EUROPEAN CHEMICALS AGENCY

Helsinki, 10 February 2020

Addressees
Registrants of JS_HMX/Octogen listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
10/07/2013

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine
EC number: 220-260-0
CAS number: 2691-41-0

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

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of **16 November 2020**.

A. Requirements applicable to 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, EU B.13/14. /OECD TG 471), using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102 with the Substance.

2. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method EU C.3./OECD TG 201) with the Substance

Conditions to comply with the requests

Each addressee of this decision is bound by the requests for information listed above.

Appendix A to this decision states the reason for the request for information.

The test material used to perform the required studies must be selected and reported in accordance with the specifications prescribed in the Appendix entitled Observations and technical guidance.

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 requests to comply with Annex VII of REACH

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 1 to 10 tonnes or more per year must contain, as a minimum, the information specified in Annex VII to the REACH Regulation.

1. *In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.)

An *in vitro* gene mutation study in bacteria is a standard information requirement in Annex VII to REACH.

In the registration dossier you have provided five studies "equivalent or similar to OECD Guideline 471 (Bacterial Reverse Mutation Assay)" as a weight of evidence approach to cover this information requirement.
We have assessed the information and noted the following shortcomings.

(a) Weight of Evidence

You have adapted the standard information requirement according to Annex XI, Section 1.2. Weight of evidence (WoE) of REACH, by providing five negative Bacterial Reverse Mutation Assays in your dossier. The assays are with the Substance and with the following strains:

i. 1977 study: TA 98, TA 100, TA 1535, TA 1537 and TA 1538
ii. 1980 study: TA 98, TA 100, TA 1535, TA 1537 and TA 1538
iii. 1984 study: TA 98, TA 100, TA 1535, TA 1537 and TA 1538
iv. 1992 study: TA 98 and TA 100
v. 1999 study: TA 98 and TA 100

Annex XI, Section 1.2 states that there may be sufficient WoE from several independent sources of information leading to assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

According to ECHA Guidance R.4.4, a WoE adaptation involves an assessment of the relative values/weights of the different sources of information submitted based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance of the information for the given regulatory endpoint. Subsequently, relevance, reliability, consistency and results of these lines of evidence must be balanced in order to decide whether they provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

In the present case, the WoE adaptation may allow concluding on gene mutation of the Substance in bacteria, if the sources of information provide sufficient information on the dangerous property foreseen to be investigated in an *in vitro* gene mutation study in bacteria performed in accordance with the OECD TG 471 (1997). One of the key parameters of this test guideline includes that the test must be performed with 5 strains: four strains of *S. typhimurium* (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101).

We have assessed to what extent the sources of information submitted enable a conclusion on this dangerous property and identified the following deficiency:

The reported data for the studies you have provided did not include results for the appropriate 5 strains, that is the required fifth strain, *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli*

WP2 uvrA (pKM101).

As there is no source of information in your dossier which investigates the fifth strain, it is not possible to evaluate the possible hazardous property for gene mutation in bacteria covered by this information requirement. Therefore, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular hazardous property foreseen to be investigated in an OECD TG 471.

Your adaptation is rejected and the information requirement is not fulfilled

(b) Other data

In your dossier you also provide the following information:

(i.) Two *in vitro* gene mutation studies in mammalian cells with the analogue substance perhydro-1,3,5-trinitro-1,3,5-triazine (EC no 204-500-1) and with the Substance; and

(ii.) Two *in vivo* studies (micronucleus (OECD TG 474) and rodent dominant lethal (OECD TG 478) studies) with the analogue substance perhydro-1,3,5-trinitro-1,3,5-triazine (EC no 204-500-1).

Under REACH the study provided must be an *in vitro* gene mutation study in bacteria.

However, the above studies do not address the key parameters foreseen to be investigated in an OECD TG 471 study. More specifically, the provided *in vitro* information (i.) relate to a different test from the OECD TG 471 as these studies investigate mammalian cells and not bacteria, and the *in vivo* studies (ii.) do not investigate gene mutation but chromosomal aberration. Therefore, the studies in (ii.) are not appropriate to clarify potential positive results in the fifth strain of the *in vitro* gene mutation study in bacteria.

Therefore, the information requirement is not fulfilled.

To fulfil the information requirement for the Substance, the *in vitro* gene mutation study in bacteria (OECD TG 471) should be performed using one of the following strains: *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102.

2. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)

Growth inhibition study aquatic plants is a standard information requirement in Annex VII of REACH.

You have provided:

- a key study by [redacted] (publication, 1997) not performed according to any recommended guideline;
- a supporting study by [redacted] (publication, 1978) performed according to the Algal Assay Procedure: Bottle Test (U.S EPA, 1971).

Although you do not explicitly claim an adaptation, ECHA understands that the information provided was submitted in order to meet the required information by way of adaptation under Annex, Section XI 1.1.2. This adaptation rule enables registrants to claim that the data from experiments not carried out according to GLP or the test methods referred to in Article 13(3) can be considered equivalent to data generated by those test methods where a number of cumulative conditions are met, in particular:

1. Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3),
2. Adequate and reliable documentation of the study is provided.

OECD TG 201/EU C.3 are the recognised methods for this information requirement. Both methods specify that the test endpoint is inhibition of growth, expressed as the logarithmic increase in biomass during the exposure period. Additonally, one of the validity criteria of these methods is that the mean coefficient of variation for section-by-section specific growth rates (days 0-1, 1-2, 2-3 and 3-4, for 96-hour tests) in the control cultures should not be above 35%. Another requirement of the the test methods is that there must be analytical monitoring of exposure concentrations.

On the study by [redacted] (1997):

- you report that the key parameter investigated is the inhibition of growth after 96 hours based on growth rate. However, the publication by [redacted] (1997) specifies that the endpoint measured in this study is % inhibition of growth (i.e. yield) after 96 hours of exposure;
- you report that an analytical determination of exposure concentrations was conducted. However, the publication by [redacted] (1997) only refers to the analytical determination of TNT and its metabolites but not of HMX. For HMX, only results expressed as nominal concentrations are reported in the publication;
- no data on section-by-section (days 0-1, 1-2, 2-3 and 3-4) specific growth rates are available.

On the study by [redacted] (1978):

- you report that the key parameter investigated is the inhibition of growth after 96 hours based on cell numbers (i.e. yield);
- you report that the publication by [redacted] (1978) does not specify if an analytical monitoring of exposure concentrations was conducted;
- no data on section-by-section (days 0-1, 1-2, 2-3 and 3-4) specific growth rates are available.

We have assessed the information provided in your technical dossier and in the corresponding publications and we identified the same issues in both studies:

A. The key parameter investigated is the inhibition of growth after 96 hours (i.e. 96h-EC50) based on yield rather than growth rate (logarithmic increase in biomass). Therefore these studies do not provide an adequate coverage of the key parameter foreseen to be investigated in the corresponding test methods referred to in Article 13(3).

B. No data is available on the analytical monitoring of exposure concentrations. Therefore these studies do not provide a reliable coverage of the reported key parameter.

C. No data on section-by-section specific growth rates are available. Therefore these published studies do not provide adequate documentation to verify whether all validity criteria of the test methods referred to in Article 13(3) were fulfilled. In particular, the documentation is insufficient to verify if:
   - the biomass in the control cultures increased exponentially by a factor of at least 16 within the 72-hour test period (i.e. specific growth rate ≥ 0.92 /day);
   - the mean coefficient of variation for section-by-section specific growth rates

(days 0-1, 1-2, 2-3 and 3-4, for 96-hour tests) in the control cultures did not exceed 35%.

Therefore, your adaptation is rejected and the information requirement is not fulfilled.

Appendix B: Procedural history

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 the REACH Regulation.

The compliance check was initiated on 08 November 2018.

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 within 30 days of the notification.

ECHA did not receive any comments within the 30 days.

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

ECHA received proposals for amendment and modified the draft decision by adding the information request for an In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.) under A.1.

ECHA invited you to comment on the proposed amendments and referred the modified draft decision to the Member State Committee.

You did not provide any comments on the proposed amendment(s).

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-67 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix C: Observations and technical guidance

1. The substance subject to the present decision is provisionally listed in the Community rolling action plan (CoRAP) for the start of substance evaluation in 2020.

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

3. 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 the Member States.

4. 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 shall 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[2]'.

5. Test material

   Selection of the test material

   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 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.

   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.

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

Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[3].

6. List of references of the ECHA Guidance documents[3]

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 in this decision.

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)4

Physical-chemical properties
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.

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.

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

Appendix D: 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 fufilled
[redacted]	[redacted]	[redacted]