EUROPEAN CHEMICALS AGENCY

Helsinki, 19 July 2018

Addressee: [redacted]

Decision number: TPE-D-2114428715-46-01/F
Substance name: butan-2-one O,O',O''-(vinylsilylidyne)trioxime
EC number: 218-747-8
CAS number: 2224-33-1
Registration number: [redacted]
Submission number: [redacted]
Submission date: 11.03.2016
Registered tonnage band: 1-10T

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA examined your testing proposal(s) and decided as follows.

Your testing proposal is accepted and you are requested to carry out:

Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route using the analogue substance butan-2-one O, O', O''-(methylsilylidyne)trioxime (CAS no 22984-54-9, EC no 245-366-4).

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective Annex, and an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by ***26 July 2019***. You shall also update the chemical safety report, where relevant.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. Advice and further observations are provided in Appendix 3.

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, shall 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] by Ofelia Bercaru, Head of Unit, Evaluation E3

[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

The decision of ECHA is based on the examination of the testing proposal submitted by you for the registered substance butan-2-one O,O',O''-(vinylsilylidyne)trioxime (CAS no 2224-33-1, EC no 218-747-8; hereafter referred to as "target substance").

You propose a testing strategy intending to fulfil the standard information requirement for

- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

In your testing strategy you propose to test the analogue substance butan-2-one O, O', O''-(methylsilylidyne)trioxime (CAS no 22984-54-9, EC no 245-366-4) (hereafter referred to as "source substance"). The results from the structural analogue will then be used to adapt the standard information requirements by using read-across and grouping approach following Annex XI, Section 1.5. of the REACH Regulation. ECHA has considered first the scientific validity of the proposed read-across and grouping approach (preliminary considerations; Section 0, below), before assessing the testing proposed (Section 1, below).

0. Grouping of substances and read-across approach

a. Legal Background on ECHA's assessment of the grouping of substances and read-across hypothesis

The evaluation by ECHA of testing proposals submitted by registrants aims at ensuring that generation of information is tailored to real information needs. To this end, it is necessary to consider whether programmes of testing proposed by you are appropriate to fulfil the relevant information requirements and to guarantee the identification of health and environmental hazards of substances. In that respect, the REACH Regulation aims at promoting wherever possible the use of alternative means, where equivalent results to the prescribed test are provided on health and environmental hazards.

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated whenever possible by means other than vertebrate animal tests, including information from structurally related substances (grouping of substances and read-across), "*provided that the conditions set out in Annex XI are met*".

The first Recital and the first Article of the REACH Regulation establish the "*promotion of alternative methods for assessment of hazards of substances*" as an objective pursued by the Regulation. In accordance with that objective, ECHA considers whether a prediction of the relevant properties of the substance subject to the present decision by using the results of the proposed tests is plausible based on the information currently available.

b. Description of the proposed grouping and read-across approach

You have provided the following arguments to justify the read-across approach:

"*VOS and Butan-2-one O, O', O''-(methylsilylidyne) trioxime (MOS; CAS 22984-54-9) are part of an existing category (OECD SIDS, 2009). They are known to hydrolyse rapidly to release three equivalents of methylethylketoxime (CAS No. 96-29-7; MEKO) and one equivalent of reactive methyl- or vinyl-substituted silanetriols.*"

On the basis of all evaluated data, the similarity of the analogue group members of the oximino silanes category is justified on basis of the physico-chemical properties, toxicological, ecotoxicological profiles. The similarity assessment [OECD HPV SIDS, 2009] has been performed on the basis of process information, structural features,

physicochemical properties, and environmental behaviour as both substances hydrolyse rapidly to liberate three moles of methylethylketoxime (CAS No. 96-29-7; MEKO) and one mole of reactive methyl- or vinyl-substituted silanetriols".

"The key points that the members share are:
(i) Common origin
(ii) Similar structural features
(iii) Similar physicochemical properties
(iv) Common properties for environmental fate & eco-toxicological profile
(v) Similar metabolic pathways
vi) Common levels and mode of human health related effects".

"In conclusion, the read-across from MOS to VOS is adequate, based on the structural similarity of the parent substances and the similar hydrolysis products".

c. Information submitted to support the grouping and read-across approach

You have provided the following documents as separate attachments in IUCLID, Section 13, relevant to the testing proposed:

- A read-across justification document: [redacted] describing substance-specific read-across hypothesis and justification.
- [redacted]). The document is summarising the available physico-chemical and toxicological data on the target, source and other related substances.
- [redacted] The document is an overview of the grouping and read-across methods of Reconsile REACH submissions. The document describes the general principles applied but does not provide any substance-specific information. According to the report, "*each CSR needs to describe clearly whether Category, Analogue or QSAR methods have been applied, and which endpoints they are applied to, and the IUCLID entries must be consistent with this*". Based on this document, ECHA understands that you intend to apply analogue approach as a basis for data gap filling which are further justified in each registration dossier and CSR.

In addition, you have provided the following human health studies on the target substance:

- acute oral toxicity (OECD 425)
- acute oral toxicity (equivalent or similar to OECD 401, two studies)
- acute oral toxicity (equivalent or similar to EPA OPPTS 870.1100)
- acute dermal toxicity (OECD 402)
- eye irritation (OECD 405)
- eye irritation (CFR Title 16, Subchapter C, Federal Hazardous Substances Act Part 1500.42, revised 1978-01-01)
- Ames test (OECD 471)
- In vitro Mammalian Chromosome Aberration Test (OECD 473)
- Mammalian Erythrocyte Micronucleus Test (OECD 474)

and studies on the source substance:

- skin sensitisation (OECD 406)
- range-finding for the OECD 422 study (7-days)

- Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test (OECD 422)

and a study on methyl ethyl ketoxime (CAS no 96-29-7)

- Sub-chronic toxicity (90-day) (OECD 408)

d. ECHA analysis of the grouping approach and read-across hypothesis in light of the requirements of Annex XI, 1.5.

ECHA notes that the registrants of oximino silanes have grouped the substances in 'Analogue group', including the substance subject to the current decision, but the category approach is not proposed. Based on the substance specific justification for read-across approach and supporting information provided by you, ECHA understands that no category hypothesis /justification has been included and the proposed prediction is based on the source substance.

According to ECHA's understanding the proposed read-across hypothesis is based on

- common origin of the substances,
- structural similarity,
- similar physico-chemical properties,
- similar metabolic pathway and similar hydrolysis product, and
- similar toxicity of the target and source substances.

ECHA notes that in your read-across justification document you have provided a short summary of the manufacturing processes, i.e. common origin of the substances.

In the following, ECHA examines whether the substances have indeed similar properties or that they would follow a regular pattern in their properties, before assessing the scientific validity of your hypothesis.

(i) Structural (dis)similarities and their impact on prediction

Structural similarity is a prerequisite for applying the grouping and read-across approach, but ECHA does not accept in general or this specific case that structural similarity *per se* is sufficient to enable the prediction of human health properties of a substance, since structural similarity does not always lead to predictable or similar human health properties. It has to be justified why such prediction is possible in view of the identified structural differences and the provided evidence has to support such explanation. In particular, the structural similarities must be linked to a scientific explanation of how and why a prediction is possible.

You have described the structural similarities between target and source substances by explaining that both substances contain three methylethylketoxime groups. You further explain that the difference between the substances is a methyl (in the source substance) or a vinyl group (in the target substance) in the fourth position on the silicon atom.

You state that the substances belong to an existing category: OECD HPV program; HPV Category, SIDS Oximino Silanes Category, 2009. ECHA notes that the OECD category of Oximino Silanes consists only of two substances, i.e. the target and source substances, and cannot therefore be considered a category.

ECHA notes that you have not provided information on how the structural differences in the parent substances and consequently in the silanol hydrolysis products may impact the

toxicity of the substances and thus affect the possibility to predict properties of the target substance from the data obtained with the source substance.

However, ECHA considers that the submitted toxicokinetic and toxicological data provides evidence to support your read-across approach as discussed in section (ii) under the headings "toxicokinetics", "hydrolysis" and "toxicological data" below.

(ii) Similar properties or regular pattern as a result of structural similarity

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"*. One prerequisite for a prediction based on read-across therefore is that the substances involved are structurally similar and are likely to have similar properties. One important aspect in this regard is the analysis of the data matrix to compare the properties of source and target substances and to establish whether indeed they are similar or follow a regular pattern.

In your read-across justification you state that physico-chemical parameters/properties of target and source substances are similar. ECHA observes that the physico-chemical properties of target and source substances are in the same/similar range.

Hydrolysis

ECHA understands that the hypothesis relies also on the assumption that both target and source substances undergo rapid hydrolysis producing *"respective silanetriol hydrolysis products and methylethylketoxime"*.

ECHA observes that based on the hydrolysis study (OECD 111) the source substance hydrolyses rapidly (at pH 7 and 2°C, less than 1 minute). ECHA notes that the target substance is also expected to hydrolyse rapidly. The common hydrolysis product is methylethylketoxime (CAS No. 96-29-7; MEKO), and non-common hydrolysis products are methyl- or vinyl-substituted silanetriols formed from the source and target substances, respectively.
ECHA observes that you have provided sufficient evidence to demonstrate that the hydrolysis of the target and source substances is rapid and that the common hydrolysis product ([redacted] moles of MEKO) and non-common hydrolysis products ([redacted] mole of vinylsilanetriol and methylsilanetriol) are formed from the target and source substances.

Condensation of the silanols

You explain that the silanol hydrolysis products may undergo condensation reactions leading to the formation of siloxane dimers, oligomers and polymers and state that:
"depending on the pH and concentration of the substance, the reactive methyl or vinyl substituted silanetriols (at concentrations greater than 500 mg/l) can condense to form highly cross-linked, high molecular weight polymers, further reducing the potential for exposure (OECD, 2009d)".

ECHA observes that you have not addressed sufficiently the impact of the possible condensation of the silanols on toxicity. However, ECHA notes that since both methyl- and vinyl silanols are silanetriols the condensation reactions are expected to be similar.

Toxicokinetics

You state that *"due to the rapid hydrolysis, relevant oral, dermal and inhalation systemic exposure would be to the hydrolysis products"*.

You state that no toxicokinetic data is available for the target and source substances. However, you have provided toxicokinetic information on the common hydrolysis product, MEKO, and non-common hydrolysis products vinylsilanetriol and methylsilanetriol. ECHA observes that since the hydrolysis of the parent substances is very rapid, toxicokinetic assessment of the hydrolysis products is relevant. ECHA notes that based on the physico-chemical properties of vinylsilanetriol and methylsilanetriol, toxicokinetic properties of these hydrolysis products are expected to be similar. ECHA further notes that due to rapid hydrolysis systemic exposure is expected to be to the hydrolysis products as claimed by you.

Toxicological data

You claim that the target and source substances have similar toxicity profiles and "*common levels and mode of human health related effects*".

Based on the data provided ECHA notes that the target and source substances and the common hydrolysis product MEKO, have similar acute oral and dermal toxicity profiles, are classified as eye irritants and skin sensitisers and are not genotoxic.

You claim that the critical effects are haematological effects mainly caused by MEKO. You further claim that since similar toxic effects "*at comparable doses*" were observed in studies conducted with the source substance and MEKO, read-across from the source substance to the target substance is appropriate. ECHA observers that based on the oral OECD 422 and OECD 408 studies conducted with the source substance and MEKO, respectively, similar effects were observed, such as anaemia, haematopoiesis and hemosiderin deposits. ECHA notes that the NOAEL and LOAEL values are in similar range (NOAELs of 10 and 25/30 mg/kg bw/day for the source substance and MEKO, respectively). ECHA observers that you have classified the target and source substances and MEKO as STOT RE Cat 2 based on haematotoxic effects.

Regarding fertility and developmental toxicity, you have provided an oral OECD 422 study conducted with the source substance, in which no reproductive effects were observed at the highest dose (250 mg/kg bw/day). In addition, in the read-across justification document you state that MEKO is not classified for developmental toxicity and refer to a pre-natal developmental toxicity study (OECD 414) conducted with MEKO in which no adverse effects were observed.

The non-silanol hydrolysis products

ECHA notes that you have addressed the toxicity of the non-common hydrolysis products, vinylsilanetriol and methylsilanetriol, by referring to oral OECD 422 studies conducted with trimethoxy(vinyl)silane (CAS no 2768-02-7) and trimethoxy(methyl)silane (CAS no 1185-55-3), which are hydrolysed to the same hydrolysis products as the target and source substances subject to the current decision. No adverse effects on reproductive parameters were observed in these studies.

ECHA considers that you have provided sufficient evidence to demonstrate that the hydrolysis of the target and source substances is rapid and that the common hydrolysis product ([redacted] moles of MEKO) and non-common hydrolysis products ([redacted] mole of vinylsilanetriol and methylsilanetriol) are formed from the target and source substances. In addition, there is sufficient evidence to demonstrate that the repeated-dose and reproductive toxicity profiles of the source substance and the common hydrolysis product MEKO are similar, and that MEKO is expected to be responsible for the effects observed in the repeated-dose toxicity studies. In addition, the two other supporting substances (trimethoxy(vinyl)silane

(CAS no 2768-02-7) and trimethoxy(methyl)silane (CAS no 1185-55-3)) show no adverse effects on reproductive parameters, suggesting that the non-common hydrolysis products do not impact the toxicity profiles of the target and source substances.

ECHA concludes that the data provided provides sufficient evidence to conclude that there is an adequate basis for predicting the human health properties of the target substance from the data obtained with the source substance.

e. Conclusion on the read-across approach

Based on the above considerations ECHA concludes that you have provided adequate and reliable information to demonstrate that the proposed read-across approach is plausible for the endpoint in consideration.

ECHA therefore concludes that the criteria of Annex XI, Section 1.5, are met, and consequently the testing proposed on the read-across substance is appropriate to fulfil the information requirement of the substance subject to the present decision.

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

a) Examination of the testing proposal

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.

A pre-natal developmental toxicity study for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for a pre-natal developmental toxicity study in rats according to EU B.31./OECD TG 414 by the oral route with the analogue substance butan-2-one O, O', O''-(methylsilylidyne)trioxime (CAS 22984-54-9, EC no 245-366-4).

ECHA has evaluated your proposal to perform the test with the analogue substance butan-2-one O, O', O''-(methylsilylidyne)trioxime (CAS 22984-54-9, EC no 245-366-4). Based on the data submitted by you, ECHA concludes that you have provided adequate and reliable information to demonstrate that the read-across approach is plausible for the pre-natal developmental toxicity endpoint as explained in Section 0 "Read-across approach" of this decision, and your adaptation of the information requirement can be accepted.

ECHA considers that the proposed study performed with the analogue substance butan-2-one O, O', O''-(methylsilylidyne)trioxime (CAS 22984-54-9, EC no 245-366-4) is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

You proposed testing with the rat as a first species. According to the test method EU B.31/OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed with the rat or rabbit as a first species.

You proposed testing by the oral route. ECHA agrees that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information*

requirements and chemical safety assessment (version 6.0, July 2017) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

In your comments on the draft decision, you noted that there might have been a mistake in ECHA request, as ECHA has accepted a testing proposal on an analogue substance while requesting to conduct the test with the registered substance. ECHA acknowledged an administrative mistake and amended the request in the draft decision.

b) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed study with the butan-2-one O, O', O''-(methylsilylidyne)trioxime (CAS 22984-54-9, EC no 245-366-4): Pre-natal developmental toxicity study in a first species (rats or rabbits), oral route (test method: EU B.31./OECD TG 414).

Notes for your consideration

For the selection of the appropriate species you are advised to consult ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017), Chapter R.7a, section R.7.6.2.3.2.

ECHA notes that a revised version of OECD TG 414 was adopted this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. You should test in accordance with the revised version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788).

Appendix 2: Procedural history

ECHA received your registration containing the testing proposal for examination pursuant to Article 40(1) on 30 April 2015.

ECHA notes that the tonnage band for one member of the joint submission is 100 to 1000 tonnes per year.

ECHA held a third party consultation for the testing proposal from 25 June 2015 until 10 August 2015. ECHA did not receive information from third parties.

This decision does not take into account any updates after **11 July 2016**, 30 calendar days after the end of the commenting period.

ECHA notified you of the draft decision and invited you to provide comments. In your comments to the draft decision you provided specific considerations to the test substance requested by ECHA to be used for conducting pre-natal developmental toxicity study, subject to the current decision.

You did not update your registration dossier. ECHA took into account your comments and amended the request in the draft decision.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation

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Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided in your registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the registration at a later stage.

2. Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the Enforcement Authorities of the Member States.

3. In relation to the information required by the present decision, the sample of the substance used for the new test(s) must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants. It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new test(s) is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new test(s) must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.

4. In case the required test is conducted with an analogue substance in the context of a read-across approach, the identity of the test material used to perform the test should be specified in line with the ECHA's Practical Guide 6 "How to report on read-across". This is required to demonstrate that the test material is representative of the analogue substance identified in the read-across approach and used to predict the properties of the registered substance.