Helsinki, 15 May 2020

Addressees
Registrants of A_CAL_145 listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of a decision
26/02/2018

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Alkenes, C13-14, hydroformylation products, distn. residues
EC number: 292-429-7
CAS number: 90622-29-0

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

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of ***23 May 2022***.

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

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

   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce systemic toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation which must be followed to weaning.**

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

Your originally proposed test using an analogue substance Alkenes, C11-12, hydroformylation products, distn. residues is rejected, according to Article 40(3)(d):

- Extended one-generation reproductive toxicity study in rats, (EU B.56./OECD TG 443)

Conditions to comply with the requests

You are bound by the requests for information corresponding to the REACH Annexes applicable to your own registered tonnage of the Substance at the time of evaluation.

- Therefore you have to comply with the requirements of Annexes VII to X of REACH, if

you have registered a substance at above 1000 tpa.

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.

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.

Appendix A: Reasons for the requirement applicable to all the Registrants subject to Annex X of REACH

This decision is based on the examination of the testing proposal you submitted.

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

The basic test design of an extended one-generation reproductive toxicity study (EOGRTS) is a standard information requirement under Annex X to the REACH Regulation. Furthermore, column 2 of Section 8.7.3. defines when the study design needs to be expanded.

You have submitted a testing proposal for an EOGRTS according to OECD TG 443 by the oral route in rats with 10-week premating exposure duration to be performed with the analogue substance Alkenes, C11-12, hydroformylation products, distn. Residues, "Alchisor CAL 123" (CAS No. 90622-27-8).

You provided your considerations and you applied read-across to fulfil the respective information requirement, and no other alternative methods were available. ECHA has taken these considerations into account.

You have provided a read-across justification document in IUCLID Section 13.

You predict the properties of the Substance from the structurally similar substance: Alkenes, C11-12, hydroformylation products, distn. Residues, "Alchisor CAL 123" (CAS No. 90622-27-8); i.e. the source substance).

The relevant source studies for this reproductive toxicity endpoint that you have used in your read-across approach are:

- A 90 day repeat dose study of Alkenes, C11/C12, Hydroformylation products, distillation residues by oral gavage in rats with 28 day recovery (2014), corresponds to a 90 day repeated dose toxicity study performed according to the OECD TG 408 with additional histopathological assessment of the reproductive organs
- Prenatal Development Toxicity Study of Alkenes, C11/C12 Hydroformylation Products, Distillation Residues (CAS/No.90622-27-8) by Oral Gavage in Rats (2014), corresponds to a prenatal developmental toxicity study performed according to the OECD TG 414.

To show similarity of "toxicological characteristics", you compared the above results with the source substance with the following studies using the Substance:

- A 90 Day Study of Alkenes, C13-C14, hydroformylation products, Distn. residues (CAS/No. 90622-29-0) by Oral (Gavage) in Rats with a 28 Day Recovery Period (2015) with additional histopathological assessment of reproductive organs.
- A Prenatal Development Toxicity Study of Alkenes, C13-C14, hydroformylation products, Distn. residues (CAS/No. 90622-29-0) by Oral (Gavage) in Rats (2014).

ECHA notes that the prenatal developmental toxicity study with the Substance (2014) was submitted in a dossier update in 2015, but it is not included in the current dossier. However, ECHA has taken this study as provided in your registration with submission number [redacted] into consideration when assessing the read-across justification.

You have provided the following reasoning for the prediction of toxicological properties: "*The similarity between Alchisor CAL 123 and Alchisor CAL 145 is based on their composition,*

particularly the high degree of structural similarity between constituents. The constituents of both substances include common functional groups (including hydroxyl, carboxyl, ethyl and ester groups) in similar relative contributions (w/w%). This provides a sufficient basis to support identification of Alchisor CAL 123 and Alchisor CAL 145 as analogue substances such that data from one analogue can be used in a read across approach for the other."

Furthermore: *"the results of the 90-day and developmental toxicity studies conducted on both CAL 123 and CAL 145 serve to anchor these two substances together with respect to their toxicological characteristics. These results show that both substances can be regarded of low toxic potency with respect to the repeat dose and developmental toxicity potential."* [...] *"Given the relative low expected toxicity of these materials and the fact that CAL 145 is almost certainly to be less bioavailable than CAL 123, we believe the results of the EOGRTS study CAL 123 may very likely overestimate, rather than under estimate, the reproductive toxicity of CAL 145."*

ECHA understands that you predict the properties of the Substance ("Alchisor CAL 145") using a read-across hypothesis which assumes that different substances have the same type of effects. The properties of your Substance are predicted to be quantitatively equal to those of the source substance (*'both substances can be regarded of low toxic potency'*). Furthermore, your justification refers to a worst-case approach (*'the results of the EOGRTS study CAL 123 may very likely overestimate, rather than under estimate, the reproductive toxicity of CAL 145'*).

ECHA's assessment

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 (read-across approach).

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance R.6 and related documents.

ECHA notes the following shortcomings with regards to the predictions of toxicological properties:

A) Read-across hypothesis

A read-across hypothesis needs to be provided, establishing why a prediction for a toxicological property is reliable. This hypothesis should be based on recognition of the structural similarities and differences between the source substance(s) and your Substance[2]. It should explain why the differences in the chemical structures should not influence the toxicological properties or should do so in a regular pattern.

Your read-across hypothesis is that the similarity in chemical structure and in some of the toxicological properties (i.e. repeat-dose and developmental toxicity) between the source substance and your Substance is a sufficient basis for predicting the properties of your Substance for other endpoints (reproductive toxicity).

[2] *Guidance on information requirements and chemical safety assessment*, Chapter R.6: QSARs and grouping of chemicals.

Similarity in chemical structure and similarity of some of the physicochemical and toxicological properties (repeat-dose and developmental toxicity) does not necessarily lead to predictable or similar human health properties in other endpoints, namely reproductive toxicity. As described above, a well-founded hypothesis is needed to establish a reliable prediction for a toxicological property, based on recognition of the structural similarities and differences between the source substance and your Substance.

Despite of the degree of similar functional groups and chemical structures between constituents of the source substance and your Substance, these UVCBs have different chain length distribution of the reported constituents.

Furthermore, ECHA notes that your dossier only contains results of repeat-dose and prenatal developmental toxicity studies. These studies do not address parameters of sexual function and fertility (e.g. there are no investigations on mating in these studies) and they do therefore not inform if the Substance and the source substance are similar with respect to these parameters as investigated in an extended one-generation reproductive toxicity study. ECHA cannot conclude if there is a likelihood that the substances have similar toxicological properties with respect to sexual function and fertility.

B) Read-across hypothesis contradicted by existing data

Annex XI, Section 1.5. provides that "substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances. The ECHA Guidance[3] indicates that "*it is important to provide supporting information to strengthen the rationale for the read-across*". The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substance. The observation of differences in the toxicological properties between the source substance(s) and the Substance is a warning sign. An explanation for such a difference resulting in a contradiction between the similarities in properties claimed in the read-across hypothesis and the observation of different properties needs to be provided and supported by scientific evidence.

As indicated above, your read-across hypothesis is based on the assumption that "*Given the relative low expected toxicity of these materials and the fact that CAL 145 is almost certainly to be less bioavailable than CAL 123, we believe the results of the EOGRTS study CAL 123 may very likely overestimate, rather than under estimate, the reproductive toxicity of CAL 145.*"

The available set of data on the target and source substances indicates differences in the toxicological properties of the substances. More specifically, in the 90-day repeat-dose studies with comparable dose levels, liver effects were observed at ≥300 mg/kg bw/day for the target substance (i.e. CAL 145), and only at 1000 mg/kg bw/day for the source substance (i.e. CAL 123).

In your comments, you challenged ECHA´s conclusion that the available data for the proposed target and source substances indicates differences in the toxicological properties of these substances. In detail, you claimed that the liver effects can be regarded as adaptive and not toxic, which is consistent with the no-observed-adverse-effect level (NOAEL) of 1000 mg/kg/day that was reported for both materials.

[3] Guidance on information requirements and chemical safety assessment (version 6.0, July 2017), Chapter R.6, Section R.6.2.2.1.f

In the provided 90-day studies the source substance show liver effects at higher dose than the Substance. In this context the effects, adaptive or not, do not support your statement that the Substance is expected to be less bioavailable than the source substance, and that the results of the EOGRTS study with the source substance (CAL 123) would likely overestimate, rather than under-estimate, the reproductive toxicity of the Substance (CAL 145).
This contradicts your read-across hypothesis whereby the target substance (CAL 145) would be less bioavailable, with limited toxic potential, than the source substance (CAL 123).

Therefore you have not demonstrated and justified that a reproductive toxicity study with the source substance would 'very likely overestimate' the reproductive toxicity of the Substance. In your comments, you also refer to animal welfare reasons to justify performing the OECD TG 443 study with the source substance. The OECD TG 443 is a standard information requirement under Annex X and if the proposed read-across adaptation with the source substance is not plausible, the study must be performed with the Substance.

3. Conclusion

As explained above (shortcomings A and B), the provided information is not sufficient to support your read-across hypothesis. Therefore, the information requirement is not fulfilled.

a) The specifications for the 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 if there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA Guidance[1]. In this specific case ten weeks exposure duration is supported by the lipophilicity of the Substance (logKow = 6 at 25°C) to ensure that the steady state in parental animals has been reached before mating.

Therefore, the requested premating exposure duration is ten weeks.

In order to be compliant and not to be rejected due to too low dose levels, the highest dose level must 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 with the other cohorts being tested at the same dose levels. 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 existing relevant data to be used for dose level setting, it is recommended that results from a range-finding study (or range finding studies) are reported with the main study.

You must provide a justification with your study report that demonstrate that the dose level selection meets the conditions described above.

Cohorts 1A and 1B

Cohorts 1A and 1B belong to the basic study design and shall be included.

Extension of Cohort 1B

If the Column 2 conditions of 8.7.3., Annex X are met, Cohort 1B must be extended.

The extension is inter alia required, if the use of the registered substance is leading to significant exposure of consumers and professionals (column 2, first paragraph, point (a) of Section 8.7.3., Annex X) and if there are indications that the internal dose for the registered substance will reach a steady state in the test animals only after an extended exposure (column 2, first paragraph, lit. (b), second indent of Section 8.7.3., Annex X).

The use of the Substance is leading to significant exposure of consumers and professionals because the Substance is used by professionals as agrochemicals, process chemicals in paper, textile and leather industry, fuel, cleaning products, metalworking fluid/rolling oil, lubricants, binder and release agent and in coating (PROCs 1, 2, 3, 4, 5, 6, 7, 8a, 8b, 9, 10, 11, 13, 15, 16, 17, 18, 19) and by consumers e.g. as biocides (e.g. disinfectants, pest control products), anti-freeze products, coating products, fillers, putties, plasters, modelling clay, finger paints, lubricants, greases, polishes, waxes, air care products and washing and cleaning products.

Furthermore, there are indications that the internal dose for the Substance will reach a steady state in the test animals only after an extended exposure. Specifically, the $\log K_{ow}$ for the substance is above 4.5 indicating potential accumulation.

Therefore, the Cohort 1B must be extended.

The F2 generation must be followed to weaning allowing assessment of nursing and lactation of the F1 parents and postnatal development of F2 offspring. Investigations for F2 pups must be similar to those requested for F1 pups in OECD TG 443 and described in OECD GD 151[4]. It is recommended to aim at 20 litters per dose group.

Species and route selection

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

Outcome

Under Article 40(3)(c) of REACH, you are requested to carry out the additional test, as indicated above, with the Substance.

Further expansion of the study design

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 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].

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4 http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2013)10&doclanguage=en

5 ECHA Guidance R.7a, Section R.7.6.2.3.2.

6 ECHA Guidance R.7a.

In your comments, you note that your registration is not a joint submission even though the draft decision refers to it. However, according to REACH-IT, your registration is a joint submission of which you are currently the only registrant, and the DD relies on the information submitted in REACH-IT.

Appendix B: Procedural history

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 26 February 2018.

ECHA held a third party consultation for the testing proposals from 2 November 2018 until 17 December 2018. ECHA did not receive information from third parties.

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).

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 C: Observations and technical guidance

1. This testing proposal examination decision does not prevent ECHA from initiating 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 your Member State(s).

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 must 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. Selection of the test material(s) for UVCB substances

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. Any constituents that have harmonised classification and labelling according to the CLP Regulation (Regulation (EC) No 1272/2008) must be identified and quantified using the appropriate analytical methods.

The OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, Number 11 [ENV/MC/CHEM(98)16] requires a careful identification of the test material and description of its characteristics. In addition, the Test Methods Regulation (EU) 440/2008, as amended by Regulation (EU) 2016/266, requires that "*if the test method is used for the testing of a* [...] *UVCB* [...] *sufficient information on its composition should be made available, as far as possible, e.g. by the chemical identity of its constituents, their quantitative occurrence, and relevant properties of the constituents*".

In order to meet this requirement, all the constituents of the test material used for each test must be identified as far as possible. For each constituent the concentration value in the test material must be reported in the Test material section of the endpoint study record.
Technical Reporting of the test material for UVCB substances

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

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

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" on the ECHA website[8].

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

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]

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
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

[8] https://echa.europa.eu/manuals
[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

Appendix D: 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 fulfilled
[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.