Helsinki, 11 March 2019

Addressee: [redacted]

Decision number: TPE-D-2114461502-56-01/F
Substance name: 3,6-bis(4-chlorophenyl)-1H,2H,4H,5H-pyrrolo[3,4-c]pyrrole-1,4-dione
EC number: 401-540-3
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 20/12/2017
Registered tonnage band: Over 1000

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation ((EC) No 1907/2006) (the REACH Regulation), ECHA examined your testing proposal(s) and decided as follows.

While your originally proposed test for Sub-chronic toxicity study (90-day), oral route (OECD TG 408) using the registered substance is rejected, you are requested to perform:

1. **Sub-chronic toxicity study (90-day), inhalation route (Annex IX, Section 8.6.2.; test method: OECD TG 413) in rats using the registered substance.**

Your testing proposal is accepted and you are requested to carry out:

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

The Sub-chronic toxicity study (90-day) by the inhalation route shall be performed before you conduct the pre-natal developmental toxicity study in point 2. After performing the 90-day study you shall reconsider the most appropriate route of exposure for the pre-natal developmental toxicity study.

You are required to submit the requested information in an updated registration dossier by **20 September 2021**.

The reasons for 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. The results of the Sub-chronic toxicity study (90-day) will be used, among other relevant information, to decide on the study design of the Extended one generation reproductive toxicity study. Therefore, your testing proposal for Extended one-generation reproductive toxicity study will be addressed after having received the results of the Sub-chronic toxicity study (90-day).

ECHA
EUROPEAN CHEMICALS AGENCY

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 Ofelia Bercaru, 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

The decision of ECHA is based on the examination of the testing proposals submitted by you and scientific information submitted by third parties.

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

a) Examination of the testing proposal

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.

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. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for a sub-chronic toxicity study (90 day) in rats by the oral route according to OECD TG 408.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Sub-chronic toxicity (90-day): oral. ECHA notes that 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.

You proposed testing by the oral route. It is noted that testing by the oral route of administration could be considered. In the technical dossier and/or chemical safety report the registered substance is indicated to be a powder. However, judging from the information you provided, the inhalation route is considered a more appropriate route of administration for testing. In the technical dossier and/or chemical safety report uses with spray application are reported that may generate aerosols of inhalable size. Information provided on granulometry indicates that the substance includes a significant proportion ([redacted] %) of particles of an inhalable size (<13.2 µm). Hence, the criteria listed in Annex IX, Section 8.6.2., column 2 with regard to the appropriateness of testing by the inhalation route are met. In addition, there is a potential concern for local respiratory tract effects following inhalation exposure because the substance is of low water solubility and consequently there is a potential for accumulation of the substance in the lungs. However, the potential concern for effects in the respiratory tract is not assessed in the dossier. Consequently, information on the oral route is considered to be less relevant than information obtained by the inhalation route to investigate local respiratory tract effects.

Therefore, ECHA considers that the inhalation route is the most appropriate route of administration for testing. Hence, the test shall be performed by the inhalation route using the test method OECD TG 413.

You proposed testing in rats. According to the test method OECD TG 413 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

There is evidence that the lower respiratory tract is the primary site of deposition and retention of the registered substance because the substance is insoluble in water and respirable. Therefore, you are requested to perform BAL fluid analysis as specified in the OECD TG 413.

In your comments to the draft decision you indicated your agreement with ECHA's assessment. You also requested an extension of the deadline to provide the information from the requested sub-chronic (90-day) toxicity study. Among the arguments provided to support your request, you stressed that the properties of the registered substance require the inclusion of post-exposure periods of 1 month and possibly 6 months in the in vivo experimental phase of the study to investigate the clearance kinetics and to conduct lung burden measurements. The OECD test guideline 413 adopted on 25 June 2018 indicates that "*Measurements of lung burden, which inform on pulmonary deposition and retention of particles in the lung, should be done when a range-finding study or other relevant information suggests that inhaled test particles are poorly soluble and likely to be retained in the lung*" and to that purpose "*one or two satellite groups of 5 males per concentration may be added to measure lung burden at different post=exposure time points*". The decision on the inclusion of additional post-exposure observation (PEO) time points and on the spacing of the PEO time points is at your discretion, taking into account the information obtained in a range-finding study and considering whether lung clearance and lung burden measurements can be aligned.

The request for the extension of the deadline is further addressed below in section "Deadline to submit the requested information".

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

A third party has indicated that "*The substance is insoluble in water and organic solvent. A study of toxicokinetics in the rat is reported, using single oral gavage doses of 100 and 1000 mg/kg bw/d of the substance (radiolabelled). Based on the results of this study, it is concluded that the substance is not bioavailable. Very small amounts of radioactivity detected in the urine were attributed to faecal contamination from the metabolism cage. Levels of radioactivity detected in the blood were only marginally above the limit of detection. The substance is of low acute oral and inhalation toxicity and is not an irritant or sensitiser. A 28-day toxicity study reports a NOAEL of 1000 mg/kg bw/d in the absence of any adverse effects of treatment. Findings in this study were limited to red discoloration of the faeces (consistent with excretion of the test material (a red dye) and staining of the skin and do not therefore provide any evidence of systemic bioavailability. A developmental toxicity study in the rat is also available similarly reports a NOAEL of 1000 mg/kg bw (the highest dose level) and no evidence of systemic bioavailability. The substance is not classified for human health endpoints and therefore meets the definition of a 'low (sub)acute toxicity profile' according to Taylor et al (2014), Taylor & Andrew (2017). It is therefore unlikely that the proposed 90-day study will demonstrate a lower NOAEL for human-relevant effects, particularly given the demonstrated absence of systemic bioavailability following oral dosing. The value of the proposed 90-day study is therefore questioned.*"

ECHA understands that the third party comments refers to the specific rules for adaptation from the standard information requirement of Annex IX, 8.6.2 for a sub-chronic toxicity study listed in Annex IX, 8.6.2 column 2, 4th indent whereby the sub-chronic toxicity study does not need to be conducted if "*the substance is unreactive, insoluble and not inhalable and there is no evidence of absorption and no evidence of toxicity in a 28-day 'limit test', particularly if such a pattern is coupled with limited human exposure*". Based on the information provided in the technical dossier, the substance subject to this decision is of limited solubility in water. The particle size reported in the technical dossier indicates a D50 of 13.2 micrometer, suggesting that the substance may be inhaled. No evidence of absoprtion and of toxicity was detected up to the limit dose in a 28-day repeated dose toxicity study conducted in rats via the oral route with the substance subject to this decision. Based on the information on uses reported in the technical dossier, exposure of professional and consumers may occur. Since this substance is not classified for any hazard, no exposure scenarios characterising the extent of such exposure were required to be developed and reported. In the absence of this information ECHA considers that it is not possible to confirm that only limited human exposure occurs. This assessment is in line with the statement made by the registrant in its considerations on alternative to conducting testing whereby it is indicated that "*the substance is inhalable and human expsoure is not limited*". Therefore, ECHA concludes that the conditions for adapting the information requirement of Annex IX, 8.6.2 for a sub-chronic toxicity study (90- day) according to the provisions of Annex IX, 8.6.2 column 2, 4th indent are not all met.

c) Outcome

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the additional study with the registered substance subject to the present decision: Sub-chronic toxicity study (90-day) in rats, inhalation route (test method: OECD TG 413) while your originally proposed test for Sub-chronic toxicity study (90-day) (test method: OECD TG 408) is rejected according to Article 40(3)(d) of the REACH Regulation.

Notes for your considerations:

You submitted a testing proposal for an Extended one-generation reproductive toxicity study (Annex X, 8.7.3.). However, this testing proposal is not addressed in this decision because the results of the Sub-chronic toxicity study (90-day) are considered crucial to inform on the study design of the Extended one-generation reproductive toxicity study. Therefore, you are required to perform the Sub-chronic toxicity study (90-day) first, and submit the results by the deadline indicated above.

Together with providing the results for the requested Sub-chronic toxicity study (90-day), you may also consider updating your testing proposal for the Extended one-generation reproductive toxicity study. The updated testing proposal should include a justification for the design of the Extended one-generation reproductive toxicity study 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 Sub-chronic toxicity study (90-day).

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

a) Examination of the testing proposal

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.

Pre-natal developmental toxicity studies on two species are part of the standard information requirements for 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 dossier contains a pre-natal developmental toxicity study in rats as first species. However, there is no information available for a pre-natal developmental toxicity study in a second species. Consequently there is an information gap for Annex X, Section 8.7.2. and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for a pre-natal developmental toxicity study in a second species (rabbits) according to OECD TG 414 by the oral route.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Sub-chronic toxicity (90-day): oral. ECHA notes that 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.

ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex X, Section 8.7.2. of the REACH Regulation.

You proposed testing with the rabbit as a second species. The test in the first species was carried out with rats. According to the test method OECD 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed with the rabbit as a second species.

You proposed testing by the oral route. Based on the information available in the dossier, ECHA agrees 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 solid, ECHA concludes that testing should be performed by the oral route.

Subsequent to a Proposal for Amendment (PfA) from a Member State Competent Authority, ECHA requests that you reconsider the most appropriate route after you have performed the 90-day study by inhalation. If there are clear indications, based on observed toxicity, that the registered substance has greater systemic bioavailability after inhalation exposure as compared with oral exposure, then you shall reconsider the route of exposure and use the route with greater systemic bioavailability of the substance for the pre-natal developmental toxicity study (PNDT).

In your comments to the PfA, you provided detailed scientific considerations for the choice of route of exposure. Summarising, you consider that the oral route remains most appropriate, whilst considering that, if the substance is considered to be orally non-bioavailable, you should determine the next steps based on all available data, including the results of the 90-day study. Thus you propose to remove the request for PNDT from this decision, and to address the PNDT endpoint in a subsequent decision. ECHA agrees that it is

essential to review all available data after the conduct of the 90-day study, and determine the most appropriate route of exposure at that time, as set out above. ECHA considers it is not necessary to remove the request for the PNDT from this decision, as you have sufficient time to review the results of the 90-day study before conducting the PNDT study.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

A third party has indicated that "*The substance is insoluble in water and organic solvent. A study of toxicokinetics in the rat is reported, using single oral gavage doses of 100 and 1000 mg/kg bw/d of the substance (radiolabelled). Based on the results of this study, it is concluded that the substance is not bioavailable. Very small amounts of radioactivity detected in the urine w3ere attributed to faecal contamination from the metabolism cage. Levels of radioactivity detected in the blood were only marginally above the limit of detection. The substance is of low acute oral and inhalation toxicity and is not an irritant or sensitiser. A 28-day toxicity study reports a NOAEL of 1000 mg/kg bw/d in the absence of any adverse effects of treatment. Findings in this study were limited to red discoloration of the faeces (consistent with excretion of the test material (a red dye) and staining of the skin, and do not therefore provide any evidence of systemic bioavailability. A developmental toxicity study in the rat is also available similarly reports a NOAEL of 1000 mg/kg bw (the highest dose level) and no evidence of systemic bioavailability. Taking into account the available toxicological data showing an absence of systemic toxicity and bioavailability, the proposed second species PNDT study is not required on scientific grounds and is not in the interests of animal welfare. It can be reliably predicted that a study will not demonstrate any relevant toxicological effects.*"

ECHA understands that the third party comments refers to the specific rules for adaptation from the standard information requirement of Annex X, 8.7 for a pre-natal developmental toxicity study in Annex X, 8.7.2 column 2, 3rd indent whereby the study does not need to be conducted if "*the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure*". According to the information provided in the technical dossier, the systemic bioavailability of the substance subject to this decision is limited after oral administration. No evidence of toxicity was detected up to the limit dose in a 28-day repeated dose toxicity study conducted in rats via the oral route with the substance subject to this decision. Based on the information on uses reported in the technical dossier, exposure of professional and consumers may occur. However, as this substance is not classified for any hazard, no exposure scenarios characterising the extent of such exposure were required to be developed and reported. In the absence of this information ECHA considers that it is not possible to confirm that there is no or no significant human exposure. Therefore, ECHA concludes that the conditions for adapting the information requirement of Annex X, 8.7.2 for a pre-natal developmental toxicity study according to the provisions of Annex X, 8.7 column 2, 3rd indent are currently not all met.

c) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are thus requested to carry out the proposed study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in a second species (rabbit), oral route (test method: OECD TG 414).

Notes for your consideration

You are reminded that before performing a pre-natal developmental toxicity study in a second species you must consider the specific adaptation possibilities of Annex X, Section 8.7., column 2 and general adaptation possibilities of Annex XI (e.g. Annex XI, Section 1.2.). If the results of the 90d-study with other information enable such adaptation, testing in the second species should be omitted and the registration dossier should be updated containing the corresponding adaptation statement.

Deadline to submit the requested Information

In the draft decision communicated to you the time indicated to provide the requested information from an inhalation sub-chronic toxicity study (90-day) was 12 months from the date of adoption of the decision. In your comments on the draft decision, you requested an extension of the timeline to 30 months. You sought to justify this request by referring to time required to complete the necessary administrative preparations, the need to develop a sensitive bioanalytical method and to conduct a dose-range-finding study. You also stressed that the properties of the registered substance require the inclusion of post-exposure periods of 1 month and possibly 6 months in the *in vivo* experimental phase of the study to investigate the clearance kinetics and to conduct lung burden measurements.

ECHA has taken the information provided in the comments into account and considers that the time periods for the individual steps (administration in total 6 months, range finding 8 months and main study 16 months) are overestimated. Therefore ECHA-S has partially granted the request. The Sub-chronic toxicity study (90-day) by the inhalation route shall be performed before you conduct the pre-natal developmental toxicity study. ECHA has set the deadline to provide all the information requested in this decision to 30 months.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 3 January 2018.

ECHA held a third party consultation for the testing proposals from 26 March 2018 until 11 May 2018. ECHA received information from third parties (see Appendix 1).

This decision does not take into account any updates after **3 September 2018**, 30 calendar days after the end of the commenting period.

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 amended the deadline.

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

ECHA received proposal(s) for amendment and modified the draft decision.

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

ECHA referred the draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-63 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided in your registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the 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 the Member States.

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.