Helsinki, 16 February 2021

as consolidated following decision ED-0038.01

Addressees
Registrant(s) of 701-314-7_JS_EM_LR as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
13/09/2019

Registered substance subject to this decision ("the Substance")
Substance name: Alkenes, C6-11 (branched), hydroformylation products, distn. residues, heavy cracked fraction
EC number: 701-314-7
CAS number: NS

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

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***30 January 2023***.

Requested information must be generated using the Substance unless otherwise specified.

A. Information required from all the Registrants subject to Annex IX of REACH

1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.; test method: OECD TG 408) by oral route, in rats, with the Substance

Reasons for the request(s) are explained in the following appendix:

- Appendices entitled "Reasons to request information required under Annexes VII to X of REACH", respectively.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

How to comply with your information requirements

To comply with your information requirements you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also update the chemical safety report, where relevant, including any changes to classification

and labelling, based on the newly generated information.

You must follow the general testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". In addition, you should follow the general recommendations provided under the Appendix entitled "General recommendations when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

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 A: Reasons for the requirements applicable to all the Registrants subject to Annex IX of REACH

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

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

You have adapted the standard information requirement mentioned above according to Annex XI, Section 1.2 of REACH (Weight of Evidence).

In support of your adaptation, you have provided the following sources of information:

(i) Supporting 28d RDT study ([redacted] 1990) according to EU Method B.7 (Repeated Dose (28 Days) Toxicity, Oral) with the Substance;
(ii) Reference to the U.S. EPA HPV Challenge Program Submission [redacted] 2003) of a substance with a similar compositional profile (CAS#68526-82-9), study equivalent or similar to OECD Guideline 413 (Subchronic Inhalation Toxicity: 90-Day Study (1987);
(iii) The OECD Guideline 473 (In vitro Mammalian Chromosome Aberration Test) and OECD Guideline 476 (In vitro Mammalian Cell Gene Mutation Test) studies;

Based on the presented sources of information, you argue that the available data gives sufficient information to conclude on the sub-chronic toxicity because: *"The overall weight of the evidence does not justify the additional use of animal testing."*.

Additionally, you have submitted an adaptation based on read-across in accordance with Annex XI, section 1.5. and to support your adaptation, you have provided the following source of information:

[redacted] Read-across adaptation of OECD Guideline 413 (Subchronic Inhalation Toxicity: 90-Day Study) based on analogue substance Alkenes, C6-10, hydroformylation products, high-boiling" (CAS#68526-82-9), [redacted]

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

A. Weight of evidence

Annex XI, Section 1.2 states that there may be sufficient weight of evidence 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.

According to ECHA Guidance R.4, a weight of evidence adaptation involves an assessment of the relative values/weights of the different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance and coverage of the information for the given regulatory information requirement. Subsequently, relevance, reliability, coverage, consistency and results of these

sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the (dangerous) property investigated by the required study.

Annex XI, section 1.2 requires that adequate and reliable documentation is provided to describe your weight of evidence approach.

You have not included a justification for your weight of evidence adaptation, which would include an adequate and reliable (concise) documentation as to why the sources of information provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Irrespective of the above mentioned deficiencies on the documentation, which in itself leads to the rejection of the adaptation, ECHA has assessed the provided sources of information.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.6.2 at Annex IX includes similar information that is produced by the OECD TG 408. At general level it includes information on repeated dose toxicity in live animals for comparable or longer exposure duration.

In more detail, sub-chronic repeated dose toxicity study (90 day) includes at least three dose levels, clinical observations, ophthalmological examination, haematology, clinical biochemistry, urinalysis, full detailed gross necropsy and subsequent histopathology and at least 20 animals per dose group and exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3), in this case 90 days.

The source of information (*i.*), 28d repeated dose toxicity study, provides relevant information on short term repeated dose toxicity on live animals. In more detail, it includes i.e. clinical and functional observations, body weight measurent, clinical biochemistry, histopathology, gross necropsy and organ weights in at least 10 animals per dose group.

The source of information (*ii.*), subchronic inhalation toxicity study with an analogue substance, provides relevant information on some key elements similar to OECD TG 408, such as similar exposure duration. In more detail, the study covers clinical observations, body weight measurements, clinical chemistry, gross necropsy and organ weights.

However the information provided on sub-chronic toxicity is limited and does not cover all relevant and essential aspects as defined above.

More in particular, the source of information (*i.*) does not have sufficient study duration and the number of animals does not meet the requirements as required in OECD TG 408.

The source of information (*ii.*) has particular attention to the respiratory tract and it does not cover all relevant and essential aspects as defined above. In particular, full histopathology, thyroid hormone level measurements, parameters related to spermatogenesis, sperm and oestrous cycle are missing. Finally, the oral route is the default one for sub-chronic toxicity studies as it is assumed that oral route of exposure maximises systemic availability (internal dose) of most substances.

The source of information (*iii.*) does not inform on repeated dose toxicity in live animals, as the OECD TG 473 and OECD TG 476 are *in vitro* studies on mammalian cells which only provide information on structural chromosomal aberrations in cultured mammalian somatic cells and mammalian cell gene mutations, respectively.

Taken together, the information that the relevant sources of information *(i.), (ii.)* and *(iii.)* provide can be summarised as following:

- Short-term repeated dose toxicity study (*i.*) provides information on clinical and functional observations, organ weights, histopathology and clinical biochemistry, but does not include sufficient exposure duration and number of animals.
- Subchronic inhalation toxicity study (*ii.*) provides information on clinical observations, body weight measurements, clinical chemistry, gross necropsy and organ weights with sufficient exposure duration. However, it does not cover all relevant information as described in OECD TG 408, such as full histopathology and hormone level measurements. Moreover, the oral route is the default one for sub-chronic toxicity studies.
- The *in vitro* studies (*iii.*) do provide information on mammalian cell mutagenicity but does not correspond to the information requirement of this endpoint.

Therefore, a significant amount of essential investigations are limited or totally lacking that would inform on sub-chronic repeated dose toxicity in order to conclude on these aspects.

It is not possible to conclude, based on any source of information alone or considered together, and taking into account the lack of proper justification for the WoE adaptation, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 408 study. Therefore, your adaptation according to Annex XI, Section 1.2. is rejected and the information requirement is not fulfilled.

B. Read-across

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 summaries of the source studies.[2]

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance[3] and related documents[4, 5].

Predictions for properties

You have provided the following reasoning for the prediction of toxicological properties (in the IUCLID section 7.5.2): *"Several criteria justify the use of the read-across approach to fill a data gap for the registered substance "Alkenes C6-C11, hydroformylation products, distn. Residues, heavy cracked fraction" with the following substance "Alkenes, C6-10, Hydroformylation Products, High-Boiling". The read across substance has similar manufacturing process, similar composition and similar physic-chemical properties as the registered substance."* and *"The same types of molecules (alcohols, esters, and ethers) in*

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

[3] 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

[4] 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)

[5] 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

similar carbon ranges are present in both substances. Because the components have similar structures, they are metabolized by common pathways. Thus neither components nor metabolites with differentiating toxicological properties are expected in the two substances."

ECHA understands that you predict the properties of the Substance using a read-across hypothesis, which assumes that different compounds have the same type of effects. The properties of your Substance are predicted to be qualitatively and quantitatively equal to those of the source substance.

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

Missing supporting information

Annex XI, Section 1.5 of the REACH Regulation states that "*physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s)*". For this purpose "*it is important to provide supporting information to strengthen the rationale for the read-across*"[6]. 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 other category members.

Supporting information must include bridging studies to compare properties of the category members and to support your prediction, which is based on similarity of the relevant toxic properties.

As indicated above, your read-across hypothesis is based on the assumption that the similar composition of the target and source substances cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the target and source substance is necessary to confirm that both substances cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design for the target and the source substances.

The data set reported in the technical dossier does not include relevant, reliable and adequate information for the Substance to support your read-across hypothesis.

In the absence of such information, you have not established that the target and the source substances are likely to have similar properties. Therefore, you have not provided sufficient supporting information to strengthen the rationale for the read-across.

Missing information on the formation of common compound

As indicated above, your read-across hypothesis is based on similar manufacturing process, similar composition and similar physico-chemical properties.

You have not provided any experimental data to document the presumed similar metabolisation of the target and the source substances.

In the absence of this information, you have not provided supporting evidence establishing the transformation of the Substance as assumed in your read-across hypothesis. Therefore, you have not provided sufficient supporting information to strengthen the rationale for the

[6] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.2.1.f

read-across.

As explained above, your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. Therefore, your adaptation is rejected and it is necessary to perform testing on your Substance.

Route of exposure

As noted already under the WoE issue, oral route is the default one for subchronic toxicity studies because it is assumed to maximise systemic availability (internal dose) of most substances and the key investigations in OECD TG 408 are more comprehensive.

Based on the above, the information you provided does not fulfil the information requirement. Your adaptations according to Annex XI 1.2. and 1.5. are rejected and the information requirement is not fulfilled.

In your comments to the draft decision, you agree to conduct the requested OECD TG 408 study with the Substance.

Information on the design of the study to be performed

Referring to 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.

Therefore the sub-chronic toxicity study must be performed according to the OECD TG 408, in rats and with oral administration of the Substance.

Appendix B: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. Test methods, GLP requirements and reporting

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

2. 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.

3. 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 on How to report robust study summaries[7].

B. Test material

1. *Selection of the Test material(s)*

   The Test Material used to generate the new data must be selected taking into account the following:
   a) the boundary composition(s) of the Substance,
   b) 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.

2. *Information on the Test Material needed in the updated dossier*

   a) You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
   b) The reported composition must include the careful identification and description of the characteristics of the Tests Materials in accordance with OECD GLP (ENV/MC/CHEM(98)16) and EU Test Methods Regulation (EU) 440/2008 (Note, Annex), namely all the constituents must be identified as far as possible as well as their concentration. Also any constituents that have harmonised classification and labelling according to the CLP Regulation must be identified and quantified using the appropriate analytical methods,

With that detailed information, ECHA can confirm whether the Test Material is relevant for the Substance.
Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[8].

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

Appendix C: Procedure

The information requirement for an Extended one-generation reproductive toxicity study (EOGRTS; Annexes IX or X, Section 8.7.3.) is not addressed in this decision. This may be addressed in a separate decision once the information from the Sub-chronic toxicity study (90-day) requested in the present decision is provided; due to the fact that the results from the 90-day study is needed for the design of the EOGRTS. Similarly the information requirement for a Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.) is not addressed in this decision; as the EOGRTS will cover the same parameters.

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

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The compliance check was initiated on 02/10/2019.

The decision making followed the procedure of Article 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 did not amend the request(s).

Deadline to submit the requested information in this decision

The timeline indicated in the initial draft decision to provide the information requested was 27 months from the date of adoption of the decision.

In your comments on the draft decision, you requested an extension of the timeline to 33 months. However, after the expiry of the commenting period, you informed ECHA on 14 August 2020 that the extension of the deadline was no longer needed. Therefore ECHA did not modify the deadline of this decision.

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.

Following an appeal registered as Case A-001-2021, on 15 February 2021 the Executive Director of ECHA rectified the decision in accordance with Article 93(1) of the REACH Regulation (decision ED-0038.01), by withdrawing from the decision the following information requests:

(A.2) Soil simulation testing (EU C.23./OECD TG 307)
(A.3) Sediment simulation testing (EU C.24./OECD TG 308)
(A.4) Identification of degradation products (EU C.23/OECD TG 307 or EU C.24/OECD TG 308)
(B.1) Pre-natal developmental toxicity study (OECD TG 414)

Appendix D: List of references - ECHA Guidance[9] and other supporting documents

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 where relevant.

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 where relevant.

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

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, 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.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

[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

OECD Guidance documents[11]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

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

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

[11] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Appendix E: Addressees of this decision and the corresponding information requirements applicable to them

You must provide the information requested in this decision for all REACH Annexes applicable to you.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]

Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.