Helsinki, 30 August 2016

[redacted]

Decision number: CCH-D-2114342672-51-01/F
Substance name: tetrahydrofurfuryl alcohol
EC number: 202-625-6
CAS number: 97-99-4
Registration number: [redacted]
Submission number: [redacted]
Submission date: 04.04.2013
Registered tonnage band: 100 to 1000 tonnes per year

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. **Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral route with the registered substance, specified as follows:**
   - **At least two 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) with extension to mate the Cohort 1B animals to produce the F2 generation;**
   - **Cohorts 2A and 2B (Developmental neurotoxicity); and**
   - **Cohort 3 (Developmental immunotoxicity);**
2. **Classification and labelling in accordance with the CLP Regulation (Annex VI, Section 4)**

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 of the REACH Regulation. In order 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 an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by **6 September 2018**. You shall also 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. 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, shall 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 Ofelia Bercaru, Head of Unit, Evaluation E3

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

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH 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 IX of the REACH Regulation, if the available repeated dose toxicity studies (e.g. 28-day or 90-day studies, OECD TGs 421 or 422 screening studies) indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity. If the conditions described in column 2 of Annex IX are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

1.1. The information requirement

ECHA considers that adverse effects on reproductive organs or tissues and other concerns in relation with reproductive toxicity are observed. More specifically, you submitted five studies showing adverse effects on reproductive organs:
(i) a combined repeated-dose and reproductive/developmental toxicity screening study was performed (OECD TG 422, reliability 1), showing effects on testis at 150 mg/kg bw/day or above;
(ii) a 28-day repeated dose toxicity study was performed (similar to an OECD TG 407, reliability 2) showed signs of toxicity to testes at 150 mg/kg bw/day, and above;
(iii) three 90-day repeated dose toxicity studies (OECD TG 408, oral route with relialibity 2; OECD TG 411, dermal route with relialibity 2; and OECD TG 413 inhalation route with relialibity 2) that consistently indicated adverse effects on male reproductive organs.

Pursuant to Annex IX, Section 8.7.3. an extended one-generation reproductive toxicity study is thus an information requirement for registrations of the registered substance.

In the technical dossier you have provided a study record for a key study, which is a combined repeated-dose and reproductive/developmental toxicity screening study (OECD TG 422), and you have also provided four supporting studies which are repeated-dose toxicity studies (as listed above). However, these studies do not provide the information required by Annex IX, Section 8.7.3., because they do 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: at least 20 pregnant females, and an extensive postnatal evaluation of the F1 generation.
In addition, the criteria for extension of the Cohort 1B are met for the registered substance and there is a particular concern for developmental neurotoxicity and/or developmental immunotoxicity according to column 2 of Annex IX, Section 8.7.3. and information for those properties are missing. 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 IX, Section 8.7.3.

The technical dossier does not contain an adaptation in accordance with column 2 of Annex IX, Section 8.7.3. or with the general rules of Annex XI for this standard information requirement.

ECHA notes that you have submitted a "Repr. 2" self-classification. However ECHA points out that the substance has a harmonised classification as Repr. 1B/ H360 Df, and that the substance is listed in Annex VI of the CLP Regulation (Harmonised Classification and Labelling). While you have not explicitly claimed an adaptation, ECHA notes the column 2 provision of Annex IX, 8.7. stating that "*[I]f a substance is known to cause developmental toxicity, meeting the criteria for classification as toxic for reproduction category 1A or 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment, then no further testing for developmental toxicity will be necessary. However, testing for effects on fertility must be considered.*" ECHA therefore considers whether testing for effects for fertility is necessary.
In view of the consistency, nature and the potency of the effects seen on male reproductive organs (see above), which trigger the information requirement of extended one-reproductive toxicity study at Annex IX, ECHA further considers that there is a particular concern for effects on fertility which needs to be addressed to inform on the proper risk management measures regarding effects on fertility.

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 to Annex IX, Section 8.7.3. is required. The following refers to the specifications of this required study.

1.2. The specifications for the required study

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 the ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.6 (version 4.1, October 2015), the starting point for deciding on the length of the 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 if 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* R.7a, chapter R.7.6 (version 4.1, October 2015). In this specific case, animals of Cohort 1B are mated to produce the F2 generation and, thus, the premating exposure duration will be 10 weeks for these Cohort 1B animals and the fertility parameters will be covered allowing an evaluation of the full spectrum of effects on fertility in these animals. Thus, shorter premating exposure duration for parental (P) animals may be considered. However, the premating period shall not be shorter than two weeks and must be sufficiently long to reach a steady-state in reproductive organs as advised in the ECHA Guidance. The consideration should take into account whether the findings from P animals after a longer premating exposure duration would provide important information for interpretation of the findings in F1 animals, e.g. when considering the potential developmental origin of such findings as explained in ECHA guidance.

Extension of Cohort 1B

If the column 2 conditions of 8.7.3., Annex IX are met, Cohort 1B must be extended, which means that the F2 generation is produced by mating the Cohort 1B animals. This extension provides information also on the sexual function and fertility of the F1 animals.

The use of the registered substance is leading to significant exposure of professionals because the registered substance is used by professionals (wide dispersive uses of the registered substance in agrochemicals and adhesives) with the corresponding PROCs 4 and 8a.

Furthermore, from the repeated-dose and toxicity studies (OECD TG 422, OECD TG 407, OECD TG 408, OECD TG 413), there are indications for endocrine-disrupting modes of action because of the following observations in reproductive/ endocrine organs and parameters due to hormonal change: reduced prostate, epididymal and testes weights, necrosis of the seminiferous tubular epithelium and lower sperm production, prolonged oestrus cycle and gestation length.

Therefore, ECHA concludes that Cohort 1B must be extended to include mating of the animals and production of the F2 generation because the uses of the registered substance is leading to significant exposure of professionals and there are indications of modes of action related to endocrine disruption from the available *in vivo* on the registered substance.

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

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 IX. 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 derived from available *in vivo* 28-day repeated dose toxicity and inhalation 90-day repeated dose toxicity studies show evidence of neurotoxicity on the function of the central nervous system as stated by you: *"increase in motor activity in females of the 150 mg/kg group, increase in motor activity accompanied with decrease in motor activity and prone position in both sexes of the 600 mg/kg group were noted."* Also "*[T]he decrease in the grip strength of hindlimbs in the male of the 600 mg/kg group was considered to be [a] finding related to the effect on the function of the central nervous system". "The predominant clinical finding was intermittent whole-body spasms in all treated groups that were frequent and exposure-related. Hypoactivity and excessive grooming were occasionally observed in males and females at 500 ppm. One hour after exposure, concentration-related hyperactivity was reported in all treated groups, and yellow urogenital matting and salivation at 500 ppm."*
ECHA notes that similar findings were reported in the combined repeated-dose and reproductive/ developmental toxicity screening study, OECD TG 422.

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* studies on the registered substance.

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

Cohort 3

The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity as described in column 2 of 8.7.3., Annex IX.

ECHA notes that existing information on the registered substance derived from an available *in vivo* 28-day repeated dose toxicity, combined repeated-dose and reproductive/ developmental toxicity screening (OECD TG 422) and oral 90-day repeated dose toxicity studies show evidence of substance-related effects on thymus, which are not secondary according to you: *"... decrease in the thymus weight in both sexes of the 600 mg/kg group, and histopathologically, atrophy of thymus were noted. These thymic changes were considered to be not due to the secondary effect caused by toxicological stress but direct effect of the test substance on thymus because the enlargement of the adrenal gland was not accompanied."*
ECHA notes that similar findings were reported in the combined repeated-dose and reproductive/ developmental toxicity screening study, OECD TG 422.

ECHA concludes that the developmental immunotoxicity Cohort 3 needs to be conducted because there is a particular concern on (developmental) immunotoxicity based on the results from the above-identified *in vivo* studies on the registered substance.

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 4.1, October 2015) R.7a, chapter 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.

1.3. Outcome

Based on the available information, 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:

- At least two 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) with extension to mate the Cohort 1B animals to produce the F2 generation;
- Cohorts 2A and 2B (Developmental neurotoxicity); and
- Cohort 3 (Developmental immunotoxicity).

2. Classification and labelling in accordance with the CLP Regulation (Annex VI, Section 4)

Pursuant to Article 10(a)(iv) of the REACH Regulation the technical dossier shall include the classification and labelling for the registered substance in accordance with the CLP Regulation, as specified in Annex VI, Section 4 of the REACH Regulation.

You have classified the registered substance as Repr. 2.with specific effects: "*Males: lower prostate, epididymal and testes weights, necrosis of the seminiferous tubular epithelium and lower sperm production. Females: prolonged oestrus cycle and gestation length. Foetal resorption or mummification and dead pups on PND 1*".

However the registered substance has a harmonised classification as Repr. 1B/ H360 Df pursuant to Annex VI of the CLP Regulation,which is legally binding (Article 4(3) of the CLP Regulation). The self-classification in the technical dossier proposes a less stringent classification, which is not acceptable according to the CLP Regulation.

As explained above, the information provided for the registered substance in the technical dossier does not meet the information requirement.

Therefore, pursuant to Article 41(1)(a) and (3) of the REACH Regulation, you are requested to submit the following information for the registered substance subject to the present decision: a classification and labelling in accordance with the CLP Regulation.

This information must be provided in Section 2 of the IUCLID dossier.

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 19 November 2015.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation:

ECHA notified you of the draft decision and invited you to provide comments. ECHA did not receive any comments by the end of the commenting period.

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) for amendment.
ECHA received proposal(s) for amendment and did not modify the draft decision.

ECHA invited you to comment on the proposed amendment(s).

ECHA referred the 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 during its MSC-48 meeting and ECHA took the decision according to Article 51(6) 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 request(s) in this decision, or to fulfil otherwise the information requirement(s) 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 test(s) 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 test(s) 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 test(s) must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.