EUROPEAN CHEMICALS AGENCY

Helsinki, 10 February 2020

Addressees
Registrant of [redacted] listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
15/02/2018

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: N-methylaniline
EC number: 202-870-9
CAS number: 100-61-8

Decision number: [Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/D)]

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of ***17 February 2021***.

Requirement applicable to the Registrant subject to Annex IX of REACH[1]

1. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) in one species (rat or rabbit), oral route, with the Substance;

2. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method OECD TG 210) with the Substance.

Conditions to comply with the requests

You are bound by the request for information corresponding to the REACH Annexes applicable to your own registered tonnage of the Substance at the time of evaluation.

Therefore you have to comply with the requirements of Annexes VII, VIII and IX of REACH, if you have registered a substance at 100-1000 tpa.

The Appendices state the reasons for the requests for information to fulfil the requirements set out in the respective Annexes of REACH.

The Appendix entitled Observations and technical guidance addresses the generic approach for the selection and reporting of the test material used to perform the required studies and provides generic recommendations and references to ECHA guidance and other reference documents.

You must submit the information requested in this decision by the deadline indicated above in an updated registration dossier and also update the chemical safety report, where relevant,

[1] Testing required under this Annex can only be started or performed after the decision has been adopted according to Article 51.

including any changes to classification and labelling, based on the newly generated information. The timeline has been set to allow for sequential testing where relevant.

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[2] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

[2] 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 A: Reasons for the requests to comply with Annex IX of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier registered at 100 to 1000 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII-IX to REACH.

1. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in one species

A Pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is a standard information requirement under Annex IX to REACH.
In your technical dossier you provided the following information with analogue substances:

1. a developmental toxicity study (oral route) with aniline (EC no. 200-539-3), performed similar to OECD TG 414 ([redacted] 1985); and
2. a publication: "*Evaluation of 60 Chemicals in a Preliminary Developmental Toxicity Test*" in mice (Hardin *et al.*, 1987) (non guideline study), including aniline (EC no. 200-539-3), *p*-nitroaniline (EC no. 202-810-1) and N,N-dimethylaniline (EC no. 204-493-5).

We have assessed the available data from your dossier and note the following:

> Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide a justification for the read-across including a hypothesis, explanation of the rationale for the prediction of properties and robust study summary(ies) of the source study(ies).
>
> However, you did not provide such documentation.
>
> In the absence of such documentation, ECHA cannot verify that the properties of your Substance can be predicted from the data on the selected source substances.

Based on the above, the information you provided does not fulfil the information requirement.

Therefore, a PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit as preferred species with oral[3] administration of the Substance.

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

Long-term toxicity testing on fish is a standard information requirement in Annex IX to REACH.

You have submitted an OECD TG 212 study.

We have assessed this information and identified the following issues:

Incompliance with OECD TG 212

Tests on substances must be conducted in accordance with the OECD test guidelines or another recognised international test method (Article 13(3) of REACH).

[3] ECHA Guidance R.7a, Section R.7.6.2.3.2.

To be considered compliant and to generate information concerning the lethal and, to a limited extent, sub-lethal effects of the Substance on the life-cycle stages (embryo and Sac-fry) and species tested, the study has to meet the key parameters of OECD TG 212.

The relevant key parameter(s) of this test guideline for your preformed study includes:

- Exposure duration for zebrafish: An embryo stage, which is 3 - 5 days, and, following this, a Sac-fry stage, which is 8 – 10 days

In the OECD TG 212 study you have provided the fish species used, Zebrafish, were exposed to the Substance for a duration of 96 hours. Currently, your Risk Characterisation Ratio (RCR) values for several exposure scenarios indicate risk for the environment.

This study does not have the required exposure duration according to OECD TG 212 for the fish species, Zebrafish, because the exposure does not cover the relevant life-cycle stage of the Sac-fry which for this species is 8 – 10 days, following the embryo stage.

Therefore, this study does not fulfil the conditions set out in OECD TG 212 and the information provided does not fulfil the information requirement.

In your comments on the draft decision you outline that the available data are limited and are challengeable (information based on QSAR or read across with other substances, whose method is not very well detailed), therefore you consider to submit a testing proposal as part of Annex IX (the option of performing an experimental test to fill the gap of information seems the best as it is the most scientifically robust). ECHA notes that there is no need to submit a testing proposal for the long-term toxicity to fish endpoint as the same endpoint is already addressed and the relevant study is requested by this compliance check decision.

Comparison of OECD TG 210 vs OECD TG 212

According to ECHA Guidance R.7b, an OECD TG 210 test is the most sensitive of the standard long-term fish toxicity tests available as it covers several life stages of the fish from the newly fertilised egg, through hatch to early stages of growth. The OECD TG 210 is also the only suitable test currently available for examining the potential toxic effects of bioaccumulation. Furthermore, the use of OECD TG 212 is not advised due to animal welfare issues (FISH TOXICITY TESTING FRAMEWORK, OECD Series on Testing and Assessment, No. 171).

In your comments on the draft decision, you outline that several tests exist for the endpoint of long-term toxicity to fish. While you acknowledge that the OECG TG 212 method is less sensitive than the OECD TG 210 method, you point out that the OECG TG 212 study is shorter and less expensive. The Guidance indicates that the OECD TG 212 method is an alternative to OECD TG 210 for substances having a log Kow<4, which is the case of N-methylaniline. Therefore, you ask whether ECHA would accept an OECD TG 212 study instead of an OECD TG 210 study.

ECHA notes that OECD TG 212 is a test during which exposure to the test substance starts from the newly fertilised egg to the end of the sac-fry stage. For OECD TG 210, exposure also starts from fertilised eggs but is continued until the juvenile life-stage is reached. As explained in the introduction of OECD TG 212, "*only tests incorporating all stages of the life-cycle of fish are generally liable to give an accurate estimate of the chronic toxicity of chemicals to fish, and [...] any reduced exposure with respect to life stages may reduce the sensitivity and thus underestimate the chronic toxicity*". For this reason, OECD TG 212 is considered insensitive relatively to OECD 210.

ECHA further notes that OECD TG 212 allows for considerable variations in its design (e.g. number of test chambers, test concentrations, starting number of fertilised eggs). It is thus regarded as less reliable than an OECD 210 test.

Finally, the OECD FISH TOXICITY TESTING FRAMEWORK implicitly acknowledges that larvae used in an OECD 212 test could be subject to pain when it recommends that larvae with severe deformities should be terminated to avoid suffering. This test is performed without any external food supply. It should normally be stopped just before the yolk sac of any larvae has been completely absorbed or before mortality by starvation starts in the controls. However, the exact point at which this occurs may be difficult to define in practice. The lack of feeding could be considered unacceptably distressful for the test organisms. As such this test, which is sometimes termed as the "fish starvation test" (e.g. https://www.oecd-ilibrary.org/docserver/9789264221437-en.pdf?expires=1571648956&id=id&accname=guest&checksum=56A906873CF171D1C405D5C920E79C98), is ethically problematic.

Therefore, ECHA considers that that an OECD TG 210 study is appropriate and suitable. On the contrary, OECD TG 212 study is not the most sensitive for the purpose of addressing the information requirement of long-term toxicity to fish, independent of the test substance's physical chemical properties and therefore not appropriate and not acceptable.

Appendix B: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of registration dossiers after the date on which you were notified the draft decision according to Article 50(1) of the REACH Regulation.

The compliance check was initiated on 14 January 2019.

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 within 30 days of the notification.

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

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) and referred the modified draft decision to the Member State Committee.

You did not provide any comments on the proposed amendment(s).

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-68 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix C: Observations and technical guidance

1. This compliance check decision does not prevent ECHA from initiating further compliance checks at a later stage on the registrations present.

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. Test guidelines, GLP requirements and reporting

   Under Article 13(3) of REACH, all new data generated as a result of this decision needs to be conducted according to the test methods laid down in a European Commission Regulation or according to international test methods recognised by the Commission or ECHA as being appropriate.

   Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses shall be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

   Under Article 10 (a) (vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide: 'How to report robust study summaries'[4].

4. Test material

   Selection of the test material(s)

   The registrants of the Substance are responsible for agreeing on the composition of the test material to be selected for carrying out the tests required by the present decision. The test material selected must be relevant for all the registrants of the Substance, i.e. it takes into account the variation in compositions reported by all members of the joint submission. The composition of the test material(s) must fall within the boundary composition(s) of the Substance.

   While selecting the test material you must take into account the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected test material must contain that constituent/ impurity.

   Technical reporting of the test material

   The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and their concentration values. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

   Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[5].

[4] https://echa.europa.eu/practical-guides
[5] https://echa.europa.eu/manuals

5. List of references of the ECHA Guidance and other guidance/ reference documents[6]

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 in this decision.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 in this decision.

ECHA Read-across assessment framework (RAAF, March 2017)[7]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

OECD Guidance documents[8]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD23.

Guidance Document on Mammalian Reproductive Toxicity Testing and Assessment – No 43, referred to as OECD GD43.

[6] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[7] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[8] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Appendix D: List of the registrant to which the decision is addressed and the corresponding information requirement is applicable

Registrant Name	Registration number	(Highest) Data requirements to be fufilled
[redacted]	[redacted]	[redacted]