Committee for Risk Assessment

RAC

Annex 1

Background document

to the 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

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

8 June 2018

CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

International Chemical Identification:

Trimethoxyvinylsilane

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

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

Index Number: **Not applicable**

Contact details for dossier submitter:

Swedish Chemicals Agency

Esplanaden 3a, P.O Box 2

SE-172 13 Sundbyberg, Sweden

kemi@kemi.se

+46 8 519 41 100

Version number: 2 **Date: 170329**

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON TRIMETHOXYVINYLSILANE; TRIMETHOXY(VINYL)SILANE

Note on confidential information

Please be aware that this report is intended to be made publicly available. Therefore it should not contain any confidential information. Such information should be provided in a separate confidential Annex to this report, clearly marked as such.

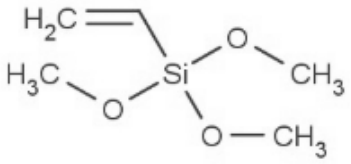
CONTENTS

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Names in the IUPAC nomenclature or other international chemical name	Trimethoxy(vinyl)silane Ethenyl(trimethoxy)silane ethenyltrimethoxysilane Silane, ethenyltrimethoxy- Vinyl trimethoxysilane vinylsilane Vinyltrimethoxysilan Vinyltrimethoxysilane
Other names (usual name, trade name, abbreviation)	A-171M BRB Silanil 276 Crosslinker TP-3625 DOW CORNING(R) Z-6300 SILANE Dynasylan(R) VTMO GENIOSIL® XL 10 KBM-1003 SILAN V-TRIMETHOXY SILQUEST A-171 SILANE Silquest A-171W Silquest A-171« silane Silquest Y-9818 silane Silquest« A-171B silane TP 3625

	TSL8310 Vernetzer VERNETZER ME 16 VS-1034 Xiameter(R) OFS-6300 XL-PEarl 10 silane Y-11386
EC number	220-449-8
EC name	Trimethoxyvinylsilane
CAS number	2768-02-7
Molecular formula	C5H12O3Si
Structural formula	
SMILES notation (if available)	O(C)[Si](OC)(OC)\C=C
Molecular weight or molecular weight range	148.2
Degree of purity (%)	Not relevant

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self- classification and labelling (CLP)**
Trimethoxyvinylsilane	99-100%	-	Current self-classification in the lead registration: Flam. Liq. 3, H226 Acute Tox. 4, H332 STOT RE 2, H373 (oral, bladder) In addition, the following hazard classes are notified among the 22 other aggregated self-classifications in the C&L Inventory: 4/22 Flam. Liq. 2, H226 2/22 Eye Dam. 1, H318 9/22 Skin Irrit. 2, H315 8/22 Eye Irrit. 2, H319 5/22 STOT SE 3, H335 1/22 Asp. Tox. 1, H304 1/22 Muta 1B, H340 1/22 Carc 1B, H350 1/22 Carc. 2, H351 1/22 Aquatic Acute 1, H400 1/22 Not classified

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self- classification and labelling (CLP)**	**The impurity contributes to the classification and labelling**
Impurity 1	-	-	-	No
Impurity 2	-	-	-	No

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
-	-	-	-	-	-

Table 5: Test substances (non-confidential information) (this table is optional)

Identification of test substance	Purity	Impurities and additives (identity, %, classification if available)	Other information	The study(ies) in which the test substance is used
Dynasylan VTMO	See confidential Annex I	See confidential Annex I	Contains trimethoxyvinylsilane	Study report, 1993;1994
Silcat R	See confidential Annex I	See confidential Annex I	Contains trimethoxyvinylsilane	Study report, 1999
Silquest A-171 Silane	See confidential Annex I	See confidential Annex I	Contains trimethoxyvinylsilane	Study report, 1996
A-171	See confidential Annex I	See confidential Annex I	Contains trimethoxyvinylsilane	Study report, 2000

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 6:

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	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 entry										
Dossier submitters proposal	xxx-xxx-xx-x	Trimethoxyvinylsilane	220-449-8	2768-02-7	Skin Sens. 1B	H317	GHS07 Wng 	H317	-	-	-
Resulting Annex VI entry if agreed by RAC and COM	xxx-xxx-xx-x	Trimethoxyvinylsilane	220-449-8	2768-02-7	Skin Sens. 1B	H317	GHS07 Wng 	H317	-	-	-

Table 7: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	*hazard class not assessed in this dossier*	No
Flammable gases (including chemically unstable gases)	*hazard class not assessed in this dossier*	No
Oxidising gases	*hazard class not assessed in this dossier*	No
Gases under pressure	*hazard class not assessed in this dossier*	No
Flammable liquids	*hazard class not assessed in this dossier*	No
Flammable solids	*hazard class not assessed in this dossier*	No
Self-reactive substances	*hazard class not assessed in this dossier*	No
Pyrophoric liquids	*hazard class not assessed in this dossier*	No
Pyrophoric solids	*hazard class not assessed in this dossier*	No
Self-heating substances	*hazard class not assessed in this dossier*	No
Substances which in contact with water emit flammable gases	*hazard class not assessed in this dossier*	No
Oxidising liquids	*hazard class not assessed in this dossier*	No
Oxidising solids	*hazard class not assessed in this dossier*	No
Organic peroxides	*hazard class not assessed in this dossier*	No
Corrosive to metals	*hazard class not assessed in this dossier*	No
Acute toxicity via oral route	*hazard class not assessed in this dossier*	No
Acute toxicity via dermal route	*hazard class not assessed in this dossier*	No
Acute toxicity via inhalation route	*hazard class not assessed in this dossier*	No
Skin corrosion/irritation	*hazard class not assessed in this dossier*	No
Serious eye damage/eye irritation	*hazard class not assessed in this dossier*	No
Respiratory sensitisation	*hazard class not assessed in this dossier*	No
Skin sensitisation	-	Yes
Germ cell mutagenicity	*hazard class not assessed in this dossier*	No
Carcinogenicity	*hazard class not assessed in this dossier*	No
Reproductive toxicity	*hazard class not assessed in this dossier*	No
Specific target organ toxicity-single exposure	*hazard class not assessed in this dossier*	No
Specific target organ toxicity-repeated exposure	*hazard class not assessed in this dossier*	No
Aspiration hazard	*hazard class not assessed in this dossier*	No
Hazardous to the aquatic environment	*hazard class not assessed in this dossier*	No
Hazardous to the ozone layer	*hazard class not assessed in this dossier*	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

There is no harmonised classification and labelling for trimethoxyvinylsilane.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

[B.] Justification that action is needed at Community level is required.

Requirement for harmonised classification by other legislation or process.

https://www.echa.europa.eu/web/guest/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table/-/dislist/details/0b0236e1807e6fe3

5 IDENTIFIED USES

Trimethoxyvinylsilane is used in polymers, adhesives and sealants, coating products, non-metal-surface treatment products and laboratory chemicals.

6 DATA SOURCES

Data for trimethoxyvinylsilane are taken from the publically disseminated REACH Registration Dossier (ECHA, 2016) or from full study reports on skin sensitisation made available by the Registrant(s).

7 PHYSICAL AND CHEMICAL PROPERTIES

The data comes from the publically disseminated REACH Registration Dossier for trimethoxyvinylsilane (ECHA, 2016) and are taken from the key study or, in the absence of a key study, the study with the highest reliability score.

Table 8: Summary of physical and chemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	Liquid	Reach Registration Dossier (ECHA, 2016)	Observed
Melting/freezing point	-97°C	Reach Registration Dossier (ECHA, 2016)	Measured
Boiling point	123°C	Reach Registration Dossier (ECHA, 2016)	Measured, equivalent to OECD Guideline 103
Relative density	0.97g/cm³ at 20°C	Reach Registration Dossier (ECHA, 2016)	Measured, equivalent to OECD Guideline 109
Vapour pressure	11.9 hPa at 20°C	Reach Registration Dossier (ECHA 2016)	Measured
Surface tension	No data	Reach Registration Dossier (ECHA 2016)	Waived
Water solubility	Not applicable	Reach Registration Dossier (ECHA 2016)	Not determined due to very fast hydrolysis of the substance

Property	Value	Reference	Comment (e.g. measured or estimated)
Partition coefficient n-octanol/water	Not applicable	Reach Registration Dossier (ECHA 2016)	Not determined due to very fast hydrolysis of the substance
Flash point	23-26°C	Reach Registration Dossier (ECHA 2016)	Measured
Flammability	1.40% (lower flammable limit value) 23.94% (the higher flammable limit value)	Reach Registration Dossier (ECHA 2016)	Measured, ASTM E918-83 standard method
Explosive properties	No data	Reach Registration Dossier (ECHA 2016)	Waived
Self-ignition temperature	-	-	-
Oxidising properties	No data	Reach Registration Dossier (ECHA 2016)	Waived
Granulometry	-	-	-
Stability in organic solvents and identity of relevant degradation products	No data	Reach Registration Dossier (ECHA 2016)	Waived
Dissociation constant	No data	Reach Registration Dossier (ECHA 2016)	Waived
Viscosity	0.6 mPa s at 25°C	Reach Registration Dossier (ECHA 2016)	Measured, equivalent to OECD Test Guideline 114

8 EVALUATION OF PHYSICAL HAZARDS

Not evaluated in this dossier.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

No data.

10 EVALUATION OF HEALTH HAZARDS

10.1 Acute toxicity - oral route

Not evaluated in this dossier.

10.2 Acute toxicity - dermal route

Not evaluated in this dossier.

10.3 Acute toxicity - inhalation route

Not evaluated in this dossier.

10.4 Skin corrosion/irritation

Not evaluated in this dossier.

10.5 Serious eye damage/eye irritation

Not evaluated in this dossier.

10.6 Respiratory sensitisation

Not evaluated in this dossier.

10.7 Skin sensitisation

Trimethoxyvinylsilane hydrolyses quickly when it comes in contact with water to vinylsilanetriol and methanol. The hydrolysis half-life of trimethoxyvinylsilane is short - about 0.2 h at pH 7 and 20-25°C. This property has been carefully considered when the relevance of the studies was evaluated, especially when it comes to the choice of vehicle. The purity of the tested substance has also been taken into account. The five disseminated skin sensitisation studies were performed with four different test substances containing various levels of trimethoxyvinylsilane. The purity of these products is reported in the confidential Annex I.

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, and one negative study from 1999 with Silcat R - and three Guinea Pig Maximization Tests (GPMT) with Dynasylan VTMO (1994), Silquest A-171 Silane (1996) and A-171 (2000) which were all found to be negative. The summary table (Table 9) and detailed study summaries with DS assessments are found below.

Table 9: Summary table of animal studies on skin sensitisation

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	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 548h after challenge. 9/10 (90%) of positive control animals with positive reactions at	Study report, 1999 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**
	control group			24 and 48h after challenge.	
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 48 h 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 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	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 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.	Study report, 1996 as quoted in ECHA Dissemination, 2016
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 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	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

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

A topical dose range finding study including 3 guinea pigs was performed prior to the Buehler test. Dynasylan VTMO was tested in concentrations of 2.5%, 25%, 50% and 100%. Dilutions were made in MEH 56 corn oil. Dynasylan VTMO was found to be mildly irritant at both 50% and 100%, hence the higher of the two was used as induction dose. 25% was the highest dose causing no irritation and was therefore chosen as the challenge dose. The results from the dose range finding study are found in Table 10. In the main study 20 animals were induced with 100% test substance on day 0 (Induction Phase I), 7 (Induction Phase II) and 14 (Induction Phase III) and challenged with 25% on day 28. It was demonstrated that 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 (Table 11). Of the 13 test animals with positive reactions,10 had positive reactions reactions at both time points whereas 3 animals had positive reactions only at one time point. Responses of the individual animals are found in Table 12. Hence, in the study Dynasylan VTMO was found to be a skin sensitizer.

Table 10. Results from the dose range finding study of Dynasylan VTMO

	Animal 1				Animal 2				Animal 3			
	2.5%	25%	50%	100%	2.5%	25%	50%	100%	2.5%	25%	50%	100%
6h	O:0 E:0	O:0 E:0	O:1* E:0	O:1* E:0	O:0 E:0	O:0 E:0	O:0* E:0	O:1* E:0	O:0 E:0	O:0 E:0	O:0* E:0	O:0* E:0
24h	O:0 E:0	O:0 E:0	O:2* E:1	O:2* E:2	O:0 E:0	O:0 E:0	O:1* E:1	O:0* E:0	O:0 E:0	O:0 E:0	O:1*s E:1	O:1*s E:1
48h	O:0 E:0	O:0 E:0	O:2* E:1	O:2* E:1	O:0 E:0	O:0 E:0	O:0* E:0	O:0* E:0	O:0 E:0	O:0 E:0	O:1*s E:1	O:1*s E:1

E	Erythema and scabbing	0	No visible change
O	Edema	1	Discrete or patchy erythema/edema
*	Skin dryness	2	Moderate and confluent erythema/edema
S	Skin dander	3	Intense erythema/edema and swelling

Table 11. Incidence of post-challenge dermal responses to the test material (TM) Dynasylan VTMO and vehicle (MEH corn oil). Reactions in the test group were considered positive when they were more intense than the responses to the test material in the negative control at either timepoint.

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/edema
2	Moderate and confluent erythema/edema
3	Intense erythema/edema and swelling

Table 12: Dermal scores for individual animals in Study I following challenge with pure (100%) vehicle and 25% test material (TM) Dynasylane VTMO.

Animal	100% vehicle (MEH 56 corn oil)				25% TM in MEH 56 corn oil			
	30 h		54 h		30 h		54 h	
	E	O	E	O	E	O	E	O
1	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
3	0	0	0	0	2	2	2*	2
4	0	0	0	0	0	0	0	0
5	0	0	0	0	2	2	1*	2
6	0	0	0	0	2	2	2*	1
7	0	0	0	0	2	2	2	1
8	0	0	0	0	0	1	1	1
9	0	0	0	0	1	1	0	0
10	0	0	0	0	0	0	0	0
11	0	0	0	0	1	1	1	1
12	0	0	0	0	0	0	0	0
13	0	0	0	0	1	1	1	1
14	0	0	0	0	0	0	0	0
15	0	0	0	0	1	1	1	1
16	0	0	0	0	1	1	0	0
17	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	2*	1
19	0	0	0	0	1	1	1	1
20	0	0	0	0	2	1	1*	1

0 No visible change
1 Discrete or patchy erythema/edema
2 Moderate and confluent erythema/edema
3 Intense erythema/edema and swelling
* Skin dryness

The study was performed according to OECD TG 406 guideline under GLP with Dynasylan VTMO, a product which according to data safety sheets available online[1] contains a high level of trimethoxyvinylsilane (>98%). There is no information on the exact composition of the vehicle MEH 56 cornoil in the study report, but the choice of corn oil as vehicle is expected to prevent hydrolysis of trimethoxyvinylsilane. The study is therefore considered to provide results that are valid to assess the skin sensitisation potential of trimethoxyvinylsilane.

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

A topical dose range finding study including 8 guinea pigs was performed prior to the Buehler test in which Silcat R was tested in concentrations of 2.5%, 5%, 10%, 25%, 50% and 100%. Dilutions were made in acetone. Mild irritation was observed at both 50% and 100%, however eschar and focal eschar was observed at the highest concentration, prompting the use of 50% as induction dose in the main study. 10% was the highest concentration not to cause irritation and was therefore used as challenge dose. The results from the dose range finding study are found in Table 13. In the main study, 20 animals were induced with 50% Silcat R at day 0, 7 and 14 and challenged with 10% of the test substance at day 28. The results show that 1/10 of the test animals had positive reactions to Silcat R at 24 hours post-challenge, whereas no animals reacted at the later time point (48 hours) (Table 14). After rechallenge none of the test animals had positive skin reactions (Table 15). Negative controls had no reactions (0/10) and 9/10 of the positive controls had positive reactions to α-Hexylcinnamaldehyde (HCA) thereby confirming the reliability of the experimental design. In the study, Silcat R was found not to be a skin sensitizer.

[1] http://www.palmerholland.com/Assets/User/Documents/Product/42570/2407/MITM04137.pdf

Table 13. Results from the dose range finding study of Silcat R

Animal	2.5%	5%	10%	25%	50%	100%
1 (M)	0	-	-	-	2	1ef
2 (M)	-	0	+/-	1	-	-
3 (M)	0	-	+/-	1	-	-
4 (M)	-	0	-	-	2	2e
5 (F)	0	0	-	-	-	1ef
6 (F)	-	-	0	0	1	-
7 (F)	0	0	-	1	-	-
8 (F)	-	-	0	-	1	1ef

0 No reaction
+/- Slight patchy erythema
1 Slight confluent or moderate patch erythema
2 Moderate erythema
e Eschar
f Focal eschar

Table 14. Incidence of post-challenge dermal responses to the test material (TM) Silcat R. Grades of 1 or greater in the induction-treated test group indicated sensitization provided only grades of less than 1 were noted in the negative control group. If scores of 1 or greater were noted in the negative control group, then only those scores in the test group which exceeded the highest score noted in the negative control group were attributed to sensitization. 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 edema)

Table 15. Incidence of dermal responses following rechallenge to the test material (TM) Silcat R. Grades of 1 or greater in the induction-treated test group indicated sensitization provided only grades of less than 1 were noted in the negative control group. If scores of 1 or greater were noted in the negative control group, then only those scores in the test group which exceeded the highest score noted in the negative control group were attributed to sensitization. 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	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 edema)

Study II used a lower topical induction dose compared to Study I (50% and 100%, respectively). In addition, it was performed with a test substance which, according to SDS available online[2], contains a lower level of trimethoxyvinylsilane (≥70% to <90%) compared to Dynasylan VTMO. In the study, acetone was used as vehicle and since acetone normally contains water, it is likely that some degree of hydrolysis of trimethoxyvinylsilane occurred prior to application, reducing the dose available for uptake via the skin. The exact composition of Silcat R is not stated in the study report, however, according to the SDS it seems also to contain at least two substances both classified as skin irritants and skin corrosive. Hence, it is possible that the eschar observed after testing with 100% Silcat R in the dose range finding study, and which was the reason for selecting 50% as the induction dose, was caused by substances other than trimethoxyvinylsilane.

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

A dose range selection study was performed prior to the main study including 1 animal for intradermal exposure with 0.25, 0.5, 1.0, 2.5, 5.0, and 10.0% of Dynasylan VTMO, and 3 animals for dermal exposure with 10, 25, 50 and 100% of Dynasylan VTMO. Dilutions were made in MEH 56 corn oil. 10% Dynasylan VTMO caused mild/moderate irritation and was used in the main study as dermal induction dose. Regarding the dermal application, it was found that 50% was the highest concentration which resulted in mild/moderate irritation (selected as topical induction dose) and that 25% was the highest concentration which did not cause irritation reactions (selected as challenge dose). The main study hence included intradermal induction injections of 10 animals with 10% Dynasylan VTMO in corn oil, 10% Dynasylan VTMO in a 1:1 mixture of Freund's Complete Adjuvance (FCA): sterile saline, and a 1:1 mixture of FCA:sterile saline at day 0. Topical induction (48h occluded) was performed on day 7 with 50% Dynasylan VTMO in MEH 56 corn oil. Challenge dosing (occluded for 24h) with 25% Dynasylan VTMO in MEH 56 corn oil for the detection of sensitisation was performed 14 days after topical induction. One animal died during testing from causes not contributed to treatment with the test substance. The reading at 24 or 48 hours post-challenge demonstrated that none of the test animals (0/9) nor the negative controls (0/5) had

[2] http://msds.momentive.com/ehswww/testEbiz/e/result/report.jsp?P_LANGU=E&P_SYS=1&P_SSN=10111&P_REP=000000000000000000006&P_RES=9083&winTitle=Momentive Performance Materials

positive reactions to the test substance (Table 16). The study authors concluded that Dynasylan VTMO was not a skin sensitizer.

Table 16. Incidence of post-challenge dermal responses to Dynasylan VTMO. Reactions in the test group were considered positive when they were more intense than the responses to the vehicle and the responses to the test material (TM) in the negative control.

Group	Challenge material	Time point (h)	Dermal scores			Number of animals	Severity Index
			0	1	2		
Test	25% TM in MEH 56 cornoil	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 cornoil	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/edema
2 Moderate and confluent erythema/edema

The induction doses used in the main study may have been lower than what is recommended by the OECD TG 406. The guideline states that the highest intradermal and topical doses causing mild to moderate irritation should be used for induction. A 10% intradermal induction dose of Dynasylan VTMO caused mild/moderate irritation but was also the highest intradermal dose addressed in the dose range finding studies. It is therefore possible that if higher doses of Dynasylan VTMO would have been tested, a higher intradermal induction dose would have been selected in the main study. Moreover, the OECD 406 guideline protocol includes mixing of the test substance with FCA: sterile saline prior to one of the injections at day 0. This procedure may cause hydrolysis of trimethoxyvinylsilane. The degree of hydrolysis that occurs depends on the area of contact between the FCA and water. It may also depend on when in time prior to the injection the mixing was made (not reported in detail in the study). The use of corn oil as vehicle is expected to prevent hydrolysis of trimethoxyvinylsilane in the other steps of the GPMT procedure. It is strongly recommended by the OECD TG 406, that if negative results are obtained when using fewer animals than 20 test- and 10 control animals, further animals (up to 20 test- and 10 control animals) should be tested. However, further testing was not performed in the study. The lack of positive controls in the study in combination with the negative responses also causes concern about the reliability of the experimental design.

Study IV - GPMT using Silquest A-171 Silane (Study report, 1996)
The GPMT was proceeded by a topical dose range selection study which was performed with a total of 14 guinea pigs 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 dose site after dermal exposure to 50% and 100% of the test substance. 50% caused mild to moderate irritation whereas 100% caused moderate irritation with eschar. Hence, 50% was selected as the topical induction dose. 10% caused slight irritation and was selected for challenge. The study did not include an intradermal dose-range findig study nor an explanation for the selection of the intradermal induction dose level. In the main study,

intradermal induction consisted of 3 injections (5% Silquest A-171 Silane in acetone, 5% Silquest A-171 Silane in a 1:1 mixture of Freund's Complete Adjuvance (FCA): sterile saline, and a 1:1 mixture of FCA: sterile saline) of 20 animals on day 0. Topical induction consisted of a 48 hours occluded dermal exposure to 50% Silquest A-171 Silane in acetone at day 7, whereas the challenge dosing was performed 14 days after topical induction, and was conducted occluded during 24 hours with 10% Silquest A-171 Silane in acetone. Results show that 1/20 test animals reacted at 24 hours and that none reacted 48 hours post-challenge (Table 17). Further, that rechallenge with 10% Silquest A-171 Silane in acetone was performed by which no sensitisation reactions were detected (Table 18). Based on the absence of positive reactions following re-challenge dosing, the isolated positive reaction at 24 h post challenge was considered an irritation reaction. Negative controls were reported to have no reactions (0/10) and the reactions (10/10) of the positive controls to dinitrochlorobenzene (DCNB) confirmed the reliability of the experimental design. It was concluded that the test substance was a non-sensitizer.

Table 17. Incidence of post-challenge dermal responses to Silquest A-171 Silane. Reactions in the test group were considered positive when they were more intense than the responses to the vehicle and the responses to the test material (TM) in the negative control. Responses to DCNB were graded on an absolute basis. 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.

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

Table 18. Incidence of dermal responses following rechallenge to Silquest A-171 Silane. Reactions in the test group were considered positive when they were more intense than the responses to the vehicle and the responses to the test material (TM) in the negative control. 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.

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	20	0	0	20	0%	1.0
		48	12	8	0	0	20		0.4
Test	100% acetone	24	5	15	0	0	20	n.a	0.8
		48	20	0	0	0	20		0.0
Negative control	10% TM in acetone	24	0	10	0	0	10	n.a	1.0
		48	3	7	0	0	10		0.7
Negative control	100% acetone	24	2	8	0	0	10	n.a	0.8
		48	8	2	0	0	10		0.2

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

The OECD TG 406 guideline recommends that the highest dose causing mild to moderate irritation should be used for intradermal induction. Hence, the dose used in the main study may have been lower than recommended. As no primary irritation test was performed to assess irritation following intradermal induction, the relevance of the selected dose cannot be evaluated. However, the purity of Silquest A-171 Silane is comparable with that of Dynasylan VTMO, which indicates that a intradermal induction dose of at least 10% should have been used (Study III). In the study summary, the Study Sponsor informs that the necessary dilutions of Silquest A-171 Silane in saline during the GPMT procedure resulted in hydrolysis of the test substance. Moreover, that the use of acetone, containing an estimated 0.5% of water, as vehicle may have caused further hydrolysis. It is stated that the study, although technically valid, may not provide a proper assessment of the sensitisation potential of trimethoxyvinylsilane. This statement is not supported by data, and it is hence difficult to conclude to what extent the trimethoxyvinylsilane hydrolysed. However, there are indications that the hydrolysis product of trimethoxyvinylsilane (vinylsilanetriol) polymerizes spontaneoulsy (OECD 2009; 2013). The residual test material remaining on the skin during the primary irritation phase study performed with 50% and 100% test substance could therefore suggest that hydrolysis did occur.

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

A primary irritation study was performed prior to the GPMT including a total of 28 guinea pigs 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 and 75% (dermal, in mineral oil). Testing was also performed with undiluted A-171. 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. The selection of topical doses is not according to OECD TG 406 recommendations, but seems to have been necessary from a practical point of view, since higher concentrations than 5% of A-171 in mineral oil resulted in what is described as “polymerization” of the test substance. In addition, higher concentrations than 3% A-171 were not possible to dissolve in FCA. Hence, in the main study intradermal induction of 20 animals at day 0 consisted of injections of 5% A-171 in mineral oil, 3% A-171 in a 1:1 mixture of Freund’s Complete Adjuvance (FCA): sterile saline and a 1:1 mixture of FCA:sterile saline. Topical induction was performed occluded for 48 hours with 5% A-171 in mineral oil, 7 days after intradermal induction. The challenge dosing was performed with occluded exposure for 24 hours, on day 14 using 5% A-171 in mineral oil. The challenge exposure resulted in some positive reactions to

the test substance in the test animals (5/20) and negative controls (4/10) at the reading at 24 h, but no positive reactions were detected in test- or control animals at 48 h (Table 19). The positive reactions (9/10) to HCA of the positive controls confirmed the reliability of the experimental design. Hence, the study authors found that A-171 was not a skin sensitizer.

Table 19. Incidence of post-challenge dermal responses to the test material (TM) A-171. Reactions in the test group were considered positive when they were more intense than the responses to the vehicle and the responses to the test material in the negative control. Responses to the positive control were graded on an absolute basis since 1% HCA is known to be non-irritating. 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.

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 oil)	24	10	0	0	0	10	n.a	0.0
		48	10	0	0	0	10		0.0
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

The induction doses used in the main study are lower than what is recommended by the OECD TG 406. The guideline states that the highest intradermal and topical doses causing mild to moderate irritation should be used for induction. 5% A-171 caused mild/moderate irritation but was also for practical reasons the highest intradermal dose addressed in the dose range finding studies. The "polymerisation" of the test substance which was reported to occur at concentrations higher than 5% A-171 in mineral oil, is more likely problems with solubility. For polymerisation of trimethoxyvinylsilane to occur, the presence of water for hydrolysis is a prerequisite. Mineral oil normally do not contain any water. In addition, difficulties with solubility was reported to occur when mixing A-171 with FCA, a solution which is largely based on mineral oil. The problems to dissolve trimethoxyvinylsilane in FCA caused a further reduction of the concentration of trimethoxyvinylsilane for intradermal induction to 3%. In addition, the mixing of trimethoxyvinylsilane in FCA: sterile saline may have further lowered the dose due to hydrolysis. Similar to Study III and IV, it is difficult to assess the degree of hydrolysis of trimethoxyvinylsilane.

10.7.1 Short summary and overall relevance of the provided information on skin sensitisation

A chemical substance becomes a skin sensitizer only if a sufficient amount is absorbed through the skin and reacts with skin proteins to form haptens which, in turn, initiate an immunological response.

Hence, the internal dose of the chemical substance is the one important for an immune reaction to occur. The 5 disseminated studies have used 2 different assays, 4 different test substances and 3 different vehicles in various combinations. To envisage how these choices may affect the internal dose and thereby the outcome of the studies is challenging. Hence, a crude model was developed in an attempt to compare the internal levels of trimethoxyvinylsilane in the skin in the five studies. The model considers the purity (P) of the test substance, the probability for hydrolysis of trimethoxyvinylsilane by dilution in the vehicle (HV) and by contact with water on the skin surface (HS). Hydrolysis occurring following contact with water inside the body was assumed to be comparable in all studies and was neglected in the calculations.

The estimated internal induction dose (EID) of trimethoxyvinylsilane was calculated as follows:

$$EID_{Buehler} = P \cdot (1-HV) \cdot DI \cdot (1-HS) \quad , \qquad (1)$$

$$EID_{GPMT} = P \cdot IDI \cdot (1-HV) + P \cdot IDI \cdot (1-HV) + P \cdot (1-HV) \cdot DI \cdot (1-HS) \quad , \qquad (2)$$

where *IDI* and *DI* denote the nominal intradermal - and dermal induction dose in percent, respectively.

The estimated internal challenge dose (ECD) of trimethoxyvinylsilane was calculated as follows:

$$ECD = P \cdot (1-HV) \cdot CD \cdot (1-HS) \quad , \qquad (3)$$

where *CD* denotes the nominal challenge dose in percent.

Hydrolysis of trimethoxyvinylsilane in corn- and mineral oil was assumed not to occur and was therefore assigned a probability of 0. The likelihood of hydrolysis of trimethoxyvinylsilane in acetone and FCA: saline was determined based on the amount of water contained in the respective vehicle. Acetone was assumed to contain 0.5% water and the probability for hydrolysis was then 0.005, i.e. 0.5% of the trimethoxyvinylsilane was assumed to hydrolyse. It should however be noted that the water content may be higher depending on the storage time of the acetone prior to use and also the storage time of the dilutions of test substances prior to the application (no detailed information was given in the studies). Over time, ketones form ketals and at the same time, water is produced. Short chain ketones such as acetone react quite rapidly. FCA and saline was used in a 1:1 mixture and the probability for hydrolysis was hence assumed to be 0.5, i.e. 50% of the added trimethoxyvinylsilane may hydrolyse. As there was no detailed information on when in time prior to injection/application the mixing was performed, the storage time was not included in the calculations, although it may have a large impact on the extent of the hydrolysis. Excluding storage time of both the vehicle and the dilutions of the test material in the vehicle may underestimate the degree of hydrolysis of trimethoxyvinylsilane and therefore overestimate the calculated internal intradermal and challenge doses. The uptake of trimethoxyvinylsilane via the skin was assumed to be rapid and complete due to its small size (~150 Da), high predicted water solubility (9400 mg/l) and high predicted log K_{ow} (1.1) (ECHA, 2016b). Furthermore, 5% of the trimethoxyvinylsilane was assumed to hydrolyse in the moisture on the skin surface prior to absorption. Hence, the likelihood of hydrolysis on the skin was set to 0.05. The hydrolysis product of trimethoxyvinylsilane, vinylsilanetriol, has a high water solubility ($1 \cdot 10^6$ mg/l), but with a log K_{ow} of -2.0 it is not likely to be sufficiently lipophilic to cross the stratum corneum (ECHA, 2016b). The estimated internal induction and challenge doses of trimethoxyvinylsilane in the 5 disseminated studies are presented in Table 20.

Table 20: A crude comparison of the internal induction and challenge doses of trimethoxyvinylsilane in the 5 disseminated studies.

Study	Doses	Purity	Likelihood of hydrolysis	Estimated internal induction dose (EID)	Estimated internal challenge dose (ECD)	Sensitisation index
I Study report, 1993 (Buehler)	100% (DI) 25% (CD)	>98%*	On skin.	0.98·(1-0)·100%·(1-0.05) = **93%**	0.98·(1-0)·25%·(1-0.05) = **23%**	65%
II Study report, 1999 (Buehler)	50% (DI) 10% (CD)	>70%-<90%*, Assuming 80% (average value)	Acetone as vehicle for induction and challenge. On skin.	0.8·(1-0.005)·50%·(1-0.05) = **38%**	0.8·(1-0.005)·10%·(1-0.05) = **7%**	0%
III Study report, 1994 (GPMT)	10%+10% (IDI) 50% (DI) 25% (CD)	>98%*	Mixing with saline. On skin.	0.98·10%·(1-0) + 0.98·10%·(1-0.5) + 0.98·(1-0)·50%·(1-0.05) = **61%**	0.98·(1-0)·25%·(1-0.05) = **23%**	0%
IV Study report, 1996 (GPMT)	5%+5% (IDI) 50% (DI) 10% (CD)	97.5%-100%* Assuming 99% (average value)	Mixing with saline. Acetone as vehicle for induction and challenge. On skin.	0.99·5%·(1-0.005) + 0.99·5%·(1-0.5) + 0.99·(1-0.005)·50%·(1-0.05) = **54%**	0.99·(1-0.005)·10%·(1-0.05) = **9%**	0%
V Study report, 2000 (GPMT)	5%+3% (IDI) 5% (DI) 5% (CD)	See confid-ential annex I	Mixing with saline. On skin.	< 30% See confidential annex I	< 10% See confidential annex I	0%

*According to SDSs available online

The comparison of the estimated internal doses indicate that the highest doses of trimethoxyvinylsilane for both induction (~93%) and challenge (~23%) were used in Study I. Study I is also the only study which reports a positive result for skin sensitisation. Apart from concerns that constituents other than trimethoxyvinylsilane may have influenced the selection of the induction dose level in the second, negative, Buehler assay (Study II), a considerably lower internal level of trimethoxyvinylsilane was used for testing.

The estimated internal doses of trimethoxyvinylsilane in Study III, IV and V are also considerably lower than in Study I, which could at least partly explain the absence of positive reactions in the GPMTs. However, a comparison of the internal induction dose levels between the Buehler assay and GPMT should be made with caution, since the test protocols differ. In a GPMT the immune system is boosted by injection of FCA which makes the GPMT more sensitive compared to the Buehler assay. However, the GPMT is a maximisation test, which implicates that maximum concentrations should be used in order for the test to be fully reliable. None of the Studies III, IV or V have demonstrated that the maximum intradermal dose that causes mild to moderate irritation was used

during testing. Moreover, the GPMT test protocol introduces an opportunity for hydrolysis of trimethoxyvinylsilane by the procedure of mixing the test substance in FCA with 50% sterile saline prior to one of the intradermal injections during induction. Furthermore, the solubility issues of A-171 in mineral oil and FCA (based mainly on mineral oil) reported in Study V causes concern also for the reliability of Studies III and IV. In Study V, concentrations of A-171 higher than 3% were insoluble in FCA, however in Study III and IV, 10% and 5% of Dynasylan VTMO and Silquest A-171 Silane, respectively, were used. There seems not to be any large differences in the composition of these three test substances which raises the suspicion that the level of trimethoxyvinylsilane in FCA: saline used in Study III and IV might have been lower than what was reported, not only due to hydrolysis of the test substance but also due to precipitation. Solubility problems of the test substances in MEH 56 corn oil and acetone were not reported.

In conclusion, the positive test results obtained in Study I are considered reliable and valid for the assessment of the skin sensitisation potential of trimethoxyvinylsilane since the choice of assay and vehicle prevented hydrolysis of trimethoxyvinylsilane, and that maximal doses for induction and challenge exposure were used. Studies II-V are considered less reliable due to the markedly lower estimated internal levels of trimethoxyvinylsilane (Study II, possibly Studies III-V), the use of vehicles that likely caused hydrolysis of the test substance (Study II-V), possible precipitation of the test substance in FCA (Study III and IV) and the use of dose selection procedures which may not follow the OECD TG 406 guideline recommendations (Study III-V). These issues creates an uncertainty about the actual dose of trimethoxyvinylsilane and thereby also about the validity of the negative results in the overall assessment of the skin sensitisation potential of the substance.

10.7.2 Comparison with the CLP criteria

The CLP Regulation allows classification of skin sensitizers in one hazard category, Category 1, which comprises two sub-categories, 1A and 1B. For Category 1, when a non-adjuvant Guinea pig test method is used, a response in at least 15% of the animals is considered positive. This criteria is fulfilled for trimethoxyvinylsilane which has a positive response in 65% of the animals following the use of a 100% topical induction dose of Dynasylan VTMO (Study report, 1993). Classification into sub-categories should be performed if data is sufficient (CLP Annex I 3.4.2.2.1.1). Criteria for sub-categorisation into 1A and 1B includes data with the below indicated values (Table 21), according to the CLP Regulation (Table 3.4.3 and 3.4.4)

Table 21. Criteria for sub-category classification of skin sensitizers.

Sub-category	Assay	Response
1A	Buehler assay	≥ 15 % responding at ≤ 0.2 % topical induction dose or ≥ 60 % responding at > 0.2 % to ≤ 20 % topical induction dose
	Guinea Pig Maximization Test	≥ 30 % responding at ≤ 0.1 % intradermal induction dose or ≥ 60 % responding at > 0.1 % to ≤ 1 % intradermal induction dose
1B	Buehler assay	≥ 15 % to < 60 % responding at > 0,2 % to ≤ 20 % topical induction dose or ≥ 15 % responding at > 20 % topical induction dose
	Guinea Pig Maximization Test	≥ 30 % to < 60% responding at > 0.1 % to ≤ 1% intradermal induction dose or ≥ 30 % responding at > 1 % intradermal induction dose

According to Table 21, trimethoxyvinylsilane fulfils the criteria for sub-categorisation into 1B (≥ 15 % responding at > 20 % topical induction dose in a Buehler assay). The CLP Guidance states that care should be taken not to classify substances into category 1B if category 1A cannot be excluded (section 3.4.2.2.3.2). In Study I (Study report, 1993) the topical induction dose and response ratio were too high for category 1A to be excluded. Although the actual dose levels of trimethoxyvinylsilane used in Studies II-V (Study report 1994; 1996, 1999, 2000) are unknown due

to hydrolysis and in some cases precipitation of the test substance, they are lower than the dose level used in Study I, and no sensitisation reactions were detected. The negative results following a lower dose administration indicate that trimethoxyvinylsilane is a weak sensitizer. Sub-categorisation in 1B is therefore considered appropriate.

10.7.3 Conclusion on classification and labelling for skin sensitisation

Classification of trimethoxyvinylsilane as **Skin Sens. 1B, (H317)** is proposed.

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	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)	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	Study report, 1996 as quoted in ECHA Dissemination, 2016

performed on the hydrolysis product of Silquest A-171 Silane			Challenge dose: 10% (acetone)	After rechallenge 0/20 (0%) of test animals with positive reactions at 24 and 48h. 0/10 (0%) of 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 sensitization

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
4 Slight confluent or moderate patch erythema
5 Moderate erythema
6 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
4 Slight confluent or moderate patch erythema
5 Moderate erythema
6 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 oil)	24	10	0	0	0	10	n.a.	0.0
		48	10	0	0	0	10		0.0
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**.

10.8 Germ cell mutagenicity

Not evaluated in this dossier.

10.9 Carcinogenicity

Not evaluated in this dossier.

10.10 Reproductive toxicity

Not evaluated in this dossier.

10.11 Specific target organ toxicity-single exposure

Not evaluated in this dossier.

10.12 Specific target organ toxicity-repeated exposure

Not evaluated in this dossier.

10.13 Aspiration hazard

Not evaluated in this dossier.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Not evaluated in this dossier.

12 EVALUATION OF ADDITIONAL HAZARDS

Not evaluated in this dossier.

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14 ANNEXES

Annex I – Confidential information on compositions and impurities.