EUROPEAN CHEMICALS AGENCY

Helsinki, 21 February 2020

Addressees
Registrants of JS_EC_701-281-9 listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of a decision
17 October 2018

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Propionaldehyde, reaction product with formaldehyde
EC number: 701-281-9
CAS number: NS

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

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of ***26 November 2021***.

A. Requirements applicable to all the Registrants subject to Annex IX of REACH

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, with the Substance;

B. Requirements applicable to all the Registrants subject to Annex X of REACH

1. Long-term toxicity to sediment organisms (Annex X, section 9.5.1.; test method: Sediment-water Chironomid toxicity using spiked sediment (OECD 218) or Sediment-water Lumbriculus toxicity test using spiked sediment (OECD 225) or Sediment-water Chironomid life-cycle toxicity test using spiked water or spiked sediment (OECD 233)) with the Substance.

Conditions to comply with the requests

Each addressee of this decision is bound by the requests for information corresponding to the REACH Annexes applicable to their own registered tonnage of the Substance at the time of evaluation of the jointly submitted dossier.
To identify your legal obligations, please refer to the following:

- you have to comply with the requirements of Annexes VII to IX of REACH, if you have registered a substance at 100-1000 tpa;
- you have to comply with the requirements of Annexes VII to X of REACH, if you have registered a substance at above 1000 tpa.

Registrants are only required to share the costs of information they are required to submit to fulfil the information requirements for their registration.

The Appendices state the reasons for the requests for information to fulfil the requirements

set out in the respective Annexes of REACH.

The Appendix entitled Observations and technical guidance addresses the generic approach for the selection and reporting of the test material used to perform the required studies and provides generic recommendations and references to ECHA guidance and other reference documents.

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

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.

Approved[1] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

[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 A: Reasons for the requirements applicable to all the Registrants subject to Annex IX of REACH

This decision is based on the examination of the testing proposals you submitted.

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

An appropriate *in vivo* somatic cell genotoxicity study is an information requirement under Section 8.4., Column 2, Annex IX to REACH if there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII and there are no appropriate results already available from an *in vivo* somatic cell genotoxicity study.

You have submitted a testing proposal for an *in vivo* mutagenicity test according to OECD Guideline 489 (*In Vivo* Mammalian Alkaline Comet Assay), with the justification: "*An Ames test in accordance with OECD Guideline 471 was performed using Salmonella typhimurium strains TA97a, TA98, TA100, TA102 and TA1535, with and with metabolic activation. The study showed positive results in Salmonella typhimurium strains TA97a, TA100 and TA102, both with and without metabolic activation. Therefore, the Ames test was judged to be positive and further in vivo testing is required in accordance with column 2 of Annex IX of the REACH Regulation. On this basis, the registrant considers the testing proposal for an in vivo mutagenicity (Comet) test justified*".

Your dossier contains positive results for the *in vitro* gene mutation study in bacteria (*In vitro* Bacterial Reverse Mutation Assay according to OECD TG 471, [redacted] 2010) and *in vitro* cytogenicity (*In Vitro* Mammalian Chromosome Aberration Test according to OECD TG 473, [redacted] 2010) tests. The positive *in vitro* results raise concerns on gene mutation and chromosomal aberration. Also, your dossier contains an *in vivo* mammalian somatic cell study: cytogenicity / erythrocyte micronucleus (*In Vivo* Mammalian Erythrocyte Micronucleus Test according to OECD TG 474, [redacted] 2013) conducted with the Substance providing negative results. This *in vivo* study is not appropriate to address both concerns relating to the positive *in vitro* results. It addresses only the concern relating to chromosomal aberration but not the concern relating to the gene mutation.

Therefore, further *in vivo* testing is needed and you have submitted a testing proposal for an *in vivo* mutagenicity test according to the OECD Guideline 489 (*In Vivo* Mammalian Alkaline Comet Assay) to be performed with the Substance. You did not specify the species to be used for testing. You did not specify the route for testing.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Genetic toxicity *in vivo*. 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.

Study design

The proposed test is an appropriate test to further investigate effects on gene mutations *in vivo* as described in the ECHA Guidance R.7a[2].

[2] ECHA Guidance R.7a, Section R.7.7.1 and Figure R.7.7.

According to the test method OECD TG 489, the test must 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 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.

Germ cells

A subsequent germ cell genotoxicity study (TGR/OECD TG 488, or CA on spermatogonia/OECD TG 483) may still be required under Annex IX of REACH, in case 1) an *in vivo* genotoxicity test on somatic cell is positive, and 2) no clear conclusion can be made on germ cell mutagenicity.

> Therefore, you may consider to collect the male gonadal cells collected from the seminiferous tubules (as described by e.g. O'Brien *et al.*[3]) in addition to the other aforementioned tissues, as it would optimise the use of animals. You can prepare the slides for male gonadal cells and store them for up to 2 months, at room temperature, in dry conditions and protected from light. Following the generation and analysis of data on somatic cells, in accordance to Annex IX, Section 8.4., column 2, you should consider analysing the slides prepared with gonadal cells. 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.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed study.

[3] O'Brien, J.M., Beal, M.A., Gingerich, J.D., Soper, L., Douglas, G.R., Yauk, C.L., Marchetti, F. (2014) Transgenic Rodent Assay for Quantifying Male Germ Cell Mutant Frequency. J. Vis. Exp. (90), e51576, doi:10.3791/51576

Appendix B: Reasons for the requirement applicable to all the Registrants subject to Annex X of REACH

This decision is based on the examination of the testing proposals you submitted.

1. Long-term toxicity testing to sediment organisms (Annex X, Section 9.5.1.)

Long-term toxicity testing to sediment organisms is a standard information requirement in Annex X to REACH.

You have submitted a testing proposal for this endpoint. You propose to conduct the study according to the test method Sediment-water Chironomid toxicity using spiked water (OECD TG 219).

ECHA agrees that you must conduct a sediment toxicity study to further investigate long-term toxicity to sediment organisms.

The choice of the appropriate test method depends on the properties and use patterns of the Substance. In general, the sediment spike route is most relevant for industrial chemicals. The methods: Sediment-water Chironomid toxicity test using spiked sediment (OECD TG 218), Sediment-water *Lumbriculus* toxicity test using spiked sediment (OECD TG 225) and Sediment-water Chironomid life-cycle toxicity test using spiked water or spiked sediment (OECD TG 233) are recommended for continuous and intermittent release of chemicals and as such are intended to simulate accumulated levels of chemicals persisting in the sediment. On the other hand, the OECD TG 219 using spiked water is most relevant for spray drift applications as it simulates a pesticide type spray drift event.

You have proposed to conduct the study using the test method OECD TG 219 without providing any specific justification for the chosen test method. According to the uses reported in the technical dossier the registered substance has no spray drift applications.

Taking into account the uses of the Substance, the proposed guideline OECD TG 219 is not the most appropriate. The test methods OECD TG 218, OECD TG 225 and OECD TG 233 (using spiked sediment exposure) are considered the most appropriate guidelines.

Under Article 40(3)(d), your originally proposed test is rejected and you are requested to carry out one of the tests indicated above with the Substance according to Article 40(3)(c).

Appendix C: Procedural history

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 30 October 2018, following the necessary clarification of the identity of your substance.

ECHA held a third party consultation for the testing proposals from 10 December 2018 until 24 January 2019. ECHA did not receive information from third parties.

For the purpose of the decision-making, this decision does not take into account any updates of registration dossiers after the date on which you were notified the draft decision according to Article 50(1) of REACH.

ECHA notified you of the draft decision and invited you to provide comments within 30 days of the notification.

ECHA did not receive any comments within the 30-day notification period.

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 D: Observations and technical guidance

1. This testing proposal examination decision does not prevent ECHA from initiating compliance checks at a later stage on the registrations present.

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 your Member State(s).

3. Test guidelines, GLP requirements and reporting

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

   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.

   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: 'How to report robust study summaries'[4].

4. Test material

   Selection of the test material(s)

   The registrants of the Substance are responsible for agreeing on the composition of the test material to be selected for carrying out the tests required by the present decision. The test material selected must be relevant for all the registrants of the Substance, i.e. it takes into account the variation in compositions reported by all members of the joint submission. The composition of the test material(s) must fall within the boundary composition(s) of the Substance.

   While selecting the test material you must take into account 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. Any constituents that have harmonised classification and labelling according to the CLP Regulation (Regulation (EC) No 1272/2008) must be identified and quantified using the appropriate analytical methods.

   The OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, Number 11 [ENV/MC/CHEM(98)16] requires a careful identification of the test material and description of its characteristics. In addition, the Test Methods Regulation (EU) 440/2008, as amended by Regulation (EU) 2016/266, requires that "*if the test method is used for the testing of a* [...] *UVCB* [...] *sufficient information on its composition should be made available, as far as possible, e.g. by the chemical identity of its constituents, their quantitative occurrence, and relevant properties of the constituents*".

[4] https://echa.europa.eu/practical-guides

In order to meet this requirement, all the constituents of the test material used for each test must be identified as far as possible. For each constituent the concentration value in the test material must be reported in the Test material section of the endpoint study record.

Technical reporting of the test material

The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and their concentration values. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[5].

5. List of references of the ECHA Guidance and other guidance/ reference documents[6]

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 in this decision.

ECHA Read-across assessment framework (RAAF, March 2017)[7]

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

OECD Guidance documents

[5] https://echa.europa.eu/manuals
[6] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[7] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

Guidance Document on aqueous –phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD23.

Appendix E: List of the registrants to which the decision is addressed and the corresponding information requirements applicable to them

Registrant Name	Registration number	(Highest) Data requirements to be fulfilled
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Note: where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas the decision is sent to the actual registrant.