Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

Trimethoxy(methyl)silane

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

CLH-O-0000001412-86-234/F

Adopted

14 September 2018

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: trimethoxy(methyl)silane
EC number: 214-685-0
CAS number: 1185-55-3
Dossier submitter: Sweden

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
24.10.2017	Germany		MemberState	1
Comment received				
The German CA does not agree with the proposed classification as Skin Sens. 1B; H317. The German CA is also of the opinion that, even if an agreement was achieved at MSC, the justification that action at community level is needed is poorly elaborated. In Section 7 "Physicochemical Properties" of the CLH report a predicted water solubility of 1 × 10^6 g l^-1 for the hydrolysis product methylsilanetriol was cited from the REACH registration dossier. However, the unit is wrong and the predicted water solubility according to the registration dossier amounts to 1 × 10^6 mg l^-1.				
Dossier Submitter's Response				
We thank the German CA for the comments. The classification process for trimethoxy(methyl)silane 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. Please see further explanation with the reference to the decision on the substance evaluation and minutes from MSC discussion. Please see an extract from the SEV decision for trimethoxy(methyl)silane: "By 22 February 2016 the evaluating MSCA received proposal(s) for amendment to the draft decision. The request to perform the Local lymph node assay, OECD 429 was removed from the decision based on the reasoning that available information is already sufficient to classify the substance as a skin sensitiser[2]. Consequently, the request for information on existing data on human skin sensitisation potential after exposure to the registered substance was also removed from the decision." (SEV decision for trimethoxy(methyl)silane: https://echa.europa.eu/documents/10162/0fe51b2f-137b-46e6-91fc-c36f2814fbf6) MSC discussed and unanimously agreed at the MSC-47 meeting that because the available information was considered sufficient to classify trimethoxy(methyl)silane as a skin sensitiser, there was no need to request at that stage the initially proposed LLNA.				

The substance evaluation strategy to clarify the concern for skin sensitisation of trimethoxy(methyl)silane is explained in more details in MSC minutes. 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)

You are correct regarding section 7 "Physicochemical Properties" of the CLH report. There is an error in the unit given. The predicted water solubility for the hydrolysis product methylsilanetriol according to the registration dossier amounts to 1 × 10^6 mg l^-1.

RAC's response

Thank you for the comment.

Date	Country	Organisation	Type of Organisation	Comment number
27.10.2017	Germany	Reconsile REACH consortium	Company-Manufacturer	2

Comment received

Different approaches have been used by the Swedish authorities to justify the CLH classification and labelling proposals (skin sensitization) for this and a similar substance, respectively.
For the similar substance (Trimethoxyvinylsilane - EC Number 220-449-8; CAS Number 2768-02-7) the Swedish authorities apply a crude model to discuss results of five skin sensitization tests (GPMT and Buehler tests) based on the assumed internal doses. As a result, the only positive test (Buehler) has been identified as solely relevant for classification due to estimated internal levels based on this model. Although we do not support this model at all, it is worth to mention that if this approach would have been applied in the present case as well, the test with the negative result (study report 2013) would have been identified as solely relevant for classification. This approach, however, was not followed indicating that there is no agreed and comprehensible approach how the

evaluating authority assesses such studies.

With the specific test design of the 2009 study it cannot be excluded that findings in the test group after re-challenge are unspecific reactions due to irritation. This must be considered in the evaluation.

Limitations of the 2013 study, which are discussed by the Swedish authorities, could be clarified (information from study owner). Therefore, the 2013 study is reliable and must be considered in the evaluation as well.

In a comprehensive way, Reconsile has now summarized existing and available information from human on skin sensitisation potential. Based on these data there is no indication of sensitization after decades of production and use of this substance which must also be considered in the CLH discussion.

It is the opinion of the Reconsile consortium that a weight of evidence approach as already done in the REACH dossier should be applied to conclude on the skin sensitisation potential of the substance.

Based on all available data (animal, human) it is the opinion of the Reconsile consortium that the substance has not be classified as skin sensitizer.

More detail is provided in section "Specific comments/Skin sensitization".

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Reconsile Comments on MTMS 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:

<u>Approaches for evaluating studies</u>
In the evaluation of the substance (trimethoxyvinylsilane - EC Number 220-449-8; CAS Number 2768-02-7) the Swedish Chemicals Agency applied a crude model to discuss the differences in results of the various skin sensitisation tests. This approach was undertaken in an attempt to compare the results as the 5 disseminated studies have used 2 different assays (GPMT and Buehler tests), 4 different test substances with various degrees of purity, and 3 different vehicles in combination. As stated in the CLH report for trimethoxyvinylsilane, the model should not be used for actual calculations of internal dose and that comparisons of doses between assays should be made using caution, since the sensitivity of the Buehler test and GPMT differ.

In the evaluation of the present substance (trimethoxy(methyl)silane - EC Number 214-685-0; CAS Number 1185-55-3), both studies applied the same assay, test substance and vehicle. However, the purity of the test substance was unknown in the second study of 2013, which was one of the parameters in the crude comparison model. In the CLH report for trimethoxy(methyl)silane, the crude model was not considered necessary to be able to compare the results of the two available studies.

<u>The 2009 study</u>
It is concerning that the level of skin reaction differs between the challenges, as it makes the interpretation of the results difficult. The reactions in negative control group during the first challenge has not been explained in a satisfactory manner in the study, making the results less convincing.

However, irritation screenings were conducted prior to the main study to determine the the minimal irritation concentration of the induction period and the highest nonirritating concentration for the challenge and re-challenge periods. Topical administration with trimethoxy(methyl)silane at 75% in PEG 300, resulted in slight skin reactions (grade 1, discrete or patchy erythema), but with scaling. Trimethoxy(methyl)silane at 50% in PEG 300 produced slight skin irritation (grade 1), but without scaling, and therefore this concentration was selected for the epidermal induction period. Trimethoxy(methyl)silane at 25% in PEG 300 did not result in a local skin reaction during irritation screening. Importantly, the OECD test guideline 406 allows for a re-challenge if it is necessary to clarify the results. The test guideline 406 specifies that rechallenge can be performed "where appropriate with a new control group". Hence, the 2009 study has followed test guideline 406, in contrast to the 2013 study.
In addition, the study director has made the assessment that the skin reactions are considered to be skin sensitisation rather than unspecific irritation.
Taken together, we consider the 2009 study as reliable with restriction. The study is following the OECD test guideline 406. We believe that the results after the re-challenge are an indication of trimethoxy(methyl)silane having a limited potential to cause skin sensitisation. Positive effects seen in either humans or animals for skin sensitisation will normally justify classification. Hence, we believe that trimethoxy(methyl)silane should have a harmonised classification as Skin sens. 1B.

<u>The 2013 study</u>
The clarification on the purity is important, as this was not available at the time of writing the CLH report. It would have been interesting to know if the test material came from the same manufacturer and if it contains the same impurities.
Although the study report of 2013 is negative, it has deficiencies which makes it difficult to evaluate the reliability, validity and relevance of the results. This study was not considered reliable due to: 1) non-compliance with OECD guideline 406 (failure to demonstrate that maximal doses resulting in light/moderate irritation were given for induction), 2) lack of information on preparation and storage time of the trimethoxy(methyl)silane/PEG mixture and 3) purity not reported in the study report (which has been clarified in comment 2 and 4).
It is concerning that no skin reactions were observed at either concentrations in the 2013 study. Although the study of 2013 might be a confirmatory study of the study of 2009, the OECD guideline 406 should have been followed. A concentration resulting in mild irritation should have been selected for induction and the highest nonirritating dose should be selected for the challenge.

<u>Human data</u>
The CLH dossier was prepared using all data considered relevant for CLP purposes available at the time. Stating secondary source in the CLH report is referring to the summary of information in the summary report, where a primary source would be e.g. a full study report, complete case report or scientific research paper of the documented cases of accidents. The information on humans that was provided in the summary report of 2013 and 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 trimethoxy(methyl)silane; records of searches in the scientific literature and databases for cases of trimethoxy(methyl)silane 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 trimethoxy(methyl)silane). Actual detailed human exposure levels are lacking in this information. Although this body of information may be valuable in discussions on safe use of trimethoxy(methyl)silane, it is not suitable for

classification purposes under CLP. Classification under CLP is based on intrinsic hazard and not risk.

Weight of evidence
The available data on skin sensitisation for trimethoxy(methyl)silane 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. We believe that there are deficiencies in the available data. A clear scientific explanation as to why the level of skin reaction differs between the two studies has not been provided. A speculation is that the level of hydrolysis of trimethoxy(methyl)silane is involved, but there is no data to confirm this. The hydrolysis of trimethoxy(methyl)silane in water is rapid (half-life approximately 2.2 hour at pH 7, <0.033 hours at pH 4, 0.11 hours at pH 9 and 25°C)). Since hydroxide groups are present in PEG, hydrolysis can be expected but the rate of the hydrolysis of trimethoxy(methyl)silane in PEG 300 is unknown. In the study of 2009 it is stated that the dilutions of trimethoxy(methyl)silane is freshly made throughout the study. It is not reported in the 2013 study if the test material was freshly prepared. It difficult to scientifically assess if enough of trimethoxy(methyl)silane was present in the tested material, to draw the conclusion that the result of the 2013 study is relevant for the substance for which CLH is proposed.
Importantly, the 2009 study follows the OECD guideline 406, while the 2013 study does not. In the irritation screening in the study of 2009, 75% of trimethoxy(methyl)silane caused slight irritation with scaling and 50% caused slight irritation without scaling, indicating that a suitable induction concentration might be between 75-50% of trimethoxy(methyl)silane if the testing conditions (including test material composition) are similar. In the 2013 study, the highest concentration tested was 50% of trimethoxy(methyl)silane and no skin reactions were observed. If the testing conditions were comparable, similar skin reactions would have been expected. Hence, a proper irritation screening could be crucial to establish a relevant induction concentration. The dose levels required by OECD test guideline 406 for each induction exposure should be the highest concentration of the test substance to cause mild irritation, and the concentration used for the challenge exposure should be the highest non-irritating dose. The validity and relevance of the negative test result is questionable due to the above mentioned limitations, such as deviation from the OECD test guideline 406. We believe that the positive effects for skin sensitisation seen in the 2009 study (reliable with restriction) is a cause for concern, indicating that harmonised classification of trimethoxy(methyl)silane as Skin sens. 1B is justified. We look forward to the discussions in RAC.

RAC's response
Thank you for the comment.

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
24.10.2017	Germany		MemberState	3
Comment received				
The dossier is focussed on this endpoint exclusively. The German CA has doubts that the key study is sufficient to justify classification and labelling as Skin Sens 1B. The first challenge (see p. 10, table 9) shows a result of 100 % reaction in the control group, 10 out of 10 animals reacted with erythema score 1 after 24 hours. The results of the trimethoxy(methyl)silane-treated group showed a 95 % reaction after 24 hours. The dossier submitter relies solely on the results of the re-challenge (see p. 11, table 10). Here the control did not show any reaction whereas the treated group yielded 6 out of 20 animals with erythema score 1 after 24 hours and 4 out of 20 animals with erythema				

score 1 after 48 hours.
This study contains inconsistent results and is not suitable for the justification of the proposed classification and labelling.

Dossier Submitter's Response

We thank the German CA for the comments.
This dossier is focused on this endpoint exclusively 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 more elaborate explanation under response to comment 1).
We agree that the key study contains inconsistent results. The unexplained positive skin reactions in control group I during the first challenge is concerning. However, the OECD test guideline 406 allows for a re-challenge if it is necessary to clarify the results (OECD 406, para 35, page 6). The results after the re-challenge could be an indication of trimethoxy(methyl)silane having a skin sensitisation potential. In our opinion, the study follows the OECD guideline 406 and the positive findings in the study, which is reliable with restriction, indicates that harmonised classification of trimethoxy(methyl)silane as Skin sens. 1B is justified.
The study report of 2013 is negative but it has deficiencies with deviations from the OECD test guideline 406 which makes it difficult to evaluate the reliability and significance of the results.

RAC's response

Thank you for the comment.

Date	Country	Organisation	Type of Organisation	Comment number
27.10.2017	Germany	Reconsile REACH consortium	Company-Manufacturer	4

Comment received

ANIMAL DATA
In the CLH report results of two Buehler tests are summarized.

Both reports are considered as reliable with restrictions in the Reconsile REACH dossier.

The study report of 2009 has been identified as key by the Swedish authorities. It is stated in the CLH dossier that "In conclusion, the study report of 2009 is reliable, it follows the OECD guideline 406 and it is performed with a test material of known purity. Due to the positive results of the re-challenge, the entire study is rendered positive."
In this test the results of the first challenge indicate an unspecific irritation reaction in both control and test groups at a concentration of 25% trimethoxy(methyl)silane with higher incidence in the control. In the re-challenge with a concentration of again 25% trimethoxy(methyl)silane using the same vehicle (PEG) a new control group was selected while the treated group was comprised of the same animals. With this test design a positive reaction in 30% of the animals in the test group after 24 hours and in 20% of the animals after 48 hours has been observed. No skin reaction was observed in the new control group. It must be considered that in the first challenge in the initial control group and the test group skin reactions have been observed at a concentration of 25% trimethoxy(methyl)silane. Therefore, with this test design (new control group) it cannot be excluded that findings in the (initial) test group after re-challenge are unspecific (irritation) reactions. This must be considered in the evaluation.

In the CLH report it is stated that "In the second Buehler test (study report 2013), found to be not reliable, trimethoxy(methyl)silane did not cause skin irritation. The selected concentration for induction did not cause mild-to-moderate skin irritation in the irritation

screening, as is required by the Buehler test OECD 406. In addition, the purity of the tested substance has not been reported. The validity and relevance of the negative test results is questionable due to the limitations of the study. It is noted that the study of 2013, which found the test material not sensitising, used a higher concentration of test substance (50% at induction and challenge doses), than the study of 2009 which concluded the test substance to be a sensitiser (50% at induction and 25% at re-challenge doses). However, the negative study of 2013 is considered to be not reliable due to the OECD guideline 406 deviation making the test procedure not entirely in accordance, the reporting of purity and the availability of the raw data (as specified in ECHA Guidance on information requirements and chemical safety assessment 2011)."

Concerning the limitations of the study discussed by Swedish authorities the following information can be provided:
Purity: The purity of the test substance was 95.59%. This purity is covered by the concentration range given in the REACH dossier (Typical concentration > 95%). Therefore, this purity is representative for the registered substance.
Preparation of the test material: It is assumed that the samples were prepared freshly. However, a communication with the CRO is still ongoing to clarify this issue finally.
Rationale to use a concentration of 50% for induction: In the 2009 study trimethoxy(methyl)silane showed an ambiguous positive sensitization reaction occurring at a concentration of 25% in PEG. Therefore, in the later study of 2013 a doubled concentration of 50% was chosen as the highest concentration. The sensitivity and reliability of the test system has been approved by a reliability check. The study has been performed to clarify the ambiguous results of the study from 2009.

Based on this additional information study report of 2013 and the corresponding results should be considered as reliable with restrictions and should be used in a weight of evidence approach.

Different approaches have been used by the Swedish authorities to justify the CLH classification and labelling proposals (skin sensitization) for this and a similar substance, respectively.
For the similar substance (Trimethoxyvinylsilane - EC Number 220-449-8; CAS Number 2768-02-7) the Swedish authorities apply a crude model to discuss results of five skin sensitization tests (GPMT and Buehler tests) based on the assumed internal doses. The only positive test (Buehler) has been identified as solely relevant for classification due to estimated internal levels based on this model.
Although we do not support this model at all, it is worth to mention that if this approach would have been applied in the present case as well, the test with the negative result (study report 2013) would have been identified as solely relevant for classification.

HUMAN DATA
In the CLH report in chapter 10.5.1 it is stated that "The human data (summary report 2013) is not considered relevant for the purpose of assessing skin sensitization potential of trimethoxy(methyl)silane under CLP, as this is only a summary report from a secondary source."

This is a misunderstanding as the report covers experience of one company (Wacker, 2013) which produce the substance since more than 20 years and market it since at least 14 years. The exposure situation and the experience of the plant managers and company medical doctors (based on internal data files) have been summarized in the paper. No one case of skin sensitization has been observed.

Nevertheless further activities have been started in Reconsile to summarize the experience in humans in a more comprehensive way. Such comprehensive statement is available from one company and attached as file named "Sens_Trimethoxymethylsilane_experience_humans.pdf"). Three additional files named "Annex 1_MTMS_VTMS.pdf", "Annex 2_MTMS_WACKER.pdf" and "Annex 3_MTMS_VTMS.pdf" are relevant as well for this statement.

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 Trimethoxy(methyl)silane and mixtures containing this substance at WACKER 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.

Based on the described experience in humans Trimethoxy(methyl)silane does not require classification/labelling for skin sensitization.

In addition, a more general statement from one other company is available which support these results based on experience related to two similar substances (Trimethoxyvinylsilane - EC Number 220-449-8; CAS Number 2768-02-7 and Triethoxymethylsilane - EC number 217-983-9; CAS Number 2031-67-6). Both, triethoxymethylsilane (CAS 2031-67-6) and trimethoxymethylsilane rapidly hydrolyse to the same silicon hydrolysis product methyltrisilanol. The statement is attached as file named "2768-02-7 Momentive - Medical Statement on sensitization CAS 2031-67-6 and CAS 2768-02-7.pdf".

These human data must be considered in the CLH discussion.

CONCLUSION
Based on all available data (animal, human) it is the opinion of the Reconsile consortium

that the substance has not be classified as skin sensitizer.

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

Dossier Submitter's Response

We thank the Reconsile REACH consortium for the comments and the provided data. Please see reponse to comment 2.

RAC's response

Thank you for the comment.

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	France		MemberState	5

Comment received

Could you please specify if a positive control was included in both studies?
FR questions if the overall evidence is sufficient to conclude on classification. The relevance of the first study is doubtful considering the positive responses reported in the control group at the first challenge. In the second study, we agree that the induction concentration is maybe too low. However, the induction dose is the same as in the first study and the challenge dose is higher than in the first study which was already positive. Thus, we consider that a new study should have been useful to clarify this endpoint.

Dossier Submitter's Response

We thank MS France for the comments.

Regarding positive controls:
Positive controls were indeed included in both studies.

Study report, 2009: the positive control was alpha-hexylcinnamalaldehyde.
Due to equivocal findings after the first challenge with a rapid fading of the skin reactions at the 24 hour reading (with 5% alpha-hexylcinnamalaldehyde in PEG 300), a second challenge was performed two weeks later by repeating the first challenge procedure on a new skin site (again with 5% alpha-hexylcinnamalaldehyde in PEG 300).

The incidence of positive skin reactions after the first challenge with positive control alpha-hexylcinnamalaldehyde at 5% in PEG 300 is summarised as follows:

Erythema Score	**Control Group 10 animals**		**Positive Control Group 20 animals**	
	5% in PEG 300		**5% in PEG 300**	
	24 hrs	**48 hrs**	**24 hrs**	**48 hrs**
0	10	10	10	20
1	0	0	10	0
2	0	0	0	0
3	0	0	0	0
No. with grades ≥1	0	0	10	0
No. tested	10	10	20	20
Incidence*	**0/10**	**0/10**	**10/20 (50%)**	**0/20**
Severity**	0	0	0.5	0

*Number of animals showing a response of grade 1 or greater at either 24- or 48-hour reading out if the total animals.

** Total sum of 24- and 48-hour response readings divided by the number of animals exposed (maximum of 3).

The incidence of positive skin reactions after the challenge with positive control alpha-hexylcinnamalaldehyde at 1% in PEG 300 is summarised as follows:

Erythema Score	**Control Group 10 animals**		**Positive Control Group 20 animals**	
	1% in PEG 300		**1% in PEG 300**	
	24 hrs	**48 hrs**	**24 hrs**	**48 hrs**
0	10	10	20	20
1	0	0	0	0
2	0	0	0	0
3	0	0	0	0
No. with grades ≥1	0	0	0	0
No. tested	10	10	20	20
Incidence*	**0/10**	**0/10**	**0/20**	**0/20**
Severity**	0	0	0	0

*Number of animals showing a response of grade 1 or greater at either 24- or 48-hour reading out if the total animals.
** Total sum of 24- and 48-hour response readings divided by the number of animals exposed (maximum of 3).

The incidence of positive skin reactions after the second challenge with positive control alpha-hexylcinnamalaldehyde at 5% in PEG 300 is summarised as follows:

Erythema Score	**Positive Control Group 20 animals**	
	5% in PEG 300	
	24 hrs	**48 hrs**
0	5	10
1	15	10
2	0	0
3	0	0
No. with grades ≥1	15	10
No. tested	20	20
Incidence*	**15/20 (75%)**	**10/20 (50%)**
Severity**	0.75	0.5

*Number of animals showing a response of grade 1 or greater at either 24- or 48-hour reading out if the total animals.
** Total sum of 24- and 48-hour response readings divided by the number of animals exposed (maximum of 3).

Study report, 2013: the positive control was 0.1% dinitrochlorobenzene (DNCB) in 95% ethanol.

The incidence of positive skin reactions after the challenge with positive control DNCB at 0.1% in ethanol is summarised as follows:

Reading	Hours after challenge	Group	Dose level	No. with skin reaction score 2	No. with skin reaction score 1	Total no. in group
1st reading	24	Positive control	0.1%	2	3	5
2nd reading	48	Positive control	0.1%	0	5	5

Regarding equivocal results:
We agree that there are concerning deficiencies in the studies. In our opinion, there is no satisfactory explanation provided for the different levels of skin reactions between the two challenges within the 2009 study, and when comparing skin reactions after challenge in the 2009 study with the 2013 study. A speculation for the differences in the levels of skin reactions between the two studies is that the level of hydrolysis of trimethoxy(methyl)silane is involved, but there is no data to confirm this. The rate of the hydrolysis of trimethoxy(methyl)silane in PEG 300 is unknown. In the study of 2009 it is stated that the dilutions of trimethoxy(methyl)silane is freshly made throughout the study. It is not reported in the 2013 study if the test material was freshly prepared. It difficult to scientifically assess if enough of trimethoxy(methyl)silane was present in the tested material, to draw the conclusion that the result of the 2013 study is relevant for the substance for which CLH is proposed.

Regarding induction doses:
In the irritation screening of the 2009 study, 50% of trimethoxy(methyl)silane produced slight irritation (grade 1) without scaling. The skin reactions observed in the test group in the induction phase in the main study of the 2009 study was discrete/patchy erythema (grade 1) in twelve (60%), sixteen (80%) and all (100%) of twenty test animals after each of the three induction exposures with 50% of trimethoxy(methyl)silane in PEG 300, respectively.
In contrast, no skin effects (grade 0) were observed either in the irritation screening or during the induction phase of the main study from 2013 after application of 50% trimethoxy(methyl)silane in PEG 300. This was the highest tested concentration. A proper irritation screening, as stipulated in the OECD guidline 406, could be crucial to establish a relevant induction concentration. The validity and relevance of the negative test result is questionable due to the limitations. We believe that the positive findings in the 2009 study indicates a cause for concern and that trimethoxy(methyl)silane could have the potential for skin sensitisation.

RAC's response

Thank you for the comment.

PUBLIC ATTACHMENTS
1. Reconsile Comments on MTMS CLH dossier.zip [Please refer to comment No. 2, 4]