

Helsinki, 4 July 2019

Addressee: [REDACTED]

Decision number: TPE-D-2114473788-28-01/F

Substance name: Methanal, reaction products with 1,3-bis(aminomethyl)benzene and hydroxybenzen

EC number: 701-207-5

CAS number: 1950616-36-0

Registration number: [REDACTED]

Submission number: [REDACTED]

Submission date: 22/03/2018

Registered tonnage band: 100-1000

### **DECISION ON A TESTING PROPOSAL**

Based on Article 40 of Regulation ((EC) No 1907/2006) (the REACH Regulation), ECHA examined your testing proposal(s) and decided as follows.

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

- 1. In vivo mammalian alkaline comet assay (Annex IX, Section 8.4., column 2; test method: OECD TG 489) in rats, oral route, on the following tissues: liver, glandular stomach and duodenum, using the registered substance.**

Your testing proposals are accepted and you are requested to carry out:

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

You have to submit the requested information in an updated registration dossier by **11 January 2022**. You also have to update the chemical safety report, where relevant.

The reasons for 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.

## **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<sup>1</sup> by Claudio Carlon, Head of Unit, Hazard Assessment

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<sup>1</sup> 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 proposals submitted by you and scientific information submitted by third parties.

### 1. *In vivo* mammalian alkaline comet assay (Annex IX, Section 8.4., column 2)

#### a) Examination of the testing proposal

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

"Mutagenicity" is an information requirement as laid down in Section 8.4. of Annexes VII to X of the REACH Regulation. Column 2 of Annex IX, Section 8.4. provides that "If there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII and there are no results available from an *in vivo* study already, an appropriate *in vivo* somatic cell genotoxicity study shall be proposed by the Registrant."

The technical dossier contains an *in vitro* study "*In vitro mammalian cell gene mutation test (2012)*" performed according to *OECD TG 476* with the registered substance that shows positive results. You summarise the *OECD 476* study results as follows:

*"The test substance did not induce gene-mutation in the absence of rat liver fraction S9 metabolic activation. However, the data demonstrate that the registered substance is mutagenic to mouse lymphoma cells when metabolically converted to an ultimate mutagen. The increase in the frequency of small colony mutants under the conditions of S9 metabolic activation suggests that the test substance is capable of causing chromosome damage in chromosome 11 of these mouse cells."*

You did not, however, provide any tabulated information on the small and large colonies or any other detailed quantitative data on the test results in the study record. Hence, ECHA notes that it is not possible to get a more precise insight into the type(s) of damage, i.e. point mutation and/or structural chromosome aberration, the test material has caused. The technical dossier also contains an *OECD TG 473* study (*In vitro mammalian chromosome aberration test, 2012*) conducted with the registered substance with a negative result with and without metabolic activation and therefore not indicative of inducing chromosomal aberrations. Based on the provided data, ECHA considers that the positive result in the *OECD 476* study indicates that the substance is inducing gene mutations under the conditions of the test and the main concern is on gene mutations.

An appropriate *in vivo* genotoxicity study to follow up the concern on gene mutations is not available for the registered substance. Consequently, there is an information gap.

Hence, you have submitted a testing proposal for an *In vivo single-cell-gel-electrophoresis (Comet Assay)*.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Genetic toxicity *in vivo*. ECHA notes that you provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

ECHA notes that the proposed test is an appropriate test to investigate effects on gene mutations *in vivo* as described in the ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017), Chapter R.7a, section R.7.7.1. and figure R.7.7-1.

You proposed testing in mice by the oral route.

You did not provide any scientific justification why testing should be performed in mice. According to the test method OECD TG 489, the test shall be performed in rats. Having considered the anticipated routes of human exposure and adequate exposure of the target tissue(s), performance of the test by the oral route is appropriate.

In line with the test method OECD TG 489, the test shall be performed by analysing tissues from liver as primary site of xenobiotic metabolism, glandular stomach and duodenum as sites of contact. There are several expected or possible variables between the glandular stomach and the duodenum (different tissue structure and function, different pH conditions, variable physico-chemical properties and fate of the substance, and probable different local absorption rates of the substance and its possible breakdown product(s)). In light of these expected or possible variables, it is necessary to analyse both tissues to ensure a sufficient evaluation of the potential for genotoxicity at the site of contact in the gastro-intestinal tract.

#### b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

The third party provided their considerations of the study design and stated that "*If the in vivo genetic toxicity testing proposal is confirmed by ECHA, the study design proposed by the Registrant is supported as it aims to obtain the maximum amount of information from a single study. The study proposed includes assessment of DNA damage and chromosomal endpoints, and investigation of toxicokinetic parameters intended to demonstrate adequate exposure of the target tissue(s).*"

However, the third party did not provide any scientific data which would fulfil this information requirement.

#### c) 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: *In vivo* mammalian alkaline comet assay (test method: OECD TG 489) in rats, oral route, on the following tissues: liver, glandular stomach and duodenum.

#### d) Notes for your consideration

You are reminded that according to Annex IX, Section 8.4., column 2 of the REACH Regulation, if positive results from an *in vivo* somatic cell study are available, "the potential for germ cell mutagenicity should be considered on the basis of all available data, including toxicokinetic evidence. If no clear conclusions about germ cell mutagenicity can be made, additional investigations shall be considered".

You may consider examining gonadal cells, as it would optimise the use of animals. ECHA notes that a positive result in whole gonads is not necessarily reflective of germ cell damage since gonads contain a mixture of somatic and germ cells. However, such positive result would indicate that the substance and/or its metabolite(s) have reached the gonads and caused genotoxic effects. This type of evidence may be relevant for the overall assessment of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation.

## **2. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.)**

### **a) Examination of the testing proposal**

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 rats by the oral route according to OECD TG 408.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Sub-chronic toxicity (90-day): oral. ECHA notes that you provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

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 6.0, July 2017) 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, potential inhalation-specific effects are already addressed by deriving a long-term DNEL for inhalation, local effects. Hence, the test shall be performed by the oral route using the test method OECD TG 408.

Therefore, ECHA considers that the proposed study performed by the oral route with the registered substance is appropriate to fulfil the information requirement of Annex IX, Section 8.6.2. of the REACH Regulation.

You proposed testing in rats. According to the test method OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

### **b) Consideration of the information received during third party consultation**

ECHA received third party information concerning the testing proposal during the third party consultation. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

The third party provided their considerations of the study design and stated that *"The Registrant proposes a Repeated Dose 90-Day Oral Toxicity study in the rat. While this study is a data requirement at the tonnage band at which the substance is registered. If the proposed study is confirmed by ECHA, the study design proposed by the Registrant is supported as it aims to obtain the maximum amount of information from a single study."*

However, the third party did not provide any scientific data which would fulfil this information requirement.

#### c) Outcome

ECHA notes that there are inconsistencies in the substance identifiers for the test material in the submitted testing proposal. ECHA found that following a prior CCH decision concerning the substance identity (ECHA's decision CCH-D-2114306140-72-01/F on 10 August 2015), you have incorrectly updated the name and CAS number for the test material in IUCLID Section 7.5.1. However, ECHA understands for this decision that you intend to test the registered substance.

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: OECD TG 408).

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

#### a) Examination of the testing proposal

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 in rats according to OECD TG 414 by the oral route.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (pre-natal developmental toxicity). ECHA notes that you provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

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 proposed testing with the rat as a first species. According to the test method 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 with the rat or rabbit as a first species.

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 6.0, July 2017) Chapter R.7a, Section 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.

#### b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

The third party has indicated *"The Registrant proposes a Reproductive toxicity (pre-natal developmental toxicity) study in the rat. While this study is a data requirement at the tonnage band at which the substance is registered. If the proposed studies are confirmed by ECHA, they should be performed in a step-wise manner to avoid unnecessary testing (e.g. if clearly adverse effects sufficient for classification are seen in a study in the initial species)."*

ECHA notes that it is your responsibility to consider and justify in the registration dossier any adaptation of the information requirements in accordance with Annex IX, Section 8.7., column 2, second indent. This adaptation specifies that in case the substance is known to be a germ cell mutagen (which correspond to a classification as germ cell mutagen category 1A or 1B) and appropriate risk management measures are implemented, the pre-natal developmental toxicity study does not need to be conducted.

However, ECHA notes that results of a positive *in vivo* comet assay may contribute to a classification as germ cell mutagen, but this test is usually not sufficient on its own for classification as germ cell mutagen category 1B.

ECHA also notes that the timeline has been set to allow for sequential testing.

#### c) Outcome

ECHA notes that there are inconsistencies in the substance identifiers for the test material in the submitted testing proposal. ECHA found that following a prior CCH decision concerning the substance identity (ECHA's decision CCH-D-2114306140-72-01/F on 10 August 2015), you have not yet updated the identifiers for the test material in IUCLID Section 7.8.2. However, ECHA understands for this decision that you intend to test the registered substance.

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: 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 6.0, July 2017), Chapter R.7a, Section R.7.6.2.3.2.

## **Appendix 2: Procedural history**

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 22 March 2018.

ECHA held a third party consultation for the testing proposals from 21 May 2018 until 5 July 2018. ECHA received information from third parties (see Appendix 1).

This decision does not take into account any updates after **19 December 2018**, 30 calendar days after the end of the commenting period.

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 did not receive any comments by the end of the commenting period.

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

ECHA received proposals for amendment and did not modify the draft decision.

ECHA invited you to comment on the proposed amendments.

ECHA referred the 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 during its MSC-64 meeting 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 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. 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.