ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 17 November 2017

Addressee: [redacted]

Decision number: CCH-D-2114375622-47-01/F
Substance name: MORPHOLINE
EC number: 203-815-1
CAS number: 110-91-8
Registration number: [redacted]
Submission number: [redacted]
Submission date: 12.12.2012
Registered tonnage band: [redacted]

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 morpholine hydrochloride (EC 233-029-4);**

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 morpholine hydrochloride (EC 233-029-4) 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**

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 **24 February 2021**. 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

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at [redacted] 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.

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 [redacted] 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 morpholine hydrochloride (EC 233-029-4) as test material. However, there is no information provided for a pre-natal developmental toxicity study in a second species and the technical dossier does not contain an adaptation in accordance with column 2 of Annex X, Section 8.7.2. or with the general rules of Annex XI for this standard information requirement.

Hence, 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) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

ECHA notes that the provided pre-natal developmental toxicity study in rats was performed with morpholine hydrochloride (EC 233-029-4), which is a salt of the registered substance. According to 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 (iv), "*In certain cases, testing of neutral salts of alkaline or acidic substances may be appropriate and allows investigation of intrinsic properties at adequate dose levels*". Since morpholine is an alkaline substance classified for skin corrosion, ECHA considers that testing for pre-natal developmental toxicity with its neutral salt morpholine hydrochloride as done in the rat study is more appropriate than testing with morpholine.

In your comments to the draft decision according to Article 50(1) of the REACH Regulation you agree to perform this study. However, you argue that despite its corrosivity, it may be possible to perform the requested tests with the registered substance. ECHA acknowledges that you agree to perform the requested study. However, ECHA retains its view that testing should be performed with the hydrochloride salt of morpholine due to the corrosive properties of the registered substance. Such properties are expected to mainly lead to dose-limiting local effects and systemic effects secondary to it may be masked.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with morpholine hydrochloride (EC 233-029-4): 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.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at [redacted] 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.

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* R.7a, chapter 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.

a) The information provided

You have not provided any study record of an extended one-generation reproductive toxicity study in the dossier that would meet the information requirement of Annex X, Section 8.7.3.

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.2., weight of evidence. Hence, ECHA has evaluated your adaptation with respect to this adaptation.

With regard to the adaptation according to Annex XI, Section 1.2., weight of evidence, in the technical dossier section 7.8.1, you have stated that REACH allows the assessment of the reproductive toxicity of a given chemical with the help of findings from studies with repeated administration. In addition, you have provided argumentation to support you adaptation which can be summarised as follows:

- in several subchronic and subacute studies (Conaway et al. 1984; Sander & Bürkle, 1969; Shea, 1939) no apparent adverse effects on reproductive organs were

observed in rats; the possible target organs of chronic intoxication for this substance were liver, kidneys and stomach;

- you have cited articles by BAuA, 2003, Mangelsdorf et al. 2003, and Janer et al 2007 and claimed the following: "*histopathological and organ weights parameters, taken from 90 day studies, were in fact shown to be more sensitive than fertility parameters that were measured during multi-generation studies and exposure for 4 weeks is sufficient for an assessment of male fertility by referring a literature by (Mangelsdorf et al. 2003); and if 28-day study do not show effects on organ weights nor histopathological changes in testes or ovary then the weight of evidence is that effects on reproduction also not expected (BAuA, 2003), and comparison of the NOAELs from more than hundred 90-day studies with two generation studies with the same substances were differed by a factor of two (Janer et al 2007)*";
- In the last part of your argumentation, you have also claimed that "*Information gained from a two-generation study are regarded as not necessary with respect to the fact that REACH allows assessment of reproductive toxicity of a given chemical with the help of findings from studies with repeated administration. This is in-line with the idea that the information requirements under REACH are regarded as the evaluation of endpoints which do not necessarily require data from specific studies.*"

b) ECHA's evaluation and conclusion of the provided information

Criteria applied

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 (hazardous) property with respect to the information requirement in question including an adequate and reliable documentation.

Your weight of evidence adaptation needs to address the specific dangerous (hazardous) properties of the registered substance at equivalent level as investigated in an extended one-generation reproductive toxicity study (EU B.56./OECD TG 443) which is a standard information requirement. ECHA considers that this study provides relevant information on two aspects, namely on sexual function and fertility in P1 and F1 generations (further referred to as 'sexual function and fertility') and on developmental toxicity observable peri- and postnatally in the F1 generation (further referred to as 'post-natal developmental toxicity'). Relevant elements for 'sexual function and fertility' are in particular functional fertility (mating behaviour, conception, pregnancy, parturition, and lactation) in the parental generation after sufficient pre-mating exposure and histopathological examinations of reproductive organs in both P and F1 generations. Relevant elements for 'post-natal toxicity' are in particular peri- and post-natal investigations of the F1 generation up to adulthood.

Sexual function and fertility

With respect to the aspect of sexual function and fertility of P and F1 generation, you provided reliable information from sub-chronic and chronic toxicity studies on histopathological changes in major reproductive organs which show that the reproductive organs are not affected.
However, you have not provided any information on functional fertility (mating behaviour, conception, pregnancy, parturition, and lactation) and histopathological examinations of reproductive organs in an offspring generation.

ECHA also observes your claim that "*information gained from a two-generation study are regarded as not necessary with respect to the fact that REACH allows assessment of reproductive toxicity of a given chemical with the help of findings from studies with repeated administration. This is in line with the idea that the information requirements under REACH are regarded as the evaluation of endpoints which does not necessarily require data from specific studies*". ECHA acknowledges that the information requirement can be met by providing several independent sources of information according to Annex XI, Section 1.2. (weight of evidence) of the REACH Regulation. However, as explained above, this requires that information at an equivalent level of an extended one-generation reproductive toxicity study (EU B.56./OECD TG 443) is provided to assume/conclude on the hazardous property of the substance according to Annex X, Section 8.7.3..

The literature references cited in your adaptation justification do not contain information on the registered substance nor do you explain why and how the information on various aspects of reproduction provided by an extended one-reproductive toxicity could be replaced or predicted for your substance by histopathological examinations only.

Thus, the information you provided does not support your conclusion that the substance does not have a dangerous property with respect to sexual function and fertility.

Post-natal developmental toxicity

ECHA notes that your adaptation does not address post-natal developmental toxicity. The provided information does also not cover the key elements which need to be investigated in this regard. The pre-natal developmental toxicity study according to OECD TG 414 in the rat with the salt forms of the registered substance, morpholine hydrochloride, (also available in the registration dossier but not mentioned in your adaptation justification) provides information only on pre-natal developmental toxicity and in particular does not cover the peri-and postnatal toxicity. Thus, the information you provided does not allow a conclusion on the hazardous property of the registered substance with respect to post-natal developmental toxicity.

Conclusion

Hence, the information you provided to support you adaptation, considered individually or together, 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.

c) *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 if 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 6.0, July 2017). 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. 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 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.

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) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

Substance to be tested

As indicated above under paragraph 'Pre-natal developmental toxicity', you provided a pre-natal developmental toxicity study in rats performed with the substance morpholine hydrochloride (EC 233-029-4). According to 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 (iv), "*In certain cases, testing of neutral salts of alkaline or acidic substances may be appropriate and allows investigation of intrinsic properties at adequate dose levels*". Since morpholine is an alkaline substance classified for skin corrosion, ECHA considers that testing for reproductive toxicity with its neutral salt morpholine hydrochloride as done in the pre-natal developmental toxicity study is more appropriate than testing with the corrosive free base morpholine.

Comments on the draft decision

In your comments to the draft decision according to Article 50(1) of the REACH Regulation you agree to perform this study. However, you argue that despite its corrosivity it may be possible to perform the requested tests with the registered substance. ECHA acknowledges that you agree to perform the requested study. However, ECHA retains its view that testing should be performed with the hydrochloride salt of morpholine due to the corrosive properties of the registered substance. Such properties are expected to mainly lead to dose-limiting local effects and systemic effects secondary to it may be masked.

d) Outcome

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with morpholine hydrochloride (EC 233-029-4):
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

Notes for your consideration

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the new information shows triggers which are described in column 2 of Section 8.7.3., Annex X and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter 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.

Deadline to submit the requested information in this decision

In the draft decision communicated to you, the time line to provide the requested studies and submit the study results to ECHA in a dossier update was 30 months from the date of adoption of the decision. In your comments on the draft decision, you requested an extension of this timeline to 42 months. You justified this request by explaining that agreeing on the composition of the test substance, negotiating laboratory capacity, as well as for dose-range-finders and toxicological pre-testing (OECD TG 422 study) before the main studies additional time is needed.

ECHA finds that some of the issues (such as agreement within the consortium and negotiating laboratory capacity) you raise to justify a prolongation of the deadline have already been taken into account when setting the initial deadline. However, based on the provided information on the need for dose-range-finding studies for an OECD TG 414 study in rabbits and performance of an OECD TG 422 study before the OECD TG 443 study, ECHA agrees to prolong the deadline with 9 months. Hence, the time line to submit the requested information in an updated registration dossier has been extended from 30 months to 39 months.

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 7 November 2016.

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(s).

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

ECHA received proposal(s) for amendment and did not modify 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-55 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. 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.

2. 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.

3. If the required tests are conducted with an analogue substance in the context of a read-across approach, the identity of the test material used to perform the test should be specified in line with ECHA's Practical Guide on "How to use alternatives to animal testing to fulfil your information requirements" (chapter 4.4). This is required to show that the test material is representative of the analogue substance identified in the read-across approach and used to predict the properties of the registered substance.