Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Adopted

8 June 2018

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON TRIMETHOXYVINYLSILANE; TRIMETHOXY(VINYL)SILANE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Substance name: trimethoxyvinylsilane; trimethoxy(vinyl)silane
EC number: 220-449-8
CAS number: 2768-02-7
Dossier submitter: Sweden

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
25.07.2017	Germany		MemberState	1
Comment received				
The German CA agrees with the proposed harmonised classification as skin sensitiser Sub-Category 1B.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
01.08.2017	Germany	Reconsile REACH consortium	Company-Manufacturer	2
Comment received				
In the Final Decision on a substance evaluation (ECHA; Helsinki, 04 July 2016) for this substance there is a request to summarize "Existing data on skin sensitisation potential after human exposure to trimethoxyvinylsilane." The data shall be submitted to ECHA by 11 October 2017. It is not clear why a CLH dossier has been developed before these requested data are available and have been evaluated. Therefore, it is requested to suspend the CLH discussion until an updated dossier according to the Final Decision on a substance evaluation (Helsinki, 04 July 2016) has been submitted to ECHA by Reconsile which is due on 11 October 2017. The new data have then to be evaluated by authorities, which are asked to draw a conclusion based on all available data and to decide whether a classification of the substance concerning this endpoint is still				

indicated.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Reconsile Comments on VTMO CLH dossier.zip

Dossier Submitter's Response

We thank the Reconsile REACH consortium for the comments. The classification process for trimethoxyvinylsilane on skin sensitisation was initiated because the necessity of further testing on this endpoint, to be decided in the SEV "follow up" is dependent on the RAC opinion on the currently available animal data on skin sensitisation. A RAC-opinion takes 18 months to develop and the legal deadline to request further tests for trimethoxyvinylsilane in the SEV process is 12 months after an updated dossier is submitted. We consider that information on "Existing data on skin sensitisation potential after human exposure to trimethoxyvinylsilane" requested in the SEV decision for trimethoxyvinylsilane is not necessary for classification as a skin sensitiser. Please see further explanation with the reference to SEV decision and minutes from MSC discussion. MSC unanimously agreed (by written procedure MSC-47) that because the available information was considered sufficient to classify trimethoxyvinylsilane as a skin sensitiser, there was no need to request at that stage the initially proposed LLNA. As there was no proposal to remove from the decision the request for human data this request remained. Please see decision https://www.echa.europa.eu/documents/10162/8c5b3eb0-8fec-43c4-9c0d-98f96b38cbf6

The substance evaluation strategy to clarify the concern for skin sensitisation of trimethoxyvinylsilane is in line with the one explained in more details in MSC minutes for trimethoxymethylsilane (for which SEV decision was discussed and agreed at the MSC-47 meeting, not via written procedure). Please see below the extract from MSC-47 minutes on SEV-SE-030/2013 Trimethoxy(methyl)silane (EC No. 214-685-0).

"The written procedure for MSC agreement seeking on this SEv draft decision prepared by the SE CA (eMSCA) had been terminated by the MSC Chair on request of a MSC member and the case was brought to the meeting to further discuss and clarify the proposed removal of the information request for a *Local lymph node assay (LLNA) (OECD 429 or OECD 442A or OECD 442B),* as requested in two PfAs received. In the following discussion, the eMSCA's expert and the MSC members exchanged views on the validity of the results of the positive Buehler test and the potential ways forward. The eMSCA proposed to drop the requests for LLNA and information on human experience from the DD and proceed based on the available information with a CLH proposal under the CLP Regulation such that RAC may assess its applicability for CLP-purposes. eMSCA further clarified that in the follow-up evaluation, after obtaining the information on mutagenicity testing and possibly taking into account the outcome of the CLH process, the eMSCA will reassess whether the concern for skin sensitisation remains and whether further studies should be requested. MSC supported the eMSCA's strategy to proceed with a CLH dossier first based on the currently available dataset and to assess further information needs in the follow-up evaluation stage. MSC unanimously agreed to the DD as modified at the meeting."
(MSC-47 minutes https://www.echa.europa.eu/documents/10162/22837890/msc-47_meeting_minutes_en.pdf/5c0a51cf-181b-4fa5-8818-a75becf26c8c)

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
04.08.2017	Belgium		Individual	3

Comment received

Dear Sir or Madam:

I am writing in response to the public consultation on the proposed hazard classification of

Trimethoxyvinylsilane (EC No. 220-449-8).

In its CLH report 'Proposal for Harmonized Classification and Labelling' (Vers. 2; Date: 170329), the Swedish Chemical Agency proposes to classify trimethoxyvinylsilane (EC no. 220-449-8) as Skin Sens. 1B (H317) under Regulation (EC) No 1272/2008 ('CLP Regulation'). The Swedish Chemical Agency evaluated the quality and reliability of a total of 5 in vivo skin sensitisation studies available on the substance in guinea pigs, 2 according to the Buehler test and 3 according to the maximisation test protocol. Only one of the 5 studies, a Buehler test, resulted in a positive outcome indicating a skin sensitisation potential for trimethoxyvinylsilane. Based on a self-developed model, the CLH report submitter considered a single positive Buehler test to be more sensitive than the 3 guinea pig maximisation and 1 Buehler tests on their own right and in combination.

It is my view that the CLH proposal to classify trimethoxyvinylsilane as Skin Sens. 1B is neither based on a thorough evaluation of the science nor on an appropriate application of the CLP criteria for skin sensitisation and should therefore be reconsidered.

My assessment is based on the fact that the consistent absence of a skin sensitisation potential of trimethoxyvinylsilane in four animal studies was not considered in an appropriate weight of evidence manner. Moreover, the model used by the CLH report submitter to argue the higher sensitivity of the single positive Buehler assay versus the 3 negative guinea pig maximisation and 1 Buehler tests is flawed and the actual calculations to rank order the reliability of the available animal studies are based on a chain of unsupported and partly faulty assumptions. More detail is provided in section 'specific comments/skin sensitisation'.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment TM-TMVS CLH Public Consultation-04Aug17.pdf

Dossier Submitter's Response
Thank you for the comment. It has been noted. Please see response to comment 11.
RAC's response
Thank you for the comment.

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
03.08.2017	Germany	Evonik Resource Efficiency GmbH	Company-Manufacturer	4
Comment received				
With regard to Study III - GPMT using Dynasylan VTMO (Study report, 1994) the CLH report states that "the lack of positive controls in the study in combination with the negative responses also causes concern about the reliability of the experimental design." For animal welfare reasons and others, positive controls are rarely performed in parallel to the test item. Reliability checks of test system are rather conducted on a regular basis. The above mentioned study was performed between 8 November 1993 and 16 December 1993; the most recent reliability check using 2-mercaptobenzothiazole (2-MCBT) between 16 August 1993 and 17 September 1993, revealing skin reactions in 100% of the treated animals. This has been well documented in the study report.				

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Dossier Submitter's Response
Thank you for your comment. It has been noted.
RAC's response
Thank you for the information, it has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
03.08.2017	Belgium		MemberState	5

Comment received

BE CA would thank the Swedish Chemicals Agency for submitting this proposal for Harmonised Classification and Labelling.

BE CA considers the sub-categorization in 1B for trimethoxysilane is not appropriate.

Indeed, results of study I (Buehler test, Study report 1993) are found reliable and fulfill criteria for a cat. 1 classification (≥ 15% responding when a non-adjuvant Guinea pig test method is used). The CLP Guidance also precises that a substance may be classified as a skin sensitizer on the basis of a single positive Buehler test result.

However, substances should not be sub-classified into category 1B if category 1A cannot be excluded. Accordingly, the negative results following a lower dose administration (studies II-V) confirm that trimethoxysilane might be sub-classified in 1B at first glance. Although, the possible hydrolysis of trimethoxysilane when diluted in aqueous solution as well as the solubility problems highlighted by the DS might invalidate the estimated internal induction doses (EID), giving therefore false negative results for sensitisation index. Especially, we cannot exclude that most oftrimethoxyvinylsilane might have been hydrolysed before the sensitization evaluation. Indeed, trimethoxyvinylsilane hydrolyses into vinylsilanetriol and methanol particularly quickly when it comes in contact with water (hydrolysis half-life about 0,2h at pH 7 and 20-25°C). In particular, studies III (GMPT, study report 1996) and V (GMPT, study report 2000) used organic vehicles, but trimethoxyvinylsilane was first diluted in saline solution.

In light of this knowledge, BE CA considers that category 1A cannot be excluded and trimethoxyvinylsilane should be classified in category 1.

Dossier Submitter's Response

We thank the Belgian CA for the comments. We agree that it is not possible to know to what extent hydrolysis of trimethoxyvinylsilane occurred following mixing with FCA:saline prior to intradermal induction and/or by using other vehicles containing water, and therefore the actual doses that were administered in Studies II-V are unknown. Hydrolysis could be almost complete giving false negative results for sensitisation, but could also be occurring to a smaller extent which would then only lower the administered induction/challenge doses compared to the nominal ones. We agree that category 1A cannot be excluded with absolute certainty based on the available data. However, Study II uses a lower induction dose (50%, purity of 70-90%) compared to Study I (100%, purity>98%) and a vehicle (acetone) in which hydrolysis may occur, but probably to a smaller extent. Since no positive skin sensitisation results were recorded in Study II, and if comparing to the criteria for classification in sub-category 1A (≥ 60% of the animal should have positive reactions at >0.2% to ≤20% local induction dose, alternatively ≥ 15% should have positive reactions at ≤ 0.2% local induction dose) it seems plausible that trimethoxyvinylsilane is a weak sensitiser and that classification in sub-category 1B would be appropriate.

RAC's response
Thank you for your comment.

Date	Country	Organisation	Type of Organisation	Comment number
01.08.2017	Germany	Reconsile REACH consortium	Company-Manufacturer	6

Comment received

To derive internal doses for all available tests various assumptions have been made by the Swedish authorities and a crude model has been applied. In our opinion, these assumptions are not justified sufficiently.

In general a higher bioavailability can be expected in case of a GPMT test as intradermal application is used. This is not considered in the model.

In the CLH report, penetration behaviour of the substance and the hydrolysis product vinylsilanetriol are discussed based on the physical-chemical properties. For the hydrolysis product vinylsilanetriol the logKow value is used to discuss skin penetration and a possible skin sensitization potential. Publications exist which question general phys.-chem. properties as significant for evaluating skin sensitization potential, e.g. Fitzpatrick JM et al; "Is skin penetration a determining factor in skin sensitization potential and potency? Refuting the notion of a logKow threshold for skin sensitization" J Appl Toxicol. 2017 Jan; 37(1):117-127.

Due to all these limitations a weight of evidence approach as already done by Reconsile is indicated to conclude on the skin sensitization potential of the substance. This view is also supported by ECHA's Final Decision on a substance evaluation (Helsinki, 04 July 2016) for trimethoxyvinylsilane. In this decision it is stated that "There is ambiguity in the results of the in vivo testing for the skin sensitisation potential with the use of trimethoxyvinylsilane and structurally similar substances and the weight of evidence approach may be necessary to conclude about the skin sensitisation concern."

The discussion of the GPMT as maximisation test is wrong in the CLH report. It is stated that "…the GPMT is a maximisation test, which implicates that maximum concentrations should be used in order for the test to be fully reliable." "Maximisation" in this context, however, means maximisation of exposure by intradermal application and potentiation of sensitization by the injection of Freund's Complete Adjuvant, which leads to a higher sensitivity of the test system (a factor of 2 is assumed in comparison to the Buehler test).

It is not discussed and explained in the CLH report why (if the higher sensitivity for GMPT - factor 2 - is considered) in Table 20 study III (GMPT) shows no signs of sensitization (0%) in comparison to study I (Buehler) with 65% sensitization index (estimated internal induction doses 61% vs. 93%; estimated internal challenge doses 23% vs 23%).

The already existing data concerning experience in humans (no indication of sensitization after decades of production and use of this substance) have not been considered and mentioned in the CLH report.

In the Final Decision on a substance evaluation (ECHA; Helsinki, 04 July 2016) for this substance there is a request to summarize "Existing data on skin sensitisation potential after human exposure to trimethoxyvinylsilane." The data shall be submitted to ECHA by 11 October 2017. It is further stated that "The already existing experiences from human data, if adequately analysed and reported, could add to the weight of evidence. There is

ambiguity in the results of the in vivo testing for the skin sensitisation potential with the use of trimethoxyvinylsilane and structurally similar substances and the weight of evidence approach may be necessary to conclude on the skin sensitisation concern. Reporting of already existing and available information on human on skin sensitisation potential of the trimethoxyvinylsilane is required."

Reconsile is in the process of developing such data. So far, a comprehensive statement is available from one company and attached as file named "2768-02-7 Wacker - Experience in Human Beings.pdf" (contained in "Reconsile Comments on VTMO CLH dossier.zip"). Three additional files named "2768-02-7 Wacker - Experience in Human Beings - Annex 1/2/3.pdf" are relevant as well for this statement.

Therein, the following sources have been used to evaluate the skin sensitization potential of the substance:
· Company internal data: relevant plants, number of employees, exposure description; medical surveillance
· Company internal regular health checks (especially concerning skin status) already performed on employees of the relevant plants
· Information from the Network of Departments of Dermatology for the surveillance and scientific evaluation of contact allergies
· Information from Employer's liability insurance association (BG Bau)
· Information from customer
· Comprehensive literature search

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

The following conclusion is drawn:

During more than 20 years of production (> 1000 t/a; two production sites), handling and use of trimethoxyvinylsilane and mixtures containing this substance at this company and during at least 14 years of external sale no single case of suspected contact allergy has been observed/reported. No signs of skin sensitization have been observed by the medical doctors and no skin disorders have been reported by the concerned employees during the regular health examinations, which comprise the Occupational Medical Examination G 24 "Skin disorders (not including skin cancer)". In total 855 medical check-ups of 168 employees have been performed. Relevant exposure can be expected during this time.

Information from other sources described above leads to the same conclusion. No case of skin sensitization has been observed and no such case has been reported in the scientific literature.
In contrast, a case was reported where substitution of a sealant with oximosilane crosslinker by a sealant with alkoxysilane crosslinker system lead to recurrence-free recovery of skin alterations induced by the sealant with oximosilane crosslinker.

In addition, more general statements from two other companies are available which support these results. Those are attached as files named "2768-02-7 Evonik - Experience in Human Beings.pdf" and "2768-02-7 Momentive - Medical Statement on sensitization CAS 2031-67-6 and CAS 2768-02-7.pdf" (both contained in the ZIP container "Reconsile Comments on VTMO CLH dossier.zip" as well).

Based on the described experience in humans trimethoxyvinylsilane does not require classification/labelling for skin sensitization.

These data must be considered in the CLH discussion.

It is requested to suspend the CLH discussion until an updated dossier according to the Final Decision on a substance evaluation (Helsinki, 04 July 2016) has been submitted to ECHA by Reconsile which is due on 11 October 2017. The new data have then to be evaluated by authorities, which are asked to draw a conclusion based on all available data and to decide whether a classification of the substance concerning this endpoint is still indicated.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Reconsile Comments on VTMO CLH dossier.zip

Dossier Submitter's Response

We thank the Reconsile REACH consortium for the comments and the provided data. Specific responses to the comments are given below:

Estimated internal dose

We agree that the model is crude and should not be used for actual calculations of internal dose – this is stated at page 22 of the CLH report. It is also stated in the report that comparisons of doses should be made using caution, since the sensitivity of the Buehler test and GPMT differ.

Weight of evidence

The available data on skin sensitisation data for trimethoxyvinylsilane was evaluated in a weight of evidence assessment where the quality and reliability of all studies as well as the purity of the test compounds was taken into account. Studies II-V were not considered reliable in comparison to Study I due to: 1) the high probability for hydrolysis of trimethoxyvinylsilane by mixing trimethoxyvinylsilane with saline prior to the intradermal induction and or mixing trimethoxyvinyl silane with other vehicles containing water (acetone), 2) possible non-compliance with OECD-guideline 406 (failure to demonstrate that maximal doses resulting in light/moderate irritation were given for induction), 3) lack of information on storage time of the trimethoxyvinylsilane/FCA:saline mixture and trimethoxyvinylsilane:acetone mixtures, and 4) solubility issues/possible precipitation of the test compound in some of the GPMTs.

GPMT as maximisation test

This sentence from the CLH report refers to that in two of the GPMTs (Studies III and V) it was not demonstrated that the maximal dose resulting in light to moderate irritation was used for induction. This is a deviation from OECD TG 406.

Human data

The CLH dossier was prepared using all data considered relevant for CLP purposes available at the time. Since it was agreed at MSC 47 that the existing data on skin sensitisation was sufficient for harmonised classification as a skin sensitiser (see response to comment 1), we did not consider that awaiting information on human experience was necessary. Also, the CLH process should not be suspended because the necessity of further testing on this endpoint, to be decided in the SEV "follow up", is dependent on the RAC opinion on the currently available data on skin sensitization (see also response to comment 1).

The human information that was provided during public consultation consist of statements from companies that no cases of skin sensitisation has been observed/reported in workers during several years of production, handling, use and sale of trimethoxyvinylsilane; records of searches in the scientific literature and databases for cases of trimethoxyvinylsilane skin

sensitisation which turned up empty; and a published study from BG Bau on health benefits of solvent-free adhesives used for flooring where one of the adhesives contained methoxysilanes (however not specifically mentioning trimethoxyvinylsilane). Actual detailed human exposure levels are lacking in this information. Although this body of information may be valuable in discussions on safe use of trimethoxyvinylsilane, it is not suitable for classification purposes under CLP. Classification under CLP is based on intrinsic hazard and not risk.
RAC's response
Thank you for the information.

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2017	France		MemberState	7
Comment received				
Classification of trimethoxyvinylsilane as a skin sensitizer 1B is proposed based on a Buehler test with Dynasylan VTMO which induced a positive response in 65% of the animals at 100% topical induction dose. Another Buehler test at 50% topical induction dose with Silcat R and guinea pig maximization tests with Dynasylan, VTMO, Silquest A-171 silane or A-171 did not show sensitizing potential of the test substance but the conditions of application of these tests were considered less sensitive by the DS. Based on the available data provided in the CLH report, we support the classification of trimethoxyvinylsilane as a skin sensitizer category 1. With regard to sub-category, the two Buehler assays support a classification of trimethylvinylsilane into category 1B considering that positive results are only found after 100% induction suggesting a low potency. Indeed, the second study investigating lower topical induction dose (50%) with a substance of lower purity gives negative results. However, before concluding with sufficient level of evidence for the sub-category 1B, we think that human data should be taken into account. We have noticed that during the evaluation process of this compound as mentioned in section 4, existing data on skin sensitisation potential after human exposure to trimethoxyvinylsilane have been asked to the registrant. We think that this should be reflected in the CLH report and if human data have been now made available, they should be addressed. If no human data have been currently provided, then this should be also mentioned in the report. Moreover, we think that data (in vivo/in vitro or human) on structurally similar substances – if available could also be included to strengthen the level of evidence.				
Dossier Submitter's Response				
Thank you for your support. All data relevant for classification of trimethoxyvinylsilane under CLP was considered at the time the CLH dossier was prepared. No such human data was found. Read across to structurally similar substances (such as trimethoxy(methyl)silane, CAS No 1185-55-3, for which a CLH-proposal for Skin Sens. 1B also has been submitted) was considered but not explored further for two reasons: 1) the available data for trimethoxyvinylsilane was considered sufficient for classification as skin sensitiser and 2) the chemical structure of trimethoxyvinylsilane contains a double bond and may it therefore be more reactive than trimethoxy(methyl)silane. Human experience from exposure to trimethoxyvinylsilane was submitted during public consultation, but lack in detail on actual worker exposure levels. It is therefore not considered relevant for classification purposes (see also response to comment 6).				
RAC's response				
Thank you for your comment.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON TRIMETHOXYVINYLSILANE; TRIMETHOXY(VINYL)SILANE

Date	Country	Organisation	Type of Organisation	Comment number
25.07.2017	Germany		MemberState	8
Comment received				
Concordant with the CLP criteria the evidence from the first study indicates that the test chemical is a skin sensitizer and is considered to be of sufficient quality to be taken into consideration. Further studies performed are less reliable due to some weaknesses such as e.g. incomplete conformity with the OECD guidelines. The choice of the vehicle used in these studies cannot exclude the occurrence of hydrolysis or precipitation of the test chemical, thus potentially resulting in lower doses. Therefore we agree with the proposal that trimethoxyvinylsilane should be classified as a weak sensitizer.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for the comment.				

Date	Country	Organisation	Type of Organisation	Comment number
19.07.2017	Finland		MemberState	9
Comment received				
One skin sensitisation study (Buehler test, OECD TG 406) in guinea pigs showed positive response in 65% of animals at 100% topical induction dose. The criteria for classification as Skin Sens 1B; H317 is thus met (≥ 15% responding at > 20% topical induction dose). Based on this study, classification into sub-category 1A cannot be exluded, because both the dose and the response rate were too high. In other skin sensitisation studies where lower dose levels in induction and challenge were used, no sensitisation effects were observed. This indicates that trimethoxyvinylsilane would not be a strong sensitiser. FI CA supports the proposed classification of Skin Sens. 1B; H317 May cause an allergic reaction for trimethoxyvinylsilane.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for the comment.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2017	Germany		Individual	10
Comment received				
Trimethoxyvinylsilane appears to have a weak sensitizing effect at all. Only one test report shows a sensitizing effect at high concentrations. Tests with lower concentrations show no positive reactions. However, if the substance is harmonized as sensitizing, it should also be clarified whether the labeling limit is higher than 1%.				
Dossier Submitter's Response				
Thank you for the comment. According to the Guidance on the application of the CLP Criteria, it is difficult to prove the absence of sensitising properties at certain concentration levels. An SCL above the GCL may therefore only be set in exceptional circumstances, if scientific information is adequate, reliable and conclusive for that particular skin sensitiser.				

We do not consider the data on skin sensitisation for trimethoxyvinylsilane to be sufficient for the derivation of an SCL. Hence, we consider the concentration limit of >=1% (GCL) to be appropriate.
RAC's response
Thank you for the comment.

Date	Country	Organisation	Type of Organisation	Comment number
04.08.2017	Belgium		Individual	11
Comment received				
Three of the four in vivo studies which the CLH report submitter 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. Where deviations from OECD TG 406 occurred (as per the description of CLH report submitter), these are minor with no expected impact on the study outcome. Since the full study reports are not publicly available for review, I recommend checking the quality assurance procedure of the contract laboratory of study III, before prematurely concluding that the absence of a positive control in the actual study limits its reliability. To reduce the amount of laboratory animals used for toxicity testing, contract laboratories do not always include a positive control into each skin sensitisation study, but regularly conduct positive control testing to assure the sensitivity of the different skin sensitization protocols ran within the contract laboratory. The procedure is typically stated in the study report. I agree with the Swedish Chemical Agency 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. However, it should still be considered in an overall weight of evidence context as the result of study V matches those of studies II, III and IV. The model which the CLH report submitter developed to estimate 'internal doses' resulting from the in vivo studies with trimethoxyvinylsilane presents an interesting approach to take account of potential hydrolysis of the substance under actual testing conditions, but is flawed with regard to estimating exposure and ranking the reliability of the studies for hazard classification purposes. If at all, it establishes a sort of bioavailable concentration based on a chain of unsupported assumptions, but not an internal dose. Thereby it ignores the accepted concept of dose metrics in the acquisition of skin sensitisation which has been established by Kimber et al. (2008). Moreover, 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. Following a thorough review of the scientific evidence along with the immunologic basis for skin sensitization, Kimber et al. (2008) concluded that, for topically applied substances, the dose of chemical per unit area of skin rather than the total amount of the chemical delivered is the key metric in terms of effectiveness with which sensitisation is acquired. Kimber et al. (2008) stated further that the only exception to this rule is when very small topical application sites are considered. This is however not the case for the Buehler or maximisations test where topical patches of 4-8 cm2 are being applied. The model proposed by the CLH dossier submitter is significantly hampered by not taking into account the total mass of the test substances per unit area of skin applied in the induction phase of the respective studies. This should be straightforward to determine for topical applications in the Buehler test and the topical induction of the GPMT, but it is yet unclear how to consider the first phase of the GPMT, the intradermal injection of the test substance alone and test substance mixed with the Freund's complete adjuvant in this				

context. When comparing outcomes from a Buehler test with those of the GPMT, it is particularly this intradermal induction step which increases the GPMT's effectiveness in triggering a sensitisation response and makes, along with the longer induction patch application (48 hrs in the GPMT vs 6 hrs in the Buehler assay), the GPMT more sensitive compared to the Buehler test. This is scientifically widely recognised (see for example van Loweren et al., 2008) and the reason why the regulatory community prefers the GPMT over the Buehler test for skin sensitisation hazard identification purposes. Not considering these differences in dosing with its impact on the sensitivity of the assays is a major flaw in the CLH dossier submitter's model.

Notwithstanding the lack of consideration of the sensitivity differences between the two guinea pig assays, another significant flaw in the CLH dossier submitter's is the assumption that trimethoxyvinylsilane is rapidly and completely taken up by the skin (i.e., 100%). According to Shen J. et al. (2014), for chemical substances with a molecular weight of 150 Da and a log Kow of 1.1 (i.e., the same parameters considered by the CLH dossier submitter for Trimethoxyvinylsilane), a maximum flux of 1.0 – 10 µg/cm2/h is considered leading to a proposed default absorption of 40% per 24 hrs of skin exposure. According to OECD TG 406, the induction patches in a Buehler test are applied for 6 hrs, while in a GPMT the induction patches are applied for 48 hrs. If linearity is assumed, one could estimate an absorption of 10% of the topically applied trimethoxyvinylsilane in the Buehler test and 80% of the topical induction dose in the GPMT.

Using these different absorptions in the dossier submitter's algorithm with the same assumptions of hydrolysis (Table 20) would lead to a completely different picture: For study I (positive Buehler test), one would calculate an 'estimated internal induction dose' of 9.3%. In study III (negative GPMT), one would calculate an 'estimated internal induction dose' of 52%. For the 2nd negative GPMT, study IV, an 'estimated internal induction dose' of 45% would be calculated. When looking at these very different 'intake' values, the observed sensitisation rate of 65% for study I at lower intake level is not consistent with the 3 negative GPMT studies and appears a chance finding.

This calculation example is meant for illustrative purposes only and should not be considered as support for the dossier submitter's model for the mechanistic reasons discussed before. Also, trimethoxyvinylsilane's hydrolysis rate of 5% or 50% upon contact with skin moisture or via the vehicles is purely speculative and should not be used in support of a skin sensitisation hazard classification proposal as long as not understood.

In conclusion, the CLH proposal to classify trimethoxyvinylsilane as Skin Sens. 1B is neither based on a thorough evaluation of the science nor an appropriate application of the CLP criteria for skin sensitisation. The weight of evidence from five in vivo skin sensitisation studies in guinea pigs according to the Buehler and the maximisation test protocol suggests that trimethoxyvinylsilane should not be classified as skin sensitiser. This is due to the consistent absence of a skin sensitisation potential of trimethoxyvinylsilane in four animal studies, 3 GPMT's and 1 Buehler assay versus a positive finding in a single Buehler test. The model used by the CLH report submitter to argue the higher sensitivity of the single positive Buehler assay versus the 3 guinea pig maximisation and 1 Buehler tests is flawed and the actual calculations to rank order the reliability of the available animal studies based on a chain of unsupported and partly faulty assumptions. Finally, I suggest including the review and consideration of available human exposure data in any update of the CLH report on the classification of trimethoxyvinylsilane for skin sensitisation.

References

Kimber I. et al. (2008). Dose metrics in the acquisition of skin sensitization: Thresholds and

importance of dose per unit area. Regulatory Toxicology and Pharmacology 52, 39-45.

Shen J. et al. (2014). An in silico skin absorption model for fragrance materials. Food and Chemical Toxicology 73, 164-176.

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Sincerely,

Thomas Petry, Ph.D., DABT, ERT

ECHA note – An attachment was submitted with the comment above. Refer to public attachment TM-TMVS CLH Public Consultation-04Aug17.pdf

Dossier Submitter's Response

We thank Dr. Petry for the comments. The results of studies I, II, III, IV and V were evaluated in a weight of evidence assessment taking the quality and reliability of the studies as well as the purity of the test compounds into account.

The procedure for positive controls used in Study III has been noted (see also comment 4).

The model used in the CLH report was an attempt to take into account in the weight of evidence assessment the less reliable studies II-V in which vehicles containing water was used to test the hydrolytically unstable trimethoxyvinylsilane. The model is - as stated in the CLH-report (p. 22)- crude, based on assumptions, and should be used with caution since differences in experimental design between the Buehler test and the GPMT results in differences in sensitivity. Further uncertainties and drawbacks of the model are identified in the comments above. However, the major flaw of this model is that the extent of hydrolysis of trimethoxyvinylsilane brought on by mixing with FCA:saline prior to the first intradermal injections (Study III-V) or by using other vehicles containing water (such as acetone in Study II and IV) is unknown. Therefore, the administered doses in these assays are unknown. In addition, there is no detailed information in the study reports on the time elapsed between mixing trimethoxyvinylsilane with FCA:saline/acetone and the intradermal injections/topical applications, adding further to the uncertainty of the doses. Hydrolysis of trimethoxyvinylsilane is rapid (half-life of ~0.2h at pH 7 and 25°C) which means that only a short storage time would substantially lower the nominal dose. Storage of acetone: trimethoxyvinylsilane mixtures would also increase the risk for hydrolysis. Over time, ketones form ketals and at the same time, water is produced. Short chain ketones such as acetone react quite rapidly.

When it comes to human information, all information relevant for CLP-purposes that was available at the time the CLP-dossier was prepared was taken into account. Human information was submitted during public consultation, however it is not considered to be relevant for the purpose of classification of trimethoxyvinylsilane under CLP (please see response to comment 6).

RAC's response

Thank you for the comment.

PUBLIC ATTACHMENTS

1. TM-TMVS CLH Public Consultation-04Aug17.pdf [Please refer to comment No. 3, 11]
2. Reconsile Comments on VTMO CLH dossier.zip [Please refer to comment No. 2, 6]