EUROPEAN CHEMICALS AGENCY

Helsinki, 13 December 2018

Addressee

[redacted]

Decision number
CCH-D-2114453560-54-01/F

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Methyl 5-nitrohydrogen.isophthalate
EC number: 217-793-6
CAS number: 1955-46-0

Your registration
Registration number: [redacted]
Submission number: [redacted]
Submission date: 30 May 2018
Registered tonnage band: 10-100

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA requests you to submit information generated with a test material representative of the Substance on:

1. **In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14. / OECD TG 471);**

2. **In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method: OECD TG 473) or in vitro micronucleus study (Annex VIII, Section 8.4.2, test method: OECD TG 487);**

3. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490); provided that both studies requested under 1. and 2. have negative results;**

4. **, 5. Combined repeated dose toxicity study with the reproduction/developmental toxicity screening study (Annex VIII, Section 8.6.1. and Section 8.7.1.; test method: OECD TG 422) in rats, oral route;**

You are required to submit the requested information in an updated registration dossier by ***20 April 2020***.

You are required to submit the results in a form of a robust study summary[1]. You shall also update the chemical safety report. The timeline has been set to allow for sequential testing.

[1] See ECHA Practical guide 3: https://echa.europa.eu/documents/10162/13643/pg_report_robust_study_summaries_en.pdf/

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 toxicological information requirements of Annex VIII, 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[2] by Ofelia Bercaru, Head of Unit, Evaluation E3

[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 1: Reasons

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

Your current registration dossier ([redacted] dated 30 May 2018), contains for the endpoints addressed in this Decision, adaptation arguments in the form of predictions generated with the use of QSAR models under Annex XI, Section 1.3 of the REACH Regulation. ECHA has assessed your adaptation arguments in line with the conditions specified in Annex XI of the REACH Regulation:

For the use of (Q)SAR models, according to Annex XI, Section 1.3, the results obtained from valid (Q)SAR models may be used instead of testing when the following conditions are met[4]:

- results are derived from a (Q)SAR model whose scientific validity has been established,
- the substance falls within the applicability domain of the (Q)SAR model,
- results are adequate for the purpose of classification and labelling and/or risk assessment, and
- adequate and reliable documentation of the applied method is provided.

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)

For your registration an *In vitro* gene mutation study in bacteria is a standard information requirement.

ECHA evaluated the dossier originally subject to this draft decision ([redacted] dated 20 June 2012) and rejected the proposed read-across approach. In your dossier update you replaced the read-across adaptation with a QSAR prediction.

Whilst in your comments to the draft decision you agreed to perform this test, in your current dossier ([redacted] dated 30 May 2018), you have replaced the original read-across adaptation for the Substance using a (Q)SAR model (Danish EPA Model) adaptation. ECHA has assessed the updated information according to Annex XI, Section 1.3. ECHA concludes that you have not provided any documentation containing:

1. An evaluation of the scientific validity (relevance and reliability) of the model used for the prediction,
2. An assessment of the applicability of the model to the Substance and the reliability of the individual model prediction,
3. An assessment of the adequacy of the prediction for classification and labelling and/or risk assessment.

ECHA therefore concludes that:

- The proposed adaptation is not in line with the conditions specified in Annex XI, Section 1.3., and is therefore rejected.
- Contrary to Article 3(28) of the REACH Regulation, the documentation of the endpoint study records is insufficient and does not allow an independent assessment of the adequacy of this study, its results and its use for hazard assessment.

2. In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)

For your registration, an *In vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study in a standard information requirement.

You have indicated "calculation" in the administrative section of the endpoint study record in the technical dossier for *In vitro* cytogenicity / chromosome aberration study in mammalian cells for predicting the properties of the Substance. You have claimed predicting the property by estimation using a (Q)SAR model (Danish EPA Model).

ECHA notes that you have not provided any documentation containing:

1. An evaluation of the scientific validity (relevance and reliability) of the model used for the prediction,
2. An assessment of the applicability of the model to the Substance and the reliability of the individual model prediction
3. An assessment of the adequacy of the prediction for classification and labelling and/or risk assessment.

ECHA therefore concludes that the proposed adaptation is not in line with the conditions specified in Annex XI, Section 1.3. and is therefore rejected.

In your comments to the draft decision you agreed to perform this test.

3. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

For your registration an *In vitro* gene mutation study in mammalian cells is a standard information requirement if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. is obtained. Currently your dossier does not have acceptable information on the two endpoints mentioned above. Adequate information on *in vitro* gene mutation in mammalian cells will however need to be present in the technical dossier for the Substance to meet this information requirement provided that both studies requested under 1 and 2 have negative results. ECHA set the deadline for provision of the information to allow for sequential testing.

You have indicated "calculation" in the administrative section of the endpoint study record in the technical dossier for *In vivo* mammalian germ cell study: gene mutation for predicting the properties of the Substance. You have claimed predicting the property by estimation using a (Q)SAR model (Danish EPA Model).

ECHA notes that you have not provided any documentation that containing:

1. An evaluation of the scientific validity (relevance and reliability) of the model used for the prediction,
2. An assessment of the applicability of the model to the Substance and the reliability of the individual model prediction
3. An assessment of the adequacy of the prediction for classification and labelling and/or risk assessment.

ECHA therefore concludes that the proposed adaptation is not in line with the conditions specified in Annex XI, Section 1.3. and is therefore rejected.

ECHA considers that the *in vitro* mammalian cell gene mutation tests using the *Hprt* and *xprt* genes (OECD TG 476) and the *in vitro* mammalian cell gene mutation tests using the thymidine kinase gene (OECD TG 490) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.3.

In your comments to the draft decision you indicated that this study is not a data requirement for registrations at 10-100 tonnes per year. As explained above, an *in vitro* gene mutation study in mammalian cells is an information requirement as laid down in Annex VIII, Section 8.4.3. of the REACH Regulation, "if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2." is obtained.

Also, you indicate that "since after above test there will be data available for the substance which may confirms that the substance not genetically toxic substance". In your current dossier ([redacted] dated 30 May 2018), you have provided an additional prediction that you claim you generated with the Substance using a (Q)SAR model (Danish EPA Model). However, with this additional prediction, ECHA has observed the same issues as stated above for point 1 – 3.

Therefore for this additional prediction, ECHA concludes that the proposed adaptation is not in line with the conditions specified in Annex XI, Section 1.3. and is therefore rejected.

Therefore, adequate information for this endpoint needs to be present if the studies requested under issues items 1 and 2 of this draft decision give negative results.

ECHA considers that the in vitro mammalian cell gene mutation tests using the Hprt and xprt genes (OECD TG 476) and the in vitro mammalian cell gene mutation tests using the thymidine kinase gene (OECD TG 490) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.3.

4. Short-term repeated dose toxicity (28 day), one species (Annex VIII, Section 8.6.1.)

For your registration a "short-term repeated dose toxicity study (28 days)" is a standard information requirement as laid down in Annex VIII, Section 8.6.1. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the Substance to meet this information requirement.

You have indicated "read-across based on grouping of substances (category approach)" in the administrative section of each endpoint study record for Repeated-dose toxicity (oral and inhalation). In the technical dossier you have provided automated reports generated with the OECD QSAR Toolbox for the purpose of a read-across adaptation and you have indicated that the reports aim to predict Repeated-dose toxicity, LOEL for the Subtance.

ECHA notes that:

1. You have not provided an assessment to address structural similarity/dissimilarity between the Substance and the proposed analogue(s).

2. You have not provided any read-across hypothesis establishing why the results generated with the source substance can be used to predict the results for the target substance.
3. You have not provided any experimental studies neither with the Substance nor with structurally similar analogue(s) which would substantiate the prediction. Absence of experimental data to substantiate the hypothesis for the prediction makes any adaptation based on read-across invalid as it does not allow a comparative assessment of properties of the source and target substance and hence concluding whether properties could be read across, and
4. There is no adequate robust study summary for a study to be read-across.

ECHA therefore concludes that:

- The proposed adaptation is not in line with the conditions specified in Annex XI, Section 1.5.
- Contrary to Article 3(28) of the REACH Regulation, the documentation of the endpoint study records is insufficient and does not allow an independent assessment of the adequacy of this study, its results and its use for hazard assessment.

Furthermore, you have provided the following waiving statement for the endpoint "sub-chronic toxicity: dermal": *"According to annex IX of REACH regulation, Short-term repeated dose toxicity study (28 days) does not need to be conducted if one species, male and female, most appropriate route of administration, having regard to the likely route of human exposure, unless already provided as part of Annex VIII requirements. since acute toxicity dermal route has been provided as part of annex VIII requirements."*

ECHA notes that the waiving statement you provided for the dermal route is not correct as the acute dermal toxicity study cannot be used for the waiving of the short-term repeated dose toxicity study.

When there is no information available neither for the 28-day repeated dose toxicity endpoint (EU B.7, OECD TG 407), nor for the screening study for reproductive/developmental toxicity (OECD TG 421 or TG 422) as explained below under point 5.), the conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) is preferred to ensure that unnecessary animal testing is avoided. Such an approach offers the possibility to avoid carrying out a 28-day study according to OECD TG 407, because the OECD TG 422 can at the same time fulfil the information requirement of REACH Annex VIII, 8.6.1 and that of REACH Annex VIII, 8.7.1.[3]

With regard to your comment on the proposal for amendment submitted by a Member State Competent Authority, please see section 5 below.

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. Hence, the test shall be performed by the oral route.

[3] ECHA Guidance, Section R.7.6.2.3.2., pages 484 to 485 of version 6.0 – July 2017. (https://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf)

According to the test method OECD TG 422, the test is designed for use with rats. On the basis of this default assumption ECHA considers testing should be performed with rats.

5. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

For your registration a "Screening for reproductive/developmental toxicity" is a standard information requirement.

You have indicated "read-across based on grouping of substances (category approach)" in the administrative section of one of the endpoint study records and "calculation" in the other endpoint study record for Toxicity to Reproduction. In the technical dossier you have provided an automated report generated with the OECD QSAR Toolbox for the purpose of a read-across adaptation and you have indicated that the reports aims to predict Reproductive toxicity, LOEL for the Substance.

ECHA notes that regarding your proposed read-across adaptation:

1. You have not provided an assessment to address structural similarity/dissimilarity between the Substance and the proposed analogue(s).
2. You have not provided any read-across hypothesis establishing why the results generated with the source substance can be used to predict the results for the target substance.
3. You have not provided any experimental studies neither with the Substance nor with structurally similar analogue(s) which would substantiate the prediction. Absence of experimental data to substantiate the hypothesis for the prediction makes any adaptation based on read-across invalid as it does not allow a comparative assessment of properties of the source and target substance and hence concluding whether properties could be read across, and
4. There is no adequate robust study summary for a study to be read-across.

ECHA also notes that regarding the use of the (Q)SAR model, you have not provided any documentation containing:

1. An evaluation of the scientific validity (relevance and reliability) of the model used for the prediction,
2. An assessment of the applicability of the model to the Substance and the reliability of the individual model prediction
3. An assessment of the adequacy of the prediction for classification and labelling and/or risk assessment.

ECHA therefore concludes that:

- The proposed adaptations are not in line with the conditions specified in Annex XI, Section 1.3., and Annex XI, Section 1.5. They are therefore rejected.
- Contrary to Article 3(28) of the REACH Regulation, the documentation of the endpoint study records is insufficient and does not allow an independent assessment of the adequacy of this study, its results and its use for hazard assessment.

ECHA notes that when there is no information available neither for the 28-day repeated dose toxicity endpoint (EU B.7, OECD TG 407) (as explained above under point 4.), nor for the screening study for reproductive/developmental toxicity (OECD TG 421 or TG 422), the

conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) is preferred to ensure that unnecessary animal testing is avoided. Such an approach offers the possibility to avoid carrying out a 28-day study according to OECD TG 407, because the OECD TG 422 can at the same time fulfil the information requirement of REACH Annex VIII, 8.6.1 and that of REACH Annex VIII, 8.7.1.[4]

According to the test method OECD TG 422, the test is designed for use with rats. On the basis of this default assumption ECHA considers testing should be performed with 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) Chapter R.7a, Section R.7.6.2.3.2. Since the Substance is a solid, ECHA concludes that testing should be performed by the oral route.

In your comment on a proposal for amendment submitted by a Member State Competent Authority, you have claimed that the substance has only intermediate use and that you had further changed the tonnage band of your registration from 10-100 tonner per year to 1-10 tonnes per year. Therefore you consider that the combined repeated dose toxicity study with the reproduction/developmental toxicity screening study should be removed from the decision. ECHA notes that your claims are not supported by the information in your dossier. Also, as outlined in Appendix 2 of this decision, updates of the registration dossier after the notification of the draft decision are not to be considered. Exceptionally, your initial change of the tonnage from Annex IX to Annex VIII information requirements was already taken into account. Further/later changes and updates cannot be considered in the current decision making process.

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. This period of time took into account the fact that the draft decision also requested a Sub-chronic toxicity study (90-day) and a Prenatal developmental toxicity study in the first species. Due to the tonnage band change from 100-1000 tonnes per year to 10-100 tonnes per year, these two requests have been removed from the present decision. Following a proposal for amendment from one of the Member States Competent Authorities the request for a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) was included in the decision. As a consequence, the deadline for providing the information to meet the requests in the decision has been set to 16 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

[4] ECHA Guidance, Section R.7.6.2.3.2., pages 484 to 485 of version 6.0 – July 2017. (https://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf)

Appendix 2: Procedural history

You were notified that the draft 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. Exceptionally, following your comments on the draft decision and the inter-related new and substantial information provided in the updated dossier, ECHA has taken into account all the updated information, relevant, to the draft decision. Based on the updated tonnage band and the average production and/or import volumes for the three preceding calendar years, ECHA has changed the tonnage band from 100 – 1000 tonnes per year (submission number: [redacted]) to 10 – 100 tonnes per year (Latest submission number [redacted] on 30 May 2018.)

The compliance check was initiated on 16 January 2018.

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 all the updated information of submission number [redacted]. As a result, the requests for information on Sub-chronic toxicity study (90-day), oral route in rats, and Pre-natal developmental toxicity study in a first species (rat or rabbit), oral route were removed. In addition, for the requests for information on In vitro gene mutation study in bacteria, In vitro cytogenicity study in mammalian cells or in vitro micronucleus study and In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490), only Appendix 1 was modified.

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

ECHA received proposals for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendments.

ECHA referred the draft decision to the Member State Committee.

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

In addition, you provided comments on the draft decision. These comments were not taken into account by the Member State Committee as they were considered to be outside of the scope of Article 51(5).

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-62 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 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 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 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.