EUROPEAN CHEMICALS AGENCY

Helsinki, 21 December 2016

Addressee: [redacted]

Decision number: TPE-D-2114350099-47-01/F
Substance name: 4-methylmorpholine 4-oxide, monohydrate
EC number: 231-391-8
CAS number: 7529-22-8
Registration number: [redacted]
Submission number: [redacted]
Submission date: 4 May 2016
Registered tonnage band: 1000+T

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. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats using the registered substance.**
2. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route using the registered substance.**

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

3. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56 /OECD TG 443) in rats, oral route using the registered substance.**
   - **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;**

You are requested to perform as additional test:

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

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

You are required to submit the requested information in an updated registration dossier by ***29 June 2020*** except for the information requested under point 1 for a sub-chronic toxicity study (90-day) which shall be submitted in an updated registration dossier by **3 January 2018**. You may only commence the extended one-generation reproductive toxicity study as requested under point 3 after **28 March 2018**, unless an indication to the contrary is communicated to you by ECHA before that date. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

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

Appeal

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

Authorised[1] by 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

The decision of ECHA is based on the examination of the testing proposal(s) submitted by you and scientific information submitted by third parties.

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

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

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

You have submitted a testing proposal for a sub-chronic toxicity study (90 day) in rodents by the oral route according to EU B.26/OECD TG 408.

You proposed testing by the oral route. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA agrees that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration. More specifically, even though the information indicates that human exposure to the registered substance by the inhalation route is likely, the exposure concentrations reported in the chemical safety report for the inhalation route are low (maximum 0.3 mg/m^3). Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

You did not specify the species to be used for testing. According to the test method EU B.26/OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

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: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26/OECD TG 408).

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

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

A pre-natal developmental toxicity study for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently, there is an information gap and it is necessary to provide information for this endpoint.
You have submitted a testing proposal for a pre-natal developmental toxicity study according to EU B.31/OECD TG 414.

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.

You did not specify the species to be used for testing. According to the test method EU B.31/OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent. On the basis of this default consideration, ECHA considers testing should be performed with rats or rabbits as a first species.

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 4.1, October 2015) R.7a, chapter 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.

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: Pre-natal developmental toxicity study in a first species (rats or rabbits), oral route (test method: EU B.31/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 4.1, October 2015), Chapter R.7a, section R.7.6.2.3.2.

3. Extended one-generation reproductive toxicity study (Annex [IX/X], Section 8.7.3.)

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

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 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 ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015).

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 EU B.56/OECD TG 443 oral route with the following justification and specification of the cohorts:

"Without extension of cohort 1B:
Professional and consumer exposure can't be excluded. However, the test substance was confirmed non-mutagenic in the Ames test, non-mutagenic in the mouse lymphoma assay, non-genotoxic to rat hepatocytes in the unscheduled DNA synthesis assay, negative in the Balb/3T3 in vitro transformation assay, negative in the DNA repair test in male Fischer 344 rats, and negative in the micronucleus assay using male or female ICR mice. In conclusion: the substance is considered non-genotoxic and is not classified as mutagen. The substance is not classified as PBT or vPvB. There are no indications that the internal dose will reach steady state after extended exposure: on the basis of the high water solubility and the low log Kow (-1.2), no accumulation in the body is expected (the bioaccumulation factor is below 10). In addition to its high water solubility, its low molecular weight indicates that the substance (and its metabolites) is expected to be excreted via the urine. This assumption will be confirmed when conducting the 90 days repeated dose test (OECD TG 408), as proposed in the dossier. The registrant suggests to await the results of this test before initiating the EOGRTS (OECD TG 443). There are no indications in the available studies of mode of action of the substance related to endocrine disruption. There are no structural alerts either. The substance is currently not classified as toxic to reproduction based on the results of the OECD TG 422 study included in the dossier: a NOAEL of 50 mg/kg/day (test item based) was determined for both parental fertility and reproduction and for offspring toxicity. It is assumed that the effects observed in the offspring (eg lower body weight and increased mortality of pups) are secondary to maternal toxicity.

Without cohorts 2A and 2B:
There is no indication that the substance, or any structural analogue or in another way related substance (e.g. N-methylmorpholine (EC 203-640-0; CAS 109-02-4) or N-ethylmorpholine (EC 202-885-0; CAS 100-74-3), has adverse effects on the nervous system. Based on the results of the OECD TG 422 study ([redacted]), a NOAEL of 50 mg/kg/day (test item based) was determined. Following treatment-related effects of systemic or reproductive toxicity are observed at the LOAEL level of 500 mg/kg/day: a decrease in body weight, body weight gain and food consumption (which was reversible during the recovery period), a decrease in number of implantations, corpora lutea and number of pups in dams. No mortality was observed at any dose level. No adverse effects in functional battery testing, clinical chemistry or hematology were observed.
There is no mechanism or mode of action known with an association to neurotoxicity.
Without cohort 3:
There is no indication that the substance, or any structural analogue or in another way related substance (e.g. N-methylmorpholine (EC 203-640-0; CAS 109-02-4) or N-ethylmorpholine (EC 202-885-0; CAS 100-74-3), has adverse effects on the immune system. Based on the results of the OECD TG 422 study ([redacted]), a NOAEL of 50 mg/kg/day (test item based) was determined. Following treatment-related effects of systemic or reproductive toxicity are observed at the LOAEL level of 500 mg/kg/day: a decrease in body weight, body weight gain and food consumption (which was reversible during the recovery period), a decrease in number of implantations, corpora lutea and number of pups in dams. No maternal mortality was observed at any dose level. No adverse effects in functional battery testing, clinical chemistry or hematology were observed.
There is no mechanism or mode of action known with an association to immunotoxicity.

Study plan:
Dosing of NMMO to rats via oral gavage during 10 weeks for parental animals. There are no indications to extend the premating dosing period for longer than two weeks.
Dose selection will be done on the basis of the results of the OECD 408 test results (90 day repeated dose study) (still to be performed)."

ECHA considers that the proposed study design requires modification to fulfil the information requirement of Annex X, Section 8.7.3. of the REACH Regulation. The modification relates to the premating exposure period and dose-level setting (please see further justification below).

Information from studies to be conducted before the extended one-generation reproductive toxicity study

The sub-chronic toxicity study shall be conducted before the extended one-generation reproductive toxicity study and the results from that study shall be used, among other relevant information, to decide on the study design of the extended one-generation reproductive toxicity study following ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015).The sub-chronic toxicity study may provide information on effects that is relevant for triggers (e.g. weight changes and histopathological observations of organs as indication(s) of one or more modes of action related to endocrine disruption which may meet the toxicity-trigger for extension of Cohort 1B or as evidence of specific mechanism/modes of action and/or neurotoxicity and/or immunotoxicity which may meet the particular concern criteria for developmental neurotoxicity and/or developmental immunotoxicity cohorts).

Premating exposure duration and dose-level setting

You proposed that there are no indications to extend the premating dosing period for longer than two weeks and that dose selection will be done on the basis of the results of the OECD 408 test results (90 day repeated dose study) (still to be performed).

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). Furthermore, as the extension of the Cohort 1B animals is not triggered, a ten -week premating exposure duration should be the starting point.

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 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* R.7a, chapter R.7.6 (version 4.1, October 2015).

Therefore, ECHA agrees that the criteria to extend the Cohort 1B are not met.

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* R.7a, chapter R.7.6 (version 4.1, October 2015).

Therefore, ECHA agrees that the criteria to include Cohorts 2A and 2B are not met.

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* R.7a, chapter R.7.6 (version 4.1, October 2015).

Therefore, ECHA agrees that the criteria to include Cohort 3 are not met.

Species and route selection

You proposed testing in rats. 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.

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 4.1, October 2015) R.7a, chapter 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.

Outcome

Therefore, pursuant to Article 40(3)(b) of the REACH Regulation, you are requested to carry out the modified study 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.

Currently, the extension of Cohort 1B and the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) are not requested. However, the sub-chronic toxicity study (90-day) requested in this decision (request 1) and/or any other relevant information may trigger changes in the study design. Therefore, the sub-chronic toxicity study (90-day) is to be conducted first and the study results submitted to ECHA in a dossier update by **3 January 2018**. If, on the basis of this update and/or other relevant information, a need for changes to the study design is identified, ECHA will inform you by **28 March 2018** (i.e. within three months after expiry of the 12-month deadline to provide the sub-chronic toxicity study (90-day)) of its intention to initiate a new decision making procedure under Articles 41, 50 and 51 of the REACH Regulation to address the design of the extended one-generation reproductive toxicity study. If you do not receive a communication from ECHA by **28 March 2018**, the request of the present decision for the extended one-generation reproductive toxicity study remains effective and you may commence the conduct of the study and the results will need to be submitted by the deadline given in this decision **29 June 2020**.

In your comments to the proposals for amendment submitted by Member State Competent Authorities, you disagreed with the proposals to introduce a 12-month deadline for submitting the results of the requested sub-chronic toxicity study (90-day) to allow re-assessment of the design of the extended one-generation reproductive toxicity study. You considered that the 12-month deadline would unnecessarily restrict the flexibility to conduct the studies. You furthermore indicated that if the re-assessment would be necessary, the overall deadline should be extended beyond the overall deadline of 42 months. ECHA emphasises that a re-assessment of the study design of the extended one generation reproductive toxicity study after the submission of the results of the sub-chronic toxicity study is aimed to provide clarity to you as regards the study design needed to meet the standard information requirement. ECHA considers that if it comes to the conclusion that no revision of the design is needed, the remaining time of approximately 27 months, which includes time for planning and scheduling the study, is sufficient for providing the information on the extended one-generation reproductive study. As indicated in the previous paragraph, if the Agency considers that the study design of the extended one-generation reproductive toxicity study may need to be revised, a new decision-making process to amend the design will be initiated. This decision will then also specify a new deadline to meet the request for the extended one-generation reproductive toxicity study. This new decision-making process will follow the standard procedure as outlined in Articles 50 and 51 of the REACH Regulation and thus includes the possibility for you to provide comments and the Member State Competent Authorities to submit proposals for amendment.[2]

Note for your considerations:

When submitting the study results of the sub-chronic toxicity study (90-day) you are invited to also include in the registration update your considerations whether changes in the study design are needed (see also *ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.6 (version 4.1, October 2015)*).

[2] Further information on this sequential testing can be found in chapter 4 "*Missing relevant information*" of ECHA's technical report "*How ECHA identifies the design for the extended one-generation reproductive toxicity study (EOGRTS) under dossier evaluation*" available in the Internet at https://echa.europa.eu/publications/technical-scientific-reports

Furthermore, after having commenced the extended one-generation reproduction toxicity study in accordance with the ECHA decision, you may also expand this study to address a concern identified during the conduct of it and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the changes in the study design 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.

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

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

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).

As outlined above under 2, ECHA has approved your testing proposal for a pre-natal developmental toxicity study in a first species according to EU B.31/OECD TG 414. ECHA notes that you registered your substance for 1000 tonnes or more per year and that your technical dossier does not contain information on a pre-natal developmental toxicity study in a second species (Annex X, Section 8.7.2.). Consequently, there is an information gap and it is necessary to provide information for this endpoint.

According to the test method EU B.31/OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed in a second species (rabbit or rats), 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 4.1, October 2015) R.7a, chapter 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.

Outcome

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the additional study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in a second species (rabbits or rats), oral route (test method: EU B.31/OECD TG 414).

Notes for your consideration

Before performing a pre-natal developmental toxicity study in a second species you should consider the specific adaptation possibilities of Annex X, Section 8.7.2., column 2 and general adaptation possibilities of Annex XI. If the results of the test in the first species or any other new information enable such adaptation, testing in the second species should be omitted and the registration dossier should be updated containing the corresponding adaptation statement and underlying scientific justification.

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

Appendix 2: Procedural history

ECHA received your registration containing the testing proposal(s) for examination pursuant to Article 40(1) on 15 September 2014.

ECHA held a third party consultation for the testing proposal(s) from 16 February 2015 until 2 April 2015. ECHA did not receive information from third parties.

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

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

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend the request(s).

After submitting the draft decision to the lead Registrant HUNTSMAN EUROPE LIMITED (registration number 01-2119974591-29-0000 and submission number UX607271-08), there has been a lead registrant change. The current lead registrant is the addressee of this draft decision (registration number 01-2119974591-29-0001, submission number PQ615843-14).

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

ECHA received proposal(s) for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendment(s).

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-51 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 request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the Enforcement Authorities of the Member States.

3. In relation to the information required by the present decision, the sample of the substance used for the new test(s) 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 test(s) 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 test(s) must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.