EUROPEAN CHEMICALS AGENCY

Helsinki, 4 July 2019

Addressee: [redacted]

Decision number: CCH-D-2114465658-33-01/F
Substance name: 2-benzofuran-1,3-dione, addition product with 2-(2-hydroxyethoxy)ethanol, ethoxylated
EC number: 701-218-5
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 29/01/2018
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. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) in rats with the registered substance**

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

You are required to submit the requested information in an updated registration dossier by **12 July 2021** except for the information requested under point 1. for a sub-chronic toxicity study (90-day) which shall be submitted in an updated registration dossier by **13 July 2020.** You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

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.

This decision does not address the information requirement of the Extended one-generation reproductive toxicity study according to Annex X, Section 8.7.3. of the REACH Regulation.

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 **Wim De Coen**, Head of Unit, 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 1: Reasons

1. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)

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.

A "sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have not provided any study record of an sub-chronic toxicity study by the oral route in the dossier that would meet the information requirement of Annex IX, Section 8.6.2. Instead you have provided the following adaptation:

"Waiving for OECD TG 408: A subacute oral toxicity study (28-days; [redacted] 2010) with the test substance revealed no toxicological effects for female rats and only slight liver findings for male rats in the high dose group (1000 mg/kg). The study director concluded on these liver findings in males (centrilobular vacuolisation that proved to be hepatocellular fat deposition, and eosinophilia) that they might be indicative for an (adverse) influence on fat metabolism. The derived NOAELs were thus 1000 mg/kg bw for females and 300 mg/kg bw for males. However, it is not assumed that a longer study duration (i.e. 90 days) would substantially change the outcome and thus the hazard assessment of the substance. Taking into account that for the substance no risk characterization has to be done (since it does not meet the criteria for classification as dangerous (in accordance with Directive 67/548/EEC) with regard to human health or is assessed to be a PBT or vPvB) and having regard to the objective and general rule stipulated in REACH that testing on vertebrate animals animal shall be undertaken only as a last resort, a subchronic (90-days) repeated dose toxicity study with the test substance is omitted".

In support of your adaptation you have provided the following study record:

- Key study: Subacute repeated dose 28-day toxicity study in rats, oral gavage (OECD 407, certified GLP) with the registered substance, [redacted], 2010, reliability 1.

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.2. (weight of evidence). Hence, ECHA has evaluated your adaptation with respect to this provision.

An adaptation pursuant to Annex XI, Section 1.2. requires sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property with respect to the information requirement in question including an adequate and reliable documentation while the information from each single source alone is regarded insufficient to support this notion.

Your weight of evidence adaptation needs to address the specific dangerous (hazardous) properties of the registered substance with respect to a sub-chronic toxicity study OECD TG

408). Relevant elements are in particular exposure route, duration and levels, two genders, sensitivity and depth of investigations to detect specific organ toxicity.

However, ECHA notes that your adaptation does not meet the criteria for an adaptation based on weight of evidence (Annex XI, Section 1.2), because the exposure duration of the study on which the argumentation is based is less than 90 days and the number of animals per dose group is significantly lower than in the 90 day sub-chronic toxicity study (OECD TG 408). Therefore, the sensitivity of the provided 28-day study is much lower than that of a 90-day study.

Hence, the source of information you provided, together with your justification for the adaptation, do not allow to assume/conclude on the dangerous (hazardous) property of the registered substance with respect to the information requirement for Annex IX, Section 8.6.2. Therefore, the general rules for adaptation laid down in Annex XI, Section 1.2. of the REACH Regulation are not met and your adaptation of the information requirement is rejected.

In your comments to the initial draft decision, you proposed to perform a 90-day oral study with the analogue substance 2-benzofuran-1,3-dione, addition product with (2R,3R,4R,5S)-hexane-1,2,3,4,5,6-hexol and 2-(2-hydroxyethoxy)ethanol, propoxylated (EC number: 601-238-3) to fulfil the information requirements for this endpoint. You also provided a justification for your read-across approach. ECHA acknowledges your intention to update your dossier with read-across information and a reference to a testing proposal for an analogue substance. However, although read-across between the two substances could be plausible, there is no information currently available to fulfil the information requirement for a sub-chronic toxicity study.

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.

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. More specifically, even though the information indicates that human exposure to the registered substance by the inhalation route is likely (uses include industrial and non-industrial/professional spraying), the available oral 28-day study gives an indication of potential systemic toxicity (liver findings) that requires further information on repeated dose toxicity by the oral route.

Hence, the test shall be performed by the oral route using the test method OECD TG 408.

According to the test method OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

Notes for your considerations:

The Extended one-generation reproductive toxicity study (EOGRTS) according to Annex X, Section 8.7.3. is not part of this decision because the results of the Sub-chronic toxicity study (90-day) are considered crucial to inform on the study design of the EOGRTS.

Therefore, the results of the 90-day should be used, among other relevant information, to decide on the study design of the EOGRTS.

ECHA may therefore launch a separate compliance check at a later stage addressing the EOGRTS information requirement.

Alternatively, you may also consider submitting a testing proposal for an EOGRTS together with the results of the requested 90-day. The testing proposal should include a justification for its study design following ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017), taking into account the results of the 90-day.

2. 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 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.

In your comments to the initial draft decision, you proposed to perform a second species pre-natal developmental toxicity study with the analogue substance 2-benzofuran-1,3-dione, addition product with (2R,3R,4R,5S)-hexane-1,2,3,4,5,6-hexol and 2-(2-hydroxyethoxy)ethanol, propoxylated (EC number: 601-238-3) to fulfil the information requirements for this endpoint. You also provided a justification for your read-across approach. ECHA acknowledges your intention to update your dossier with read-across information and a reference to a testing proposal for an analogue substance. However, although read-across between the two substances could be plausible, there is currently no information available to fulfil this information requirement.

Accordingly, 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 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: OECD TG 414) in a second species (rabbit) by the oral route.

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 1 April 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.

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

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 will result in a notification to the enforcement authorities of your Member State.

3. In carrying out the tests required by the present decision, it is important to ensure that the particular sample of substance tested 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. If the registration of the substance covers different grades, the sample used for the new tests must be suitable to assess these.

   Furthermore, 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.