EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000003130-92-06/F Helsinki, 20 August 2013

**DECISION ON A TESTING PROPOSAL SET OUT IN A REGISTRATION PURSUANT TO ARTICLE 40(3) OF REGULATION (EC) NO 1907/2006**

**For 2-{N-[2,6-Diamino-4-oxo-4H-pyrimidin-(5Z)-ylidene]-hydrazino}-5-methyl-benzenesulfonic acid, (EC No 700-002-8 ), registration number: [redacted]**

**Addressee: [redacted]**

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

I. Procedure

Pursuant to Article 40(1) of the REACH Regulation, ECHA has examined the following testing proposal submitted as part of the registration dossier in accordance with Articles 10(a)(ix) and 12(1)(d) thereof for 2-{N-[2,6-Diamino-4-oxo-4H-pyrimidin-(5Z)-ylidene]-hydrazino}-5-methyl-benzenesulfonic acid, (EC No 700-002-8), by [redacted] (Registrant).

- Developmental toxicity / teratogenicity study (OECD 414).

This decision is based on the registration dossier as submitted with submission number [redacted], for the tonnage band of 10 to 100 tonnes per year. This decision does not take into account any updates after 8 March 2013, the date upon which ECHA notified its draft decision to the Competent Authorities of the Member States pursuant to Article 51(1) of the REACH Regulation.

This decision does not imply that the information provided by the Registrant in his 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.

The examination of the testing proposal was initiated upon the date when receipt of the complete registration dossier was confirmed on 07 June 2012.

ECHA held a third party consultation for the testing proposal from 16 July 2012 until 30 August 2012. ECHA did receive information from third parties (see section III below).

On 21 November 2012 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision.

On 22 November 2012 ECHA received comments from the Registrant agreeing to ECHA's draft decision.

On 8 March 2013 ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals to amend the draft decision within 30 days of the receipt of the notification.

Subsequently, one Competent Authority of a Member State submitted a proposal for amendment to the draft decision.

On 11 April 2013 ECHA notified the Registrant of that proposal for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on that proposal for amendment within 30 days of the receipt of the notification.

ECHA reviewed the proposal for amendment received and decided not to amend the draft decision.

On 22 April 2013 ECHA referred the draft decision to the Member State Committee.

The Registrant did not provide any comments on the proposed amendment.

After discussion in the Member State Committee meeting on 11-14 June 2013, a unanimous agreement of the Member State Committee on the draft decision was reached on 13 June 2013. ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Decision

The originally proposed test for a pre-natal developmental toxicity study (Annex IX, 8.7.2.; test method: EU B.31/OECD 414) to be carried out using the registered substance 2-{N-[2,6-Diamino-4-oxo-4H-pyrimidin-(5Z)-ylidene]-hydrazino}-5-methyl-benzenesulfonic acid is rejected pursuant to Article 40(3)(d) of the REACH Regulation.

III. Statement of reasons

The decision of ECHA is based on the examination of the testing proposal submitted by the Registrant for the registered substance and scientific information submitted by third parties.

**1. Pre-natal developmental toxicity study**

a) Examination of the testing proposal

Pursuant to Article 40(3)(d) of the REACH Regulation, ECHA may reject a proposed test.

Data from a pre-natal developmental toxicity study is not a standard information requirement according to Annex VIII, 8.7.1 of the REACH Regulation. According to REACH Annex VIII 8, 8.7.1, column 2, a pre-natal developmental toxicity study may be proposed by the Registrant instead of the screening study "in cases where there are serious concerns about the potential for adverse effects on fertility or development". The standard information requirement is a screening study for reproductive/developmental toxicity (OECD421 or OECD 422). Such a study is not available in the dossier.

The Registrant states in Section 7.8.2 of the registration dossier that *"based on the log Pow of less than -1 and the absence of systemic toxicity at the limit dose of the subacute toxicity study, it is unlikely that the substance is taken up by the body in significant amounts and that therefore, effects on reproductive function - if any - are unlikely to be picked up in a screening study of low statistical power such as the OECD 421."* Furthermore, the Registrant mentions that *"Considering the log Pow, transfer of the test substance or metabolites into the milk and effects via lactation are not expected. Overall, as no effects on reproductive organs were observed upon subacute toxicity and as transfer into the milk is unlikely, a*

*developmental toxicity study (OECD 414) is considered the adequate study to fill the data gap for reproductive toxicity."*

The Registrant further argues why, for reasons of low toxicity and low availability of the substance from lactation, there is no need to conduct the screening study and therefore a prenatal developmental toxicity study is proposed. The Registrant also points out that the OECD 421/422 screening study would have low statistical power and therefore effects are unlikely to be seen. As a consequence, the Regisrant has waived the reproductive/ developmental toxicity screening study.

In view of the ECHA, it appears that the Registrant has demonstrated low toxicity in the 28-day repeated dose toxicity study where a NOAEL of 1000 mg/kg (highest dose tested) was obtained. This supports the Registrant's view that the substance is of low toxicity. Also acute toxicity tests (oral and dermal) show low toxicity ($LD_{50}$ in both is >2000 mg/kg). Although the observations from the subacute toxicity test and physico-chemical information imply low absorption from the gut, there are no toxicokinetic studies to corroborate that. The Registrant has not included any information in the dossier that raises concerns for general systemic toxicity.

With regard to the statistical power, the Registrant rightly points out that it is likely to be lower for the screening studies than for an OECD 414 study, which recommends that each test and control group should contain a sufficient number of females to result in approximately 20 female animals with implantation sites at necropsy, whereas an OECD 422 would contain only 8 animals per group. Also in the OECD 421 test guideline, which does not inspect developmental parameters, the number of animals per dose group would be only half of what is recommended in the OECD 414 test guideline. However, it is important to note that test protocols OECD 414 and OECD 421 examine the effects of different endpoints and, therefore, are not comparable as such.

The substance is a pigment, which is used in industrial and professional settings and in consumer products. In addition, articles handled by consumers contain the substance. Therefore, there is potential for wide dispersive exposure, which could potentially be a cause for concern.

However, the available toxicological information does not indicate the existence of serious, or even any, concerns relating to the potential for adverse effects on fertility or development. Therefore, the arguments given by the Registrant do not fulfil the criteria of Annex VIII column 2.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation. The information did not change ECHA's assessment of the testing proposal.

Third party information

In its comments, the third party mentions that *"Column 2 of Annex VIII of the REACH Regulation states that a screening study is not required if a pre-natal developmental toxicity study is available, or if a pre-natal developmental toxicity study is proposed due to 'serious concerns' for adverse effects on development. Chapter R7a (R.7.6.6.3) of the REACH guidance further notes that a pre-natal developmental toxicity study may be preferred to a screening study at this tonnage band, if Stage 1 and 2 assesment identifies a specific alert for developmental toxicity. This does not appear to be the case for this substance."*

The third party therefore proposes not to perform the study unless the Registrant is confident that they will, in the short term, be increasing manufacture/import such that it will be updating the dossier for this substance under Annex IX where the prenatal developmental toxicity study is a standard requirement.

ECHA acknowledges the third party opinion.

c) Outcome

The proposed test for a pre-natal developmental toxicity study (Annex IX, 8.7.2.; test method: EU B.31/OECD 414) to be carried out using the registered substance 2-{N-[2,6-Diamino-4-oxo-4H-pyrimidin-(5Z)-ylidene]-hydrazino}-5-methyl-benzenesulfonic acid is rejected pursuant to Article 40(3)(d) of the REACH Regulation.

IV. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Article 51(8) of the REACH Regulation. Such appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on the ECHA's internet page at http://echa.europa.eu/appeals/app_procedure_en.asp. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

[redacted]
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Director of Regulatory Affairs