EUROPEAN CHEMICALS AGENCY

Helsinki, 16 June 2020

Addressees
Registrants of [redacted] EC# 214-685-0 listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
08/02/2018

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Trimethoxy(methyl)silane
EC number: 214-685-0
CAS number: 1185-55-3

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

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of ***21 September 2021***

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

1. Skin sensitisation (Annex VII, Section 8.3.) with the Substance

   i. *in vitro/in chemico* skin sensitisation information on molecular interactions with skin proteins (OECD TG 442C), inflammatory response in keratinocytes (OECD TG 442D) and activation of dendritic cells (OECD TG 442E)(Annex VII, Section 8.3.1.); and

   ii. Only if the *in vitro/in chemico* test methods specified under point 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);

Conditions to comply with the requests

Each addressee of this decision is bound by the requests for information corresponding to the REACH Annexes applicable to their own registered tonnage of the Substance at the time of evaluation of the jointly submitted dossier.

To identify your legal obligations, please refer to the following:

- you have to comply with the requirements of Annex VII of REACH, if you have registered a substance at 1-10 tonnes per annum (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- you have to comply with the requirements of Annexes VII and VIII of REACH, if you have registered a substance at 10-100 tpa;
- you have to comply with the requirements of Annexes VII, VIII and IX of REACH, if

you have registered a substance at 100-1000 tpa;

- you have to comply with the requirements of Annexes VII to X of REACH, if you have registered a substance at above 1000 tpa.

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

The Appendices state the reasons for the requests for information to fulfil the requirements set out in the respective Annexes of REACH.

The Appendix entitled Observations and technical guidance addresses the generic approach for the selection and reporting of the test material used to perform the required studies and provides generic recommendations and references to ECHA guidance and other reference documents.

You must submit the information requested in this decision by the deadline indicated above in an updated registration dossier and also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information.

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.

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 requests to comply with Annex VII of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier registered at 1 to 10 tonnes or more per year must contain, as a minimum, the information specified in Annex VII to REACH.

1. Skin sensitisation (Annex VII, Section 8.3.)

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

You have provided the following *in vivo* information which you use as part of a weight of evidence adaptation according to REACH Annex XI, Section 1.2:

i. [redacted] 2013, according to OECD 406 (Skin sensitisation) with the Substance in guinea pig.
ii. [redacted] 2009, according to OECD 406 (Skin sensitisation) with the Substance in guinea pig.
iii. Sensitisation data in humans provided in IUCLID Section 7.10.4:
   - [redacted] (2017) [redacted] (2017)

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.4.4, 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 of the information for the given regulatory endpoint. Subsequently, relevance, reliability, 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.

ECHA has assessed your adaptation and identified the following issues.

1. Lack of documentation for the adaptation

You have provided a justification for the weight of evidence adaptation as follows: "*Two in vivo skin sensitisation studies ([redacted], 2013 and [redacted], 2009) in guinea pigs conducted according to the Buehler Test protocol together with information on workers form a weight of evidence for the skin sensitising potential of trimethoxy(methyl)silane. In the first test conducted by [redacted] (2009) the test substance was found to be sensitising. However, in a more recent test the result was negative ([redacted], 2013).*

Two trimethoxy(methyl)silane manufacturers have provided statements which confirm that there have been no cases of skin sensitisation amongst workers during more than 20 years of manufacture (see IUCLID Section 7.10.4) ([redacted], 2017; [redacted], 2017)."

However, your justification does not 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 could lead to the rejection of the adaptation, ECHA has assessed the provided sources of information.

2. Sources of information

The sources of information must provide sufficient weight of evidence to conclude that the information requirement for skin sensitisation, as specified in all of the available test guidelines (*in vitro* and *in vivo*[2]), is fulfilled by integrating and weighing the evidence e.g. the following aspects are covered: A) whether the substance causes skin sensitisation, and B) whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A), in case, the substance is considered to be a skin sensitiser.

ECHA has assessed to what extent the sources of information submitted enables a conclusion on these properties A) and B) and identified the following deficiencies:

A) Assessment if the Substance causes skin sensitisation

You have provided three studies (i. to iii.) to address whether the Substance causes skin sensitisation.

1) Study (iii.)

This study does not provide information relevant to assess whether the Substance causes skin sensitisation. This is due to the reported exposure being at such a low level that it cannot inform on the potential hazard of the Substance i.e. whether the Substance causes skin sensitisation, as explained below.

For human skin sensitisation studies to be considered relevant, specific conditions need to be met e.g. adequate extent of exposure (ECHA Guidance R.7a, section R.7.3.5.2).

In the document entitled "[redacted]" included in the endpoint study record "[redacted], 2017" under IUCLID section "7.10.4 Sensitisation data (humans)", you have provided information on the exposure situations in workers, including the estimated dermal exposures (ECTOC TRA, mg/kg/day) and the area of dermal exposure (cm^2). You also state that based on your experience there is no indication of sensitising properties of the Substance in the working environment or have been received from customers.

Based on the information provided, the highest dermal exposure, when looking at all of the exposure scenarios, is estimated to be for workers ca. [redacted] $\mu g/cm^2$/day (assuming a weight of 70 kg) and for consumers ca. [redacted] $\mu g/cm^2$/day (assuming a weight of 70 kg). The reported estimated exposures are very low and cannot inform about potential hazardous properties of the substance i.e. whether the substance can cause skin sensitisation. For comparison, substances requiring classification as moderate skin sensitisers (Cat 1B according to CLP), in the human repeat insult

[2] OECD TGs 442C, 442D, 442E, 429, 442A, 442B and 406

patch test threshold for no observed effect level (NOEL) has been described as ranging between several hundreds to thousands in µg/cm^2 (Basketter et al, 2014[3]). Therefore, when humans have been exposed to concentrations around tens of µg/cm^2/day, as in the documentation on worker exposure you provided, this cannot be considered high enough to conclude that the substance does not have a hazardous property.

2) Studies (i.) and (ii.)

These studies are considered relevant for assessment of whether the Substance causes skin sensitisation, but have deficiencies regarding reliability, as described below.

For *in vivo* skin sensitisation studies to be considered reliable, the study must follow the principles of the test method (OECD TG 406), which include that:

a) The concentration used for induction should be the highest to cause mild-to-moderate skin irritation
b) The concentration used for challenge should be the highest non-irritant concentration.

The reported data for the studies you have provided showed that:

a) The concentration used for induction did not cause mild-to-moderate skin irritation as required by the OECD TG 406 (study i.)
b) The concentration used for the first challenge caused skin irritation and the study was considered by you as equivocal due to methodological issues (study ii.)

Therefore, the provided studies do not follow the principles of the test method and cannot be used to fulfil the information requirement.

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

As the currently available data does not allow to conclude whether the Substance causes skin sensitisation, this is not assessed.

Conclusion

Taken together, although some sources of information as indicated above, provide relevant information, they have major issues related to reliability. Testing the Substance at appropriate doses, as indicated above, is required in order to assess whether the Substance has a hazardous property.

Therefore, it is not possible to conclude whether your Substance causes skin sensitisation or not. Consequently, your adaptation is rejected and the information requirement is not fulfilled.

In your comments on the draft decision you agree with the need to conduct an additional skin sensitisation test.

Information on the design of the studies to be performed

[3] Basketter et al (2014), Categorization of Chemicals According to Their Relative Human Skin Sensitizing Potency (Dermatitis)

To fulfil the information requirement for the Substance for skin sensitisation, *in vitro/in chemico* studies (OECD TG 442C, 442D and 442E) are considered suitable. In case *in vitro/in chemico* methods are not suitable for the Substance or the results cannot be used for classification and risk assessment an *in vivo* skin sensitisation study must be performed and the murine local lymph node assay (LLNA) (OEDC TG 429) is considered as the appropriate study, for the following reasons:

In your comments on the draft decision you argue that *in vitro/in chemico* methods are not suitable for the Substance. You refer to a substance evaluation final decision for another alkoxysilane, 3-trimethoxysilylpropyl methacrylate (EC number: 219-785-8, CAS number: 2530-85-0) where ECHA concluded that the suitability of *in vitro/in chemico* methods was uncertain. The reasons being that the substance (EC number: 219-785-8) rapidly hydrolyses in water and given that the *in vitro/in chemico* methods require incubation with the test material for at least 24 hours in an aqueous solution, significant hydrolysis would be likely to occur preventing an assessment of the sensitisation potential of the parent (neat) substance.

ECHA notes that the Substance is also likely to hydrolyse rapidly in water. If it can be proven, that the *in vitro/in chemico* methods are not suitable for the Substance, an adaptation for not performing those studies must be included in the dossier (Annex VII, section 8.3.1., column 2).

The LLNA (OEDC TG 429) is the first-choice method for *in vivo* testing. Other tests can only be used in exceptional circumstances when an appropriate justification is provided (Annex VII, section 8.3.2.).

You have provided the following arguments against the suitability of the LLNA: "*The current accepted and preferred method for skin sensitisation testing according to the REACH Regulation (EC No 1907/2006) and CLP Regulation (EC No 1272/2008) is the murine local lymph node assay (LLNA). A validated test method, OECD TG 429 (OECD 2010) is available for the LLNA. The guideline acknowledges the limits of the LLNA, and states that there are instances where 'test substance classes or substances containing functional groups shown to act as potential confounders' make the use of guinea pig tests more appropriate. It is concluded that the LLNA is not applicable where the properties of the test material cause interference in the accuracy of the LLNA (OECD 2010). The statement in the OECD TG 429 is given with reference to the findings of Basketter et al. (2009a), who demonstrated false positives in silicon based substances which had previously been demonstrated to be non-sensitisers in the guinea pig maximisation test (GPMT).*

The importance of available evidence from guinea pig results, consideration of chemical reactivity, epidermal bioavailability and clinical and experimental human data are emphasised as central to reaching appropriate regulatory decisions for substances which have been shown to fall outside the specificity of the LLNA (Basketter et al., 2009b). The non-applicability of the LLNA for silicone based substances has also been demonstrated by Petry et al. (2012). The sensitisation potential of polyfunctional silicone materials was tested in a comparative study investigating the GPMT and the LLNA assays, which found the five tested substances to be negative in the GPMT whereas they were concluded to be weak to moderate skin sensitisers in the LLNA (Petry et al., 2012)."

You refer to the results from studies investigating the suitability of the LLNA assay to identify skin sensitisation potential of alkoxysilanes (Basketter, et al., 2009a and b; Petry et al., 2012) which indicated that testing of substances from the group of alkoxysilanes in the LLNA assay may lead to false positive results. However, the publicly available reports cited in the justification are considered as insufficient evidence to conclude that the LLNA is not suitable for this group of substances. Several limitations are noted in this respect:

- Basketter et al., 2009a: In the publication only one polyaminofunctional siloxane (specific substance details was not provided) was tested in the LLNA and GPMT (OECD TG 406). Discordant results were obtained, i.e. LLNA positive and GPMT negative. In the LLNA this polyaminofuctional siloxane showed marked ear thickness increase at the two highest concentrations and marginal increase in the low dose (amount of increase not specified). The author considered that "*Irritancy remains as a confounding characteristic regardless of the assay/methodology for skin sensitization and in this situation one cannot be certain what role it plays in this particular assay.*". The Substance under consideration is not a polyfunctional siloxane nor irritating to the skin and you have not explained the relevance of this information for the Substance.

- Basketter et al., 2009b: The publication discusses in general terms that no assay is perfect and examines how to deal with uncertainties such as irritancy and structural alerts (or the lack thereof). The publication does not provided any argumentation that would be specific for the Substance.

- Petry et al., 2012: In this publication there are results for five polyfunctional siloxanes (mainly propylpi-pyridyl functionalized silicone substances). These substances are substantially different to the Substance (e.g. in size and side chain structure) and you have not explained the relevance of this information for the Substance.

- Furthermore, other studies concluded that at the present there is a lack of mechanistic information for these allegedly false positive findings (Basketter 2011[4]) .

To conclude, there is no appropriate, Substance specific justification to consider that the LLNA is unsuitable.

[4] Basketter D., Kimber I (2011). Skin irritation, false positives and the local lymph node assay: a guideline issue? Reg. Toxicol. Pharmacol. 61, 137–140.

Appendix B: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of registration dossiers after the date on which you were notified the draft decision according to Article 50(1) of REACH.

The compliance check was initiated on 25 April 2019.

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

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of the Member States.

3. Test guidelines, GLP requirements and reporting

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

   Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses shall be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

   Under Article 10 (a) (vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide: 'How to report robust study summaries'[5].

4. Test material

   Selection of the test material(s)

   The registrants of the Substance are responsible for agreeing on the composition of the test material to be selected for carrying out the tests required by the present decision. The test material selected must be relevant for all the registrants of the Substance, i.e. it takes into account the variation in compositions reported by all members of the joint submission. The composition of the test material(s) must fall within the boundary composition(s) of the Substance.

   While selecting the test material you must take into account the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected test material must contain that constituent/ impurity.

   Technical reporting of the test material

   The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and their concentration values. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

   Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[6].

[5] https://echa.europa.eu/practical-guides
[6] https://echa.europa.eu/manuals

5. List of references of the ECHA Guidance and other guidance/ reference documents[7]

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 in this decision.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 in this decision.

ECHA Read-across assessment framework (RAAF, March 2017)[8]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

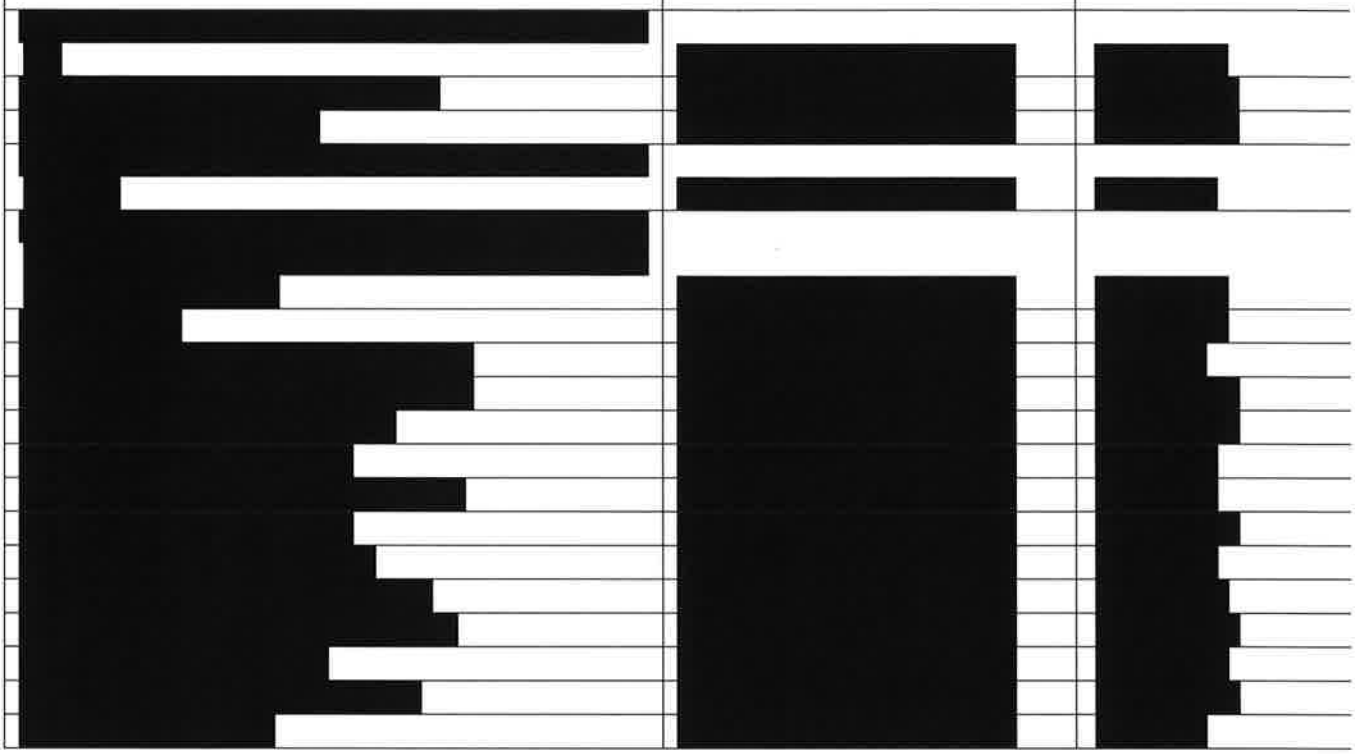
PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

OECD Guidance documents[9]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD23.
Guidance Document on Mammalian Reproductive Toxicity Testing and Assessment – No 43, referred to as OECD GD43.

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

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 fufilled
		

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.