SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Trimethoxy(methyl)silane

EC No 214-685-0

CAS No 1185-55-3

Evaluating Member State(s): Sweden

Dated: 16 June 2020

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Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2013

Before concluding the substance evaluation a Decision to request further information was issued on 4 July 2016.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

Trimethoxy(methyl)silane was originally selected for substance evaluation in order to clarify concerns about:

- Human health – potential skin sensitiser
- Exposure - wide dispersive use
- Consumer use
- Aggregated tonnage

During the evaluation also other concerns were identified. The additional concerns were:

- Mutagenicity
- Derivation of DNELs

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Dossier evaluation was performed and a compliance check decision (CCH) was issued which is being prepared for publication in 2020. The CCH is requesting further skin sensitisation information. Additionally, a testing proposal decision has requested an extended one-generation reproductive toxicity study and pre-natal developmental toxicity studies in rats and rabbits by 18 June 2021

Harmonised classification as Skin Sens. Category 1B was proposed by the Swedish CA in May 2017. The Risk Assessment Committee (RAC) opinion was adopted in September 2018: "should not be classified as skin sensitiser due to inconclusive data".

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State to the following conclusions, as summarised in the table below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION	
Conclusions	**Tick box**
Need for follow-up regulatory action at EU level	
Harmonised Classification and Labelling	
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level	X

Based on the CCH and TPE outcomes, the MSCA may consider a new CLH proposal.

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

4.1.1. Harmonised Classification and Labelling

Not applicable. Based on future data coming from CCH and TPE outcomes, the MSCA may consider a new CLH proposal.

4.1.2. Other EU-wide regulatory risk management measures

Not applicable.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1. No need for regulatory follow-up at EU level

Table 2

REASON FOR REMOVED CONCERN The concern could be removed because	Tick box
Clarification of hazard properties/exposure	X
Actions by the registrants to ensure safety, as reflected in the registration dossiers	

A mammalian alkaline comet assay, according to the OECD TG 489, was performed subsequent to the substance evaluation decision. The results were negative. The evaluating MSCA concluded that there was no remaining concern for mutagenicity.

The concern for skin sensitisation was not clarified in this evaluation. The information on skin sensitisation was identified as a data gap for a standard information requirement and, following an inconclusive opinion by RAC handed over to ECHA to be requested under compliance check.

The Registrant(s) provided information on the reasoning behind the choice of assessment factors used for derivation of DNELs. The Registrant(s) also provided further information on exposure estimations for the worker and consumer use of products containing the substance. The evaluating MSCA concluded that no further information was needed for risk assessment.

5.2. Other actions

Not applicable.

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Not applicable.

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

Trimethoxy(methyl)silane was originally selected for substance evaluation in order to clarify concerns about:

- Human health – potential skin sensitiser
- Exposure - wide dispersive use
- Consumer use
- Aggregated tonnage

During the evaluation also other concerns were identified. The additional concerns were:

- Mutagenicity
- Derivation of DNELs

Table 4

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Skin Sensitisation	An *in vivo* skin sensitisation test (OECD TG 429) was requested in the initial draft decision, but was removed at the MSC-47 (25-29 April 2016), based on the reasoning that the available data may be sufficient to classify the substance. The Risk Assessment Committee concluded: "no classification due to inconclusive data". As this information was a standard data requirement, compliance check was considered the most appropriate process to request it under. Therefore, the test was requested under compliance check.
Mutagenicity	An *in vivo* Mammalian alkaline comet assay (OECD TG 489) was performed following the SEv decision, which was negative. No further action.
DNEL derivation	Justification for use of lower assessment factors than default for derivation of DNELs was provided, following the SEv decision. No further action.
Worker and consumer exposure	Information on exposure estimation for workers and consumers was updated in the registration(s). No further action.

7.2. Procedure

Trimethoxy(methyl)silane (TMMS) was included in the Community Rolling Action Plan (CoRAP) for substance evaluation (SEv) in 2013, by the competent authority of Sweden. The scope of the evaluation was human health, targeted to concerns for skin sensitisation, mutagenicity and risk assessment.

The initial draft decision, notified to the competent authorities of the other member states and ECHA in January 2016, included a request for an *in vivo* assay (OECD TG 429) to address the skin sensitisation concern. However, this request was removed from the decision, based on the reasoning at MSC-47 (25-29 April 2016) that the available information may be sufficient to classify the substance as a skin sensitiser.

The SEv decision was issued in July 2016, with request for information on mutagenicity (OECD TG 489), derivation of DNELs and exposure of consumers and professional users.

In May 2017 the Swedish CA submitted a classification dossier for the substance with the proposal Skin Sens., Category 1B.

In September 2018 the Risk Assessment Committee (RAC) opinion was adopted. RAC concluded: "Overall, all the available information is of limited reliability and in combination does not allow a conclusion on the skin sensitising potential of TMMS. Therefore, RAC is of the opinion that TMMS should not be classified as skin sensitiser due to inconclusive data".

In February 2018 the registration(s) were updated. An *in vivo* Mammalian alkaline comet assay, according to the OECD TG 489 was provided. Also, information on derivation of DNELs and exposure assessment was updated. The evaluating MSCA assessed the new information in the follow-up evaluation and concluded that no further information on these endpoints was needed.

The request to clarify the skin sensitisation potential was handed over to CCH, as this information was identified as a data gap for a standard information requirement. Information to clarify the potential for skin sensitisation was requested in the CCH decision which is being prepared for publication in 2020.

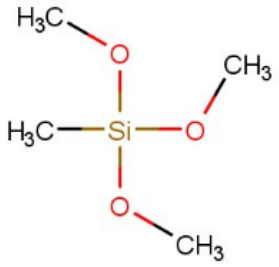
7.3. Identity of the substance

Table 5

SUBSTANCE IDENTITY	
Public name:	Trimethoxy(methyl)silane
EC number:	214-685-0
CAS number:	1185-55-3
Index number in Annex VI of the CLP Regulation:	-
Molecular formula:	C4H12O3Si
Molecular weight range:	136 g/mol
Synonyms:	METHYLTRIMETHOXYSILANE Alkoxyalkylsilane

Type of substance: Mono-constituent

Structural formula:



7.4. Physico-chemical properties

Table 7

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	Liquid
Vapour pressure	29,9-147,1 hPa at 20-50°C
Water solubility	91-1000 g/L 20°C
Partition coefficient n-octanol/water (Log Kow)	-2,4-0,7 at 20°C
Flammability	Highly flammable
Flash point	7,7°C at 101 kPa
Explosive properties	Non-explosive
Oxidising properties	Non-oxidising

7.5. Manufacture and uses

7.5.1. Quantities

Table 8

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t	☐ 10 – 100 t	☐ 100 – 1000 t	☒ 1000- 10,000 t	☐ 10,000-50,000 t
☐ 50,000 – 100,000 t	☐ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☐ > 1000,000 t	☐ Confidential

7.5.2. Overview of uses

Table 9

USES	Use(s)
Uses as intermediate	Intermediate in the production of polymers or resins
Formulation	Formulation or re-packing at industrial sites and in manufacturing
Uses at industrial sites	Coatings, adhesives and sealants products Textile treatment products Building and construction work Machinery and vehicles Electrical, electronic and optical equipment Plastic and mineral products (e.g. plasters, cement) Textile, leather or fur
Uses by professional workers	Coatings, adhesives and sealants products Textile treatment products Building and construction work
Consumer Uses	Adhesives and sealants Coating products Textile treatment products
Article service life	Indoor and outdoor use of long-life materials with low release rate, e.g. furniture, toys and building material

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

None.

The RAC opinion was inconclusive for skin sens. Therefore, no entry in Annex VI of CLP could be proposed by RAC.

7.6.2. Self-classification

In the registration(s):

Flam. Liq. 2	H225

The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory:

Skin Irrit. 2	H315
Eye Irrit. 2	H319
STOT SE 3	H335 (respiratory irritation)
Skin Sens. 1	H317
Skin Sens. 1B	H317
Flam. Gas 2	H221
Acute Tox. 4	H302
Acute Tox.4	H332
Flam. Liq. 3	H226

7.7. Environmental fate properties

Not evaluated.

7.8. Environmental hazard assessment

Not evaluated.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

Not evaluated. See section 7.9.9. for an overview of toxicokinetics information.

7.9.2. Acute toxicity and Corrosion/Irritation

Not evaluated.

7.9.3. Sensitisation

The concern for skin sensitisation was based on unreliability of the available animal and human data on trimethoxy(methyl)silane and uncertainty in the overall evidence from the structurally similar substances.

One *in vivo* Buehler test (OECD TG 406) with trimethoxy(methyl)silane was positive (Unpublished study report 2009). However, the study was considered unreliable as positive reaction in the negative control animals was reported. A second Buehler study was negative (Unpublished study report 2013). However, this study had also limitations, as the starting concentration selected for induction was not the highest to cause mild-to-moderate skin irritation, as required by the OECD TG 406. Thus, the evaluating MSCA considered that overall the existing *in vivo* data were inconclusive.

The concern could not be clarified by a weight of evidence approach, based on available data on the structurally similar substances. Negative results of studies with other alkoxysilanes, including Guinea pig maximisation test with triethoxy(methyl)silane, EC 217-983-9 (Unpublished study report 1992) and trimethoxy(vinyl)silane, EC 220-449-8 (Unpublished study report 2000) and positive Buehler study with trimethoxy(vinyl)silane (Unpublished study report 1993) were reported.

Regarding information on human exposure the Registrant(s) provided a summary report (Unpublished study report 2013) stating: only acute slight redness, but no case of skin sensitisation has been observed. Based on the experience of the plant managers and the application experts with direct relations to the customers there is no indication/information of sensitising properties of trimethoxy(methyl)silane and of mixtures containing this substance.

The Registrant(s) concluded that although the available animal data for the group of alkoxysilanes was not consistent, considering the human data, indicating no skin sensitisation potential, further *in vivo* testing was unnecessary. However, in the evaluating MSCA's view the information provided on human exposure was not satisfactory to address the skin sensitisation potential. The report did not include methodical analysis of the populations exposed to trimethoxy(methyl)silane at work or as consumers, but rather referred to a lack of information.

To clarify the skin sensitisation concern an *in vivo* Local Lymph Node Assay (LLNA), according to the OECD TG 429 was requested in the initial SEv draft decision. The test was requested to generate the necessary information for classification and subcategorization of the substance into category 1A or 1B. However, this request was removed at the MSC meeting, based on the reasoning that the available data may be

sufficient to classify the substance. Consequently, the Swedish CA submitted a CLH dossier with the proposal for classification as Skin Sens. 1B. The conclusion of the Risk Assessment Committee was "no classification due to inconclusive data".

Thus, the need for further information to clarify the concern remained. As this information was identified as a standard information requirement under REACH, CCH was considered the most appropriate process to obtain it. Therefore, information on skin sensitisation was requested under CCH, which is being prepared for publication in 2020.

7.9.4. Repeated dose toxicity

Not evaluated.

7.9.5. Mutagenicity

Available information indicated a concern for mutagenicity, both gene mutation and clastogenicity potential, for the substance. The concern for induction of gene mutation was based on the positive result from an *in vitro* mammalian cell gene mutation assay, according to the OECD TG 476 (Unpublished study report 2002). A dose-dependent increase in mutant frequency was observed with metabolic activation in mouse lymphoma cells. At concentrations causing a positive response in the mutant frequency more small than large colonies were formed, suggesting the substance may cause chromosomal aberrations.

The available *in vivo* micronucleus assay, according to the OECD TG 474 was negative (Unpublished study report 2002). However, the result of this study was considered uncertain, as no clear evidence that the substance had reached the target cells (bone marrow) was provided. Although the clinical signs and mortality indicated bioavailability, evaluation of bone marrow cells showed no signs of toxicity. Thus, the need to clarify the potential to cause chromosomal aberrations *in vivo* remained.

In the SEv decision an *in vivo* mammalian alkaline comet assay, according to the OECD TG 489, in rats was requested. The Registrant(s) carried out the comet assay, via the inhalation route. DNA damage was assessed in lung, liver and bone marrow (Unpublished study report 2017). A dose-range finding study was conducted first. The substance was administrated as a vapour by nose only inhalation, for 4 hours on three consecutive days to one group of three males and three females. The maximum dose was set to 20 mg/L, based on the subchronic inhalation toxicity studies with the substance, where mortality and clinical effects were observed at 22 and 44 mg/L for 14 days and at 2 and 9 mg/L for 90 days (Unpublished study reports 2007 and 2008). Reduced body weight gain in all males and one female and body weight loss in two females was noted at 20 mg/L.

The main study was conducted in two sessions. In session one 20 mg/L and in session two 5 and 10 mg/L were tested. Each session included a negative and a positive control. No statistically significant increase in the mean Tail Intensity (%) was observed in the tested tissues. The Tail Intensity at 5, 10 and 20 mg/L was 9.13%, 7.03% and 12.29% in bone marrow, 6.80%, 10.06% and 3.66% in liver and 4.52%, 6.33% and 8.42% in lung. All values were within the range of the historical negative controls (1.92-17.26% for bone marrow, 0.13-27.12% for liver and 0.69-37.02% for lung).

The negative control mean Tail Intensity in bone marrow and liver in session one (18.43% and 35.76%) were above the upper limit of the range. However, since these were only slightly above the range and the positive control caused severe DNA damage, the assays were considered acceptable and it was concluded that the test substance does not cause DNA damage.

The evaluating MSCA concluded that no further mutagenicity testing was needed.

7.9.6. Carcinogenicity

Not evaluated.

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

Not evaluated

7.9.8. Hazard assessment of physico-chemical properties

Not evaluated.

The substance is classified as Flammable Liquid Category 2 (H225: Highly flammable liquid and vapour). This is on the basis of a flash point of 7.7°C and a measured boiling point of 102°C. Lower and upper explosion limits are 1.5 vol% and 27 vol%.

7.9.9. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

In the registration(s) long-term DNELs for systemic effects are derived for the inhalation, dermal and oral route.

The dermal and inhalation DNELs are based on NOAEC=560 mg/m^3 from a subchronic inhalation study in rats. The effects observed included decreased body weights and histopathology findings in kidney and urinary bladder. The oral DNEL is derived from the NOAEL=50 mg/kg bw/day from a repeated dose toxicity screening study, according to the OECD TG 422. The effects observed were changes in weight and/or histopathology in organs including liver, thymus, duodenum and thyroid at or above 250 mg/kg bw/day.

For DNEL derivation the assessment factor used for the intraspecies extrapolation is lower than ECHA's guidance recommendation. This results in less conservative DNELs and bring some of the RCR values below 1. Therefore, under SEv a justification was requested for the use of lower than default assessment factor.

The registration(s) were updated with a justification for the use of lower intraspecies assessment factor. The justification was based on the toxicokinetics information. Physiologically based pharmacokinetic and toxicokinetic (PBTK) models were used to predict absorption, distribution, metabolism and excretion properties of the substance. Based on these predictions the substance is hydrolysed, absorbed and excreted rapidly. In moist medium, trimethoxy(methyl)silane hydrolyses with a half-life of 2.2 hours at pH 7 and 25°C, generating methylsilanetriol and methanol. Following oral exposure, at pH 2 in the stomach, the substance is predicted to hydrolyse to methylsilanetriol within 5 seconds at 37.5°C.

The substance and its hydrolysis product are absorbed to the blood, after inhalation or oral exposure, based on their molecular weight and water solubility. Systemic availability of the substance following these exposure routes is supported by effects observed in the acute and repeated dose toxicity studies (Unpublished study reports 1963, 2005 and 2007).

No study of the metabolism of trimethoxy(methyl)silane is available. However, data from analogue substances indicate no evidence of biodegradation once hydrolysis and subsequent biodegradation of alkoxy/acetoxy groups has been taken into account (Unpublished study report 2013). It was therefore concluded that the substance and its hydrolysis product are not recognised by mammalian metabolic systems. Since this hydrolysis occurs without enzymatic involvement, it was considered appropriate to reduce the intraspecies assessment factor from 5 to 2.2 for workers and from 10 to 3.2 for the general population, by exclusion of the toxicokinetic element of the assessment factor.

The soluble fraction of trimethoxy(methyl)silane in blood is approximately 97% and of methylsilanetriol >99%, suggesting that once absorbed, both substances are likely to be eliminated via the kidneys in urine and excreted from the body.

The evaluating MSCA agreed to the reasoning behind derivation of DNELs.

7.9.10. Conclusions of the human health hazard assessment and related classification and labelling

Trimethoxy(methyl)silane is a flammable liquid and is self-classified, accordingly (see section 7.9.8).

The substance is also self-classified as irritant for eyes, skin and the respiratory tract.

Based on the evaluated available information, no further classification is warranted for the substance. However, depending on the CCH and TPE outcomes, the MSCA may consider a new CLH proposal.

7.10. Assessment of endocrine disrupting (ED) properties

Not evaluated.

7.11. PBT and VPVB assessment

Not evaluated.

7.12. Exposure assessment

7.12.1. Human health

In the registration(s) exposure scenarios are presented for production and the following uses:

- Monomer in the production of silicone polymers or silicone resins
- Intermediate in the production of other organosilicon substances
- Coatings
- Non-metal surface treatment
- Sealants
- Electronics applications
- Textiles applications
- Laboratory reagent in research and development

The exposure scenarios are based on information in the public domain or provided by the producer companies. Direct exposure of workers and the general population to the parent substance or its hydrolysis products may occur via the inhalation and dermal routes. Exposure of the general population may also occur via the oral route.

The substance is known to evolve methanol during curing of products. Due to the hazardous properties of methanol, exposure to methanol is also considered in the risk characterisation of end use of products containing the substance for professional and consumer uses. Methanol was not risk assessed for industrial workers since measures are already in place.

For some of the exposure scenarios, e.g. use of sealant products, it is indicated that the concentration of the monomeric silane in the products is lowered due to polymerisation, compared to the amount initially added to the formulation. Thus, lower concentration were used for the exposure estimations. Subsequent to the request in the SEv decision the Registrant(s) provided studies to support use of lower concentrations (Unpublished study report 2013 and 2010).

The provided studies describe common sealant formulation processes and demonstrate that the residual concentration, at the point of use, of crosslinker in the sealant is reduced. The reports are based on data from 40 analysed samples across 6 different formulations. The range of concentrations that has been tested reflects the composition of the products on the market. In the study from 2013, three formulations with the concentrations 2%, 2,2% and 2,8% of trimethoxy(methyl)silane were tested. Final concentrations were measured to 0,8%, 0,4% and 0,6%, respectively (reduced by about 60-80%).

7.12.2. Environment

Not evaluated.

7.12.3. Combined exposure assessment

Not evaluated.

7.13. Risk characterisation

The described use scenarios for trimethoxy(methyl)silane result in exposure of workers and consumers/general population. The evaluating MSCA notes that the calculated Risk Characterization Ratios (RCRs) for the described uses are below 1.

7.14. References

All the studies referred to are cited in the registration(s).

7.15. Abbreviations

CAS	Chemical abstracts service
CCH	Compliance check
CLH	Harmonised classification
CLP	Classification, labelling and packaging (Regulation (EC) No 1272/2008)
CMR	Carcinogenic, Mutagenic or Reprotoxic
CoRAP	Community Rolling Action Plan
CSR	Chemical safety report
DNEL	Derived no effect level
ECHA	European Chemicals Agency
eMSCA	Evaluating Member State Competent Authority
EOGRTS	Extended one-generation reproductive toxicity study
MSC	Member State Committee
MSCA	Member State Competent Authority
NOAEL	No observed adverse effect level
NOEL	No observed effect level
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
PBT	Persistent, Bioaccumulative, Toxic
RAC	Risk Assessment Committee
TMMS	Trimethoxy(methyl)silane