ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 29 March 2017

Substance name: 3-trimethoxysilylpropyl methacrylate
EC number: 219-785-8
CAS number: 2530-85-0
Date of Latest submission(s) considered[1]: 8 July 2016
Decision/annotation number: Please refer to the REACH-IT message which delivered this communication (in format SEV-D-XXXXXXXXXX-XX-XX/F)
Addressees: Registrant(s)[2] of 3-trimethoxysilylpropyl methacrylate (Registrant(s))

DECISION ON SUBSTANCE EVALUATION

1. Requested information

Based on Article 46(1) of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), you are requested to submit the following information on the registered substance 3-trimethoxysilylpropyl methacrylate:

1. Skin sensitisation; test method: EU B.42/OECD 429. The study shall be performed with freshly prepared test solutions of the registered substance and the choice of vehicle shall be scientifically justified.

2. *In vivo* mammalian alkaline comet assay; test method OECD 489 in rats, inhalation route using an aerosolised atmosphere of the registered substance, on the following tissues: nasal epithelium, lungs, liver and if technically feasible the larynx. The study shall be performed with freshly prepared test solutions of the registered substance and the choice of vehicle shall be scientifically justified.

3. Exposure:

3.1 Worker – Industrial and professional; Improved characterisation of the tasks/processes covered in the following contributing exposure scenarios: process category (PROC) 5 in exposure scenario 4; PROC 8a in exposure scenarios 6 and 11; PROC 10 and 13 in exposure scenarios 7, 8 and 12; and PROC 10, 11 and 19 in exposure scenario 9. The information shall include:

- Description of the scope of the specific task/process covered by each PROC;
- Justification for the task duration chosen for exposure modelling taking into account the task description and the practicality of limiting task duration as a risk management measure, where relevant;

[1] This decision is based on the registration dossier(s) on the day until which the evaluating MSCA granted an extension for submitting dossier updates which it would take into consideration.

[2] The terms Registrant(s), dossier(s) or registration(s) are used throughout the decision, irrespective of the number of registrants addressed by the decision.

ECHA
EUROPEAN CHEMICALS AGENCY

- All model input parameters required to derive the exposure estimates;
- Details of additional exposure modifiers applied to the exposure estimate either within or outside the model (including local exhaust ventilation (LEV), gloves);
- The percentile distribution of the model output chosen, where relevant for the model.

3.2 Worker – Industrial and professional; Improved characterisation of the potential for aerosol generation in PROCs 5, 8a, 8b, 9, 10 and 13 in all relevant exposure scenarios related to industrial and professional use. The information shall include an improved task description to determine if aerosol generation is expected. Where aerosol generation is expected, a local inhalation exposure estimate shall be provided using an appropriate exposure model. All assumptions and model input parameters used to derive the exposure estimate shall be documented.

3.3 Worker – Professional; Consumer; Improved characterisation of the exposure to workers (exposure scenario 13) and consumers (exposure scenario 15) from the use of sealants. The information shall include the typical use profile of professional and consumer sealants and further justification to support the choice of model input and output parameters where these deviate from the default values and approaches.

3.4 Consumer; Improved characterisation of the exposure from the use of coatings (exposure scenario 10). The information shall include further justification to support the choice of mass transfer rate for the inhalation exposure estimate, the approach used to derive the dermal exposure estimate and clarification on whether use in consumer spray coatings is supported by the registrants. Where use in consumer spray products is supported, a long-term local inhalation exposure estimate shall be provided using an appropriate exposure model. All assumptions and model input parameters used to derive the exposure estimate shall be documented.

3.5 Worker – Industrial; Improved characterisation of the approach used to characterise the risk related to combined exposure in the Chemical Safety Report (CSR).

3.6 Worker – Industrial and professional; Exposure assessment for spray tasks or processes (PROCs 7 and 11) for the following registered uses; industrial formulation of coatings and preparations, industrial and professional use of sealants/adhesives and industrial use of non-metal surface treatments, which are not addressed in the corresponding exposure scenario in the joint CSR. The information shall include a long-term local inhalation exposure estimate, if required, using an appropriate exposure model. All assumptions and model input parameters used to derive the exposure estimate shall be documented.

You shall provide an update of the registration dossier(s) containing the requested

ECHA
EUROPEAN CHEMICALS AGENCY

information, including robust study summaries and, where relevant, an update of the CSR by **6 July 2018**. The deadline takes into account the time that you, the Registrant(s), may need to agree on who is to perform any required tests.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. Further information, observations and technical guidance, as appropriate, are provided in Appendix 3. Appendix 4 contains a list of registration numbers for the addressees of this decision. This Appendix is confidential and not included in the public version of this decision.

2. Who performs the testing

Based on Article 53 of the REACH Regulation, you are requested to inform ECHA who will carry out the study/ies on behalf of all Registrant(s) within 90 days. Instructions on how to do this are provided in Appendix 3.

3. Appeal

You can appeal this decision to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, shall be submitted to ECHA in writing. An appeal has a suspensive effect and is subject to a fee. Further details are described under http://echa.europa.eu/regulations/appeals

Authorised[3] by Leena Ylä-Mononen, Director of Evaluation

[3] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

ECHA
EUROPEAN CHEMICALS AGENCY

Appendix 1: Reasons

Based on the evaluation of all relevant information submitted on 3-trimethoxysilylpropyl methacrylate and other relevant available information, ECHA concludes that further information is required in order to enable the evaluating Member State Competent Authority (MSCA) to complete the evaluation of whether the substance constitutes a risk to human health.

The evaluating MSCA will subsequently review the information submitted by you and evaluate if further information should be requested in order to clarify the concern for skin sensitisation, mutagenicity (clastogenicity) and worker and consumer exposure.

REQUEST 1 - Skin sensitisation

The Concern(s) Identified

A concern for skin sensitisation has been identified. The concern is based on ambiguous results in a guinea pig maximisation test (GPMT) on the registered substance as reported in the registration data, an uncertainty in the robustness of the read-across to two negative GPMT studies on two structural analogues presented in the registration data and the fact that a number of methacrylate substances are classified as skin sensitisers in Annex VI to CLP. The registered uses of the substance indicate the potential for dermal exposure to workers (industrial and professional) and consumers. Therefore, there is a need to clarify the concern for skin sensitisation.

Why new information is needed

The registration data contains a GPMT in which animals were intradermally induced with a 5% mixture of 3-trimethoxysilylpropyl methacrylate in cottonseed oil (Klimisch reliability score 4). Positive responses were observed in the test group: 6/20 mild (grade 1) and 14/20 moderate (grade 2) at 24 hours and 15/20 mild and 5/20 moderate at 48 hours. However, a high incidence of positive responses was also observed in the negative control groups: following challenge with 3-trimethoxysilylpropyl methacrylate, 9/10 mild and 1/10 moderate responses were observed at 24 hours and 6/10 mild reactions were observed at 48 hours. When challenged with the cottonseed oil vehicle, 10/10 and 2/10 mild reactions were observed at 24 and 48 hours, respectively. You considered that the high incidence of mild reactions in all groups indicated a possible irritant effect of the cottonseed oil vehicle. The study report author concluded that the increased incidence and duration of responses observed in the test group may indicate a potential for dermal sensitisation under the conditions of the study. You concluded the result was ambiguous. The registration data also contains two GPMT studies (Klimisch reliability score 2) with the structural analogues 2-Propenoic acid,2-methyl-(trimethoxysilyl)methyl ester (CAS No. 54586-78-6) and 2-Propenoic acid,2-methyl-(dimethoxymethylsilyl)methyl ester (CAS No. 121177-93-3). In both studies, no sensitisation reactions were observed following topical challenge with 100% test material.

You have proposed a read-across approach from the two structural analogues, 2-

ECHA
EUROPEAN CHEMICALS AGENCY

Propenoic acid,2-methyl-(trimethoxysilyl)methyl ester and 2-Propenoic acid,2-methyl-(dimethoxymethylsilyl)methyl ester, to address the skin sensitisation endpoint for the registered substance on the basis that all three substances have similar toxicological properties due to the presence of a methacrylate group in the side chain, propylmethacrylate in the case of the registered substance and methylmethacrylate in the case of the two structural analogues. In addition, you note that all three substances share a common hydrolysis product, methanol and have similar physiochemical properties. The registration data includes a data matrix which compares the available physico-chemical data for the registered substance and the two structural analogues, in particular, water solubility, partition coefficient n-octanol/water, vapour pressure and hydrolysis. The data matrix report also states that the registered substance is part of an analogue group of twelve structurally similar substances all of which contain one or more (meth)acrylate groups. The two structural analogues selected for read across for skin sensitisation are also included in this analogue group. ECHA notes that one of the analogue group members, acrylic acid, 3-(trimethoxysilyl)propyl ester (EC No. 419-560-6) is listed on Annex VI to the CLP Regulation as a skin sensitiser category 1.

ECHA notes that the data matrix does not contain any human health toxicological data for the two structural analogues other than the results of the skin sensitisation studies. Therefore, ECHA considers that the available information does not support your conclusion that the substances have "similar toxicological properties". Also, ECHA notes that while the reported physico chemical properties of the registered substance and the two structural analogues may be considered similar, the physico-chemical data provided for both structural analogues are primarily predicted or calculated values rather than measured data. ECHA's Practical Guide 6 (ECHA 2012a) states that for data gap filling by read-across, "in general, experimental data is preferred to non-test data for physico-chemical endpoints."

ECHA's Read-Across Assessment Framework (RAAF) (ECHA 2015a) describes a method to assess whether a read-across case is compliant under REACH. In particular, for an analogue approach where the read-across hypothesis is based on different compounds having the same type of effects, the RAAF identifies the need to demonstrate a "common underlying mechanism" and outlines specific considerations in the case of predictions of absence of effects. ECHA notes that no specific explanation is provided in the registration data as to the underlying mechanism for the predicted absence of a skin sensitising effect for the registered substance other than to note that the registered substance and the two structural analogues all contain a methacrylate group in the side chain and all have similar physiochemical properties. Similarly, no information is provided to describe how the structural differences are not expected to influence toxicological properties. No toxicological data, other than the skin sensitisation data, are reported for the two structural analogues and therefore it is not possible to compare toxicity profiles for the registered substance and the two analogues. Based on the lack of evidence, ECHA considers that the available information does not support the hypothesis that the substances have a common underlying mechanism with respect to the predicted absence of skin sensitising effects.

ECHA notes that a number of alkyl methacrylate esters are classified for skin

ECHA
EUROPEAN CHEMICALS AGENCY

sensitisation in Annex VI to CLP and no explanation is provided in the registration data as to why the presence of a methacrylate group in the registered substance and the two structural analogues results in an absence of a skin sensitising effect, when in a number of other alkyl methacrylate substances, the presence of a methacrylate group results in a skin sensitising effect. It is noted that one of the analogue group members (EC number 419-560-6) identified by you is classified as a skin sensitiser in Annex VI to CLP. The registration data does not contain an explanation as to why this substance was not selected as an analogue for read-across for the skin sensitisation endpoint or why the remaining analogue group members were not included in the data matrix.

The RAAF also identifies the need to demonstrate the absence of "bias that influences the prediction". No information is included in the registration data regarding how the two analogue substances used for read-across were chosen from the members of the analogue group identified by the registrants. Similarly, no information is provided as to why the other members of the analogue group or other methacrylate substances were not considered relevant for the read-across. As discussed above, as other methacrylate substances are known to be skin sensitisers (e.g. those listed as skin sensitisers in Annex VI to CLP), there is concern that the selected two analogue substances may underestimate the skin sensitisation potential of the registered substance. Therefore, ECHA considers that the read-across is not sufficiently justified and thus the skin sensitisation potential of 3-trimethoxysilylpropyl methacrylate cannot be determined based on the available data.

In consideration of the available *in vivo* testing options, ECHA considers that a local lymph node assay (LLNA) is appropriate to determine the skin sensitisation potential of the registered substance. The LLNA provides information that is adequate for classification and labelling as it not only determines whether the substance is a skin sensitiser or not, but also generates information needed for potency assessment and thus information that can be used to sub-categorise skin sensitisers in category 1A or 1B according to the CLP Regulation. In the event that sub-categorisation into category 1A is warranted, classification and labelling of professional and consumer products containing the registered substance at >0.1 % will be required. This would result in improved communication of hazards to both workers and consumers. Currently there are no regulatory measures which address the potential concern for skin sensitisation.

Considerations on the test method and testing strategy

The LLNA (OECD 429) is the required method to determine the skin sensitisation potential of 3-trimethoxysilylpropyl methacrylate. The LLNA is the default *in vivo* study to address the skin sensitisation endpoint under REACH. Due to the hydrolytic instability of the registered substance the study shall be conducted with freshly prepared test solutions of the registered substance in an appropriate vehicle. The selection of the vehicle shall be scientifically justified and should be chosen to minimise the rate of hydrolysis of the registered substance.

As an alternative to the LLNA, the Adverse Outcome Pathway (AOP) for skin sensitisation has identified a number of *in chemico/in vitro* studies which address the three key

ECHA
EUROPEAN CHEMICALS AGENCY

events in the skin sensitisation pathway (OECD 2012). In particular, the *in chemico/*in *vitro* methods (OECD 442D, OECD 442D and OECD 442E) address three of the key events, namely peptide/protein binding, keratinocyte response and monocytic/dendritic cell response, respectively. As outlined in ECHA Guidance R.7.a section R.7.3 (ECHA 2016), due to the complexity of the skin sensitisation endpoint a combination of these alternative test methods and other types of data is currently required to identify skin sensitisers.

ECHA notes that the predicted water solubility of the registered substance is 2200 mg/L and it undergoes rapid hydrolysis in contact with water (half-life of < 2 hours at pH 4, 7 and 9) to form the hydrolysis products 3-(trihydoxysilyl)propyl methacrylate and methanol. In addition, it is stated in the registration data that condensation reactions may occur in solution and the rate and extent of condensation is dependent on the nominal loading, temperature and pH of the test system. The registration data notes that condensation reactions are expected to become important at nominal concentrations above 1000 mg/L resulting in the formation of insoluble polymeric particles and gels over time. There is no information in the registration data regarding the stability of the registered substance in other solvents. ECHA notes that the *in chemico/in vitro* test methods require incubation with the test material for at least 24 hours in an aqueous solution buffered to various pHs. Therefore, given the rapid hydrolysis and limited solubility of the registered substance in water and the propensity of the hydrolysis products to polymerise in water there is uncertainty regarding whether the registered substance could be successfully tested in the relevant *in chemico/in vitro* tests. ECHA notes that the LLNA can be conducted with neat test material or using a non-aqueous based solvent which would minimise hydrolysis. ECHA concludes that for this specific substance, the LLNA study is most appropriate to conclude on the skin sensitisation concern.

A proposal for amendment by one MSCA proposed that the registrants be given the option of conducting appropriate *in vitro* testing (OECD 442C, 442D and 442E) or the LLNA. In response, ECHA considers that due to the physico-chemico properties of the registered substance discussed above, the applicability of the *in chemico/in vitro* test methods for the registered substance is uncertain. Therefore, ECHA considers that for this specific case the LLNA is more appropriate than the *in chemico/in vitro* studies and the decision was not amended.

Alternative approaches and proportionality of the request

The request for an LLNA (OECD 429) is suitable and necessary to obtain information that will clarify whether there is a risk for skin sensitisation for workers and consumers. More explicitly, between different available alternatives, it is the least onerous way to obtain information. The possible alternative of using a combination of *in chemico/in vitro* methods outlined in the AOP for skin sensitisation may not generate the required information due to the instability of the registered substance in aqueous solutions.

If the results of the LLNA, once obtained, confirm that the registered substance is a skin sensitiser, it will allow authorities to consider further regulatory risk management in the

ECHA
EUROPEAN CHEMICALS AGENCY

form of harmonised classification and labelling. ECHA notes that there is no experimental study available at this stage that will generate the necessary information without the use of vertebrate animals.

Consideration of the Registrants' comments on the draft decision and proposals for amendment

In response to the draft decision, you indicated your agreement to perform a study to address the concern for skin sensitisation. However, you stated that you consider the LLNA not to be a suitable study for silicon based substances. In support of this view you provided further justification in a dossier update which was taken into account by the evaluating MSCA. In that update you proposed to conduct a guinea pig maximisation test (GPMT, OECD 406) instead of the requested LLNA and referred to the findings of three publications discussing the instances of false positive and negative results in LLNAs in general, and specifically with polyfunctional and polyaminofunctional siloxanes (Basketter et al., 2009a, Basketter et al 2009b & Petry et al., 2012).

ECHA notes that the registered substance differs from the substances referenced in the publications in a number of ways: the registered substance is not irritating to skin or eyes and thus irritation is not expected to be a confounding factor in the LLNA, it has a structural alert for skin sensitisation (methacrylate group), it is a reactive substance and has predicted moderate dermal penetration rate based on molecular weight.

ECHA acknowledges that there are certain classes of substances for which the LLNA may not be appropriate and which may lead to false positive or false negative results. ECHA notes that you have not proposed a hypothesis or mechanism of action as to why the LLNA is unsuitable for the registered substance specifically. In addition, the influence of the methacrylate moiety of the registered substance was not addressed by you. Therefore, ECHA considers that you have not demonstrated the relevance of the information provided to the registered substance.

ECHA Guidance R.7.a section R.7.3 (ECHA 2016) states that the LLNA is the preferred test method for new *in vivo* testing for skin sensitisation and *"the use of the standard guinea pig tests to obtain new data on the skin sensitisation potential of a substance will be acceptable only in exceptional circumstances and will require scientific justification."* The LLNA has advantages over the standard guinea pig tests, not least in that it allows for an assessment of potency and thus subcategorization into category 1A or 1B under CLP and that it is less onerous in terms of animal welfare.

ECHA considers that a sufficiently robust scientific justification to deviate from the LLNA, as the preferred method for new *in vivo* testing for the skin sensitisation endpoint, has not been presented. Therefore, the request in the decision has not been amended.

In response to a proposal for amendment, you reiterated your concerns that the LLNA is not a suitable study for silicone based substances and your preference to conduct the GPMT. In addition to the GPMT, you proposed the Buehler assay as an appropriate alternative. However, you did not provide any additional scientific justification to deviate from the LLNA. Therefore, the decision was not amended.

ECHA
EUROPEAN CHEMICALS AGENCY

Conclusion

Therefore, based on the substance evaluation and pursuant to Article 46(1) of the REACH Regulation, ECHA concludes that you are required to carry out the following study using the registered substance subject to this decision: skin sensitisation; test method: EU B.42/OECD 429. The study shall be performed with freshly prepared test solutions of the registered substance and the choice of vehicle shall be scientifically justified.

REQUEST 2 - *In vivo* mammalian alkaline comet assay

The Concern(s) Identified

A concern for mutagenicity (clastogenicity) has been identified. The concern is based on a positive *in vitro* chromosome aberration test in both the presence and absence of metabolic activation. The positive result in the absence of metabolic activation also indicates a possible concern for a direct action of the substance as a DNA damaging agent at the sites of initial contact. The most significant effect observed in the available repeated dose inhalation studies was the formation of laryngeal granulomas, accompanied by squamous metaplasia of the overlying epithelium. This indicates a possible site of contact effect of the registered substance following aerosol exposure. The available *in vivo* mammalian erythrocyte micronucleus study was conducted by the intraperitoneal route and thus is not appropriate to address the concern for clastogenicity at the site of direct contact following aerosol exposure. The registered uses of the substance indicate the potential for aerosol generation from spray applications and thus inhalation exposure. Therefore, there is a need to clarify the concern for clastogenicity.

Why new information is needed

The registration data contains an *in vitro* chromosome aberration study in Chinese Hamster Ovary (CHO) cells with the registered substance in which a statistically significant increase in the incidence of chromosome aberrations was observed in the presence and absence of metabolic activation. In an *in vitro* sister chromatid exchange (SCE) assay with CHO cells, no increase in the incidence of SCEs was observed in the presence or absence of metabolic activation. In a follow up *in vivo* erythrocyte micronucleus study in mice, in which the registered substance was administered as single intraperitoneal doses of 2500, 4000 and 5000 mg/kg, no increase in the incidence of micronuclei in peripheral blood derived erythrocytes was observed. It is noted however that a lower number of cells were analysed than recommended in OECD 474, indicating a possible lower sensitivity of the study to detect micronuclei. No concern for gene mutation was identified from the available *in vitro* gene mutation studies.

ECHA notes that the positive result in the absence of metabolic activation in the *in vitro* chromosome aberration study indicates a possible concern for a direct action of the registered substance as a DNA damaging agent at sites of initial contact. This concern is not completely addressed by the available *in vivo* micronucleus study since the

ECHA
EUROPEAN CHEMICALS AGENCY

intraperitoneal route of administration does not allow an evaluation of the effects at the site of initial contact.

From the available repeated dose inhalation studies, a concern for local effects in the respiratory tract following aerosol exposure was identified. The most significant effect observed was the formation of laryngeal granulomas, which was observed after only two exposures and for which no recovery was observed in a one year recovery period following a 90-day exposure period. In three of the reported studies (one 90-day and two 28-day), squamous metaplasia of the mucosal epithelium overlying the laryngeal granulomas was also observed as a separate finding to the formation of granulomas. In the 90-day study, this lesion had reversed in the majority of animals within 1 month post treatment with only 3/64 animals displaying the lesion during the remainder of the recovery period: 1 male at week 66 necropsy and 2 females at weeks 18 and 66 necropsies. No recovery period was included in the 28-day studies. It is noted that in the remainder of the repeated dose toxicity studies, the presence of squamous metaplasia was not analysed as a separate finding to laryngeal granuloma formation. ECHA notes that while the squamous metaplasia observed in the repeated dose toxicity studies appears not to be accompanied by any additional findings (e.g. dysplasia or cellular atypia) which might cause a concern for a pre-neoplastic effect, the longest study duration was 90-days and thus may be too short to definitively conclude there is no concern. No effect on laryngeal tissue was observed in a 9-day vapour study with the registered substance.

ECHA considers there is a need to clarify the concern relating to whether aerosol inhalation of the registered substance may cause a genotoxic effect in the upper respiratory tract, as the initial site of contact following inhalation exposure.

ECHA considers that an *in vivo* comet assay is required to determine the genotoxic potential of the registered substance following aerosol inhalation exposure. This data would allow for a conclusion on whether the registered substance is genotoxic and in particular whether it is a site of contact DNA damaging agent following aerosol exposure. In the case of a positive result, the data would also support classification and labelling as mutagenic category 2 H341 and the classification and labelling of mixtures as mutagenic category 2 H341 where the concentration of the registered substance is ≥ 1.0% w/w. This would thus influence the risk management of the substance. Currently there are no regulatory measures which address the potential concern for genotoxicity.

Considerations on the test method and testing strategy

The *in vivo* comet assay (OECD 489) is the required method to determine the potential for genotoxicity via chromosome aberration. The comet assay allows for the assessment of both chromosome aberrations and gene mutations and can be used to assess a variety of tissues, including tissues at the sites of direct contact.

The requested comet assay shall be performed in the rat. Due to the hydrolytic instability of the registered substance the study shall be conducted with freshly prepared test solutions and the choice of vehicle shall be scientifically justified. As the formation of

ECHA
EUROPEAN CHEMICALS AGENCY

laryngeal granulomas and accompanying squamous cell metaplasia was observed in aerosol rather than vapour inhalation repeated dose studies, ECHA considers that the *in vivo* comet assay should be conducted with an aerosolised atmosphere of the registered substance which mimics the worst case test conditions of the aerosol inhalation repeated dose toxicity studies reported in the registration data. Therefore, the highest tested concentration used in the repeated dose toxicity studies of 15% w/w, or the highest technically achievable concentration, and the lowest pH should be used. The following tissues shall be sampled and analysed: the nasal epithelium, lungs and liver. ECHA acknowledges that there may be technical challenges to testing laryngeal tissue and therefore the larynx shall be sampled and analysed if technically feasible. The nasal epithelium, larynx and lungs are selected as the initial sites of contact following aerosol exposure and the nasal epithelium and larynx tissue are also the target tissues in the aerosol repeated dose inhalation studies. The liver is selected as the primary site of metabolism. In accordance with OECD 489, the study shall include an appropriate concurrent positive control administered by the inhalation route.

A proposal for amendment by one MSCA noted that the comet assay has not yet been validated in the nasal or laryngeal tissues and therefore the results may not be reliable. Instead, the MSCA proposes that the study be conducted via the oral route and the stomach (as site of first contact), intestines and liver are analysed. The MSCA also notes that since the purpose of the study is hazard identification, rather than risk assessment, the choice of exposure route is more flexible. While ECHA acknowledges that the purpose of the study is hazard identification and also that it may be technically more difficult to analyse the laryngeal tissue in the comet assay, ECHA considers that there are substance specific reasons to request the comet assay via the inhalation route in this case. All of the available repeated dose toxicity studies were performed via the inhalation route with an aerosolised atmosphere of the registered substance. The most significant effect was the formation of laryngeal granulomas and this effect was noted after only two exposures. The size of the laryngeal granulomas formed was dependent on the starting concentration and pH of the test solution. As the composition of test atmospheres were not analysed in the majority of the repeated dose toxicity studies, it is not clear what portion of the atmosphere was made up of the registered substance and what portion was the hydrolysis products or if the formation of laryngeal granulomas was as a result of exposure to particulate matter rather than the registered substance. In addition, ECHA notes that as the hydrolysis rate of the registered substance increases with decreasing pH, administration via the oral route may result in a composition of the administered test solution which is not reflective of the test atmospheres in the available repeated dose toxicity studies.

Therefore, given the uncertainty in the mechanism of action for the laryngeal granuloma formation and the limitations of the available repeated dose toxicity data, ECHA considers in this case the inhalation route is appropriate. Therefore the decision was not amended.

ECHA advises you to consider examining gonadal cells when conducting the comet assay as it would optimise the use of animals. ECHA notes that a positive result in whole

ECHA
EUROPEAN CHEMICALS AGENCY

gonads is not necessarily reflective of germ cell damage since gonads contain a mixture of somatic and germ cells. However, such positive result would indicate that the substance and/or its metabolite(s) have reached the gonads and caused genotoxic effects. This type of evidence may be relevant for the overall assessment of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation as mutagenic category 1B.

Alternative approaches and proportionality of the request

The request for an *in vivo* comet assay (OECD 489) is suitable and necessary to obtain information that will clarify whether there is a concern for genotoxicity and in particular, in the sites of direct contact following aerosol exposure. The registered uses of the substance indicate the potential for aerosol generation from spray applications and thus inhalation exposure. Therefore, there is a need to clarify the concern for genotoxicity. As an alternative to the *in vivo* comet assay, a transgenic rodent (TGR) somatic and germ cell mutation assay is also suitable to investigate site of direct contact effects. ECHA considers that between different available alternatives, the *in vivo* comet assay is the least onerous way to obtain information. The results of the *in vivo* comet assay, once obtained, will confirm whether the registered substance is genotoxic and hence if classification for mutagenicity is warranted. ECHA notes that there is no experimental study available at this stage that will generate the necessary information without the use of vertebrate animals.

Consideration of Registrants' comments on the draft decision and proposals for amendment

In response to the draft decision, you indicated your agreement to undertake the requested study. In response to the proposal for amendment to conduct the study via the oral route, you indicated your agreement to conduct the study via the inhalation route.

Conclusion

Therefore, based on the substance evaluation and pursuant to Article 46(1) of the REACH Regulation, ECHA concludes that you are required to carry out the following study using the substance subject to this decision: *in vivo* mammalian alkaline comet assay; test method OECD 489 in rats, inhalation route using an aerosolised atmosphere of the registered substance, on the following tissues: nasal epithelium, lungs, liver and if technically feasible the larynx. The study shall be performed with freshly prepared test solutions of the registered substance and the choice of vehicle shall be scientifically justified.

REQUEST 3.1 - Worker – Industrial and professional; Improved characterisation of the tasks/processes

The Concern(s) Identified

For the identified exposure scenarios, the tasks or processes covered by the selected

ECHA
EUROPEAN CHEMICALS AGENCY

process categories (PROCs) are not clearly characterised in the Chemical Safety Report (CSR). In addition, not all the exposure model assumptions and input parameters used to generate the inhalation and dermal exposure estimates are documented in the CSR. Without a clear description of both the task or process and the assumptions used to generate the exposure estimate, it is not possible for the evaluating MSCA to conclude on whether the modelled exposure estimate is representative of the task or process, and thus whether the risk is adequately controlled.

Why new information is needed

A brief description of the activities and technical processes covered by each exposure scenario is documented in the CSR. ECHA notes that the descriptions are generic; for example in some cases the description refers to "alkoxysilanes" in general and is thus not specific to the registered substance or it describes uses across a number of sectors. In this context, the scope of the tasks or processes covered by the selected PROCs is not clearly documented and therefore it is not possible for the evaluating MSCA to conclude on whether the modelled exposure estimate is representative of the actual task being undertaken and thus whether exposure is adequately controlled. In particular, ECHA notes that the task description for the following PROCs is not clearly documented: PROC 5 in exposure scenario 4; PROC 8a in exposure scenarios 6 and 11; PROC 10 and 13 in exposure scenarios 7, 8 and 12; and PROC 10, 11 and 19 in exposure scenario 9.

With respect to the exposure modelling, ECHA notes that for these PROCs a number of the modelling assumptions are not clearly documented in the CSR. Dermal exposure estimates for; PROC 5 in exposure scenario 4, PROC 8a in exposure scenarios 6 and 11, PROC 10 in exposure scenarios 7, 8, 9, 12, PROC 11 in exposure scenario 9, PROC 13 in exposure scenario 12 and PROC 19 in exposure scenario 9 were derived using Riskofderm v2.0. In each case, the CSR includes limited information on the scope of the task intended to be covered by the selected PROC and does not report all model input parameters and exposure modifiers used to generate the exposure estimate. In particular, the dermal exposure operation (DEO) unit selected in Riskofderm is not documented in the CSR.

With respect to the dermal exposure estimates for PROC 5 in exposure scenario 4 and PROC 8a in exposure scenarios 6 and 11, there is no information in the CSR to indicate if aerosol generation is relevant for these tasks. ECHA observes that for example confirmation of the potential for aerosol generation is a specific input parameter when running DEO Unit 1 in Riskofderm. ECHA notes that the potential for aerosol generation could significantly increase the exposure estimate. With respect to PROC 8a, one of the modelling assumptions is that the task is automated or semi-automated. As PROC 8a covers transfer tasks at non-dedicated facilities (ECHA 2015b) and the exposure estimate is intended to cover a range of industrial settings, ECHA considers that this assumption may not represent a reasonable worst case.

With respect to PROC 10 in exposure scenario 9, the task duration used to generate the dermal exposure estimate appears to be outside the applicability domain of Riskofderm

ECHA
EUROPEAN CHEMICALS AGENCY

(445 minutes). Therefore, further justification is required to support the use of the model for the selected task duration.

With respect to PROC 11 in exposure scenario 9, the CSR indicates that the exposure scenario covers the use of decorative coatings or primers by professionals. ECHA considers that there is some uncertainty regarding the types of professional applications covered by this exposure scenario, in particular whether professional use in vehicle refinishing is covered. ECHA notes that in exposure scenario 8, relating to industrial use of coatings, the following is stated "the spraying technologies used by vehicle refinishing body shops are to a certain extent depending on their size". However, no reference to vehicle refinishing body shops is included in exposure scenario 9. ECHA notes that the choice of model input parameters used to generate the exposure estimates for exposure scenario 9 may not be representative for professional vehicle refinishing tasks. Thus, without clarification regarding the tasks and processes covered by PROC 11, it is not possible for the evaluating MSCA to conclude on whether the modelled exposure estimate is representative of all professional uses, including professional use in vehicle refinishing.

With respect to PROC 10 and PROC 13 in exposure scenarios 7, 8 and 12, Part A of the CSR lists limiting the task duration as a risk management measure: for PROC 10 the task duration is limited to < 15 minutes and for PROC 13 the task duration is limited to <1 hour in exposure scenarios 7 and 8 and < 30 minutes in exposure scenario 12. The dermal and inhalation exposure estimates have been generated assuming these exposure durations. ECHA notes that for exposure scenarios 7 and 8, the CSR states that the typical application method for the final products is "rolling, brushing or spraying" and that as a worst case, a default exposure of > 4 hours is assumed for the exposure scenarios. No information is provided on typical application method for exposure scenario 12. ECHA notes that if a longer task duration is assumed, the exposure estimate is significantly increased. As these exposure scenarios cover industrial uses and according to the CSR are intended to cover uses in a number of industry sectors ECHA considers that further information is required on the tasks covered by these PROCs in order to conclude on whether the modelled exposure estimates are representative of the actual task being undertaken and the practicality of limiting task duration as a risk management measure.

Therefore, further information on the model assumptions and the scope of the task to be covered by the exposure estimate is required to enable the evaluating MSCA to conclude on whether the modelled exposure estimate is representative of the actual task being undertaken and thus whether exposure is adequately controlled.

Considerations on the method

You are required to provide further details of the tasks and processes covered by PROC 5 in exposure scenario 4; PROC 8a in exposure scenarios 6 and 11; PROC 10 and 13 in exposure scenarios 7, 8 and 12; and PROC 10, 11 and 19 in exposure scenario 9. In addition, for the listed PROCs, you are required to provide all assumptions and model

ECHA
EUROPEAN CHEMICALS AGENCY

input parameters used to derive the exposure estimates, including the density correction factor used, direction of application assumed, whether a correction factor for concentration was applied, the use rate (and number of batches per shift, if applicable) assumed, whether a modification factor for local exhaust ventilator (LEV) was applied to the exposure estimate either within or outside the model and how a glove modification factor was applied to the exposure estimate where both hand and body dermal exposure estimates are generated. For dermal exposure estimates generated using Riskofderm, the DEO unit selected shall be provided. With respect to PROC 10 and PROC 13 in exposure scenarios 7, 8 and 12, you are required to provide further justification for the task duration, taking into account the task description and the practicality of limiting task duration as a risk management measure in these exposure scenarios. The percentile distribution of the model output chosen, where relevant for the model, shall also be provided.

Alternative approaches and proportionality of the request

The request for improved characterisation of the tasks/processes covered by the exposure scenarios in the CSR is suitable and necessary to obtain information that will clarify whether there is a risk to workers. There is no equally suitable alternative way available of obtaining this information. If the information, once obtained, confirms that there is a risk to workers, it will allow authorities to consider further regulatory risk management.

Consideration of Registrants' comments

In response to the draft decision, you indicated your agreement to provide improved information addressing the exposure concerns. As no information was provided in an update of the registration dossier, the decision was not amended.

Conclusion

Therefore, based on the substance evaluation and pursuant to Article 46(1) of the REACH Regulation, ECHA concludes that you are required to submit the following information on the substance subject to this decision: Worker – Industrial and professional; Improved characterisation of the tasks/processes covered in the following contributing exposure scenarios: PROC 5 in exposure scenario 4; PROC 8a in exposure scenarios 6 and 11; PROC 10 and 13 in exposure scenarios 7, 8 and 12; and PROC 10, 11 and 19 in exposure scenario 9. The information shall include:

- Description of the scope of the specific task/process covered by each PROC;
- Justification for the task duration chosen for exposure modelling taking into account the task description and the practicality of limiting task duration as a risk management measure, where relevant;
- All model input parameters required to derive the exposure estimates;
- Details of additional exposure modifiers applied to the exposure estimate either

ECHA
EUROPEAN CHEMICALS AGENCY

within or outside the model (including local exhaust ventilation (LEV), gloves);

- The percentile distribution of the model output chosen, where relevant for the model.

REQUEST 3.2 - Worker – Industrial and professional; Improved characterisation of the potential for aerosol generation

The Concern(s) Identified

The CSR states that local inhalation exposure is "linked specifically to aerosol exposure" and therefore local inhalation exposure estimates are provided only for spray applications, i.e. PROC 7 (industrial spraying) and PROC 11 (non-industrial spraying). ECHA notes that a number of other PROCs identified in exposure scenarios for industrial and professional uses in the CSR have the potential for aerosol generation but the reported inhalation exposure estimates do not address the potential for aerosol inhalation. The leading effect observed in the available inhalation repeated dose toxicity studies was the formation of laryngeal granulomas following aerosol exposures. Without further clarification on the potential for aerosol generation in all exposure scenarios related to industrial and professional use, it is not possible for the evaluating MSCA to conclude on whether there is a concern for local inhalation exposure and thus whether the risk for local effects in the respiratory tract following aerosol exposure is adequately controlled.

Why new information is needed

ECHA notes that several PROCs identified in the worker exposure scenarios in the CSR may have the potential for aerosol generation, for example PROC 5, 8a, 8b, 9, 10 and 13. The CSR includes limited information on the tasks intended to be covered by these PROCs and therefore it is not possible for the evaluating MSCA to conclude on whether aerosol exposure is likely, whether the modelled inhalation exposure estimate is representative of the actual task being undertaken and thus whether exposure is adequately controlled.

The evaluating MSCA considers that mixing and blending (PROC 5) and transfer tasks (PROC 8a and 8b) have the potential for aerosol generation, in particular at non-dedicated facilities. Regarding tasks covered by PROC 9 (transfer of substance/mixture into small containers), ECHA Guidance R.12 (ECHA 2015b) specifically mentions the potential for aerosol emissions. According to ECHA Guidance R.12, PROC 10 covers a number of tasks including the application of coatings which may have the potential for exposure from splashes. PROC 13 (treatment of articles by dipping or pouring) may have the potential for aerosol generation depending on how the articles are handled.

Therefore, further information on the tasks covered by these PROCs and the potential for aerosol generation is required to enable the evaluating MSCA to conclude on whether the modelled inhalation exposure estimates are representative of the actual tasks being undertaken and thus whether the risk for local effects in the respiratory tract following aerosol exposure is adequately controlled.

ECHA
EUROPEAN CHEMICALS AGENCY

Considerations on the method

You are required to provide further information on the potential for aerosol generation in all relevant industrial and professional exposure scenarios. This shall include an improved task description for PROCs 5, 8a, 8b, 9, 10 and 13 to determine if aerosol generation is expected. Where aerosol generation from these PROCs is expected, a local inhalation exposure estimate shall be provided using an appropriate exposure model. All assumptions and model input parameters used to derive the exposure estimate shall be documented.

Alternative approaches and proportionality of the request

The request to provide further information on the potential for aerosol generation is suitable and necessary to obtain information that will clarify whether there is a risk to workers for local effects in the respiratory tract following aerosol exposure. There is no equally suitable alternative way available of obtaining this information. If the information, once obtained, confirms that there is a risk to workers, it will allow authorities to consider further regulatory risk management.

Consideration of Registrants' comments

In response to the draft decision, you indicated your agreement to provide improved information addressing the exposure concerns. As no information was provided in an update of the registration dossier, the decision was not amended.

Conclusion

Therefore, based on the substance evaluation and pursuant to Article 46(1) of the REACH Regulation, ECHA concludes that you are required to submit the following information on the substance subject to this decision: Worker – Industrial and professional; Improved characterisation of the potential for aerosol generation in PROCs 5, 8a, 8b, 9, 10 and 13 in all relevant exposure scenarios related to industrial and professional use. The information shall include an improved task description to determine if aerosol generation is expected. Where aerosol generation is expected, a local inhalation exposure estimate shall be provided using an appropriate exposure model. All assumptions and model input parameters used to derive the exposure estimate shall be documented.

REQUEST 3.3 - Worker – Professional; Consumer; Improved characterisation of the exposure from the use of sealants

The Concern(s) Identified

The exposure estimates for professional (exposure scenario 13) and consumer (exposure scenario 15) use of sealants have been generated using the ConsExpo model. A number of deviations from the default model parameters have been applied to generate the exposure estimates and the resulting exposure estimates are significantly lower than those obtained by the evaluating MSCA using the default parameters. In addition, limited

ECHA
EUROPEAN CHEMICALS AGENCY

information is provided on the use profile of such sealants. ECHA considers that the justification provided by you for the choice of input and output parameters and the description of the product uses is not sufficient to conclude on whether the modelled exposure estimates are representative of the expected use and thus whether the risk is adequately controlled.

Why new information is needed

A number of model input parameters used in the CSR deviate from the default parameters. In particular, for the mass transfer rate, the CSR has used a value derived from a study in which air concentrations of an analogue substance, methyltrimethoxysilane, were measured from a simulated use of a sealant containing that substance ([redacted]). ECHA notes a number of limitations regarding the use of this data. No physico-chemical data were provided on the analogue substance, methyltrimethoxysilane, to conclude on whether this substance is an acceptable substance for surrogate monitoring. The study used a direct reading instrument to measure background levels and not personal monitoring and therefore the air concentrations measured may not be representative of actual personal exposure levels. Also, the study involved the use of one tube of sealant over 1.5 hours although the study report notes that a typical professional user "may use up to 12 cartridges of sealant on a typical day". It is not clear from the CSR how many tubes of sealant would be expected to be used per day and thus whether this study result is representative of actual use by professionals. For the dermal exposure estimates for professional and consumer use, the diffusion coefficient value was modified. This approach was justified in the CSR by the statement that "the diffusion of a substance through a polymer is 1000 times slower compared to a solvent". No further supporting evidence for this statement is provided. ECHA notes that the use of the modified mass transfer rate and diffusion coefficient lead to significant reductions in inhalation and dermal exposure estimates, respectively. ECHA considers that the existing information is not sufficient to support the use of these modifications.

With respect to dermal exposure estimates, the ConsExpo default model for joint sealants is the dermal constant rate model whereas for assembly sealants it is the dermal instant application model (RIVM 2007b). In the CSR, the dermal exposure estimate for professional use of sealants and consumer use of assembly sealants use the diffusion model instead of the appropriate default model. No justification for this deviation from the default model is provided.

For professional use, a number of other model input parameters deviate from the default ConsExpo values without adequate supporting justification, including the room volume and the ventilation rate. The ConsExpo modelling scenario assumed an exposure frequency of once per day and an applied amount of 3.1 kg. No information is provided in the CSR regarding the typical number of cartridges used by professional users per day or the volume per cartridge. Also the modelling scenario chosen appears to cover the use of joint sealants. Since the CSR contains limited information on the types of end uses of

ECHA
EUROPEAN CHEMICALS AGENCY

such sealants, it could not be concluded that the model scenario for professional use of assembly sealants was not relevant.

According to ECHA Guidance R.15 (ECHA 2015c) the starting point for consumer exposure assessment is to calculate the exposure during one use event. For products used infrequently (i.e. less than 12 times per year), the approach is to refine the risk characterisation rather than average out the exposure over a longer duration. ECHA notes that the dermal exposure estimates for both assembly and joint sealants taken forward for risk characterisation have been averaged over a longer period of time. No justification is provided in the CSR for this approach.

Considerations on the method

You are required to provide further information to support the choice of model input and output parameters where these deviate from the model default values. In particular, you are required to provide further robust justification to support the use of modified input parameters for the mass transfer rate and diffusion coefficient. In addition, further information is required on the typical use profile of professional and consumer sealants and justification for the approach used to derive the consumer exposure estimates.

Alternative approaches and proportionality of the request

The request to provide further information to support the choice of model input and output parameters and on the typical use profile of professional sealants is suitable and necessary to obtain information that will clarify whether there is a risk to workers and consumers. There is no equally suitable alternative way available of obtaining this information. If the information, once obtained, confirms that there is a risk, it will allow authorities to consider further regulatory risk management.

Consideration of Registrants' comments

In response to the draft decision, you indicated your agreement to provide improved information addressing the exposure concerns. As no information was provided in an update of the registration dossier, the decision was not amended.

Conclusion

Therefore, based on the substance evaluation and pursuant to Article 46(1) of the REACH Regulation, ECHA concludes that you are required to submit the following information on using the substance subject to this decision: Worker – Professional; Consumer; Improved characterisation of the exposure to workers (exposure scenario 13) and consumers (exposure scenario 15) from the use of sealants. The information shall include the typical use profile of professional and consumer sealants and further justification to support the choice of model input and output parameters where these deviate from the default values and approaches.

ECHA
EUROPEAN CHEMICALS AGENCY

REQUEST 3.4 - Consumer; Improved characterisation of the exposure from the use of coatings

The Concern(s) Identified

The exposure estimates for consumer use of coatings (exposure scenario 10) have been generated using the ConsExpo model. A deviation from the default mass transfer rate method has been used to derive the inhalation exposure estimate without justification. The approach used to derive the dermal exposure estimate appears not to be in line with ECHA guidance. In addition, there is some uncertainty regarding the use profile of such coatings, in particular whether they are supplied to consumers for spray use. The leading effect observed in the available inhalation repeated dose toxicity studies was the formation of laryngeal granulomas following aerosol exposures. ECHA considers that the available information is not sufficient to conclude on whether the modelled exposure estimates are representative of the expected use and thus whether the risk is adequately controlled.

Why new information is needed

The CSR indicates that the exposure estimates were generated using the ConsExpo model defaults for brushing and rolling of painting products. With respect to the mass transfer rate, the Langmuir's method is set as default in ConsExpo for the exposure modelling of brushing and rolling of solvent rich paint products (RIVM 2007a). ECHA notes that although the CSR indicates that the Langmuir's method was applied, the exposure estimate reported in the CSR could only be replicated by the evaluating MSCA using the Thibodeaux' method. The Thibodeaux' method is the appropriate approach for waterborne systems (RIVM 2007a). No information is provided in the CSR to justify deviating from Langmuir's method for non-waterborne systems. ECHA notes that the use of the modified mass transfer rate leads to a significant reduction in inhalation exposure estimate. ECHA considers that the existing information is not sufficient to support the use of this modification.

ECHA notes that the introductory text to the exposure scenario indicates that the typical application methods are "rolling, brushing or spraying". However, the inhalation exposure estimate in the CSR does not take into account spray use and thus the potential for aerosol exposure. As the leading human health effect observed in the available inhalation repeated dose toxicity studies was the formation of laryngeal granulomas following aerosol exposures, further information is required regarding whether such consumer coating products are supplied for spray use.

According to ECHA Guidance R.15 (ECHA 2015c) the starting point for consumer exposure assessment is to calculate the exposure during one use event. For products used infrequently (i.e. less than 12 times per year), the approach is to refine the risk characterisation rather than average out the exposure over a longer duration. ECHA notes that the dermal exposure estimate taken forward for risk characterisation has been averaged over a longer period of time. No justification is provided in the CSR for this approach.

ECHA
EUROPEAN CHEMICALS AGENCY

Considerations on the method

You are required to provide further information to support the choice of mass transfer rate used for the inhalation exposure estimate. In addition, further information is required on whether use in consumer spray coatings is supported. Where use in consumer spray products is supported, a long-term local inhalation exposure estimate shall be provided using an appropriate exposure model.

Alternative approaches and proportionality of the request

The request to provide further information to support the choice of mass transfer rate and the approach used to derive the dermal exposure estimates, and to clarify whether use in consumer spray coatings is supported is suitable and necessary to obtain information that will clarify whether there is a risk for inhalation exposure. There is no equally suitable alternative way available of obtaining this information. If the information, once obtained, confirms that there is a risk, it will allow authorities to consider further regulatory risk management.

Consideration of Registrants' comments

In response to the draft decision, you indicated your agreement to provide improved information addressing the exposure concerns. As no information was provided in an update of the registration dossier, the decision was not amended.

Conclusion

Therefore, based on the substance evaluation and pursuant to Article 46(1) of the REACH Regulation, ECHA concludes that you are required to carry out the following study using the substance subject to this decision: Consumer; Improved characterisation of the exposure from the use of coatings (exposure scenario 10). The information shall include further justification to support the choice of mass transfer rate for the inhalation exposure estimate, the approach used to derive the dermal exposure estimate and clarification on whether use in consumer spray coatings is supported by the registrants. Where use in consumer spray products is supported, a long-term local inhalation exposure estimate shall be provided using an appropriate exposure model. All assumptions and model input parameters used to derive the exposure estimate shall be documented.

REQUEST 3.5 - Worker – Industrial; Improved characterisation of the approach used to assess risk characterisation for combined exposure.

The Concern(s) Identified

For each industrial use scenario, the CSR has identified the possibility for simultaneous exposure of workers from more than one task or process. In order to assess this potential risk, risk characterisation ratios (RCRs) for two selected PROCs have been combined. Where the combined RCR value indicates the risk is not adequately controlled, further refinements are made including application of additional risk management

ECHA
EUROPEAN CHEMICALS AGENCY

measures. No justification is provided in the CSR for the approach used, in particular for the choice of PROCs to determine the combined RCR and whether these represent a worst case assessment. Also, the additional risk management measures applied are not reflected in the corresponding exposure scenario or in Part A of the CSR. Without a clear description of the approach taken to characterise the risk related to combined exposure and any additional risk management measures applied, it is not possible for the evaluating MSCA to conclude on whether modelled exposure estimates presented in the exposure scenarios are representative of the actual exposure to the worker and thus whether the risk is adequately controlled.

Why new information is needed

The risk characterisation of combined exposures to industrial workers addresses the potential for simultaneous exposure to a single worker during various tasks or processes within a given exposure scenario. The approach applied in the CSR combines the highest RCRs from two PROCs to determine the overall combined RCR. No information is provided to justify the choice of PROCs, including why only two PROCs were selected. In addition, no information is provided on whether the risk characterisation related to combined exposure represents a realistic scenario for a given worker, for example taking into account the actual process covered by the exposure scenario, the task durations and a normal working day. It is also not clear whether certain tasks in a given exposure scenario should not be performed by the same worker.

Where the combined RCR indicates an unacceptable risk, further risk management measures have been applied. These include reducing the task duration further (e.g. from 1 hour to less than 15 minutes). ECHA notes that no information is provided on the practicality of limiting the task duration in the context of the task description in the corresponding exposure scenario. Also in some cases a further refinement to take account of the use of respiratory protective equipment has been applied. ECHA notes that the additional risk management measures applied to the risk characterisation for combined exposure are not reflected in the corresponding exposure scenarios or in part A of the CSR.

For exposure scenario 1, an unacceptable risk is identified in the CSR for simultaneous exposure from PROCs 2 and 9. The refinement applied includes replacing PROC 2 with PROC 3 in the risk characterisation for combined exposure. ECHA notes that no justification for this approach is provided and no information is included in the CSR as to whether this combination of tasks (i.e. PROCs 9 and 2) represent a "use advised against".

For exposure scenario 11, an unacceptable risk is identified in the CSR for simultaneous exposure and the following conclusion is drawn: "there are no routes of simultaneous exposure that demonstrate safe use for this scenario". No refinement of the risk characterisation and no further advice regarding risk reduction measures are documented in the CSR, either in the exposure scenario or part A of the CSR.

Therefore, ECHA considers that there is some uncertainty regarding the risk characterisation related to simultaneous exposure of workers during different tasks or processes.

According to ECHA Guidance Part E (ECHA 2012b), where a risk characterisation shows the risk is not controlled, a further iteration of the chemical safety assessment is required by refining the exposure information or introducing new risk management measures. ECHA Guidance R.14 (ECHA 2015d) states that refinement of exposure estimation can be made using a higher tier model. Such higher tier models may also allow the calculation of a time weighted average exposure to take account of combined tasks.

As a concern for simultaneous exposure has been identified in the CSR, ECHA considers that further information is required on the approach used in the CSR to characterise the risk related to combined or simultaneous exposure to industrial workers.

Considerations on the method

You are required to provide further information on the approach used to characterise the risk related to combined exposure, taking into account the task descriptions in the exposure scenario. In particular you are required to clarify the choice of PROCs and whether the risk characterisation related to combined exposure represents a realistic scenario for a given worker. Where an unacceptable risk is identified and there is a need to further refine the exposure estimates, an appropriate higher tier exposure model shall be used.

Alternative approaches and proportionality of the request

The request to provide further information on the approach used to characterise the risk related to combined exposure is suitable and necessary to obtain information that will clarify whether there is a risk. There is no equally suitable alternative way available of obtaining this information. If the information, once obtained, confirms that there is a risk, it will allow authorities to consider further regulatory risk management.

Consideration of Registrants' comments

In response to the draft decision, you indicated your agreement to provide improved information addressing the exposure concerns. As no information was provided in an update of the registration dossier, the decision was not amended.

Conclusion

Therefore, based on the substance evaluation and pursuant to Article 46(1) of the REACH Regulation, ECHA concludes that you are required to carry out the following study using the substance subject to this decision: Worker- Industrial; Improved characterisation of the approach used to characterise the risk related to combined exposure in the CSR.

ECHA
EUROPEAN CHEMICALS AGENCY

REQUEST 3.6. - Worker – Industrial and professional; Missing exposure assessment for spray applications

The Concern(s) Identified

ECHA notes that some registration dossiers report industrial and professional spray tasks or processes (PROCs 7 and 11) which are not supported in the corresponding exposure scenario in the joint CSR. These were noted for the following registered uses; industrial formulation of coatings and preparations, industrial and professional use of sealants/adhesives and industrial use of non-metal surface treatments. The leading effect observed in the available inhalation repeated dose toxicity studies was the formation of laryngeal granulomas following aerosol exposure. In the absence of an exposure assessment for spray applications for these uses, it is not possible for the evaluating MSCA to conclude on whether there is a concern for long-term local inhalation exposure, and thus whether the risk for local effects in the respiratory tract following aerosol exposure is adequately controlled.

Why new information is needed

Some registration dossiers report spray tasks or processes (PROCs 7 and 11) for the following uses; industrial formulation of coatings and preparations, industrial and professional use of sealants/adhesives and industrial use of non-metal surface treatments. These registration dossiers refer to the joint CSR however the corresponding exposure scenarios in the joint CSR do not include an exposure assessment for spraying. No individual CSRs (whole or partial) are provided. An exposure assessment to address the potential for long-term local inhalation of aerosolised 3-trimethoxysilylpropyl methacrylate is required for the reported spray activities for these uses, to allow the evaluating MSCA to conclude on whether the risk for local effects in the respiratory tract following aerosol exposure is adequately controlled. The information shall include a long-term local inhalation exposure estimate, if required, using an appropriate exposure model. All assumptions and model input parameters used to derive the exposure estimate shall be documented.

Considerations on the method

Exposure assessment is required for the registered uses containing spray tasks or process types (PROC 7 or 11) with the description; industrial formulation of coatings and preparations, industrial and professional use of sealants/adhesives and industrial use of non-metal surface treatments which are not covered by the corresponding exposure scenario in the joint CSR. As part of the exposure assessment, a local inhalation exposure estimate shall be provided, if required, using an appropriate exposure model. All assumptions and model input parameters used to derive the exposure estimate shall be documented.

Alternative approaches and proportionality of the request

The request to provide further information on the potential for aerosol generation is suitable and necessary to obtain information that will clarify whether there is a risk to

ECHA
EUROPEAN CHEMICALS AGENCY

workers for local effects in the respiratory tract following aerosol exposure. There is no equally suitable alternative way available of obtaining this information. If the information, once obtained, confirms that there is a risk to workers, it will allow authorities to consider further regulatory risk management.

Consideration of Registrants' comments

In response to the draft decision, you indicated your agreement to provide improved information addressing the exposure concerns. As no information was provided in an update of the registration dossier, the decision was not amended.

Conclusion

Therefore, based on the substance evaluation and pursuant to Article 46(1) of the REACH Regulation, ECHA concludes that you are required to submit the following information on the substance subject to this decision: Worker – Industrial and professional; Exposure assessment for spray tasks or processes (PROCs 7 and 11) for the following registered uses; industrial formulation of coatings and preparations, industrial and professional use of sealants/adhesives and industrial use of non-metal surface treatments, which are not addressed in the corresponding exposure scenario in the joint CSR. The information shall include a long-term local inhalation exposure estimate, if required, using an appropriate exposure model. All assumptions and model input parameters used to derive the exposure estimate shall be documented.

ECHA
EUROPEAN CHEMICALS AGENCY

References

Basketter, D., Ball, N., Cagen, S., Carillo, JC., Certa, H., Eigler D., Garcia, C., Esch, H., Graham, C., Haux, C., Kreiling, R., Mehling A. (2009a). Application of weight of evidence approach to assessing discordant sensitisation datasets: implications for REACH. Reg. Toxicol. Pharmacol., **55**, 90-96

Basketter D., McFadden JF., Gerberick F., Cockshott A., Kimber I. (2009b) Nothing is perfect, not even the local lymph node assay: a commentary and the implications for REACH. Contact Dermatitis, **60**, 65-69.

[redacted]

ECHA 2012a. Practical Guide 6: How to report read-across and categories, version 2.0, December 2012, ECHA-10-B-11.1-EN

ECHA 2012b. Guidance on information requirements and chemical safety assessment, Part E: Risk characterisation, version 2.0, November 2012. ECHA-12-G-16-EN

ECHA 2015a. Read-Across Assessment Framework, May 2015. ECHA-15-R-07-EN

ECHA 2015b. Guidance on information requirements and chemical safety assessment, Chapter R.12: Use description, version 3.0, December 2015. ECHA-15-G-11-EN

ECHA 2015c. Guidance on information requirements and chemical safety assessment, Chapter R.15: Consumer exposure estimation, draft version 3.0, October 2015

ECHA 2015d. Guidance on information requirements and chemical safety assessment, R.14: Occupational exposure assessment, draft version3.0, November 2015.

ECHA 2016. Guidance on information requirements and chemical safety assessment, Chapter R.7a: Endpoint specific guidance, version 5.0, December 2016

OECD 2012. The Adverse Outcome Pathway for Skin Sensitisation Initiated by Covalent Binding to Proteins; Part 1: Scientific Evidence. Series on Testing and Assessment No.168.

Petry, T., Bosch, A., Coste, X., Dupuis, V., Eigler, D., Germain, P. (2012). An assessment of the skin sensitisation hazard of a group of polyfunctional silicones using a weight of evidence approach. Reg. Toxicol. Pharmacol., **64**, 305-314

RIVM 2007a. Paint products fact sheet to assess the risks for the consumer; Updated version for ConsExpo 4.0, August 2007. Report number 320104008

RIVM 2007b. Do-It-Yourself products fact sheet to assess the risks for the consumer; July 2007. Report number 320104007.

ECHA
EUROPEAN CHEMICALS AGENCY

Appendix 2: Procedural history

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to human health/suspected sensitiser, further evaluation of repeated dose toxicity and reproductive toxicity data; exposure/wide dispersive use, consumer use, exposure of workers, high (aggregated) 3-trimethoxysilylpropyl methacrylate CAS No 2530-85-0 (EC No 219-785-8) was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2015. The updated CoRAP was published on the ECHA website on 17 March 2015. The Competent Authority of Ireland (hereafter called the evaluating MSCA) was appointed to carry out the evaluation.

Pursuant to Article 45(4) of the REACH Regulation the evaluating MSCA carried out the evaluation of the above substance based on the information in your registration(s) and other relevant and available information.

In the course of the evaluation, the evaluating MSCA identified additional concerns regarding mutagenicity (clastogenicity).

The evaluating MSCA considered that further information was required to clarify the following concerns: skin sensitisation, mutagenicity and exposure of workers and consumers. Therefore, it prepared a draft decision pursuant to Article 46(1) of the REACH Regulation to request further information. It submitted the draft decision to ECHA on 8 March 2016.

The decision making followed the procedure of Articles 50 and 52 of the REACH Regulation.

ECHA notified you of the draft decision and invited you to provide comments.

Registrant(s)' commenting phase

ECHA received comments from you and forwarded them to the evaluating MSCA without delay.

By 8 July 2016 you submitted update(s) of the registration dossier(s). The evaluating MSCA took the information in the updated registration dossier(s) into account, and it is reflected in the Reasons (Appendix 1).

Proposals for amendment by other MSCAs and ECHA and referral to Member State Committee

The evaluating MSCA notified the draft decision to the Competent Authorities of the other Member States and ECHA for proposal(s) for amendment

Subsequently, the evaluating MSCA received proposal(s) for amendment to the draft decision and modified the draft decision. They are reflected in the Reasons (Appendix 1).

ECHA referred the draft decision, together with your comments, to the Member State Committee.

ECHA invited you to comment on the proposed amendment(s).

ECHA
EUROPEAN CHEMICALS AGENCY

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

In addition you provided comments on the draft decision, in particular proposing to conduct a guinea pig maximization test (OECD 406) instead of a LLNA. Your comments were not taken into account by the Member State Committee as they were considered to be outside of the scope of Article 52(2) and Article 51(5).

MSC agreement seeking stage

The Member State Committee reached a unanimous agreement on the draft decision during its MSC-52 meeting and ECHA took the decision according to Article 52(2) and 51(6) of the REACH Regulation.

ECHA
EUROPEAN CHEMICALS AGENCY

Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided by you in the registration(s) is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on your dossier(s) at a later stage, nor does it prevent a subsequent decision under the current substance evaluation or a new substance evaluation process once the present substance evaluation has been completed.

2. Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In relation to the required experimental study/ies, the sample of the substance to be used shall have a composition that is within the specifications of the substance composition that are given by all Registrant(s). It is the responsibility of all the Registrant(s) to agree on the tested material to be subjected to the test(s) subject to this decision and to document the necessary information on composition of the test material. The substance identity information of the registered substance and of the sample tested must enable the evaluating MSCA and ECHA to confirm the relevance of the testing for the substance subject to substance evaluation.

4. In relation to the experimental stud(y/ies) the legal text foresees the sharing of information and costs between Registrant(s) (Article 53 of the REACH Regulation). You are therefore required to make every effort to reach an agreement regarding each experimental study for every endpoint as to who is to carry out the study on behalf of the other Registrant(s) and to inform ECHA accordingly within 90 days from the date of this decision under Article 53(1) of the REACH Regulation. This information should be submitted to ECHA using the following form stating the decision number above at:
https://comments.echa.europa.eu/comments_cms/SEDraftDecisionComments.aspx

   Further advice can be found at
http://echa.europa.eu/regulations/reach/registration/data-sharing. If ECHA is not informed of such agreement within 90 days, it will designate one of the Registrants to perform the stud(y/ies) on behalf of all of them.

ECHA
EUROPEAN CHEMICALS AGENCY

Appendix 4: List of registration numbers for the addressees of this decision. This appendix is confidential and not included in the public version of this decision.

EC number: 219-785-8
CAS number: 2530-85-0
Public name: 3-trimethoxysilylpropyl methacrylate

This decision is addressed to the Registrant(s) of the above substance with active registration pursuant to Article 6 of the REACH Regulation on the date on which the draft for the decision was first sent for comments. If Registrant(s) ceased manufacture upon receipt of the draft decision pursuant to Article 50(3) of the REACH Regulation, they did not become addressee(s) of the decision. A list of all the relevant registration numbers of the Registrant(s) that are addressees of the present decision is provided below: