Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

Trimethoxy(methyl)silane

EC Number: 214-685-0
CAS Number: 1185-55-3

CLH-O-0000001412-86-234/F

Adopted

14 September 2018

14 September 2018

CLH-O-0000001412-86-234/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **trimethoxy(methyl)silane**

EC Number: **214-685-0**

CAS Number: **1185-55-3**

The proposal was submitted by **Sweden** and received by RAC on **15 May 2017.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Sweden has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **13 September 2017**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **30 October 2017**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Bogusław Barański**

Co-Rapporteur, appointed by RAC: **Anna Biró**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **14 September 2018** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal	TBD	trimethoxy(methyl)silane	214-685-0	1185-55-3	Skin Sens. 1B	H317	GHS07 Wng	H317			
RAC opinion	TBD	trimethoxy(methyl)silane	214-685-0	1185-55-3							
Resulting Annex VI entry if agreed by COM	TBD	trimethoxy(methyl)silane	214-685-0	1185-55-3							

GROUNDS FOR ADOPTION OF THE OPINION

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

The dossier submitter (DS) has provided the results of two *in vivo* skin sensitisation studies of trimethoxy(methyl)silane (TMMS) in guinea pigs conducted according to the Buehler protocol and, additionally, existing human data.

Animal data

The first Buehler test (study report, 2009) was performed according to OECD TG 406 (EU Method B.6) and in compliance with GLP. Purity of tested TMMS was 96.4 ± 0.2%.

An irritation screening was conducted prior to the main study to determine the mild-to-moderate irritating concentration for the induction and the highest non-irritating concentration for the challenge and re-challenge. Topical administration of TMMS at 75% in PEG 300 (polyethylene glycol of average molecular weight 300) as vehicle, resulted in slight skin reactions (grade 1, discrete or patchy erythema) with scaling. TMMS at 50% in PEG 300 produced slight skin irritation (grade 1), but without scaling, and therefore this concentration was selected for the epidermal induction period. TMMS at 25% in PEG 300 did not result in a local skin reaction during irritation screening.

In the main study the following concentrations of TMMS in PEG 300 were used: 50% for the epidermal induction period (6 hours exposure) applied once per week for three consecutive weeks of induction phase, 25% for challenge and re-challenge, 15% in PEG 300 was used additionally for re-challenge.

The animals in the control group, during induction phase, were treated with the vehicle PEG 300 only. Two weeks after the final application for induction, the control and treated animals were challenged with TMMS at 25% in PEG 300 (left flank) and PEG 300 alone (right flank).

The results of the first challenge (see table below) indicate an unspecific irritation reaction in treated and control animals because the number of positive skin reactions were approximately the same in the control as in the treated group. No positive reactions were seen in the re-challenge using 15% TMMS in PEG 300. The possible reasons for these skin reactions have not been explained in the study, making the results difficult to interpret. The irritation reaction could indicate that the chosen concentration was too high.

The re-challenge was performed to clarify the results obtained in the first challenge (as suggested by the OECD TG 406). A new irritation screening study was performed, with three naive guinea-pigs for each concentration tested. No local skin reactions were observed at 25%, 15%, 10% and 5%. Therefore, the concentrations of 25% and 15% TMMS in PEG 300 were chosen for the re-challenge. A new control group II with 10 naive male guinea-pigs were selected for the re-challenge while the treated group comprised of the same animals.

100% of control animals had positive skin reaction 24 h after first challenge with 25% TMMS in PEG 300, while after 48 h 80% of control animals had positive skin reaction. The percentage of animals with positive skin reaction in the treated group of animals was 95% and 45% after 24 and 48 h, respectively.

Considering that TMMS at 25% in PEG 300 was non-irritating in the two irritation screening experiments and also in the new control group II, the skin reactions observed in the test group in the first and second challenge, when treated at 25% in PEG 300, where recognised by the DS as skin sensitisation responses to the test material.

The presence of skin reactions of grade 1 in 30% and 20% of the test animals after 24 and 48 h, respectively, in the second challenge and, absence of any evidence of irritation in control group II, demonstrated consistency in the ability to cause limited skin reactions in the treated animals indicating weak skin sensitisation. Additionally, the DS considered these reactions, after application of TMMS at 25%, as likely to be skin sensitisation rather than irritation, given that the sensitisation reaction is dose-dependent and local skin reactions were observed at the concentration of 25% TMMS in PEG 300, while no local skin reactions were observed at the concentration of 15% TMMS in PEG 300.

The overall DS's conclusion was that the result of the first Buehler test (study report 2009) was positive and TMMS showed limited potential to cause moderate skin sensitisation in guinea-pigs.

The second Buehler test (study report, 2013), was performed according to OECD TG 406 (EU Method B.6) and in compliance with GLP. Purity of tested TMMS was reported by DS as unknown but was clarified and amended to be 99.6% in March 2018 study report, 2013.

An irritation screening was performed with the following dilutions of TMMS in PEG 300: 50%, 25%, 15% and 10%. No skin reactions were observed at either concentration so the highest tested concentration, 50% TMMS in PEG 300, was selected for the epidermal induction period (6 hours exposure) and challenge. However, this is a deviation from the OECD TG 406, as a concentration resulting in mild irritation should have been selected for induction and the highest non-irritating dose should be selected for the challenge.

No signs of toxicity were evident in any of the animals during the course of the study. No skin reaction scores were observed in any of the test animals or the negative control group 24 or 48 hours after challenge.

The overall DS's conclusion of the results of study report 2013 is that the study is negative, however the study is considered by DS as not reliable. The key points that has been considered when reaching this conclusion is firstly that the purity of the test substance has not been reported. Secondly, the test procedure significantly differs from that described by the test method in OECD TG 406 (that a concentration resulting in mild irritation should have been selected for induction, but was not). These are key points considered when evaluating data reliability (ECHA Guidance on REACH information requirements and chemical safety assessment, 2011). No scientific justification has been provided why a higher concentration was not included in the irritation screening and selected for the induction when there was no skin reaction recorded in the screening. However, since the authors of the second Buehler test knew the results of the first Buehler test, they could expect that TMMS already at concentrations 25 and 50% would be causing skin irritation, which was not confirmed in second skin irritation screening test.

It should be noted that due to physicochemical properties, TMMS hydrolyses in water (half-life approximately 2.2 hour at pH 7 and 25°C). However, the rate of the hydrolysis in PEG 300 is unknown. The skin sensitisation or skin irritation potentials of the hydrolysis products methylsilanetriol and methanol are unknown.

Human data

In the REACH registration dossier (summary report, 2013, ECHA dissemination) it is reported that during more than 20 years of production, handling and use of TMMS and mixtures containing this substance and during at least 14 years of external marketing no single case of suspected

contact allergy has been observed. Only acute slight redness, but no cases of skin sensitization has been observed.

In addition, it is also reported that, based on the experience of the plant managers (experience in production of this substance partially more than 20 years) and the company staff with direct relations to the customers, there is no indication/information of sensitizing properties of TMMS and of mixtures containing this substance. Furthermore, no other health effects have been communicated from the market.

In summary, TMMS was considered by the DS as skin sensitiser sub-category 1B based on positive results of a Buehler test (study report, 2009). Discrete or patchy erythema was recorded in 30% of the animals treated with 25% TMMS in PEG 300 at the 24 hours reading. 48 hours later, the skin reaction was still evident in 20% of the animals treated with 25% TMMS in PEG 300.

Comments received during public consultation

Two MSCAs did not agree with the proposed harmonised classification as Skin Sens. 1B; H317, based on the results of study report, 2009. These MSCAs questioned the relevance of this study considering the positive responses (100%) reported in the control group at the first challenge. One of this two MSCA noted that a new study would be useful to clarify this endpoint.

One Company-Manufacturer requested to take into account in the assessment of the skin potential of TMMS that:

- findings in the test group after re-challenge (study report, 2009) are unspecific reactions due to irritation
- good reliability of study report 2013 taking into account information from study owner (study report, 2013 amended in March 2018)
- existing and available information from human on skin sensitisation potential of TMMS

This company provided the following clarification on human data (summary report, 2013):

1. The following sources have been used to evaluate the skin sensitization potential of TMMS:

- Company internal data: relevant plants, number of employees, exposure description; medical surveillance
- Company internal regular health checks (especially concerning skin status) already performed on employees of the relevant plants
- Information from the Network of Departments of Dermatology for the surveillance and scientific evaluation of contact allergies
- Information from Employer's liability insurance association (BG Bau)
- Information from customer
- Comprehensive literature search

2. Concerning the exposure situation, company internal experience and REACH dossier data have been summarized.

During more than 20 years of production (> 1000 t/a; two production sites), handling and use of TMMS and mixtures containing this substance in several of the company production sites and during at least 14 years of external sale no single case of suspected contact allergy has been observed/reported. No signs of skin sensitization have been observed by the medical doctors and no skin disorders have been reported by the concerned employees during the regular health examinations, which comprise the Occupational Medical Examination "Skin disorders (not

including skin cancer)". In total, 855 medical check-ups of 168 employees have been performed. Relevant exposure can be expected during this time (20 years for production staff and 14 for sale).

Information from other sources described above leads to the same conclusion. No case of skin sensitization has been observed and no such case has been reported in the scientific literature.

Assessment and comparison with the classification criteria

The skin sensitisation potential of TMMS has been assessed in two Buehler tests. A study from 2009 performed with TMMS of purity 96.4 ± 0.2% and a study from 2013 with TMMS with a purity of 99.6% (study report, 2013 as amended in March 2018). Thus, purity of tested substance was higher in the test from 2013. In both studies, fresh preparation of solution in PEG 300 was made for each day of application in the main study (as clarified in the amendment of study report, 2013), therefore the possibility of hydrolysis of TMMS in PEG 300 is the same in both tests.

The first Buehler test (study report, 2009)

Based on an irritation screening study (25%, 50%, 75% and 100% TMMS in PEG 300) 50% TMMS, as the highest mildly irritant dose, was used for the skin sensitisation induction, and 25% TMMS, as the highest non-irritating dose, was used as challenge dose. 24 h and 48 h after first challenge 95% and 45% of the test animals had positive reactions in treated group, respectively. However 100% and 80% of the test animals had positive reactions in control group 24 h and 48 h after first challenge.

The results of the first challenge indicate an unspecific irritation reaction in treated and control animals, since the frequency of positive skin reactions were approximately the same in the control and in the treated group. This reaction has not been explained in a satisfactory manner in the study. The irritation reaction could indicate that the chosen concentration was too high.

Re-challenge was performed to clarify the results obtained in the first challenge. A new control group II with 10 naive male guinea-pigs were selected for the re-challenge while the treated group comprised of the same animals.

24 h and 48 h after topical re-challenge with TMMS at 25% in PEG 300, 30% (6/20) and 20% (4/20) of the test animals had positive reactions in treated group and absence of any evidence of irritation in new control group II.

After topical re-challenge with TMMS at 15% in PEG, the incidence of positive skin reactions was 0% for both treated animals and new negative control.

Table: *The results of first Buehler test (study report, 2009)*

	Control Group 10 animals		**Trimethoxy(methyl)-silane-treated Group (induction phase with 50%) 20 animals**	
	24 h	**48 h**	**24 h**	**48 h**
Primary challenge 25% on test day 29	***Control group I***		19/20 (95%)	9/20 (45%)
	10/10 (100%)	8/10 (80%)		
Re-challenge 25% on test day 43	***Control group II***		6/20 (30%)	4/20 (20%)
	0/10 (0%)	0/10 (0%)		
Re-challenge 15% on test day 43	***Control group II***		0/20 (0%)	0/20 (0%)
	0/10 (0%)	0/10 (0%)		

The second Buehler test (study report, 2013)

An irritation screening was performed (50%, 25%, 15% and 10% dilutions of TMMS in PEG 300). No skin reactions were observed at any of the concentrations so the highest tested concentration, 50% TMMS in PEG 300, was selected for induction and challenge phase. However, this is a deviation from the OECD TG 406, as a concentration resulting in mild irritation should have been selected for induction and the highest non-irritating dose should be selected for the challenge.

No signs of toxicity were evident in any of the animals during the course of the study. No skin reaction scores were observed in any of the test animals or the negative control group after 24 or 48 hours.

Human data

No TMMS human patch test are available, the 'negative' human data consist of the reporting of 'no cases observed/reported' in a few companies. The absence of cases of skin sensitisation may be due to absence of a sensitising potency of TMMS or due to low/absent exposure. The highest dermal exposure for workers reported in the registration dossier is 0.11 mg/kg bw/d, with 240 cm^2 exposed area. This converts to approximately 0.03 mg TMMS/cm^2 (0.11 * 60 kg : 240 cm^2). Compared to the exposure in the Buehler test (assuming a liquid layer of 0.5 mm, which equals 0.05 cm^3 liquid/cm^2 or 50 mg liquid/cm^2, and accounting for a 50% test concentration, the exposure is 25 mg TMMS/cm^2), the worker exposure is much lower than the exposure in the Buehler test. So, the absence of skin sensitisation in workers can most likely be explained by the low exposure levels and can therefore not be used to justify the absence of a skin sensitising potential.

Comparison with the classification criteria

The first Buehler study (2009) is considered as having low reliability due to high incidence of skin responses in the first challenge in the negative control group, inconsistency of results between the challenge and the re-challenge at the same concentration, so the results were considered equivocal and not providing sufficient evidence for classification.

In the second Buehler study (2013) the concentration chosen for induction (50%) may have been too low since it did not caused mild skin irritation in the screening and in the main study, thus not conforming to the requirement of OECD TG 406 that the tested concentration should be the highest inducing mild irritation.

However, the absence of skin sensitisation in workers cannot be regarded as an evidence of lack of sensitising properties of TMMS, since the number of exposed workers and the dermal exposure level were low.

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.**

Additional references

Final GLP report: 13-01067-G1 amended Contact hypersensitivity in albino guinea pigs, Buehler test; Final report date: November 25.2013; Amended report date: March 29, 2018; Christopher Parker

Documents provided by manufacturer during public consultation:

"Sens_Trimethoxymethylsilane_experience_humans.pdf",

"Annex 1_MTMS_VTMS.pdf",

"Annex 2_MTMS_WACKER.pdf",

"Annex 3_MTMS_VTMS.pdf"

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).