[If applicable: MSC identifiers]

Helsinki, 12 December 2018

Addressee: [redacted]

Decision number: CCH-D-2114453551-53-01/F
Substance name: Methyl 2-naphthyl ether
EC number: 202-213-6
CAS number: 93-04-9
Registration number: [redacted]
Submission number: [redacted]
Submission date: 31/10/2017
Registered tonnage band: 100-1000

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:

Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.; test method: OECD TG 443) in rats, oral route with the registered substance specified as follows:

- **At least two 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) with extension to mate the Cohort 1B animals to produce the F2 generation; and**
- **Cohort 3 (Developmental immunotoxicity).**

You have to submit the requested information in an updated registration dossier by ***21 December 2020***. You also have to update the chemical safety report, where relevant.

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.

The scope of this compliance check decision is limited to the standard information requirements of Annex IX, Section(s) 8.7.3 to the REACH Regulation.

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 Ofelia Bercaru, Head of Unit, Evaluation E3

[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

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

The basic test design of an extended one-generation reproductive toxicity study (test method 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 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[2].

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

In your comments you requested the draft decision to be split into two parts because several endpoints are dependent on each other. ECHA notes that as the extended one-generation reproductive toxicity study is the only request in this decision, it cannot be split. The original decision CCH-D-2114341959-34-01/F which contained the requests for sequential testing of a sub-chronic toxicity study and EOGRTS amongst other requests cannot be split as it is an adopted decision.

a) The information requirement

In decision CCH-D-2114341959-34-01/F ECHA concluded, after evaluating the relevant information in your registration dossier, that an extended one-generation reproductive toxicity study according Annex IX, Section 8.7.3. is required. Indeed, in that decision it was indicated that this information requirement was triggered and the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement.

In that same decision ECHA required you to provide a sub-chronic toxicity study (90-day). The decision indicated that the 90-day study shall be conducted before the extended one generation reproductive toxicity study and the results from the 90-day study shall be used, among other relevant information, to decide on the study design of the extended one generation reproductive toxicity study. However, you have not provided the results of a 90-day study; instead, you have self-classified the registered substance as STOT RE 2 based on liver and kidney effects. This endpoint is outside the scope of this decision.
ECHA notes that the information requirement of Section 8.7.3., Annex IX is triggered for the reasons set forth in decision CCH-D-2114341959-34-01/F (decision enclosed), which remain valid.

[2] ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017)

ECHA also notes that your weight-of-evidence (WoE) analysis for the information requirement of Section 8.7.3., Annex IX is based on the same information as analysed in decision CCH-D-2114341959-34-01/F, *i.e.* an OECD TG 407 study, (Q)SAR analysis, and three non-guideline read-across studies with Klimisch 4. Therefore, your WoE is rejected for the same reasons set out in that decision (enclosed), which remain valid.
Furthermore, ECHA emphasises that for this case WoE cannot be applied because key elements/parameters of the extended one-generation reproductive toxicity study cannot be addressed and there is no (Q)SAR model available which could predict information equivalent to the information generated by the extended one-generation reproductive toxicity study. Indeed, there is currently no animal-free/in vitro method that could cover important investigations such as *"the long postnatal period in the F1 generation with measurements of sexual maturation and gonad histopathology in adulthood of the offspring. This information can only be obtained after in utero and postnatal exposure and the results can currently* ***not be predicted*** *without an animal test."*[3]

In addition, the criteria for extension of Cohort 1B and inclusion of Cohort 3 are met (see below), however, these investigations are not addressed in your WoE.

In your comments, you requested to remove the request for an extended one-generation reproductive toxicity study, as existing information from the registered substance as well as from read-across data have been used to classify the substance for STOT RE 2 and Repr. 2. ECHA emphasises that the above-mentioned classifications are not valid adaptation possibilities according to Annex IX, Section 8.7., Column 2. Furthermore, ECHA notes that even though you present existing data in your comments, you have not addressed the shortcomings of your read-across and weight of evidence approaches, as laid out in the previous adopted decision (CCH-D-2114341959-34-01/F). Therefore your comments and supporting data cannot be accepted.

Consequently there is an information gap and an extended one-generation reproductive toxicity study according to Annex IX, Section 8.7.3. is required.

The following refers to the specifications of this required study.

b) The specifications for the required study

As you submitted a weight-of-evidence to fulfil the information requirement, you have not provided considerations of the study design.

Based on the available data, ECHA has re-evaluated the design of the extended one-generation reproductive toxicity study and concluded that a new decision, under Article 41 of the REACH Regulation, needs to be taken addressing the design of that study. The reasoning for extension of Cohort 1B and inclusion of Cohort 3 is given below.

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 the ECHA Guidance[2], the starting point for deciding on the length of the premating exposure period should be ten weeks to cover the full

[3] This has been also highlited in ECHA report on *"Non-animal approaches: Current status of regulatory applicability under the REACH, CLP and Biocidal Products regulations"* available at the internet at https://echa.europa.eu/publications/technical-scientific-reports

spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required if there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA Guidance[2]. In this specific case, animals of Cohort 1B are mated to produce the F2 generation and, thus, the premating exposure duration will be 10 weeks for these Cohort 1B animals and the fertility parameters will be covered allowing an evaluation of the full spectrum of effects on fertility in these animals. Thus, shorter premating exposure duration for parental (P) animals may be considered. However, the premating period shall not be shorter than two weeks and must be sufficiently long to reach a steady-state in reproductive organs as advised in the ECHA Guidance[2]. The consideration should take into account whether the findings from P animals after a longer premating exposure duration would provide important information for interpretation of the findings in F1 animals, e.g. when considering the potential developmental origin of such findings as explained in ECHA guidance.

The highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects 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 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. The extension is inter alia required, if the use of the registered substance is leading to significant exposure of consumers and professionals (column 2, first paragraph, lit. (a) of section 8.7.3., Annex IX) and if there are indications that there are indications of one or more relevant modes of action related to endocrine disruption from available in vivo studies or non-animal approaches (column 2, first paragraph, lit. (b), third indent of section 8.7.3., Annex IX).

The use of the registered substance is leading to significant exposure of consumers and professionals because the registered substance is used by professionals as washing and cleaning products (PROCs 8a, 10, 11, 13) and consumers as polish and wax blends amongst others.

In addition, there are indications for endocrine-disrupting modes of action (i.e. mechanisms interfering with hormonal action) because significantly increased levels of the hormones testosterone and oestrogen as well as changes in absolute and relative organ weights of hormone-sensitive reproductive organs/ tissues have been observed in the provided OECD TG 407 study with the registered substance.

Therefore, ECHA concludes that Cohort 1B must be extended to include mating of the animals and production of the F2 generation because the uses of the registered substance is leading to significant exposure of professionals and consumers and the 28-day repeated dose toxicity study conducted according to OECD TG 407 indicates endocrine-disruption

modes of action for the registered substance.

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 notes that existing information on the registered substance itself derived from the available OECD TG 407 study in rats show evidence of, decreased neutrophils in mid- and high-dose males, decreased basophils in females in all dosing groups, and changes in relative and absolute spleen weight particularly in females.

According to ECHA Guidance[2], "*reduced leukocyte count* [which include neutrophils and basophils] *in combination with reduced spleen weight*" are substance specific findings which indicate a particular concern justifying inclusion of the developmental immunotoxicity cohort.

ECHA concludes that the developmental immunotoxicity Cohort 3 needs to be conducted because there is a particular concern on (developmental) immunotoxicity based on the results from the above-identified *in vivo* study on the registered substance itself.

Species and route selection

According to the test method 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[2], Section R.7.6.2.3.2. Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route.

c) Outcome

Based on the available information, 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 OECD TG 443), in rats, oral route, according to the following study-design specifications:

- At least two 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) with extension to mate the Cohort 1B animals to produce the F2 generation; and
- Cohort 3 (Developmental immunotoxicity).

While the specifications for the study design are given above, you shall also submit with the new endpoint study record a scientific justification on each of the following aspects: 1) length of the premating exposure duration and dose level selection, 2) reasons for why or why not Cohort 1B was extended, 3) termination time for F2 generation, and 4) reasons for why or why not Cohorts 2A/2B and/or Cohort 3 were included.

Notes for your consideration

No triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) were identified. However, you may expand the study by including Cohorts 2A and 2B if relevant information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the available information, together with the new information shows triggers which are described in column 2 of Section 8.7.3., Annex IX and further elaborated in ECHA Guidance[2]. 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.

Deadline to submit the requested information in this decision

In the draft decision communicated to you the time indicated to provide the requested information was 24 months from the date of adoption of the decision. In your comments on the draft decision, you requested an extension of the timeline. However, you did not provide any supporting documentary evidence, as requested by ECHA. Therefore, ECHA has not modified the deadline of the decision.

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.

On 14 September 2016 ECHA issued decision CCH-D-2114341959-34-01/F.

On 31 October 2017 you provided a dossier update self-classifying the registered substance as STOT RE 2 instead of providing the results of the requested sub-chronic toxicity study (90-day).

The compliance check of the information requirement for an extended one-generation reproductive toxicity study was initiated on 13 December 2017.

On 18 December 2017 ECHA informed you that the request for an EOGRT study was withdrawn and would be addressed in this separate decision.

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

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

ECHA took into account your comments and did not amend the request or the deadline.

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

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

Appendix 3: Further information, observations and technical guidance

1. This 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.