~~Confidential~~

Helsinki, 07 September 2023

**Addressees**
Registrants of JS_226_749_5 as listed in Appendix 3 of this decision

**Date of submission of the dossier subject to this decision**
14 May 2018

**Registered substance subject to this decision ("the Substance")**
Substance name: 3-(p-methoxyphenyl)-2-methylpropionaldehyde
EC/List number: 226-749-5

**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 ***12 June 2025***.

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

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

1. *In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, OECD TG 471 (2020)).

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

2. *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.

3. Only if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. is obtained, *in vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: EU B.17./OECD TG 476 or EU B.67./OECD TG 490).

The reasons for the requests 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[1] 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

[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 for the request(s)

**Reasons related to the information under Annex VII of REACH**

## 1. *In vitro* gene mutation study in bacteria

1 An *in vitro* gene mutation study in bacteria is an information requirement under Annex VII, Section 8.4.1.

### *1.1. Information provided*

2 You have provided an *in vitro* gene mutation study in bacteria (2004) with the Substance.

### *1.2. Assessment of the information provided*

#### *1.2.1. The provided study does not meet the specifications of the test guideline*

3 To fulfil the information requirement, a study must comply with OECD TG 471 (Article 13(3) of REACH). Therefore, the following specifications must be met:

a) the number of revertant colonies per plate induced by the positive controls demonstrates the effective performance of the assay;

b) the number of revertant colonies per plate for the concurrent negative control is inside the historical control range of the laboratory;

c) the mean number of revertant colonies per plate is reported for the treated doses and the controls.

4 In the provided study:

a) it is not reported if the concurrent positive controls induced a number of revertant colonies per plate that demonstrate the effective performance of the assay as it is only indicated that the historical range of positive controls was exceeded in strain TA 1537 in experiment I with metabolic activation;

b) it is not reported if the number of revertant colonies per plate for the concurrent negative control was inside the historical control range of the laboratory. The information submitted only indicates that "*in experiment I, with metabolic activation, the number of colonies did not quite reach the lower limit of our historical control data in the solvent control of strain TA 102*";

c) the mean number of revertant colonies per plate for the treated doses and the controls was not reported.

5 In your comments on the draft decision, you agree with the above assessment. In addition, you state that the "*current study that supports the dossier has the required data and this will be added in IUCLID as response to this compliance check.* [redacted] *will not perform a new OECD 471 test, but will update the dossier with existing study.*".

6 ECHA notes your intention to update the registration dossier with the missing information. However, as you did not provide it in your comments, it is not possible to assess whether this information would resolve the issues identified above. You remain responsible for submitting compliant information by the deadline set out in the present decision.

7 In the meantime, the information currently provided in the registration dossier or in your comments on the draft decision does not cover the specifications required by the OECD TG 471.

8 Therefore, the information requirement is not fulfilled.

### *1.3. Study design*

9 To fulfil the information requirement for the Substance, the *in vitro* gene mutation study in bacteria (OECD TG 471) is considered suitable.

**Reasons related to the information under Annex VIII of REACH**

## 2. *In vitro* micronucleus study

10 An *in vitro* mammalian chromosomal aberration study or an *in vitro* mammalian micronucleus study is an information requirement under Annex VIII, Section 8.4.2.

### *2.1. Information provided*

11 You have provided an *in vitro* micronucleus study (2015) with the Substance.

### *2.2. Assessment of the information provided*

#### *2.2.1. The provided study does not meet the specifications of the test guideline*

12 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 positive controls induce responses compatible with those generated in the historical positive control database;

b) data on the cytotoxicity and the frequency of micronuclei for the treated and control cultures is reported.

13 In the provided study:

a) it is not reported if the positive control data are compatible with those generated in the historical positive control database;

b) only limited data on the cytotoxicity is provided and the frequency of micronuclei for the treated and control cultures were not reported.

14 In your comments on the draft decision, you agree with the above assessment. In addition, you state that the "*current study that supports this dossier has the required data and this will be added in IUCLID as response to this compliance check.*"

15 ECHA notes your intention to update the registration dossier with the missing information. However, as you did not provide it in your comments, it is not possible to assess whether this information would resolve the issues identified above. You remain responsible for submitting compliant information by the deadline set out in the present decision.

16 In the meantime, the information currently provided in the registration dossier or in your comments on the draft decision does not cover the specifications required by the OECD TG 487.

17 Therefore, the information requirement is not fulfilled.

### *2.3. Study design*

18 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).

#### *2.3.1. Assessment of aneugenicity potential*

19 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.

20 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).

## 3. *In vitro* gene mutation study in mammalian cells

21 An *in vitro* gene mutation study in mammalian cells is an information requirement under Annex VIII, Section 8.4.3., in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test.

### *3.1. Triggering of the information requirement*

22 Your dossier contains data for an *in vitro* gene mutation study in bacteria, and data for an *in vitro* mammalian micronucleus study.

23 The information for the in vitro gene mutation study in bacteria and for the *in vitro* mammalian micronucleus study provided in the dossier are rejected for the reasons provided in requests 1 and 2.

24 The result of the requests for an *in vitro* gene mutation study in bacteria and for an *in vitro* micronucleus study will determine whether the present requirement for an in vitro mammalian cell gene mutation study in accordance with Annex VIII, Section 8.4.3. is triggered.

25 Consequently, you are required to provide information for this information requirement, if the *in vitro* gene mutation study in bacteria and the *in vitro* micronucleus study provides a negative result.

### *3.2. Information provided*

26 You have provided an *in vitro* gene mutation study in mammalian cells (2017) with the Substance.

### *3.3. Assessment of the information provided*

#### *3.3.1. The provided study does not meet the specifications of the test guidelines*

27 To fulfil the information requirement, a study must comply with the OECD TG 476 or the OECD TG 490 (Guidance on IRs and CSA, Table.7.7-2) (Article 13(3) of REACH). Therefore, the following specifications must be met:

a) the maximum concentration tested induces 80-90% 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;

b) the concurrent positive controls induce responses that are compatible with those generated in the historical positive control database and does not induce more than 90% of cytotoxicity compared to the negative control

c) data on the cytotoxicity and the mutation frequency for the treated and control cultures are reported.

28 In the provided study:

a) the maximum tested concentration did not induce 80-90% of cytotoxicity compared to the negative control in the experiment with 4 hour exposure with metabolic activation as only 69% cytotoxicity was observed, or the precipitation of the tested substance, and it was less than 10 mM, 2 mg/mL or 2 µL/mL;

b) it is not reported if the positive control induced responses that are compatible with those generated in the historical positive control database and if it induced less than 90% of cytotoxicity compared to the negative control;

c) there are limited data on the cytotoxicity as only cytotoxicity of the highest evaluated concentration is reported, and the mutation frequency for the treated and control cultures were not reported.

29 The information provided does not cover the specifications required by the OECD TG 490.

30 Therefore, the information requirement is not fulfilled.

### *3.4. Study design*

31 To fulfil the information requirement for the Substance, either the *in vitro* mammalian cell gene mutation tests using the hprt and xprt genes (OECD TG 476) or the thymidine kinase gene (OECD TG 490) are considered suitable.

32 In the comments to the draft decision, you agree to perform a new study according to OECD TG 490.

## 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 requests.

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.

| Registrant Name | Registration number | Highest REACH Annex applicable to you |
|---|---|---|
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |

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).