~~Confidential~~

Helsinki, 13 April 2022

Addressees
Registrant(s) of JS_4427-96-7 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
07/11/2019

Registered substance subject to this decision ("the Substance")
Substance name: Vinyl ethylene carbonate
EC number: 700-261-7

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 ***19 July 2023***.

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

Information required from all the Registrants subject to Annex VII of REACH

1. Skin sensitisation (Annex VII, Section 8.3.)
   i. *in vitro/in chemico* skin sensitisation information on molecular interactions with skin proteins (OECD TG 442C) and activation of dendritic cells (EU B.71/OECD TG 442E) (Annex VII, Section 8.3.1.); and
   ii. Only if the *in vitro/in chemico* test methods specified under point 1.i.) are not applicable for the Substance or the results obtained are not adequate for classification and risk assessment, *in vivo* skin sensitisation (Annex VII, Section 8.3.2.; test method: EU B.42./OECD TG 429).

The reasons for the decision(s) are explained in Appendix 1.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you in accordance with Articles 10(a) and 12(1) of REACH. The addressees of the decision and their corresponding information requirements based on registered tonnage band are listed in Appendix 3.

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 requirements for testing and reporting new tests under REACH, see Appendix 4.

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.

Authorised[1] under the authority of Mike Rasenberg, Director of Hazard Assessment

Appendix 1: Reasons for the decision
Appendix 2: Procedure
Appendix 3: Addressees of the decision and their individual information requirements
Appendix 4: Conducting and reporting new tests under REACH

[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 1: Reasons for the decision

Contents

Reasons related to the information under Annex VII of REACH

1. Skin sensitisation

1 Skin sensitisation is an information requirement under Annex VII to REACH (Section 8.3.). Under Section 8.3., Column 1, the registrants must submit information allowing (1) A) a conclusion whether the substance is a skin sensitiser and B) whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A), and (2) risk assessment, where required.

1.1. Information provided

2 You have adapted this information requirement by using weight of evidence based on the following experimental data:

i. WoE Derek prediction skin sensitisation (2019) with the Substance;
ii. WoE skin sensitisation: in chemico (2019) according to the OECD TG 442C with the Substance, negative results;
iii. WoE skin sensitisation: Keratinosens (2019) according to the OECD TG 442D with the Substance, negative results.

3 Based on the presented sources of information, you consider that "The results obtained in the non-animal skin sensitization testing strategy represent sufficient evidence to conclude that the test item is not expected to lead to an allergic response following skin contact".

1.2. Assessment of the information provided

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

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

6 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.

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

8 You have provided the justification for your weight of evidence adaptation mentioned above.

9 However, your justification does not include any explanation 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.

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

A) Assessment whether the Substance causes skin sensitisation

11 Information that can be used to support a weight of evidence adaptation for the information requirements of Section 8.3 at Annex VII includes similar information to that investigated by the internationally recognised in vitro, in chemico and/or in vivo test methods on skin sensitisation. The key investigations of such test methods address each of the 3 key events of skin sensitisation, either individually or in an integrated approach as follows:

1. investigation of cell proliferation in the draining lymph nodes (local lymph node assay), or
2. investigation of local responses in animals or humans (guinea pig assays or human studies), or
3. investigation of molecular interaction with proteins, inflammatory response in keratinocytes and activation of dendritic cells (*in vitro* and *in chemico* assays).

12 All the sources of information (i. to iii.) provide relevant information, as they investigate predicted properties on skin sensitisation (study i.), on investigation of molecular interaction with proteins (study ii.) and inflammatory response in keratinocytes (study iii.).

13 However, the studies i. and ii. have the following deficiencies affecting the reliability of their contribution to the weight of evidence approach.

1.2.1. Reliability of the QSAR prediction (source of information i.)

14 ECHA Guidance R.6.1.6.3 states that the information specified in or equivalent to the (Q)SAR Prediction Reporting Format document (QPRF) must be provided to have adequate and reliable documentation of the applied method. For a QPRF this includes, among others, the identities of close analogues, including considerations on how predicted and experimental data for analogues support the prediction.

15 You provide a "non-sensitiser" prediction for skin sensitisation using Derek Nexus 6.0.1.

16 In the section 3.3.b of the QPRF, you provided the following information about the prediction: "Structural analogues: not applicable".

17 However, the information you provide about the prediction lacks information on the structural analogues and information on the accuracy of their prediction by the model. Without this information, ECHA cannot assess the reliability of the prediction for the Substance.

18 Furthermore, ECHA notes that the newest version of Derek Nexus (v6.1.0) produces a positive prediction for your Substance. This fact increases the concern relating to the reliability of the prediction that you provided in your registration.

19 For the reasons presented above, ECHA considers that the source of information i. is viciated by significant deficiencies that affects its contribution to your weight of evidence adaptation.

1.2.2. Reliability of study ii.

20 The Direct Peptide Reactivity assay (OECD TG 442C) investigates the key event of molecular interaction with proteins. The test guideline specifies borderline values for mean peptide depletion i.e. values close to the threshold to discriminate between negative and positive results. This range of borderline values is set in the OECD TG 442C as 3% to 6.38%. The test guideline specifies (paragraph 24) that additional testing should be conducted in case the mean peptide depletion obtained is in this range of values in the Cysteine 1:10 / Lysine 1:50 prediction model.

21 The study ii. was performed according to the Direct Peptide Reactivity assay (OECD TG 442C). You reported that the mean peptide depletion obtained from the study is 5.6% when using the Cysteine 1:10 / Lysine 1:50 prediction model.

22 Therefore, you consider that the study ii. provided negative results.

23 The predicted mean peptide depletion falls into this borderline range of values (mean depletion of 5.6%) affecting the reliability of the negative prediction. No additional testing has been conducted despite this borderline result.

24 Therefore, the negative prediction obtained from study ii. is viciated by significant deficiencies that affects its contribution to the weight of evidence adaptation.

1.2.3. Coverage of the key investigations

25 As indicated above, information that can be used to support a weight of evidence adaptation for the information requirements of Section 8.3 at Annex VII includes similar information to that investigated by the internationally recognised in vitro, in chemico and/or in vivo test methods on skin sensitisation.

26 The information from in vitro/in chemico test method(s) provided must address all three key events listed under Column 1, i.e. a) molecular interaction with skin proteins; b) inflammatory response in keratinocytes; and c) activation of dendritic cells, unless information from test methods addressing one or two of these key events allows classification and risk assessment (Section 8.3.1. Column 2, second paragraph of Annex VII to REACH).

27 Your registration dossier provides information from in vitro and in chemico test methods addressing two of the required three key events, i.e. key event 1: molecular interaction with skin proteins and key event 2: inflammatory response in keratinocytes.

28 You consider that the available results provide adequate evidence that the substance is not a skin sensitiser.

29 The issues identified with study ii. reported under section 1.2.2 also affect their contribution to a conclusion on classification and risk assessment. Specifically, the information on the key event molecular interaction with skin proteins (study ii.) cannot contribute to a conclusion on classification and risk assessment. The negative results obtained from study iii. do not constitute, on their own, a basis for concluding on classification and risk assessment for skin sensitisation.

30 Therefore the set of information included in your weight of evidence adaptation must cover all three key events of skin sensitisation.

31 You have not provided any information on the properties of the Substance relating to key event 3 and the information from the line of information i. does not reliably address this key event for the reasons presented in section 1.2.1.

32 Taken together the set of information that you have provided in your weight of evidence approach does not reliably address the key events 1 and 3. Therefore, the data provided do not cover all the key events set in the Annex VII, Section 8.3.1 and does not allow to make a conclusion whether the Substance causes skin sensitisation.

1.2.4. Conclusion on the weight of evidence

33 All the sources of information (i. to iii.) provide relevant information, as they investigate predicted properties on skin sensitisation (study i.), on investigation of molecular interaction with proteins (study ii.) and inflammatory response in keratinocytes (study iii.).

34 However, taken together, the relevant and reliable sources of information, as indicated above, lack information of essential key investigation(s): molecular interaction with proteins and activation of dendritic cells . This information is essential because they are elements of the skin sensitisation adverse outcome pathway and cannot be covered by or derived from any of the available sources of information.

35 Therefore information on these aspects is necessary for a conclusion on skin sensitisation properties of the Substance.

36 Weighing the relevant and reliable but deficient sources of information together, essential parts of information of the dangerous property is lacking or deficient as indicated above. Therefore 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 the recognised in vitro, in chemico and/or in vivo test methods on skin sensitisation.

37 Therefore, your adaptation is rejected and the information requirement is not fulfilled.

B) Assessment whether the Substance can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A)

38 To be considered compliant and enable concluding whether the Substance causes skin sensitisation, in case the substance is considered to cause skin sensitisation the information provided must allow a conclusion whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A).

39 As the currently available data does not allow to conclude whether the Substance causes skin sensitisation (see section A above), this condition cannot be assessed.

40 On this basis, the information requirement is not fulfilled.

1.3. Specification of the study design

41 To fulfil the information requirement for the Substance, information on molecular interaction with skin proteins and activation of dendritic cells (OECD TG 442C and EU B.71/OECD TG 442E) must be provided. Furthermore an appropriate risk assessment is required if a classification of the Substance as a skin sensitiser (Cat 1A or 1B) is warranted.

42 In case no conclusion on the skin sensitisation potency can be made for the Substance based on the existing in vitro/in chemico data or newly generated in vitro/in chemico data, in vivo skin sensitisation study must be performed and the murine local lymph node assay (EU Method B.42/OECD TG 429) is considered as the appropriate study for the potency estimation.

1.4. Information provided in your comments on the draft decision

43 In your comments on the draft decision, you acknowledge "that the Derek Nexus has been updated since the last Derek assessment was performed and will update the in silico assessment using the new version of Derek Nexus". You agree that, according to the latest version of the OECD TG 442C, a second run should be performed when, as in the case of study ii., the results of the first run are in the range of 3%-6.38% for the cysteine 1:10/lysine 1:50 prediction model. You indicate that you agree with ECHA's conclusions on the assessment of the coverage of the key investigations, i.e. that the studies included in the current dossier for skin sensitisation no longer reliably address key event 1 and 3. You acknowledge that additional information is needed for a conclusion on the skin sensitisation properties of the Substance.

44 You argue that Derek "indicates that the structure of the Substance contains a tertiary allylic hydroperoxide precursor for which its skin sensitizing mechanism is thought to be a pre-hapten producing a free radical generator". You claim that the Substance being a potential pre-hapten, neither of the required validated in vitro studies mentioned in OECD TG 442C and OECD TG 442E will provide sufficient information to conclusively determine the skin sensitization hazard and potency of the Substance. You specify that "for the OECD 442C, pre-haptens (i.e., chemicals activated by auto oxidation) may provide (false)

negative results" and that "the same applies to the studies in OECD 442E for which it is known that pre-haptens may provide (false) negative results". You further elaborate on the potential of the KeratoniSens assay (OECD TG 442D) to return false negative results when performed on substances with exclusive reactivity towards other nucleophiles than cysteine such as the Substance.

45 Therefore "regardless of the results of the requested in vitro skin sensitization studies, the three key events of skin sensitization AOP cannot be reliably assessed and thus no conclusion on the skin sensitisation properties of the Substance can be made. In case positive results are obtained, potency cannot be determined".

46 You conclude that "based on new information the in silico/in chemico/in vitro test methods available are not applicable for the test substance and thus the results obtained from such methods are not adequate for classification and risk assessment". As a result, you argue that an in vivo skin sensitisation study needs to be conducted, with the murine local lymph node assay (EU Method B.42/OECD TG 429) considered as the appropriate study.

47 ECHA understands that you consider that none of the in vitro test methods listed in the OECD TGs 442C, D and E are suitable to generate reliable information on skin sensitisation properties of the Substance and that you intend to perform a murine local lymph node assay. In this context, ECHA points out that:

48 The OECD TG 442C reports under paragraph 4 that "Chemicals that become sensitisers after abiotic transformation (i.e. prehaptens) are reported to be in most cases correctly detected by the test method", contrary to chemicals that require enzymatic bioacetivation to become skin sensitisers, i.e. pro-haptens. Therefore, caution is required in the dismissal of the applicability of the test methods listed in the OECD TG 442C in case you consider that the Substance is a pre-hapten, as indicated in your comments.

49 The OECD TG 442E reports in paragraph 4 that pre-haptens, and in particular pre-haptens with a slow oxidation rate may provide false negative results in the h-CLAT assay described in this test guideline. Therefore, attention needs to be paid to the rate of oxidation of the Substance when considering the applicability of the h-CLAT assay, in case you consider that the Substance is a pre-hapten, as indicated in your comments. Furthermore, the OECD TG 442E also mentions other methods such as the U-SENS assay, for which no limitations in respect to pre-haptens have been noted.

50 You further inquire in your comments:

51 On whether "only in case when structural analogues are provided by Derek (i.e., positive and misclassified results), the information on these analogues should be reported in the QPRF? In case of a negative prediction, no analogue information is available in Derek and can therefore not be provided".

52 ECHA acknowledges that Derek Nexus software does not provide information on close analogues for structures producing negative predictions and lacking misclassified features. Nevertheless, information on close analogues is a required and crucial element to assess the reliability of a prediction and thus its adequacy for the purpose of risk assessment (ECHA Guidance R.6.1.5.3). In fact, as specified in ECHA Guidance R6 chapter 6.1.5.2: "a warning should be given that a lack of alert does not always mean lack of hazard since a hazardous chemical functionality might not be known as such". For a negative prediction based on lack of alerts, information on close analogues and accuracy of their predictions is needed to support the hypothesis that the negative prediction is due to lack of hazard and not due to lack of knowledge. ECHA understands that for commercial QSAR software, information on training and test sets may not be disclosed. Note that ECHA Guidance R6 Chapter 6.1.10.1 describes the QSAR Prediction Reporting Format (QPRF) template. Section 3.3 of the template suggests that analogues could also be retrieved from other sources than the training or test sets of the models.

53 On whether, if applicable and conclusive, a defined approach as presented in the OECD TG 497 can be used to address the skin sensitisation endpoint.

54 ECHA confirms that, in case the methods included in the defined approaches are suitable for the substance and conclusive prediction is obtained, a defined approach as presented in the OECD TG 497 can be used to address the skin sensitisation information requirement of Annex VII, 8.3 provided that the results of the defined approach allows classification and risk assessment, including determination of the potency of the skin sensitisation properties of the Substance. It is the Registrant's responsibility to determine whether a defined approach is applicable and conclusive for a particular substance. More information on the use of defined approaches for skin sensitisation under REACH can be obtained in the document available at the following link on ECHA's website: https://echa.europa.eu/documents/10162/1128894/oecd_test_guidelines_skin_sensitisation_en.pdf

55 ECHA notes that during the assessment of the performance of the defined approaches to skin sensitisation, based on the extensive data set assessed, it was considered that although individual methods may have limitations towards pre- and pro-haptens, by applying a defined approach, especially the ITS v1 or v2 approach, an excellent performance was observed (Series on Testing and Assessment No. 336: Supporting Document to the Guideline (GL) on Defined Approaches (DAs) for Skin Sensitisation the, OECD 2021 available at https://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm).

References

The following documents may have been cited in the decision.

Guidance on information requirements and chemical safety assessment (Guidance on IRs & CSA)

Chapter R.4 Evaluation of available information; ECHA (2011).
Chapter R.6 QSARs, read-across and grouping; ECHA (2008).
Appendix to Chapter R.6 for nanoforms; ECHA (2019).
Chapter R.7a Endpoint specific guidance, Sections R.7.1 – R.7.7; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Chapter R.7b Endpoint specific guidance, Sections R.7.8 – R.7.9; ECHA (2017).
Appendix to Chapter R.7b for nanomaterials; ECHA (2017).
Chapter R.7c Endpoint specific guidance, Sections R.7.10 – R.7.13; (ECHA 2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Appendix R.7.13-2 Environmental risk assessment for metals and metal compounds; ECHA (2008).
Chapter R.11 PBT/vPvB assessment; ECHA (2017).
Chapter R.16 Environmental exposure assessment; ECHA (2016).

Guidance on data-sharing; ECHA (2017).

All Guidance on REACH is available online: https://echa.europa.eu/guidance-documents/guidance-on-reach

Read-across assessment framework (RAAF)

RAAF, 2017 Read-across assessment framework (RAAF), ECHA (2017)
RAAF UVCB, 2017 Read-across assessment framework (RAAF) – considerations on multi- constituent substances and UVCBs), ECHA (2017).

The RAAF and related documents are available online:
https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

***OECD Guidance documents* (OECD GDs)**

OECD GD 23 Guidance document on aquatic toxicity testing of difficult substances and mixtures; No. 23 in the OECD series on testing and assessment, OECD (2019).
OECD GD 29 Guidance document on transformation/dissolution of metals and metal compounds in aqueous media; No. 29 in the OECD series on testing and assessment, OECD (2002).
OECD GD 150 Revised guidance document 150 on standardised test guidelines for evaluating chemicals for endocrine disruption; No. 150 in the OECD series on testing and assessment, OECD (2018).
OECD GD 151 Guidance document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test; No. 151 in the OECD series on testing and assessment, OECD (2013).

Appendix 2: Procedure

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 08 June 2021.

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).

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 3: Addressees of this decision and their corresponding information requirements

In accordance with Articles 10(a) and 12(1) of REACH, the information requirements for individual registrations are defined as follows:

- the information specified in Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa;
- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;
- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

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

Appendix 4: Conducting and reporting new tests for REACH purposes

1. Requirements when conducting and reporting new tests for REACH purposes

1.1. 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[2].

1.2. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

(1) Selection of the Test material(s)
The Test Material used to generate the new data must be selected taking into account the following:
- the variation in compositions reported by all members of the joint submission,
- the boundary composition(s) of the Substance,
- 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
- 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.
- The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

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

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[3].

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