

Helsinki, 21 July 2017

Addressee: [REDACTED]

Decision number: CCH-D-2114363796-34-01/F

Substance name: reaction products of ethylene glycol, urea and paraformaldehyde

EC number: 700-934-5

CAS number: 1628834-01-4

Registration number: [REDACTED]

Submission number: [REDACTED]

Submission date: 11.03.2016

Registered tonnage band: 1000+T

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. In vivo mammalian alkaline comet assay (Annex X, Section 8.4., column 2; test method: OECD TG 489) in rats, oral route, on the following tissues: liver, glandular stomach and duodenum, with the registered substance**
or
Transgenic rodent somatic and germ cell gene mutation assays (Annex X, Section 8.4., column 2; test method: EU B.58./OECD TG 488) in transgenic mice or rats, oral route on the following tissues: liver, glandular stomach with the registered substance; germ cells shall be harvested and stored for up to 5 years

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 **28 January 2019**. You shall also update the chemical safety report, where relevant

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>.

Authorised¹ 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. **In vivo mammalian alkaline comet assay or transgenic rodent somatic and germ cell gene mutation assays (Annex X, Section 8.4., column 2)**

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Mutagenicity" is an information requirement as laid down in Annex VIII, Section 8.4. of the REACH Regulation. Column 2 of Annex X, Section 8.4. provides that "If there is a positive result in any of the *in vitro* genotoxicity studies in Annexes VII or VIII, a second *in vivo* somatic cell test may be necessary, depending on the quality and relevance of all the available data."

The technical dossier contains an *in vivo* study (mammalian erythrocyte micronucleus test) performed according to OECD TG 474 with the registered substance that shows negative results. However, ECHA considers that this test is not appropriate to address the concern for mammalian gene mutation as identified in an *in vitro* mammalian cell gene mutation test according to OECD TG 476 and in an *in vitro* comet assay, both provided in your technical dossier. More specifically, the *in vitro* tests identified mammalian gene mutation as the concern, whereas the provided *in vivo* test does not detect gene mutations but clastogenic and/or aneugenic effects of a substance. Hence, ECHA concludes that the test provided was not appropriate to follow-up a concern for gene mutations.

Furthermore, you have classified the registered substance as carcinogen category 1B based on the classification of the hydrolysis product formaldehyde. However, you did not classify the registered substance as mutagen category 2 based on the hydrolysis product formaldehyde. Therefore, there is a concern that is not appropriately addressed.

An appropriate second *in vivo* genotoxicity study to follow up the concern on gene mutations is not available for the registered substance but is necessary to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, section R.7.7.6.3, the transgenic rodent somatic and germ cell gene mutation assays ("TGR assay", OECD TG 488) and the *in vivo* mammalian alkaline comet assay ("comet assay", OECD TG 489) are suitable to follow up a positive *in vitro* result on gene mutation. Hence, ECHA considers that the TGR and the comet assay are suitable tests to follow up the concern on gene mutation for the substance subject to the decision.

In case you decide to perform the TGR assay according to the test method EU B.58/OECD TG 488, the test shall be performed in transgenic mice or rats and the substance is usually administered orally. Furthermore, the test shall be performed by analysing tissues from liver as slowly proliferating tissue and primary site of xenobiotic metabolism, and glandular stomach as rapidly proliferating tissue and site of direct contact. Moreover, ECHA notes that according to the OECD 488 the tissues (or tissue homogenates) can be stored under specific conditions and used for DNA isolation for up to 5 years. Hence, in order to limit additional animal testing male germ cells shall be collected at the same time as the other tissues, and stored up to 5 years (at or below $-70\text{ }^{\circ}\text{C}$). This duration is sufficient to allow the you or

ECHA, in accordance to Annex X, Section 8.4., column 2, to decide on the need for assessment of mutation frequency in the collected germ cells.

In case you decide to perform the comet assay 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. Furthermore, the test shall be performed by analysing tissues from liver as primary site of xenobiotic metabolism and 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 sample both tissues to ensure a sufficient evaluation of the potential for genotoxicity at the site of contact in the gastro-intestinal tract.

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you agreed to classify the registered substance as mutagen category 2 to avoid further testing. However, since you did not support your intention for such a classification with factual evidence (*i.e.* implement it yet in an update of the dossier) there is still a concern and ECHA is not in a position to remove the request yet. ECHA will evaluate the situation in the updated dossier after the deadline provided in the following ECHA decision.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision:

Transgenic rodent somatic and germ cell gene mutation assays (test method: EU B.58/OECD TG 488) in transgenic mice or rats, oral route on the following tissues: liver and glandular stomach, and collection and storage of germ cells for up to 5 years

or

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

Notes for your consideration

You are reminded that according to Annex X, 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".

In case you decide to perform the comet assay, you may consider examining gonadal cells in addition to the other aforementioned tissues, 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.

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 24 August 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 amended the requests.

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-54 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 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 your Member State.
3. In carrying out the test(s) required by the present decision it is important to ensure that the particular sample of substance tested 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. If the registration of the substance covers different grades, the sample used for the new test(s) must be suitable to assess these. Furthermore, 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.