EUROPEAN CHEMICALS AGENCY

Helsinki, 12 August 2020

Addressees
Registrants of JS_76199-85-4_Isoind listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
24/04/2013

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: 2-cyano-2-[2,3-dihydro-3-(tetrahydro-2,4,6-trioxo-5(2H)-pyrimidinylidene)-1H-isoindol-1-ylidene]-N-methylacetamide
EC number: 278-388-8
CAS number: 76199-85-4

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

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 ***22 May 2023***.

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

1. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method OECD TG 476 or TG 490) with the Substance;

2. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method OECD 421/422) in rats, oral route with the Substance;

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

1. If the Substance does not include nanoforms: Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method OECD TG 408) in rats with the Substance;

   If the Substance does include nanoforms: Sub-chronic toxicity study (90-day), inhalation route (Annex IX, Section 8.6.2.; test method OECD TG 413) in rats with the Substance. The study must include measurements of lung burden and bronchoalveolar lavage fluid (BALF) analysis as described in the current version (25 June 2018) of the test guideline;

2. 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;

ECHA
EUROPEAN CHEMICALS AGENCY

Conditions to comply with the requests

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 Annexes 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.

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

The Appendix on general considerations addresses issues relevant for several requests 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.

Authorised[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.

EUROPEAN CHEMICALS AGENCY

Appendix on general considerations

(i) Assessment of the Grouping of substances and read-across approach, in light of the requirements of Annex XI, Section 1.5.

You seek to adapt the following standard information requirements by applying a read-across approach in accordance with Annex XI, Section 1.5:

- In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

ECHA has considered the scientific and regulatory validity of your read-across approach(es) in general before assessing the specific standard information requirements in the following appendices.

Grouping of substances and read-across approach

Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (addressed under 'Predictions for toxicological properties'').

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance[2] and related documents[3, 4].

A. Predictions for toxicological properties

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).[5]

You have provided studies conducted with a substance (Pigment Yellow 139, EC number 253-256-2) other than your Substance in order to comply with the REACH information requirements. You have not provided documentation as to why this information is relevant for your Substance and for the endpoints assessed in this decision.

In the absence of a read-across justification documentation, ECHA cannot verify that the properties of your Substance can be predicted from the data on the source substance(s).

[2] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals. 2008 (May) ECHA, Helsinki. 134. pp. Available online: https://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf/77f49f81-b76d-40ab-8513-4f3a533b6ac9

[3] Read-Across Assessment Framework (RAAF). 2017 (March) ECHA, Helsinki. 60 pp. Available online: Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across)

[4] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 (March) ECHA, Helsinki. 40 pp. Available online: https://doi.org/10.2823/794394

[5] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.6.1

B. Conclusions on the read-across approach

As explained above, you have not established that relevant properties of the Substance can be predicted from data on the analogue substance. Therefore, your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and your grouping and read-across approach is rejected.

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

Under 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. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

An *in vitro* gene mutation study in mammalian cells is a standard information requirement in Annex VIII to REACH in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test.

Your dossier contains negative results for both an Ames test and an *in vitro* cytogenicity study. Therefore, the information requirement is triggered.

You have provided an *in vitro* mammalian cell gene mutation test ([redacted] 2012) performed with an analogue substance.

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. As explained in the Appendix on general considerations your adaptation is rejected. Therefore, the information requirement is not fulfilled.

To fulfil the information requirement for the Substance, both the *in vitro* mammalian cell gene mutation tests using the hprt and xprt genes (OECD TG 476) and the thymidine kinase gene (OECD TG 490) are considered suitable.

2. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

A Screening for reproductive/developmental toxicity study (test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) is a standard information requirement under Annex VIII to REACH, if there is no evidence from analogue substances, QSAR or *in vitro* methods that the Substance may be a developmental toxicant.

You have provided a Screening for reproductive/developmental toxicity study ([redacted] 2013) performed with an analogue substance.

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. As explained in the Appendix on general considerations your adaptation is rejected. Therefore, the information requirement is not fulfilled.

A study according to the test method EU B.63/OECD TG 421 or EU B.64/OECD TG 422 must be performed in rats with oral[6] administration of the Substance.

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

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

Under 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 to IX to REACH.

1. **If the Substance does not include nanoforms: Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method OECD TG 408) in rats with the Substance; If the Substance does include nanoforms: Sub-chronic toxicity study (90-day), inhalation route (Annex IX, Section 8.6.2.; test method OECD TG 413) in rats with the Substance;**

A Sub-chronic toxicity study (90 day) is a standard information requirement in Annex IX to REACH.

You have provided a sub-acute (28-day) toxicity study ([redacted] 2000) with the Substance.

In addition you have provided an adaptation according to Column 2 of Annex IX, Section 8.6.2. stating that the substance is unreactive and no adverse effects were observed in the subacute oral toxicity study.

We have assessed this information and identified the following issue(s):

Annex IX column 2 adaptation not met

As provided in Annex IX, Section 8.6.2, Column 2, you may adapt the information requirement, provided you fulfil all the following the criteria, including:

(i) the Substance is unreactive and
(ii) there is no evidence of absorption,
(iii) particularly if such a pattern is coupled with limited human exposure.

You provided the following justification: "*In accordance with column 2 of EC regulation 1907/2006, testing of subchronic toxicity is not indicated if the substance is unreactive and no adverse effects were observed in the subacute oral toxicity study. In this case, the substance showed no indication of toxicity in the OECD 421 study and the analogue showed no toxic effects in a 28-day repeated dose toxicity study (OECD 407) at 1000 mg/kg bw. As discussed in the section of toxicokinetics, the substance is considered to be too insoluble for transport across biological membranes. Therefore, no testing of subchronic toxicity is considered necessary*".

In your comments on the initial draft decision you:

- argue that "*The substance* [...] *is not flammable, not soluble, is not skin sensitizing, not irritating, not genotoxic, not bacteriotoxic in the Ames test and it does not cause cytotoxicity other then incompatibility of cultivated cells with particles in general*";
- inform that you are planning to perform biodissolution studies to provide information on the (in)solubility of the Substance;
- include results of static solubility and dissolution kinetics studies performed with 14 different pigments;
- state that "*Spraying applications (PROC 7 and 11) occur at the professional user level at controlled conditions*";
- indicate that based on health surveillance examinations, adverse health

effects suspected to be related to several pigment exposure have not been observed among workers.

You have not demonstrated that all criteria of Column 2 are met:

(i) You did not demonstrate that there is no evidence of absorption. No studies investigating toxicokinetic properties such as absorption were included in your dossier.
Regarding your comments, ECHA notes that is at your discretion to generate and provide the necessary supporting information in order to justify your adaptation.
Further, ECHA notes that the study reports included in your comments do not contain any studies performed with the Substance. No justification for the relevance of the substances used in those studies is provided, and no read-across hypothesis is included. Based on this limited amount of information it is not possible to make any conclusions on the relevance of the provided studies.

(ii) Human exposure cannot be considered as limited because widespread professional and consumer uses are reported (e.g. PROCs 7 and 11).
Regarding your comments, ECHA notes, however, that the dossier contains non-industrial spraying (PROC 11), and such use conditions can generally not be defined as strictly controlled. The dossier does not contain data (e.g. exposure scenarios) to demonstrate that the uses are limited to strictly controlled conditions or that human exposure is limited.
Regarding the health surveillance data, ECHA notes that although no adverse health effects have been observed in occupational health surveillance examinations, this information does not show proof of lack of exposure and does not support the adaptations attempted.

No study provided that meets the standard information requirement

To be considered compliant and enable concluding whether the Substance has dangerous properties and supports the determination of the No-Observed Adverse Effect Level (NOAEL), a study has to meet the requirements of OECD TG 408. The following key parameter(s) of this test guideline include, among others:
1. At least 10 female and 10 male animals should be used at each dose level (including control group)
2. Dosing of the Substance daily for a period of 90 days until the scheduled termination of the study

The repeated dose oral toxicity study (OECD TG 407) you provided does not have the required exposure duration of 90 days as required in OECD TG 408, because you indicated an exposure duration of 28 days, and it was conducted with six animals per sex per test dose group. The statistical power of the information provided is not sufficient because it does not fulfil the criterion of 20 animals (10 males + 10 females) for each test group set in OECD TG 408.

Based on the above, the information you provided does not fulfil the information requirement. Therefore, your adaptation is rejected.

Following the criteria provided in Annex IX, Section 8.6.2, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity[7]. The sub-chronic toxicity study must be performed according to the OECD TG 408, in rats and with oral

[7] ECHA Guidance R.7a, Section R.7.5.4.3.2.

administration of the Substance, because the Substance is reported to occur as a dust but with no significant proportion (>1% on weight basis) of particles of inhalable size (MMAD < 50 µm).

In your comments on the initial draft decision you mention that you are assessing your pigments in regard to their nanomaterial status and that *"It is possible that the route of exposure for repeated-dose toxicity may need to be adapted after the results have become available"*.

Based on the information currently available in the dossier, the oral route is the most appropriate route of administration.

You are however reminded of the obligations applicable to nanoforms, including characterisation (Annexes VI to IX to REACH). If the Substance has nanoforms as defined in Annex VI, introductory text, of REACH the inhalation route is the most appropriate route of administration, because the Substance is reported to occur as a dust with a significant proportion (>1% on weight basis) of particles of inhalable size (MMAD < 50 µm). In that case, the sub-chronic toxicity study must be performed according to the OECD TG 413, in rats and with inhalation administration of the Substance. Considering that the Substance is poorly soluble in water, in this case you are also requested to perform measurements of lung burden and bronchoalveolar lavage fluid (BALF), as indicated in the revised version of the OECD 413 test guideline (paragraphs 50-51) adopted on 25 June 2018.

2. 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 the information requirement according to Column 2 of Annex IX, Section 8.7. stating lack of toxicity and absorption, and no significant human exposure of the general population.

In addition, you have provided a Screening for reproductive/developmental toxicity study ([redacted] 2013) performed with an analogue substance.

We have assessed this information and identified the following issue(s):

Annex IX column 2 adaptation not met

According to Annex IX, Section 8.7., Column 2, third indent, the 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.

You provided the following justification: *"In accordance with Annex IX (8.7) of the REACH legislation, the reproductive toxicity studies do not need to be conducted if the substance is of low toxicity and there is no evidence of absorption from a toxicokinetic study and there is no significant human exposure. Lack of toxicity and therefore indirectly absorption was shown experimentally and is also plausible considering the physico-chemical properties. There is no significant human*

exposure because the substance is handled at an inhalable dust only by industry specialised for handling of dusts. The pigment is incorporated into coatings at low concentrations so that there is no significant exposure of the general population".

You have not demonstrated that all criteria are met:
(i) You have not provided any toxicokinetic data to prove that no systemic absorption occurs. The OECD TG 421 study and OECD TG 407 study provided did not investigate toxicokinetic properties such as absorption.
(ii) The reported uses of the Substance contain widespread professional and consumer uses, indicating that there is a possibility of significant human exposure (e.g. PROCs 7 and 11).

Therefore, your adaptation is rejected.

No study provided that meets the standard information requirement

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. by providing a Screening for reproductive/developmental toxicity study according to OECD TG 421, performed with an analogue substance.

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

In addition, the following endpoint-specific deficiency has been identified in your read-across adaptation:
In order to be considered compliant and enable assessing if the Substance is a developmental toxicant, the information provided has to meet the requirements of OECD TG 414 in one species. These parameters include information on structural malformations and variations.

In the study you have provided, structural malformations and variations are not investigated. Therefore, this study does not fulfil the information requirement.

Based on the above, the information you provided does not fulfil the information requirement.

A PNDT study according to the test method OECD TG 414 should be performed in rat or rabbit as preferred species with oral[8] administration of the Substance.

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

Appendix C: 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 REACH.

The compliance check was initiated on 25 March 2019.

ECHA notified you of the draft decision and invited you to provide comments

ECHA took into account your comments and amended the request under B.1. ECHA did not amend the other requests.

Included in your comments, you outlined various aspects that do not directly affect the decision making process of this draft decision, thus ECHA has dealt with it in separate communications.

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 D: 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'[9].

4. Test material

   Selection of the test material

   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 and other parameters relevant for the property to be tested. 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.

[9] https://echa.europa.eu/practical-guides

Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[10].

5. List of references of the ECHA Guidance and other guidance/ reference documents[11]

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)[12]

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[13]
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.

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

Appendix E: 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]

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.