EUROPEAN CHEMICALS AGENCY

Helsinki, 20 February 2020

Addressees
Registrants of [redacted] listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
10/06/2015

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: 5,12-dihydro-2,9-dimethylquino[2,3-b]acridine-7,14-dione
EC number: 213-561-3
CAS number: 980-26-7

Decision number: [Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/D)]

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of ***25 November 2022***.

A. Requirements applicable to all the Registrants subject to Annex VIII of REACH

1. Justification for an adaptation of a Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.) based on the study requested under Section C.; with the Substance

B. Requirements applicable to all the Registrants subject to Annex IX of REACH

1. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method OECD TG 414) in a first species (rat or rabbit), oral route with the Substance

C. Requirements applicable to all the Registrants subject to Annex X of REACH

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method OECD TG 414) in a second species (rat or rabbit), oral route with the Substance.

2. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) with the Substance in rats, oral route specified as follows:

    i. Ten weeks premating exposure duration for the parental (P0) generation;
    ii. Dose level setting shall aim to induce systemic toxicity at the highest dose level;
    iii. Cohort 1A (Reproductive toxicity);
    iv. Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.

    You must report the study performed according to the above specifications. Any expansion of the study design must be scientifically justified.

Conditions to comply with the requested information

Each addressee of this decision is bound by the requests for information corresponding to the REACH Annexes applicable to their own registered tonnage of the Substance at the time of evaluation of the jointly submitted dossier.
To identify your legal obligations, please refer to the following:

- You have to comply with the requirements of Annex VII and VIII of REACH, if you have registered a substance at 10-100 tpa;
- you have to comply with the requirements of Annexes VII, VIII and IX of REACH, if you have registered a substance at 100-1000 tpa;
- you have to comply with the requirements of Annexes VII to X of REACH, if you have registered a substance at above 1000 tpa.

Registrants are only required to share the costs of information that they are must submit to fulfil the information requirements for their registration.

The Appendix on general considerations addresses common arguments that are applicable throughout the present decision while the other Appendices state the reasons for the requests for information to fulfil the requirements set out in the respective Annexes of REACH.

The Appendix entitled Observations and technical guidance addresses the generic approach for the selection and reporting of the test material used to perform the required studies and provides generic recommendations and references to ECHA guidance and other reference documents.

You must submit the information requested in this decision by the deadline indicated above in an updated registration dossier and also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information. The timeline has been set to allow for sequential testing where relevant.

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.

Approved[1] under the authority of Christel Schilliger-Musset, Director of 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 on general considerations

(i) Assessment of the Weight of evidence adaptation under Annex XI, Section 1.2.

You have adapted the information requirements for a pre-natal developmental toxicity study in one species (a standard information requirement under Annex IX to REACH) and for a pre-natal developmental toxicity study in a second species and an extended one-generation reproductive toxicity study (standard information requirements under Annex X to REACH) by using weight of evidence (WoE) according to Annex XI, Section 1.2.

Annex XI, Section 1.2 states that there may be sufficient weight of evidence (WoE) from several independent sources of information leading to assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

In order to allow concluding on no reproductive toxicity (sexual function and fertility, and developmental toxicity) for the substance in a weight of evidence adaptation, the information in the justification must cover the key elements (parameters) foreseen to be investigated in PNDT studies requested and in an extended one-generation reproductive toxicity study with the test design as requested in this decision.

As a justification for your weight of evidence adaptation you provided in your registration dossier:

- Allegation of low toxicity (acute/sub-acute/sub-chronic effects, skin/eye irritation) among category members, which "*indicates that the substances of this category do not interact with living cells/tissues*"
- Allegation of low bioavailability based on a repeated dose toxicity study and low solubility in water and octanol.

In your comments on the initial draft decision, you refer to reproductive toxicity studies performed with different pigments, none of them showing adverse effects and you included a summary table listing 24 studies (OECD TG 414, 415, 421, 422) performed with 23 different pigments, belonging to 19 different pigment classes. The route of administration, NOAEL and study year are specified in that table.

You recognise that "*Even though they did not include specific pathological investigations regarding skeletal or visceral abnormalities, they still did not show any adverse effects on number or well-being of offspring*". You consider that "*This is a strong indication that no major abnormalities occurred regarding the prenatal development of these animals or the fertility of their parents*".

However, first, the information from repeated dose toxicity studies with your claim that "*the substances of this category do not interact with living cells/tissues*", and the solubility data, do not inform on intrinsic hazardous properties of the Substance regarding reproductive toxicity.

Second, the studies included in your dossier are indicating low toxicity of the substances, but you did not provide any justification for your claim that there is no interaction with living cells or tissues. The low solubility in water and octanol does not always mean that the substances have low solubility in biological fluids and are not bioavailable. In the absence of data demonstrating absence of bioavailability, it is not possible to conclude on bioavailability for all of the category members.

Third, you provided statements and studies that do not investigate and/or provide key elements for developmental toxicity or sexual function and fertility by mating and producing offspring. Specifically, there is no information on growth, survival, external, skeletal and visceral alterations in the developing foetuses in two two species and their relationship to maternal toxicity (key elements (parameters) in the pre-natal developmental study). Regarding to sexual function and fertility and toxicity to offspring, and their relationship to systemic toxicity, there is, among others, no information on key elements (parameters) of the extended one-heneration reproductive toxicity study (functional fertility (mating, gestation, delivery and lactation) and postnatal development of the F1 generation up to adulthood and histoapthology of their reproductive organs and tissue). In the absence of any information that is specifically required under the corresponding information requirements, your weight of evidence adaptations for Annex IX, section 8.7.2., Annex X, section 8.7.2. and Annex IX, section 8.7.3. are rejected and the information requirements are not met.

Fourth, within your weight of evidence adaptation, you refer to several sources of information stemming from substances of your category.

The sources of information included in your comments have the following deficiencies affecting their reliability:

Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide a justification for the read-across including a hypothesis, explanation of the rationale for the prediction of properties and robust study summary(ies) of the source study(ies).

i. All studies were performed with analogue substances. No justification for the selection of these substances was provided, and no read-across hypothesis was included. Only one of the substances included in your list of 24 pigments with studies on reproductive toxicity belongs to the group used for the grouping and read-across adaptation in your dossier (rejected for the reasons explained above).
Therefore the provided studies cannot be considered a reliable source of information.

ii. No adequate and reliable documentation of the source studies, in particular no robust study summaries, has been presented. The only information included on the study designs and outcomes are the test guideline, year and NOAEL. No other details on the studies were provided. Based on this limited amount of information it is not possible to conclude on the relevance or reliability of those studies.

Accordingly, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 414 or TG 443 study. Your adaptation is, therefore, rejected.

(ii) Assessment of the column 2 adaptation under Annex IX/X, Section 8.7.

In your dossier, you intend to demonstrate that your Substance is of low toxicological activity and that no systemic absorption occurs. However, for such adaptation claims the specific adaptation rule at Annexes IX/X, Section 8.7, Column 2, first paragraph, third indent applies. Hence, ECHA assesses below your adaptation according to this specific rule of adaptation.

According to Annex IX/X, Section 8.7., Column 2, first paragraph, third indent, the corresponding study does not need to be conducted if the substance is of low toxicological activity. This needs to be demonstrated with three concomitant criteria, two of them being:

i. that it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure; and
ii. that there is no or no significant human exposure.

In your dossier you provided:

i. A sub-chronic study performed with the Substance. The study suggests that the absorption of the Substance might be low (the Substance was not detected in blood and liver samples of exposed animals), but the information provided is not conclusive because it does not include, e.g., how long was the period between the last dose and collection of the samples or elimination rate data. Therefore, the information provided cannot be considered as proof of no systemic absorption.

ii. No detailed information on uses or exposure were included in the dossier. Based on the reported uses as colouring agent and pigment, significant human exposure is, however, likely.

Based on the above, your adaptation is rejected and information requirements are not met.

Appendix A: Reasons for the requests to comply with Annex VIII of REACH

In accordance with Articles 10(a) and 12(1) of REACH, a technical dossier registered at 10 to 100 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII and VIII to REACH.

1. Justification for an adaptation of the Screening for reproductive/ developmental toxicity (Annex VIII, Section 8.7.1.)

Screening for reproductive/developmental toxicity is a standard information requirement under Annex VIII to REACH. This information may take the form of a study record or a valid adaptation in accordance with either a specific adaptation rule under Column 2 of Annex VIII or a general adaptation rule under Annex XI.

The present decision requests the registrants concerned to generate and submit an extended one-generation reproductive toxicity study (EOGRTS) (see Section C.1). Once an EOGRTS is available, according to Column 2 of Annex VIII, Section 8.7.1. and in order to prevent unnecessary animal testing, a screening for reproductive/developmental toxicity does not therefore need to be conducted. While you still have to comply with the information requirement in Annex VIII, Section 8.7.1., you are requested to submit a justification for the adaptation based on Column 2 of that provision.

Appendix B: Reasons for the requests to comply with Annex IX of REACH

In accordance with Articles 10(a) and 12(1) of REACH, a technical dossier registered at 100 to 1000 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII-IX to REACH.

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

A Pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is a standard information requirement under Annex IX to REACH.

You have adapted this information requirement by using weight of evidence (WoE) according to Annex XI, Section 1.2 and ECHA understands that you have also adapted this information requirement by using an adaptation under Annex X, Section 8.7.2, column 2.

As explained in the Appendix on general considerations your adaptations are rejected and the information requirement is not fulfilled.

A PNDT study according to the test method OECD TG 414 should be performed in rat or rabbit as preferred species with oral[2] administration of the Substance.

[2] ECHA Guidance R.7a, Section R.7.6.2.3.2.

Appendix C: Reasons for the requests to comply with Annex X of REACH

In accordance with Articles 10(a) and 12(1) of REACH, a technical dossier at tonnage above 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII-X to REACH.

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

A Pre-natal developmental toxicity study in a second species is a standard information requirement in Annex X to REACH.

You have adapted this information requirement by using weight of evidence (WoE) according to Annex XI, Section 1.2 and ECHA understands that you have also adapted this information requirement by using an adaptation under Annex X, Section 8.7.2, column 2.

As explained in the Appendix on general considerations your adaptations are rejected and the information requirement is not fulfilled.

A PNDT study according to the OECD TG 414 study should be performed in rabbit or rat as the preferred second species, depending on the choice of species in the PNDT study in the first species (see section 1 of Appendix B).

The study shall be performed with oral[3] administration of the Substance.

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

The basic test design of an Extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is a standard information requirement in Annex X to REACH. Furthermore Column 2 of Section 8.7.3. defines when the study design needs to be expanded.

You have adapted this information requirement by using weight of evidence (WoE) according to Annex XI, Section 1.2 and ECHA understands that you have also adapted this information requirement by using an adaptation under Annex X, Section 8.7.2, column 2.

As explained in the Appendix on general considerations your adaptations are rejected and the information requirement is not fulfilled.

The specifications for the required study design

Premating exposure duration and dose-level setting

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 to obtain results adequate for classification and labelling and /or risk assessment. There is no substance specific information in the dossier supporting shorter premating exposure duration.[4]

Therefore, the requested premating exposure duration is ten weeks.

[3] ECHA Guidance R.7a, Section R.7.6.2.3.2.
[4] ECHA Guidance R.7a.

The highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects. A descending sequence of dose levels should be selected in order to demonstrate any dose-related effect and to establish NOAELs.

If there is no relevant data to be used for dose level setting, it is recommended that range-finding results are reported with the main study.

You have to provide a justification with your study results that demonstrates that the dose level selection meets the conditions described above.

Species and route selection

The study shall be performed in rats with oral[5] administration.

Requested cohorts

Cohort 1A and Cohort 1B without extension to mate the Cohort 1B animals to produce the F2 generation belong to the basic study design and shall be conducted.

Further expansion of the study design

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if relevant information becomes available from other studies or during the conduct of this study. Inclusion is justified if the available information meets the criteria and conditions which are described in Column 2, Section 8.7.3., Annex X. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in ECHA Guidance[6].

[5] ECHA Guidance R.7a, Section R.7.6.
[6] ECHA Guidance R.7a, Section R.7.6.

Appendix D: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of registration dossiers after the date on which you were notified the draft decision according to Article 50(1) of the REACH Regulation.

The compliance check was initiated on 14 January 2019.

ECHA notified you of the draft decision and invited you to provide comments within 30 days of the notification.

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 adopted the decision under Article 51(3) of REACH.

Appendix E: Observations and technical guidance

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

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. Test guidelines, GLP requirements and reporting

   Under Article 13(3) of REACH, all new data generated as a result of this decision needs to be conducted according to the test methods laid down in a European Commission Regulation or according to international test methods recognised by the Commission or ECHA as being appropriate.

   Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses shall be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

   Under Article 10 (a) (vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide: 'How to report robust study summaries'[7].

4. Test material

   Selection of the test material(s)

   The registrants of the Substance are responsible for agreeing on the composition of the test material to be selected for carrying out the tests required by the present decision. The test material selected must be relevant for all the registrants of the Substance, i.e. it takes into account the variation in compositions reported by all members of the joint submission. The composition of the test material(s) must fall within the boundary composition(s) of the Substance.

   While selecting the test material you must take into account the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected test material must contain that constituent/ impurity.

   Technical reporting of the test material

   The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and their concentration values. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

   Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[8].

[7] https://echa.europa.eu/practical-guides
[8] https://echa.europa.eu/manuals

5. List of references of the ECHA Guidance and other guidance/ reference documents[9]

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 in this decision.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 in this decision.

ECHA Read-across assessment framework (RAAF, March 2017)[10]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

OECD Guidance documents[11]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD23.
Guidance Document on Mammalian Reproductive Toxicity Testing and Assessment – No 43, referred to as OECD GD43.

[9] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[10] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[11] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Appendix F: List of the registrants to which the decision is addressed and the corresponding information requirements applicable to them

Registrant Name	Registration number	(Highest) Data requirements to be fufilled
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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Note: where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients, whereas the decision is sent to the actual registrant.