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Helsinki, 09 September 2022

Addressees
Registrants of Pt_cpd_EC237-706-5_PMC2016 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
17/11/2021

Registered substance subject to this decision ("the Substance")
Substance name: Tetraammineplatinum dichloride
EC number: 237-706-5

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

DECISION ON TESTING PROPOSAL(S)

Based on Article 40 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below by ***16 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. Transgenic rodent somatic and germ cell gene mutation assays (triggered by Annex VII, Section 8.4., column 2) test method: OECD TG 488 in transgenic rats, oral route on the following tissues: liver and kidney.

The reasons for the request is 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.

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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 decision
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 decision

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Reasons for the request related to the information under Annex VII of REACH

1. Transgenic rodent somatic and germ cell gene mutation assays

1 Further mutagenicity studies must be considered under Annex VII to REACH in case of a positive result in an in vitro gene mutation study in bacteria (Section 8.4., Column 2).

2 Your dossier contains positive results for the in vitro gene mutation study in bacteria (OECD TG 471, 1980a, 1979 and 2004) and positive results for the in vitro gene mutation in mammalian cells (OECD TG 490, 2017; OECD TG 476, 1998a and 1998b) which raise the concern for gene mutation.

3 Therefore, the concern for gene mutation remains and further mutagenicity studies must be considered under Annex VII.

1.1. Information provided to fulfil the information requirement

4 Your dossier also contains an adequate in vivo mammalian alkaline comet assay ("comet assay", OECD TG 489, 2020). Nevertheless, you have submitted a testing proposal for a Transgenic rodent somatic and germ cell gene mutation assay to be performed with the Substance in liver and kidney cells.

5 You provided the following justification, in relation to the comet assay (2020) available in the dossier: "*Negative results were obtained* […] *for comets in stomach, duodenum and liver, but an equivocal response was reported for comets in kidney of male rats. The equivocal conclusion was based on the fact that, although there were significant (up to 4-fold) increases in % Tail DNA compared to vehicle control responses, and a dose response, the % Tail DNA frequencies fell within the laboratory's historical control range. However, that historical control range was constructed from a small number of previous studies in the rat kidney (n=30; historical control data from experiments performed in Feb 2012 – July 2019) and was quite wide.* […] *DNA strand breaks (comets) are an indicator of more permanent genetic changes (e.g. mutations), but may be effectively repaired or may be lethal. This result therefore needs to be further investigated, and assessment of whether these DNA strand breaks are converted to gene mutations is considered an appropriate follow up. Therefore an in vivo gene mutation assay in transgenic rats is proposed*."

6 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.

7 ECHA understands that your dossier already contains one *in vivo* mutagenicity study (comet assay) and that you report that this study gives equivocal results in kidney cells. You therefore consider that further mutagenicity studies are necessary to enable you to conclude whether the Substance has the property investigated or not. ECHA agrees that the results of the *in vivo* mutagenicity study (comet assay) are not conclusive and further *in vivo* investigation in somatic cells is therefore necessary to address the potential for gene mutation.

1.2. Test selection

8 According to the Guidance on IRs & CSA, Section R.7.7.6.3 the Transgenic rodent somatic and germ cell gene mutation assay ("TGR assay", OECD TG 488) is suitable to investigate the concern on gene mutation.

1.3. Specification of the study design

9 You proposed testing in the rat. According to the test method OECD TG 488, the test can be performed in transgenic mice or rats. However, because the comet assay with the equivocal results was done in kidney cells of male rat it is necessary to perform the TGR assay in male rats. Therefore, the TGR assay must be performed in transgenic male rats.

10 You proposed testing by the oral route. According to the test method OECD TG 488, test substance is usually administered orally.

11 Based on TG 488, you are requested to follow the 28+28d regimen, as it permits the testing of mutations in somatic tissues and as well as in tubule germ cells from the same animals.

12 You proposed to include a parallel toxicokinetic study for the purpose of demonstrating that adequate target tissue exposure to the test substance has been achieved. Because toxicokinetic study is not an information requirement under the REACH Regulation, ECHA considers that it is at your discretion to include a parallel toxicokinetic study.

13 According to the test method OECD TG 488, the test must be performed by analysing tissues from liver as slowly proliferating tissue and primary site of xenobiotic metabolism. You proposed to analyse tissues from liver and kidney. You justify the additional kidney tissue with the equivocal response reported in kidney cells of male rats in the comet assay (2020). ECHA agrees that it is of relevance to analyse the kidney tissue in male rats based on the equivocal results in the comet assay.

1.3.1. Germ cells

14 You may consider collecting the male germ cells (from the seminiferous tubules) at the same time as the other tissues, in order to limit additional animal testing. 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 (at or below −70 ºC). This duration is sufficient to allow you or ECHA to decide on the need for assessment of mutation frequency in the collected germ 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.

1.4. Outcome

15 Your testing proposal is accepted under Article 40(3)(a) and you are requested to conduct the test with the Substance, as specified above.

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).

All Guidance on REACH is 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

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 17 November 2021.

ECHA held a third-party consultation for the testing proposal(s) from 25 November 2021 until 10 January 2022. ECHA did not receive information from third parties.

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

ECHA notified you of the draft decision and invited you to provide comments.

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend the request.

In your comments on the draft decision, you also requested an extension of the deadline to provide information from 18 to 30 months from the date of adoption of the decision. You provided documentary evidence from a test laboratory indicating the scheduling timelines for the study in question to justify why an extension to the deadline is needed. In your documentary evidence, it is further explained how the specificities of the test design, in particular the additional analysis of rat kidney tissues, impact the timeline.

On this basis, ECHA has granted the request and extended the deadline to 30 months.

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: Addressees 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;

Registrant Name	Registration number	Highest REACH Annex applicable to you
[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[2].

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 and other parameters relevant for the property to be tested.

This information is needed to assess 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[3].

[2] https://echa.europa.eu/practical-guides
[3] https://echa.europa.eu/manuals