

Helsinki, 18 January 2024

**Addressee**

Registrant of JS\_204-574-5 as listed in Appendix 3 of this decision

**Date of submission of the dossier subject to this decision**

10 April 2018

**Registered substance subject to this decision ("the Substance")**

Substance name: phenylacetaldehyde

EC/List number: 204-574-5

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

**DECISION ON A COMPLIANCE CHECK**

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below by **25 July 2025**.

Requested information must be generated using the Substance unless otherwise specified.

**Information required from all the Registrants subject to Annex VIII of REACH**

1. *In vitro* micronucleus study (Annex VIII, Section 8.4.2., test method: OECD TG 487). The aneugenic potential of the Substance must be assessed with an additional control group for aneugenicity on top of the control group for clastogenicity, if the Substance induces an increase in the frequency of micronuclei.

The reasons for the request are explained in Appendix 1.

**Information required depends on your tonnage band**

You must provide the information listed above for all REACH Annexes applicable to you in accordance with Articles 10(a) and 12(1) of REACH. The addressees of the decision and their corresponding information requirements based on registered tonnage band are listed in Appendix 3.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

**How to comply with your information requirements**

To comply with your information requirements, you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also **update the chemical safety report, where** relevant, including any changes to classification and labelling, based on the newly generated information.

You must follow the general requirements for testing and reporting new tests under REACH, see Appendix 4.

**Appeal**

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to <http://echa.europa.eu/regulations/appeals> for further information.

**Failure to comply**

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised<sup>1</sup> under the authority of Mike Rasenberg, Director of Hazard Assessment

Appendix 1: Reasons for the request(s)

Appendix 2: Procedure

Appendix 3: Addressees of the decision and their individual information requirements

Appendix 4: Conducting and reporting new tests under REACH

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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 for the request(s)**

<b>Reasons related to the information under Annex VIII of REACH .....</b>	<b>4</b>
1. <i>In vitro</i> micronucleus study .....	4
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**Reasons related to the information under Annex VIII of REACH****1. *In vitro* micronucleus study**

1 An in vitro cytogenicity study in mammalian cells or an in vitro micronucleus study is an information requirement under Annex VIII, Section 8.4.2.

1.1. *Information provided*

2 You have provided:

(i) an *in vitro* micronucleus study (2016) with the Substance.

1.2. *Assessment of the information provided*

1.2.1. *The provided study (i) does not meet the specifications of the test guideline*

3 To fulfil the information requirement, the study has to be an in vitro chromosomal aberration test or an in vitro micronucleus test conducted in mammalian cells. The study must comply with the OECD TG 473 or the OECD TG 487, respectively (Article 13(3) of REACH). Therefore, the following specifications must be met:

- a) the maximum concentration tested induces 55+5% of cytotoxicity compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test concentration corresponds to 10 mM, 2 mg/mL or 2 µL/mL, whichever is the lowest;

4 In study (i):

- a) the maximum tested and evaluated concentration did not induce 55+5% of cytotoxicity compared to the negative control, and it did not induce the precipitation of the tested substance, and it was less than 10 mM, 2 mg/mL or 2 µL/mL.

5 In your comments on the draft decision, you agree with the deficiency identified under a) above as the "*concentration response curve of the cytotoxicity was so steep, that the OECD 487 test guideline recommended window of 55+5% cytotoxicity was not met.*".

6 However, based on the following arguments you disagree with the request:

- "*[...] due to the known cytotoxicity the dilution steps have already been reduced to 1.75 fold, so well below the test guideline recommended concentration spacing.*"
- "*Even with this narrow concentration spacing, the adequate window of cytotoxicity was not hit in the experiments.*"
- "*While in a new study the concentration spacing could be narrowed down even further, hitting the adequate window of cytotoxicity would remain a gamble and the adequate window of cytotoxicity would only be hit by chance.*"

7 ECHA understands that the concentration response curve of the cytotoxicity is steep, but re-emphasize the requirements of the OECD TG 487:

- "*For test chemicals demonstrating little or no cytotoxicity, concentration intervals of approximately 2 to 3 fold will usually be appropriate.*"
- "*Where cytotoxicity occurs, the test concentrations selected should cover a range from that producing cytotoxicity as described in paragraph 29 [55 ± 5% cytotoxicity] and including concentrations at which there is moderate and little or no cytotoxicity.*"

- 8 In the study (i), the concentrations analysed do not even reach 30% of cytotoxicity as the highest concentrations evaluated in 3 different experimental conditions caused only 27.1% (short-term exposure without metabolic activation), 2.1% (short-term exposure with metabolic activation) and 2.5% (long-term exposure without metabolic activation) of cytotoxicity.
- 9 In your comments to the draft decision, you refer also to a recent publication ( [REDACTED] 2022) with the following information and arguments:
- "[...] [REDACTED] (2022) analysed the datasets of 292 chemicals tested in the *in vitro* micronucleus test"
  - "Chemicals were tested with 19 concentrations up to 200  $\mu$ M using dilution steps of 1.25-fold."
  - "Of all tested chemicals 157 were identified as positive"
  - "In 55 positive experiments (with or without S9 metabolic activation), cytotoxicity limited the concentration range that provided useful results."
  - "Even with the 1.25-fold concentration spacing, in 15 of the 55 experiments, i.e., 27 %, the adequate cytotoxicity range of 55+5% cytotoxicity (corresponding to 40-50 % relative survival in the paper) was not hit due to the steepness of the cytotoxicity concentration-response."
  - "Therefore, a further narrowing down of the dilution steps would not ensure that the adequate window of cytotoxicity would or could be met for cytotoxic test items with a very steep cytotoxicity concentration-response."
  - "By inspecting the [REDACTED] (2022) results for the 50 substances that were considered positive for the induction of micronuclei and that induced cytotoxicity (lower than 50% relative survival) in the positive experiments, it can be concluded that all of the substances would also have been identified as positive if a 1.75 fold concentration spacing had been used."
- 10 Therefore, you conclude on the provided study (i) that "While the adequate window of cytotoxicity was not met even with a narrow concentration spacing of 1.75 fold, there is no scientific evidence that this may have led to a false negative conclusion on the substance with regard to induction of micronuclei *in vitro*."
- 11 However, in terms of cytotoxicity achieved in an *in vitro* experiment, ECHA notes that [REDACTED] (2022) comes to a similar conclusion as the current draft decision by stating "In cases where the test did not achieve the minimum specified top threshold for cytotoxicity, the negative result was considered inconclusive" (page 7021 of the publication). This is in line with the OECD TG 487 requirements.
- 12 On this basis, the information provided does not cover the specifications(s) required by the OECD TG 487. Your comments on the draft decision do not change the assessment's outcome.
- 13 Therefore, the information requirement is not fulfilled.

### 1.3. Study design

- 14 According to the Guidance on IR & CSA, Section R.7.7.6.3., either the *in vitro* mammalian chromosomal aberration ("CA") test (test method OECD TG 473) or the *in vitro* mammalian cell micronucleus ("MN") test (test method OECD TG 487) can be used to investigate chromosomal aberrations *in vitro*. However, while the MN test detects both structural chromosomal aberrations (clastogenicity) and numerical chromosomal aberrations (aneuploidy), the CA test detects only clastogenicity, as OECD TG 473 is not designed to

measure aneuploidy (see OECD TG 473, paragraph 2). Therefore, you must perform the MN test (test method OECD TG 487), as it enables a more comprehensive investigation of the chromosome damaging potential in Vitro. Moreover, in order to demonstrate the ability of the study to identify clastogens and aneugens, you must include two concurrent positive controls, one known clastogen and one known aneugen [1] (OECD TG 487, paragraphs 33 to 35).

*1.3.1. Assessment of aneugenicity potential*

- 15 If the result of the MN test is positive, i.e. your Substance induces an increase in the frequency of micronuclei, you must assess the aneugenic potential of the Substance.
- 16 In line with the OECD TG 487 (paragraph 4), you should use one of the centromere labelling or hybridisation procedures to determine whether the increase in the number of micronuclei is the result of clastogenic events (i.e. micronuclei contain chromosome fragment(s)) and/or aneugenic events (i.e. micronuclei contain whole chromosome(s)).

[1] According to the TG 487 (2016) "At the present time, no aneugens are known that require metabolic activation for their genotoxic activity" (paragraph 34).

## References

The following documents may have been cited in the decision.

### ***Guidance on information requirements and chemical safety assessment (Guidance on IRs & CSA)***

- Chapter R.4 Evaluation of available information; ECHA (2011).  
Chapter R.6 QSARs, read-across and grouping; ECHA (2008).  
Appendix to Chapter R.6 for nanoforms; ECHA (2019).  
Chapter R.7a Endpoint specific guidance, Sections R.7.1 – R.7.7; ECHA (2017).  
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).  
Chapter R.7b Endpoint specific guidance, Sections R.7.8 – R.7.9; ECHA (2017).  
Appendix to Chapter R.7b for nanomaterials; ECHA (2017).  
Chapter R.7c Endpoint specific guidance, Sections R.7.10 – R.7.13; ECHA (2017).  
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).  
Appendix R.7.13-2 Environmental risk assessment for metals and metal compounds; ECHA (2008).  
Chapter R.11 PBT/vPvB assessment; ECHA (2017).  
Chapter R.16 Environmental exposure assessment; ECHA (2016).

***Guidance on data-sharing***; ECHA (2017).

***Guidance for monomers and polymers***; ECHA (2012).

***Guidance on intermediates***; ECHA (2010).

All guidance documents are available online: <https://echa.europa.eu/guidance-documents/guidance-on-reach>

### ***Read-across assessment framework (RAAF)***

- RAAF, 2017 Read-across assessment framework (RAAF); ECHA (2017).  
RAAF UVCB, 2017 Read-across assessment framework (RAAF) – considerations on multi- constituent substances and UVCBs; ECHA (2017).

The RAAF and related documents are available online:

<https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across>

### ***OECD Guidance documents (OECD GDs)***

- OECD GD 23 Guidance document on aquatic toxicity testing of difficult substances and mixtures; No. 23 in the OECD series on testing and assessment, OECD (2019).  
OECD GD 29 Guidance document on transformation/dissolution of metals and metal compounds in aqueous media; No. 29 in the OECD series on testing and assessment, OECD (2002).  
OECD GD 150 Revised guidance document 150 on standardised test guidelines for evaluating chemicals for endocrine disruption; No. 150 in the OECD series on testing and assessment, OECD (2018).  
OECD GD 151 Guidance document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test; No. 151 in the OECD series on testing and assessment, OECD (2013).

**Appendix 2: Procedure**

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

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The compliance check was initiated on 24 August 2022.

The deadline of the decision is set based on standard practice for carrying out OECD TG tests. It has been exceptionally extended by 6 months from the standard deadline granted by ECHA to take into account currently longer lead times in contract research organisations.

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.

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

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.



**Appendix 3: Addressee(s) of this decision and their corresponding information requirements**

In accordance with Articles 10(a) and 12(1) of REACH, the information requirements for individual registrations are defined as follows:

- the information specified in Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa;
- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;
- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

<b>Registrant Name</b>	<b>Registration number</b>	<b>Highest REACH Annex applicable to you</b>
██████████	██████████████████	██████████

Where applicable, the name of a third-party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.

## **Appendix 4: Conducting and reporting new tests for REACH purposes**

### **1. Requirements when conducting and reporting new tests for REACH purposes**

#### **1.1 Test methods, GLP requirements and reporting**

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

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

(3) 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 on How to report robust study summaries (<https://echa.europa.eu/practical-guides>).

(4) Under the introductory part of Annexes VII/VIII/IX/X to REACH, where a test method offers flexibility in the study design, for example in relation to the choice of dose levels or concentrations, the chosen study design must ensure that the data generated are adequate for hazard identification and risk assessment.

#### **1.2 Test material**

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

##### **(1) Selection of the Test material(s)**

The Test Material used to generate the new data must be selected taking into account the following:

- the variation in compositions reported by all members of the joint submission,
- the boundary composition(s) of the Substance,
- 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.

##### **(2) Information on the Test Material needed in the updated dossier**

- You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
- The reported composition must include all constituents of each Test Material and their concentration values.

With that detailed information, ECHA can confirm whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers (<https://echa.europa.eu/manuals>).