according to OECD guideline 443 in compliance with GLP. The test substance will be administered by the oral route. The basic configuration of EOGRTS will be performed as based on the toxicological profile of the substance there are no concern-driven scientific triggers for the performance of the F2 generation (extension of Cohort 1B), developmental neurotoxicity (DNT; cohorts 2A and 2B) and/or developmental immunotoxicity (DIT; cohort 3) cohorts.

1) Extension of Cohort 1B and termination time for F2: extension not justified

According to column 2 (specific rules for adaptation from column 1) point 8.7.3 of the amended REACH Annex X, extension of cohort 1B to include the F2 generation shall be proposed by the registrant based on the following conditions being met (a and any of b(i), b(ii) or b(iii)). See also: Chapter R.7a: Endpoint sepcific guidance Version 5.0 - December 2016:

A. The substance has uses leading to significant exposure of consumers or professionals, taking into account, inter alia, consumer exposure from articles

No – The substance has no uses leading to significant exposure of consumers or professionals. The substance has only industrial use (6 Solvay sites in the European Union).

B (i). The substance displays genotoxic effects in somatic cell mutagenicity tests in vivo which could lead to classifying it as Mutagen Category 2, or

No – The substance is not classified as Mutagen Category 1A or 1B or 2. The substance produced negative results in the reliable combined micronucleus/alkaline Comet assay with rats, suggesting that the substance is not genotoxic in vivo.

B (ii). There are indications that the internal dose for the substance and/or any of its metabolites will reach a steady state in the test animals only after an extended exposure, or

No – The toxicokinetic behaviour of the substance gives no hints for very slow clearance (see results of 90-day study). The results of the 90-day study suggest that 2-amylanthraquinone is readily metabolized in the body, undergoing primarily an oxidation of the aliphatic chain, followed by subsequent sulfonation and glucuronic acid conjugation, followed by excretion in urine. The NOAEC/LOAEC of the subchronic study is not more than 3 times lower than that the NOAEC/LOAEC from a subacute study. Therefore there are no indications that the internal dose for the substance and/or any of its metabolites will reach a steady state in the test animals only after an extended exposure.

B (iii) There are indications of one or more relevant modes of action related to endocrine disruption from available in vivo studies or non-animal approaches

No - There are no indications based on the available study results that endocrine disruption is a relevant mode of action for the substance. In particular, no effects on reproductive organs or tissues or effects on the thyroid were evidenced in the available repeated dose toxicity studies. There were also no effects on gestation in the available developmental toxicity study. The substance also does not have a structural similarity to steroid hormones. Therefore, based on the above considerations, the registrant does not believe that there is a basis for extending cohort 1B to include the F2 generation.

2) Inclusion of Cohorts 2A and 2B (developmental neurotoxicity, DNT): not justified

The registrant does not believe there is a need to include cohorts 2A and 2B in the test design. This is based on:

• Neurobehavioural observations (arena and Functional Observational Battery testing) and motor activity assessment performed as part of the subchronic toxicity study, did not indicate any neurotoxic potential of the test material.

3) Inclusion of Cohort 3 (developmental immunotoxicity, DIT): not justified

The registrant does not believe there is a need to include cohort 3 in the test design. This is based on:

• the substance has not caused biologically significant changes in haematology/clinical chemistry and/or organ weight associated with immunotoxicity such as reduced leucocyte count in combination with reduced spleen weight in repeated dose studies

• the substance has not caused significant effects to immunology organs such as thymus atrophy in repeated dose studies

The highest dose level will be selected in agreement with the testing laboratory and study director with the aim to induce some toxicity, in order to allow a conclusion on whether potential effects on reproduction are considered to be secondary, non-specific consequence of other toxic effects seen. "

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (extended one-generation reproductive toxicity study). ECHA notes that you provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirements for which testing is proposed. ECHA has taken these considerations into account.

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). Ten weeks exposure duration is supported also by the lipophilicity of the substance to ensure that the steady state in parental animals has been reached before mating..

The highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity (cf. OECD TG 443 para 21 & 22). 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 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 X 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.

You proposed not to include an extension of Cohort 1B and provided justifications following the criteria described in column 2 of Section 8.7.3 of Annex X and detailed in ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

Therefore, ECHA agrees 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.

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.

You proposed not to include Cohorts 2A and 2B and provided justifications following the criteria described in column 2 of Section 8.7.3 of Annex X and detailed in ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

Therefore, ECHA agrees 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.

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 X.

You proposed not to include Cohort 3 and provided justifications following the criteria described in column 2 of Section 8.7.3 of Annex X and detailed in ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

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

Species and route selection

You proposed testing in rats. According to the test method 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.

You proposed testing by the oral route. ECHA agrees 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.

Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed study with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method 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 systemic 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;

When you update your registration dossier with the new endpoint study record for the extended one-generation reproductive toxicity study, you shall include the scientific reasoning for length of the premating exposure duration and dose level selection, as explained in the ECHA Guidance on information requirements and chemical safety assessment (version 6.0, July 2017), Chapter R.7a, Section R.7.6.2.3.2, Stage 4.4 (iii) under the header "Study design for the extended one-generation reproductive toxicity study.

Notes for your consideration

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, currently there are no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and/or Cohort 3 (developmental immunotoxicity).

3. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

Examination of the testing proposal

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 fish" is a standard information requirement as laid down in Annex IX, Section 9.1.6. 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 fish using the test method Fish, early-life stage toxicity test, OECD TG 210 with the following justification:

"Long term toxicity testing with fish is considered to be required, based on the following considerations:

- Chronic toxicity was observed in Daphnia magna, at concentrations below the water solubility. Therefore chronic toxicity in fish at concentrations below the water solubility could occur, which should be investigated for this substance that is continuously discharged to surface waters. It is unknown whether Daphnia magna is the most sensitive species.

-The highest RCR (for freshwater) is [redacted], based on an average measured concentration in an effluent that is discharged to a river. Because of this RCR it is considered required to further refine the PNEC for freshwater. To reduce the uncertainty in the environmental risk assessment due to the lack of this sensitive fish test.

-The FELS test is considered to be an essential information requirement for the PBT assessment of this substance that is continuously discharged to surface waters. The substance is not readily biodegradable while the substance has also some bioaccumulation potential (BCF = 1215)."

ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 9.1.6 of the REACH regulation.

There were no indications in the dossier from the short-term toxicity studies on aquatic species that fish would be significantly more sensitive than aquatic invertebrates or algae. Nevertheless, acute toxicity was already found in the aquatic acute toxicity tests and a difference in sensitivity was found with Fish seemingly the most sensitive.
Furthermore, you already conducted a long term aquatic invertebrates toxicity study as per OECD TG 211. The results of this long term toxicity test on Daphnia show a NOEC = 0.084 mg/L and an estimated EC50 = 0.131 mg/L which as explained is below the known water solubility of your substance (0.15 mg/L).

Due to the potential continuous release of your substance to the aquatic compartment and its potentially Persistent and potentially Bioaccumulative properties, ECHA agrees that the Fish long term toxicity test should be performed to refine the PNEC for freshwater and facilitate the PBT assessment of the substance.

Outcome

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: Fish, early-life stage (FELS) toxicity test (Annex IX, 9.1.6.1.; test method: Fish, early-life stage toxicity test, OECD TG 210).

Notes for your consideration

Due to the low solubility of the substance in water and its potential adsoprtion properties (Log Kow and LogKoc) you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b, table R. 7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested long-term ecotoxicity tests and for calculation and expression of the result of this test.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 26 July 2017.

ECHA held a third party consultation for the testing proposals from 27 September 2017 until 13 November 2017. ECHA did not receive information from third parties.

This decision does not take into account any updates after **6 April 2018**, 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 did not receive any comments by the end of the commenting period.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

ECHA received proposal for amendment and did not modify the draft decision.

ECHA invited you to comment on the proposed amendments.

ECHA referred the draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-61 written procedure and ECHA took the decision according to Article 51(6) 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 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 the Member States.

3. In carrying out the tests 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 tests must be suitable to assess these.

   Furthermore, 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.