EUROPEAN CHEMICALS AGENCY

Helsinki, 22 September 2017

Addressee: [redacted]

Decision number: CCH-D-2114371729-35-01/F
Substance name: Hexahydro-1,3,5-trimethyl-1,3,5-triazine
EC number: 203-612-8
CAS number: 108-74-7
Registration number: [redacted]
Submission number: [redacted]
Submission date: 26/08/2016
Registered tonnage band: Over 1000

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

1. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a second species (rabbit), oral route with the registered substance;**

2. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce some toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation; and**
   - **Cohorts 2A and 2B (Developmental neurotoxicity).**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI to the REACH Regulation. To ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective annex, and adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by **30 March 2020**. You also have to update the chemical safety report, where relevant.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and advice and further observations are provided in Appendix 3.

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.

Authorised[1] by Claudio Carlon, Head of Unit, Evaluation E2

[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

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Pre-natal developmental toxicity studies (test method EU B.31./OECD TG 414) on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

The technical dossier contains information on a pre-natal developmental toxicity study in rats by the oral route using the registered substance as test material.

However, there is no information provided for a pre-natal developmental toxicity study in a second species.

You have sought to adapt this information requirement according to Annex XI, Section 3.2.(a). You provided the following justification for the adaptation:

"...The REACH legal text indicates that the study on a second species can be omitted if, taking account the outcome of the first test and all other relevant available data, an adaptation pursuant to REACH Annex X, Section 8.7, Column 2 or pursuant to REACH Annex XI can be justified. No Column 2 adaptations are relevant under Annex X, as the substance is not known to be a genotoxic carcinogen, not known to be a germ cell mutagen, nor does the substance meet the criteria of low toxicological activity or no systemic adsorption. A waiver for omission of a second pre-natal developmental toxicity study is instead presented in accordance with substance tailored exposure driven testing, REACH Annex XI (3.2a)..."

"...No significant exposure during manufacture and identified uses is anticipated as the operational conditions and risk management measure implemented in support of the qualitative risk characterisation are designed to render exposure to the substance as negligible...The strict operational conditions and risk management measures prescribed for the leading health effect are designed to render exposure to the substance as negligible...The use of this substance is restricted to the industrial sector..."

"...The registrant has derived a DNEL based on the results of an OECD 422 study (NOAEL ≥100 mg/kg bw/day) and an OECD 414 study on a single species (rat) (NOAEL ≥120 mg/kg bw/day), which has only been used as a supporting DNEL for quantitative confirmation that the qualitative operational conditions and risk management measures protect against the effects seen in the OECD 422 study. Additionally, no effects on reproduction or development were observed in either study and the DNEL was derived from the NOAEL related to repeated dose toxicity. The registrant considers that the footnote to Annex XI 3.2 (a) (ii) clearly does not limit the application of this waiver to pre-natal developmental toxicity testing on a second species.

There is no increased uncertainty resulting from the omission of the additional OECD 414 study. Sections 9 and 10 of the Chemical Safety Report prescribe a comprehensive suite of operational conditions and risk management measures for all identified uses of the substance. When considering all the data presented in the risk assessment at present, conducting the additional OECD 414 study will not alter the current approach to risk management..."

"...The risk characterisation ratios for long-term systemic effects via the inhalation route were well below 1 for all identified uses of this substance, indicating that risks are adequately controlled. This quantitative assessment was conducted to ensure that the operational conditions and risk management measures prescribed as part of the qualitative risk assessment also controlled the other significant health hazards associated with the substance, in this case specific target organ toxicity – repeated exposure category 2."

However, ECHA notes that your adaptation does not meet the general rule for adaptation of Annex XI, Section 3.2.(a) because the first and third criteria are not met.

(i) The first criterion (i) of Annex XI, Section 3.2. (a) requires that the results of the exposure assessment covering all relevant exposures throughout the life cycle of the substance demonstrate the absence of or no significant exposure in all scenarios of the manufacture and all identified uses. You have estimated exposure levels via inhalation by using tier 1 exposure modelling tool (ECETOC TRA version 3). You should demonstrate that no significant exposure occurs. For PROCs 4 and 8a this has not been achieved (see (ii) below). ECETOC TRA version 3 is a conservative model for estimating exposure and according to ECETOC TRA version 3: Technical Report No. 114, July 2012, the tool provides few opportunities for the exposure assessor to provide exposure modifiers in their assessment (a banding approach for reporting vapour pressure, technical measures for controlling inhalation limited to local exhaust ventilation). The Registered Substance falls in the band of low vapour pressure (340Pa at 20^0C), but falls close to the medium vapour pressure band (threshold 500Pa at 20^0C). In the context of determining no significant exposure, ECHA does not consider the use of a tier 1 model with few input parameters and a substance vapour pressure close to the cut-off for the next vapour pressure band that would yield a 5-fold increase in the estimated inhalation exposure for PROCs 4 and 8a to be a thorough and rigorous exposure assessment. To demonstrate absence of or no significant exposure as part of a thorough and rigorous exposure assessment, higher tier exposure modelling or preferably measured data should be used.

(ii) The third criterion (iii) of Annex XI, Section 3.2.(a) requires that the results of the exposure assessment show that exposures are always well below the derived PNECs or DNELs. The DNEL (based on a screening study) was calculated as 0.35 mg/m^3. For the PROCs that indicate potential for exposure [PROCs 4 and 8a], the estimated exposure concentrations reported in the CSR were [redacted] mg/m^3 and [redacted] mg/m^3, with risk characterisation ratios of [redacted] and [redacted], respectively. Hence, based on the information provided in the active technical dossier, the estimated exposure concentrations cannot be considered as being "*well below*" the derived DNEL.

For the adaptation set in Annex XI, Section 3.2.(a) to be fulfilled, all conditions (i) to (iii) need to be met. Hence since the first and third criteria are not met, Annex XI, Section 3.2.(a) is not fulfilled. Therefore, your adaptation of the information requirement is rejected.

In your comments to the draft decision you indicated that you would like "*to consider strengthening the waiver argument by providing higher-tier exposure data to confirm compliance with Annex XI, Section 3.2(a) criteria i and iii*". ECHA notes your intention to strengthen your adaptation according to the general rules contained in Annex XI of the REACH Regulation. ECHA notes that for any such adaptation to comply with the respective information requirement, it needs to (1) be scientifically justified, referring and conforming to the appropriate rules in the respective annex, and (2) be supported with adequate and reliable documentation. As part of the follow-up evaluation phase, pursuant to Article 42 of the REACH Regulation, ECHA will only assess the latest update you submit, for compliance with the REACH requirements after the deadline stated in the decision.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

The test in the first species was carried out by using a rodent species (rat). According to the test method EU B.31./OECD 414, the rabbit is the preferred non-rodent species. On the basis of this default assumption, ECHA considers that the test should be performed with rabbit as a second species.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a second species (rabbit) by the oral route.

2. Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

The basic test design of an extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X. If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

a) The information provided

You have not provided any study record of an extended one-generation reproductive toxicity study in the dossier that would meet the information requirement of Annex X, Section 8.7.3.

In the technical dossier you have provided a key study record for a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD TG 422) ([redacted], 2010). You also provided the following justification:

"Whilst it is acknowledged that the available OECD 422...does not address all aspects of reproduction and development that can be derived from an OECD 443 study, the available study is sufficient in order to conclude that no reproductive toxicity was observed at any dose level tested...No observed adverse effect levels (NOAELs) for reproductive and developmental parameters, based on actual dose ingested, were ≥100 mg/kg bw/day...Whilst the OECD 422 study has some limitations compared to the higher-tier OECD 443 study, safe use has been demonstrated when considering the full human health hazardous property profile of MMA triazine derived from the entire toxicological database. Additionally, the OECD 414 pre-natal developmental toxicity, both the maternal and developmental NOAEL were ≥120 mg/kg bw/day, with no maternal or developmental adverse effects noted in the study. The leading health effects identified for MMA triazine are skin corrosion, eye damage and sensitisation (Skin Corr. 1C, Eye Damage 1 and Skin Sens. 1A), which would not change regardless of the outcome of the OECD 443 study proposed for this tonnage band. The leading health effects do not have a threshold and the substance is therefore considered "high hazard" due to the potency of the effects observed. As there was no applicable dose-response relationship, no quantitative DNEL/DMEL can be derived. As a result of this hazard profile, human health risk assessment has to be conducted qualitatively. A DNEL of 0.353 mg/m3 has been derived for long-term systemic effects via the inhalation route based on the results of the OECD 422 study."

Reproduction toxicity is a separate information requirement/hazard class and a different property of a substance than those local effects the substance is already classified for. Thus, skin corrosion, eye damage, or skin sensitisation are not properties that allow an adaptation for information on reproductive toxicity.

The available OECD TG 422 study does not provide the information required by Annex X, Section 8.7.3. because it does not cover key elements, such as exposure duration, life stages and statistical power of an extended one-generation reproductive toxicity study. More specifically, the main missing key elements are: 10 weeks pre-mating exposure duration, at least 20 pregnant females per group, and an extensive postnatal evaluation of the F1 generation. In addition, there is a particular concern for developmental neurotoxicity according to column 2 of Annex X, Section 8.7.3. and information for those properties are missing.

Additionally, you have sought to adapt this information requirement Annex XI, Section 3.2.(a). You provided the following justification for the adaptation:
"In support of the qualitative risk assessment conducted for this substance, a supporting exposure assessment and risk characterisation was conducted for long-term exposure via the inhalation route. This quantitative assessment was conducted to ensure that the operational conditions and risk management measures prescribed as part of the qualitative risk assessment also controlled the other significant health hazards associated with the substance, in this case specific target organ toxicity – repeated exposure category 2. The quantitative risk characterisation ratios for all identified uses of the substance were <1, indicating that risks are adequately controlled throughout the substance's life cycle..."

"No significant exposure during manufacture and identified uses is anticipated as the operational conditions and risk management measure implemented in support of the qualitative risk characterisation are designed to render exposure to the substance as negligible..."

"Whilst the registrant has derived a DNEL from a screening test for reproductive toxicity, this has only been used as a supporting DNEL for quantitative confirmation that operational conditions and risk management measures protect against the effects seen in the OECD 422 study. Additionally, no effects on reproduction were observed in the screening test and the DNEL was derived from the NOAEL related to repeated dose toxicity. The registrant considers that the footnote to Annex XI 3.2 (a) (ii) does not consider situations where the exposure to a substance can be mitigated due to other hazardous properties constituting the leading health effect of the substance, in this case a full suite of qualitative primary hazard conclusions for the substance.There is no increased uncertainty resulting from the omission of the OECD 443 studies. Sections 9 and 10 of the Chemical Safety Report prescribe a comprehensive suite of operational conditions and risk management measures for all identified uses of the substance. When considering all the data presented in the risk assessment at present, conducting the OECD 443 study will not alter the current approach to risk management."

"The risk characterisation ratios for long-term systemic effects via the inhalation route were well below 1 for all identified uses of this substance, indicating that risks are adequately controlled. In conclusion, the registrant believes that instead of recommending that further animal testing be conducted, consideration should be given to the hazardous properties of MMA triazine, namely it is a corrosive and sensitising substance and this is the leading health effect."

However, your adaptation does not meet the general rule for adaptation of Annex XI; Section 3.2.(a), because all three criteria (i, ii and iii) are not met:

(i) As already explained above, under the pre-natal developmental toxicity study (section "1." above, criterion 3.2(a)(i) is not met.

(ii) According to footnote (1) of the second criterion (ii) for 3.2.(a), "*a DNEL derived from a screening test for reproductive/developmental toxicity shall not be considered appropriate to omit a prenatal developmental toxicity study or a two-generation reproductive toxicity study*". You argue that this footnote "*does not consider situations where the exposure...can be mitigated due to other hazardous properties... in this case a full suite of qualitative primary hazard conclusions for the substance".* ECHA notes that this criterion specifically refers to the DNEL and/or PNEC derivation, hence the other qualitative hazard conclusions reported for the other endpoints in the CSR cannot be used to omit the extended one-generation study. Moreover, as already indicated above, in the technical dossier there is no fertility study that fulfils this endpoint. Hence, you cannot claim that the other hazardous properties constitute "*the leading health effect of the substance"*, as there is clearly no scientific basis to substantiate such a claim. With specific reference to the footnote, ECHA notes that the only DNEL in the dossier is based on a screening study, so criterion 3.2(a)(ii) is not met.

(iii) As already explained above, under the pre-natal developmental toxicity study (section "1." above), criterion 3.2(a)(iii) is not met.

For the adaptation set in Annex XI, Section 3.2. (a) to be fulfilled, all conditions (i) to (iii) need to be met. Hence, since all three criteria are not met, Annex XI, Section 3.2.(a) is not fulfilled. Therefore, your adaptation of the information requirement is rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint. Thus, an extended one-generation reproductive toxicity study according Annex X, Section 8.7.3. is required. The following refers to the specifications of this required study.

b) The specifications for the study design

Premating exposure duration and dose-level setting

To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to ECHA Guidance, the starting point for deciding on the length of premating exposure period should be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

The highest dose level shall aim to induce some toxicity to allow comparison of effect levels and effects of reproductive toxicity with those of systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

If there is no existing relevant data to be used for dose level setting, it is recommended that results from a conducted range-finding study (or range finding studies) are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

Cohorts 2A and 2B

The developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity as described in column 2 of 8.7.3., Annex X. When there are triggers for developmental neurotoxicity, both the Cohorts 2A and 2B are to be conducted as they provide complementary information.

ECHA notes that existing information on the registered substance itself derived from an available *in vivo* study - combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD TG 422) ([redacted] 2010) - shows evidence of *"(minimal-slight) degeneration of the retina (atrophy)"* in 3 out of 5 females examined at 100 mg/kg bw/day (highest dose). Based on these findings you classify the substance for specific target organ toxicity repeated exposure 2 (STOT RE 2) *"eyes (degeneration of retina in females), oral route."*

According to ECHA's Guidance document[2], concerns justifying the inclusion of the developmental neurotoxicity cohorts include: *"abnormalities observed in the central nervous system or nerves"*, such as *"changes in brain weight or in specific neural areas not secondary to body weight"*, *"changes in brain volume or specific neural areas, obtained e.g. from morphometry/stereology measurements"* and *"(histo)pathological findings in brain, spinal cord and/or nerves (e.g. sciatic nerve)"*. In the screening study ([redacted] 2010) severe effects were observed in the retina (leading to STOT RE 2 classification). Because the retina is considered as being part of the central nervous system and is actually brain tissue, there is a particular concern for developmental neurotoxicity due to degeneration of retina.

ECHA concludes that the developmental neurotoxicity Cohorts 2A and 2B need to be conducted because there is a particular concern on (developmental) neurotoxicity based on the results from the above-identified *in vivo* study - combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD TG 422) ([redacted] 2010).

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Species and route selection

According to the test method EU B.56./ OECD TG 443, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in rats.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

c) Outcome

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443), in rats, oral route, according to the following study-design specifications:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce some toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation; and
- Cohorts 2A and 2B (Developmental neurotoxicity).

[2] ECHA's Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7a: Endpoint specific guidance, version 6.0, July 2017 (https://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf/e4a2a18f-a2bd-4a04-ac6d-0ea425b2567f)

Notes for your consideration

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B and Cohort 3 if new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the new information shows triggers which are described in column 2 of Section 8.7.3., Annex X and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017). You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented. The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 10 March 2017.

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.

ECHA took into account your comments and did not amend the request(s).

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

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

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

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.

3. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.