Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

trimethoxyvinylsilane; trimethoxy(vinyl)silane

EC Number: 220-449-8
CAS Number: 2768-02-7

CLH-O-0000001412-86-214/F

Adopted

8 June 2018

8 June 2018

CLH-O-0000001412-86-214/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: **trimethoxyvinylsilane; trimethoxy(vinyl)silane**

EC Number: **220-449-8**

CAS Number: **2768-02-7**

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 **20 June 2017**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **4 August 2017**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Anna Biro**

Co-Rapporteur, appointed by RAC: **Boguslaw Baranski**

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

8 June 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	Trimethoxyvinylsilane	220-449-8	2768-02-7	Skin Sens. 1B	H317	GHS07 Wng	H317			
RAC opinion	TBD	trimethoxyvinylsilane; trimethoxy(vinyl)silane	220-449-8	2768-02-7	Skin Sens. 1B	H317	GHS07 Wng	H317			
Resulting Annex VI entry if agreed by COM	TBD	trimethoxyvinylsilane; trimethoxy(vinyl)silane	220-449-8	2768-02-7	Skin Sens. 1B	H317	GHS07 Wng	H317			

GROUNDS FOR ADOPTION OF THE OPINION

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

The skin sensitisation potential of trimethoxyvinylsilane has been assessed in five studies: two Buehler assays - one positive study from 1993 with Dynasylan VTMO as test substance (Study I), and one negative study from 1999 with Silcat R (Study II). There were also three Guinea Pig Maximization Tests (GPMT) with Dynasylan VTMO (1994), (Study III); Silquest A-171 Silane (1996), (Study IV); and A-171 (2000), (Study V) which were all found to be negative. The summary of the tests can be found in the Table below.

The trimethoxyvinylsilane content of the test materials used is confidential, nevertheless from the Safety Data Sheets available online, the Dossier Submitter (DS) stated that Dynasylan VTMO contains >98%, Silcat R contains ≥70% to <90%, Silquest A-171 Silane contains 97.5% to 100%, and A-171 contains unknown/confidential % of trimethoxyvinylsilane.

In Study I (Buehler, Dynasylan VTMO) using 100% induction and 25% challenge doses in MEH 56 corn oil, 65% (13/20) of the test animals had positive reactions to Dynasylan VTMO at 30 and/or 54 hours post application whereas none (0/10) of the negative controls reacted. The doses were based on a preliminary study. In the study, Dynasylan VTMO was found to be a skin sensitiser.

In Study II (Buehler, Silcat R) using 50% induction and 10% challenge doses, with acetone as vehicle, 1/10 of the test animals had positive reactions to Silcat R at 24 hours post-challenge, whereas no animals reacted at 48 hours. The doses were based on a topical range finding study. In this study, Silcat R was not skin sensitising.

In Study III (GPMT, Dynasylan VTMO) with 10% intradermal induction dose, 50% topical induction dose, and 25% as challenge dose in MEH 56 corn oil, none of the test animals (0/9) nor the negative controls (0/5) had positive reactions at 24 or 48 hours post-challenge. The doses were based on a preliminary study. Dynasylan VTMO was not skin sensitising in the test.

In Study IV (GPMT, Silquest A-171 Silane) using 5% intradermal induction dose, 50% topical induction dose and 10% challenge dose in acetone, 1/20 test animals reacted at 24 hours and none at 48 hours post-challenge. After rechallenge with 10% Silquest A-171 Silane in acetone, no sensitisation reactions were observed. No intradermal dose-range finding study was performed. Silquest A-171 Silane was not skin sensitising.

In Study V (GPMT, A-171), based on a preliminary study, the following doses were used: intradermal induction dose: 3% (FCA:saline) and 5% (mineral oil), topical induction dose: 5% (mineral oil) and challenge dose: 5% (mineral oil). All doses were the highest that could possibly be achieved due to problems with solubility/precipitation both in mineral oil and FCA:saline. Positive reactions in the test animals (5/20) and negative controls (4/10) were found at 24h, but none were detected in test or control animals at 48h. In this study A-171 was not sensitising.

***Table**. Summary of skin sensitisation tests*

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance,**	**Dose levels duration of exposure (vehicle)**	**Results**	**Reference**
Buehler test (Study I) OECD TG 406, 1981 GLP	Guinea pig Dunkin Hartley Female 20/test group 10/neg control group	Dynasylan VTMO	Induction dose (day 0, 7 and 14): 100% Challenge dose (day 28): 25% (MEH 56 corn oil)	Sensitising 13/20 (65%) of test animals with positive reactions at 30 and 54h after challenge. 0/10 (0%) control animals with positive reactions at 30 and 54h after challenge.	Study report, 1993 as quoted in ECHA Dissemination, 2016
Buehler test (Study II) Current EPA guidelines GLP	Guinea pig Hartley Albino Male (m) and female (f) 10(m)+10(f)/test group 5(m)+5(f)/neg control group 5(m)+5(f)/pos control group	Silcat R	Induction dose (day 0, 7 and 14): 50% (acetone) Challenge dose (day 28): 10% (acetone)	Not sensitising 1/20 (5%) of test animals with positive reactions at 24h and 0/20 (0%) of test animals with positive reactions at 48h after challenge. 0/10 (0%) of negative control animals with positive reactions at 24 and 48h after challenge. 9/10 (90%) of positive control animals with positive reactions at 24 and 48h after challenge.	Study report, 1999 as quoted in ECHA Dissemination, 2016
Guinea pig maximization test (GPMT) (Study III) OECD TG 406, 1981 GLP May not have used the highest dose causing mild/moderate irritation for intradermal induction	Guinea pig Dunkin Hartley and Pirbright White Male 10/test group (1 died during testing) 5/neg control group	Dynasylan VTMO	Intradermal induction dose:10% (FCA:saline and MEH 56 corn oil) Topical induction dose: 50% (MEH 56 corn oil) Challenge dose: 25% (MEH 56 corn oil)	Not sensitising 0/9 (0%) of test animals with positive reactions at 24 and 48h after challenge 0/5 (0%) of control animals with positive reactions at 24 and 48h after challenge	Study report, 1994 as quoted in ECHA Dissemination, 2016
Guinea pig maximization test (GPMT) (Study IV) OECD TG 406 GLP Study is according to Study Sponsor performed on the hydrolysis product of Silquest A-171 Silane	Guinea pig Hartley Albino 10(m)+10(f)/test group 5(m)+5(f)/neg control group 5(m)+5(f)/pos control group	Silquest A-171 Silane	Intradermal induction dose: 5% (FCA:saline and acetone) Topical induction dose: 50% (acetone) Challenge dose: 10% (acetone)	Not sensitising 1/20 (5%) of test animals with positive reactions at 24h and 0/20 (0%) test animals with positive reactions at 48h after challenge After rechallenge 0/20 (0%) of test animals with positive reactions at 24 and 48h. 0/10 (0%) of	Study report, 1996 as quoted in ECHA Dissemination, 2016

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure (vehicle)	Results	Reference
				negative control animals with positive reactions at 24 and 48h after challenge. 10/10 (100%) of positive control animals with positive reactions at 24 and 48h after challenge.	
Guinea pig maximization test (GPMT) (Study V) OECD TG 406, 1992 GLP May not have used the highest dose causing mild/moderate irritation for intradermal induction.	Guinea pig Hartley Albino 10(m)+10(f)/test group 5(m)+5(f)/ neg control group 5(m)+5(f)/ pos control group	A-171	Intradermal induction dose: 3% (FCA:saline) and 5% (mineral oil) Topical induction dose: 5% (mineral oil) Challenge dose: 5% (mineral oil)	Not sensitising 5/20 (25%) of test animals with positive reactions at 24h and 0/20 (0%) with positive reactions at 48h after challenge. 4/10 (40%) of negative control animals with positive reactions at 24h and 0/10 (0%) with positive reactions at 48h after challenge. 9/10 (90%) of positive control animals with positive reactions after challenge.	Study report, 2000 as quoted in ECHA Dissemination, 2016

Trimethoxyvinylsilane hydrolyses quickly when it comes in contact with water to vinylsilanetriol and methanol. The hydrolysis half-life of trimethoxyvinylsilane is short, about 0.2h at pH 7 and 20-25°C.

The DS developed a crude model to calculate estimated internal induction doses and estimated internal challenge doses achieved in the five studies, taking into consideration the purity of the substance, the doses used, and the probability of hydrolysis of the substance in FCA:saline, the water content of acetone, and on the skin surface. The DS concluded that the highest estimated internal induction (~93%) and challenge (~23%) doses were achieved in Study I, the only study which reported a positive result for skin sensitisation. Study II used lower doses both for induction and challenge. Studies III to V (GPMT) might not have used the highest concentration to avoid causing mild to moderate irritation for intradermal induction. Based on the solubility issues of A-171 in mineral oil and FCA (based mainly on mineral oil) reported in Study V, the DS raised concerns for the reliability of Studies III and IV, where 10% and 5% of Dynasylan VTMO and Silquest A-171 Silane, respectively, were used in FCA:saline.

In summary, trimethoxyvinylsilane had a positive response in 65% of the animals following the use of a 100% topical induction dose of Dynasylan VTMO. The DS thus concluded that the substance meets the criteria for skin sensitiser Category 1B (in a non-adjuvant Guinea pig test method, a response in at least 15% of the animals is achieved at > 20 % topical induction dose).

The DS further reported that in Study I the topical induction dose and response ratio were too high for category 1A to be excluded. However, because the dose levels of trimethoxyvinylsilane used in Studies II to V were lower than the dose level used in Study I and no sensitisation reactions

were detected, the DS concluded that trimethoxyvinylsilane is a weak sensitiser. Subcategorisation in 1B is therefore considered appropriate by the DS.

Comments received during public consultation

One MSCA agreed with the proposed harmonised classification as skin sensitiser subcategory 1B, based on the evidence of the first (positive) study, deeming the further studies less reliable, and stating that the vehicle used in these studies cannot exclude the occurrence of hydrolysis or precipitation of the test chemical, thus potentially resulting in lower doses.

Another MSCA considered the sub-categorization in 1B for trimethoxysilane not appropriate, as subcategory 1A cannot be excluded due to hydrolysis of trimethoxysilane when diluted in aqueous solution as well as the solubility problems that might invalidate the estimated internal induction doses, giving false negative results for sensitisation index, and proposed category 1 without subcategorisation.

The third MSCA supported a classification as skin sensitiser 1, stating that the evidence of the two Buehler assays support a classification into category 1B, however, suggested that human data that was requested from the registrant during the evaluation process of this compound should be taken into account, if available. The MSCA also suggested to take into account data on structurally similar substances.

The fourth MSCA supported the proposed classification of Skin Sens. 1B; H317.

One Company-Manufacturer requested to suspend the CLH discussion until the summary on "Existing data on skin sensitisation potential after human exposure to trimethoxyvinylsilane" requested in the final decision on substance evaluation (Helsinki, 04 July 2016) which was submitted to ECHA on 11 October 2017, has been evaluated by authorities. An attachment with several documents was submitted with this comment:

- A comprehensive statement from one company (4 attached documents) concluded that during more than 20 years of production (> 1000 t/a; two production sites, ca 140 employees), handling and use of trimethoxyvinylsilane and its mixtures on the company site and during at least 14 years of external sale no single case of suspected contact allergy has been observed/reported. No signs of skin sensitisation have been observed by the medical doctors and no skin disorders have been reported by the employees during the regular health examinations, which comprise the occupational medical examination G 24 "Skin disorders (not including skin cancer)". In total, 855 medical check-ups of 168 employees have been performed. In a comprehensive (validated) literature search no publication could be identified which reported sensitising effects of the substance.
- One company stated that the employees of the concerned plant are examined by company medical doctors on a regular basis. Over the time period 2007 – 2017 of production/processing/handling, no signs of skin sensitisation have been observed by the medical doctors and no skin disorders have been reported by employees during the regular examinations.
- A medical statement from another company declared that production staff, currently under health surveillance, have never reported, throughout the course of medical history from 1996 to date, awareness of signs/symptoms of skin reactions/skin sensitisation related to exposure to Silquest A-137 silane (CAS# 2031-67-6) and Silquest A-171 silane (CAS # 2768-02-7).

Another Company-Manufacturer criticized the crude model used to derive internal doses in the CLH dossier, and asked why already existing data concerning experience in humans (no indication of sensitisation after decades of production and use of this substance) have not been considered and mentioned in the CLH report. The same set of attachments as the previous one were submitted with this comment, with a summary of the documents. The Company-Manufacturer

stated that based on the described experience in humans trimethoxyvinylsilane does not require classification/labelling for skin sensitisation and requested to suspend the CLH discussion with the same reasoning as the previous Company-Manufacturer.

The third Company-Manufacturer noted that positive controls are rarely performed in parallel to the test item. Reliability checks of test system are rather conducted on a regular basis. It gave the dates and data of the reliability check closest to Study III, which the DS had deemed unreliable partially because of the lack of a positive control.

One individual commented that three of the four *in vivo* studies, which the DS did not consider in its final evaluation (i.e., Studies II, III, IV), are of good quality and largely in line with OECD TG 406 and should not therefore be dismissed. The commenter recommended to check the quality assurance procedure of the contract laboratory of Study III as laboratories regularly conduct positive control testing to assure the sensitivity of the different skin sensitisation protocols. The commenter agreed that due to the observed precipitation and polymerisation of the test substance, the outcome of Study V should be regarded with a certain degree of uncertainty. They also criticized the model in the CLH dossier to estimate the internal induction and challenge doses, stating that it ignores the accepted concept of dose metrics in the acquisition of skin sensitisation which has been established by Kimber *et al.* (2008). The model does not take into account the basic principle of the GPMT to maximise exposure by intradermally injecting the test substance, thereby bypassing the skin barrier, and to increase the sensitivity of the animal (compared to the Buehler test) by concurrent injection of Freund's complete adjuvant, along with the longer induction patch application (48h in the GPMT vs 6h in the Buehler assay). The assumed the skin absorption rate used in the model was also criticized.

Another individual commented that if the substance is harmonized as sensitising, it should also be clarified whether the labelling limit is higher than 1%.

Assessment and comparison with the classification criteria

The skin sensitisation potential of trimethoxyvinylsilane has been assessed in five studies, 2 Buehler assays and 3 GPMTs, performed with four different test materials containing various concentrations of trimethoxyvinylsilane.

Study I - Buehler test using Dynasylan VTMO (Study report, 1993)

The study was performed according to OECD TG 406 guideline under GLP with Dynasylan VTMO, a product which contains a high level of trimethoxyvinylsilane (>98%). Based on a topical range finding study (2.5%, 25%, 50% and 100% in MEH 56 corn oil), 100% Dynasylan VTMO, as the highest mildly irritant dose, was used as the induction dose and 25% Dynasylan VTMO, as the highest non-irritating dose, was used as challenge dose. 65% (13/20) of the test animals had positive reactions to Dynasylan VTMO at 30 and/or 54 hours post application while none (0/10) of the negative controls reacted. In the study, Dynasylan VTMO was found to be a skin sensitiser.

Table. Results of Study I (Buehler, Dynasylan VTMO (TM))

Group	Challenge material	Time point (h)	Dermal scores				Number of animals	Incidence index
			0	1	2	3		
Test	25% TM in MEH 56 corn oil	30	8	7	5	0	20	65%
		54	9	6	5	0	20	
Test	100% vehicle (MEH 56 corn oil)	30	20	0	0	0	20	n.a.
		54	20	0	0	0	20	
Negative control	25% TM in MEH 56 corn oil	30	10	0	0	0	10	n.a.
		54	10	0	0	0	10	

Negative control	100% vehicle (MEH 56 corn oil)	30	10	0	0	0	10	n.a.
		54	10	0	0	0	10	

0 No visible change
1 Discrete or patchy erythema/oedema
2 Moderate and confluent erythema/oedema
3 Intense erythema/oedema and swelling

Study II - Buehler test using Silcat R (Study report, 1999)

The study was performed according to current EPA guidelines under GLP, with Silcat R, which contains ≥70% to <90% trimethoxyvinylsilane. Based on a topical range finding study (2.5%, 5%, 10%, 25%, 50% and 100% in acetone), 50% Silcat R in acetone was used as induction dose (the highest mildly irritant dose not causing eschar). The eschar observed at the 100% topical dose might have been caused by the substances mentioned in the SDS of Silcat R classified as skin irritant and skin corrosive (Dibutyltin Dilaurate 3 - <5% (Skin Corr.: 1C) and Dicumyl Peroxide 5 - <10% (Skin Irrit.: 2)), leading to a lower than optimal induction dose. 10% Silcat R in acetone, as the highest non-irritant dose, was used as challenge dose. 1/10 of the test animals had positive reactions to Silcat R at 24 hours post-challenge, whereas no animals reacted at 48 hours. After rechallenge none of the test animals had positive skin reactions. Negative controls had no reactions (0/10) and 9/10 of the positive controls had positive reactions to α-Hexylcinnamaldehyde. In the study, Silcat R was found not to be a skin sensitiser.

Table. Results of Study II (Buehler, Silcat R) The incidence index is the number of animals with post-challenge sensitisation reactions at either 24 or 48 hours divided by the total number of animals. The severity index for a group is the sum of the post-challenge test grades divided by the total number of the animals tested. In the calculations, a score of 0.5 was used for +/- reactions.

Group	Challenge material	Time point (h)	Dermal scores					Number of animals	Incidence Index	Severity index
			0	+/-	1	2	3			
Test	10% TM in acetone	24	3	16	1	0	0	20	5%	0.5
		48	9	11	0	0	0	20		0.3
Negative control	10% TM in acetone	24	9	1	0	0	0	10	n.a.	0.1
		48	9	1	0	0	0	10		0.1
Positive control	50% HCA in acetone	24	0	2	4	4	0	10	90%	1.3
		48	0	1	3	6	0	10		1.6

0 No reaction
+/- Slight patchy erythema
1 Slight confluent or moderate patch erythema
2 Moderate erythema
3 Severe erythema (with or without oedema)

Table. Results of Study II (Buehler, Silcat R, rechallenge)

Group	Challenge material	Time point (h)	Dermal scores					Number of animals	Incidence index	Severity index
			0	+/-	1	2	3			
Test	10% TM in acetone	30	11	8	1	0	0	20	0%	0.3
		54	14	6	0	0	0	20		0.2
Negative control	10% TM in acetone	30	5	4	1	0	0	10	n.a.	0.3
		54	9	1	0	0	0	10		0.1

0 No reaction
+/- Slight patchy erythema
1 Slight confluent or moderate patch erythema
2 Moderate erythema
3 Severe erythema (with or without oedema)

Study III - GPMT using Dynasylan VTMO (Study report, 1994)

The study was performed according to OECD TG 406 guideline under GLP, with Dynasylan VTMO, which contains a high level of trimethoxyvinylsilane (>98%). A dose range selection study was performed in 1 animal for intradermal exposure with 0.25%, 0.5%, 1.0%, 2.5%, 5.0%, and 10.0%, and in 3 animals for dermal exposure with 10%, 25%, 50% and 100% of the test substance. The vehicle for dilutions was MEH 56 corn oil. 10% Dynasylan VTMO (the highest to be tested) caused mild/moderate irritation and was used in the main study as intradermal induction dose. 50% was the highest concentration which resulted in mild/moderate irritation and it was selected as topical induction dose, and 25% was the highest concentration which did not cause irritation reactions and it was selected as challenge dose. At 24 or 48 hours post-challenge none of the test animals (0/9) nor the negative controls (0/5) had positive reactions to the test substance. In the study Dynasylan VTMO was found not to be a skin sensitiser.

Table. Results of Study III (GPMT, Dynasylan VTMO)

Group	Challenge material	Time point (h)	Dermal scores			Number of animals	Severity Index
			0	1	2		
Test	25% TM in MEH 56 corn oil	24	9	0	0	9	0.0
		48	9	0	0	9	0.0
Test	100% vehicle (MEH 56 corn oil)	24	9	0	0	9	0.0
		48	9	0	0	9	0.0
Negative control	25% TM in MEH 56 corn oil	24	5	0	0	5	0.0
		48	5	0	0	5	0.0
Negative control	100% vehicle (MEH 56 corn oil)	24	5	0	0	5	0.0
		48	5	0	0	5	0.0

0 No visible change
1 Discrete or patchy erythema/oedema
2 Moderate and confluent erythema/oedema

Study IV - GPMT using Silquest A-171 Silane (Study report, 1996)

The study was performed according to OECD TG 406 guideline under GLP with Silquest A-171 Silane, with a trimethoxyvinylsilane content comparable to Dynasylan VTMO. A topical dose range selection study was performed in 14 animals, with 0.5, 1.0, 2.5, 5.0, 10, 25, 50 and 100% Silquest A-171 Silane. Dilutions were made in acetone. Residual test material remained on the dosed site after dermal exposure to 50% and 100% of the test substance. 50% was the highest dose to cause mild to moderate irritation without eschar, and was selected as the topical induction dose. 10% caused slight irritation and was selected for challenge. No intradermal dose-range finding study was performed and no explanation was given for the selection of 5% as the intradermal induction dose. 1/20 test animals reacted at 24 hours, while none reacted 48 hours post-challenge. After rechallenge with 10% Silquest A-171 Silane in acetone, no sensitisation reactions were detected. Based on the absence of positive reactions following re-challenge dosing, the isolated positive reaction at 24h post challenge was considered an irritation reaction. Negative controls had no reactions (0/10) and 10/10 of positive controls to dinitrochlorobenzene (DCNB) had reactions. It was concluded that the test substance was a non-sensitiser. According to the study sponsor, the study was conducted on the hydrolysis products of Silquest A-171 Silane, as the necessary dilutions in saline during the GPMT procedure resulted in hydrolysis of the test substance.

Table. Results of Study IV (GPMT, Silquest A-171 Silane). Responses to DCNB were graded on an absolute basis.

Group	Challenge material	Time point (h)	Dermal scores				Number of animals	Incidence index	Severity index
			0	1	2	3			
Test	10% TM in acetone	24	0	19	1	0	20	5%	1.1
		48	14	6	0	0	20		0.3
Test	100% acetone	24	8	12	0	0	20	n.a.	0.6
		48	19	1	0	0	20		0.1
Negative control	10% TM in acetone	24	4	6	0	0	10	n.a.	0.6
		48	4	6	0	0	10		0.6
Negative control	100% acetone	24	8	2	0	0	10	n.a.	0.2
		48	10	0	0	0	10		0.0
Positive control	0.1% DCNB in 80% ethanol	24	0	6	2	2	10	100%	1.6
		48	0	2	6	2	10		2.0
Positive control	80% ethanol	24	10	0	0	0	10	n.a.	0.0
		48	10	0	0	0	10		0.0

0 No reaction
1 Discrete of patchy erythema
2 Moderate and confluent redness
3 Intense erythema and swelling

Study V - GPMT using A-171 (Study report, 2000)

The study was performed according to OECD TG 406 guideline under GLP, with A-171, the trimethoxyvinylsilane content of which is confidential. A primary irritation study was performed in 28 animals, with 1.0, 3.0 and 5% of A-171 (intradermal, in mineral oil and 1:1 FCA: sterile saline), 2.5, 5, 10, 25 and 50% (dermal, diluted in acetone) and 0.5, 1, 2.5, 5, 10, 15, 25, 50, 75 and 100% (dermal, in mineral oil). The 5% intradermal concentration caused mild/moderate irritation and was therefore used as induction dose. For dermal application, 5% in mineral oil was chosen for both topical induction and challenge doses. The selection of topical doses is not according to OECD TG 406 recommendations, but higher concentrations than 5% of A-171 in mineral oil resulted in what was described as "polymerization" of the test substance. In addition, higher concentrations than 3% of A-171 did not dissolve in FCA, so the intradermal injection with FCA:saline contained only 3% test material. At 24h, 5/20 tested animals and 4/10 control animals reacted, but no positive reactions were detected in test or control animals at 48 h. Therefore in this study A-171 was non-sensitising.

Table. Results of Study V (GPMT, A-171). Responses to the positive control were graded on an absolute basis since 1% HCA is known to be non-irritating.

Group	Challenge material	Time point (h)	Dermal scores				Number of animals	Incidence index	Severity index
			0	1	2	3			
Test	5% TM in mineral oil	24	15	5	0	0	20	0%	0.3
		48	20	0	0	0	20		0.0
Test	100% vehicle (mineral oil)	24	20	0	0	0	20	n.a.	0.0
		48	20	0	0	0	20		0.0
Negative control	5% TM in mineral oil	24	6	4	0	0	10	n.a.	0.4
		48	10	0	0	0	10		0.0
Negative control	100% vehicle (mineral	24	10	0	0	0	10	n.a.	0.0
		48	10	0	0	0	10		0.0

	oil)								
Positive control	1% HCA in acetone	24	1	8	1	0	10	90%	1.0
		48	6	4	0	0	10		0.4
Positive control	100% acetone	24	10	0	0	0	10	n.a.	0.0
		48	10	0	0	0	10		0.0

0 No reaction
1 Discrete or patchy erythema
2 Moderate and confluent redness
3 Intense erythema and swelling

Human information

During the public consultation, several documents were provided, from 3 different companies producing/handling the substance, stating that there were no indications of skin sensitisation as a result of potential exposure to trimethoxyvinylsilane (see "comments received during public consultation"). In a comprehensive (validated) literature search done by one of the companies, no publication could be identified which reported sensitising effects of the substance.

However, as stated in Annex I (section 3.4.2.2.4.2) of the CLP Regulation, evidence from animal studies is usually much more reliable than evidence from human exposure, and negative human data should not normally be used to negate positive results from animal studies.

Conclusion

According to Table 3.4.4. in Annex I of the CLP Regulation, category 1B is warranted when ≥15% of the animals respond at >20% topical induction dose in a Buehler assay. In a valid Buehler study, 65% of the test animals had positive reactions to Dynasylan VTMO (containing 98% trimethoxyvinylsilane) at 100% topical induction dose.

The other negative Buehler study used a lower induction dose (50%) and challenge dose (10%). Silcat R contains ≥70% to <90% trimethoxyvinylsilane, acetone was used as vehicle, and because of the water content of acetone, some hydrolysis may have occurred. This could have resulted in an even lower concentration of the test substance used. Silcat R, according to the SDS contains at least two substances classified as skin irritant or skin corrosive, which may have caused eschar in the highest (100%) dose in the preliminary study, causing the need to use a lower than optimal induction dose. The lower concentration of trimethoxyvinylsilane and/or not optimal induction dose is considered to be the reason for the negative results in the assay.

The GPMT may also not have used the optimal (the highest concentration to cause mild to moderate irritation) doses during the intradermal induction. Study III used the highest induction dose to be tested, Study IV did not have an intradermal dose-range finding study, and in Study V there were problems with the solubility of the test material. Trimethoxyvinylsilane hydrolyses quickly when it comes in contact with water to vinylsilanetriol and methanol. The hydrolysis half-life of trimethoxyvinylsilane is short, about 0.2h at pH 7 and 20-25°C. Therefore the hydrolysis of the test substance could be substantial during mixing with FCA: saline, lowering the concentration of trimethoxyvinylsilane.

The use of acetone as vehicle may further reduce the concentration of the test substance, while the use of mineral oil may cause its precipitation. The elicitation of skin sensitisation is a threshold reaction, and the use of sub-optimal doses may lead to negative results.

The results of the positive Buehler study, where a high response was achieved to a high concentration, do not make it possible to exclude Category 1A. However, on the basis of the remaining studies, especially the negative Buehler study, where lower doses were used and no sensitisation was detected, Category 1A can be excluded.

Taking into account the available data and these considerations, RAC considers that trimethoxyvinylsilane warrants classification as **skin sensitiser 1B; H317**.

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).