SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

3-trimethoxysilylpropyl methacrylate

EC No 219-785-8

CAS No 2530-85-0

Evaluating Member State(s): Ireland

Dated: 25 May 2020

Evaluating Member State Competent Authority

The Health & Safety Authority
The Metropolitan Building
James Joyce Street
Dublin D01 K0Y8
Ireland

Email: chemicals@hsa.ie

Year of evaluation in CoRAP: 2015

Before concluding the substance evaluation a Decision to request further information was issued on: 29 March 2017

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

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Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

3-trimethoxysilylpropyl methacrylate was originally selected for substance evaluation in order to clarify concerns about:

- Suspected skin sensitisation
- Wide dispersive use
- Consumer use
- Exposure of workers
- High (aggregated) tonnage

In addition to the above concerns, the published CoRAP justification document also identified concerns relating to repeated dose toxicity and reproductive toxicity. During the evaluation, additional concerns were identified relating to mutagenicity (clastogenicity).

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

A testing proposal decision has been issued by ECHA for the registered substance requesting an extended one generation reproductive toxicity study (EOGRTS, OECD 443), with a decision deadline of 10 September 2020 and a pre-natal developmental toxicity study (OECD 414) in a second species (rabbits), with a decision deadline of 15 November 2021.

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State Competent Authority (MSCA) to the following conclusions, as summarised in the table below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION Conclusions	Tick box
Need for follow-up regulatory action at EU level	X
Harmonised Classification and Labelling	X
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	

No need for regulatory follow-up action at EU level	

In addition to the conclusion that harmonised classification and labelling is needed, the evaluating MSCA identified shortcomings in the modelled worker inhalation exposure estimates presented in the registration data for some aerosol generating activities. These are further outlined in section 7.12.1.1 and in the confidential annex to this report. The evaluating MSCA calculated aerosol inhalation exposure estimates for these activities using ART v1.5 and, where no representative scenario in ART for an activity was available, ECETOC TRA v3.1. When these were compared with the DNEL for long-term local effects for the inhalation route (workers) derived by the evaluating MSCA, the resulting risk characterisation ratio (RCR) values were 1 or greater. Therefore, the evaluating MSCA concluded that based on the available information, aerosol inhalation exposure may not be adequately controlled for some worker activities. The registrants are advised to review their exposure estimates for these activities and update the registration data, as appropriate.

The evaluating MSCA also identified a concern for aerosol inhalation exposure from consumer use of spray paints containing the registered substance. The evaluating MSCA calculated an aerosol inhalation exposure estimate for this use using Cons Expo Web 1.0.6. When this estimate was compared with the DNEL for long-term local effects for the inhalation route (general population - infrequent use) derived by the evaluating MSCA, the resulting RCR is significantly greater than 1. The evaluating MSCA notes that there is some uncertainty in the registration data regarding whether paints containing the registered substance are actually supplied for spray application by consumers. However, this is a registered use of the substance and therefore based on the available information, the evaluating MSCA concluded that aerosol inhalation exposure of consumers may not be adequately controlled. The registrants are advised to clarify in their registration data whether use in consumer spray paints is supported.

Therefore, in addition to, and in parallel with, developing a proposal for harmonised classification and labelling (as discussed in section 4.1.1 below), the evaluating MSCA will further seek to clarify whether additional regulatory actions at EU level are appropriate based on the current uses reported in the registration data.

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

4.1.1. Harmonised Classification and Labelling

There is currently no entry in Annex VI of the CLP Regulation (EC) No. 1272/2008 for 3-trimethoxysilylpropyl methacrylate. The registrants have not self-classified the substance.

From the available inhalation repeated dose toxicity studies with aerosolised atmospheres of 3-trimethoxysilylpropyl methacrylate, a concern for local effects in the respiratory tract was identified. Laryngeal granulomas were observed at concentrations of ≥ 50 mg/m^3 (equivalent to 0.05 mg/L) and cytoplasmic hyalinisation of the nasal tissue was observed at concentrations ≥ 5 mg/m^3 (equivalent to 0.005 mg/L). These effects were not reversible during a 12 month recovery period following a 13 week exposure to a concentration of 100 mg/m^3. The evaluating MSCA considers that the formation of laryngeal granulomas may be an indication of functional impairment. As laryngeal granulomas were observed at ≥

0.05 mg/L in both 4 and 13/14 week studies, the evaluating MSCA concludes that classification as specific target organ toxicity – repeated exposure, category 2 (STOT-RE 2) is appropriate. As the registrants do not currently classify the substance for this endpoint, the evaluating MSCA considers that there is a need to communicate this specific hazard via harmonised classification and labelling.

4.1.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)

Not applicable.

4.1.3. Restriction

Not applicable.

4.1.4. Other EU-wide regulatory risk management measures

Not applicable.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1. No need for regulatory follow-up at EU level

Not applicable.

5.2. Other actions

Not applicable.

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Table 2

FOLLOW-UP		
Follow-up action	**Date for intention**	**Actor**
Preparation of Annex VI CLH proposal	2021	Ireland

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

3-trimethoxysilylpropyl methacrylate was originally selected for substance evaluation in order to clarify concerns about:

- Suspected skin sensitisation
- Wide dispersive use
- Consumer use
- Exposure of workers
- High (aggregated) tonnage

In addition to the above concerns, the published CoRAP justification document also identified concerns relating to repeated dose toxicity and reproductive toxicity. During the evaluation, additional concerns were identified relating to mutagenicity (clastogenicity).

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome / conclusion**
Skin Sensitisation	Based on the results of a local lymph node assay (OECD 429) with the registered substance, the evaluating MSCA concluded that the concern for skin sensitisation is not substantiated.
Repeated dose toxicity	The most significant and consistent effects observed from the available inhalation repeated dose toxicity studies (durations of between 9 days and 14 weeks) in rats with aerosolised atmospheres of the registered substance were the formation of laryngeal granulomas and cytoplasmic hyalinisation of nasal epithelium. These effects were not reversible in a 1 year follow up period following a 13 week exposure. The evaluating MSCA noted a number of limitations with the available studies; however based on a weight of evidence assessment, a concern for local effects in the respiratory tract following aerosol exposure was identified. A NOAEC of 15 mg/m^3 was identified for the formation of laryngeal granulomas and a LOAEC of 5 mg/m^3 for cytoplasmic hyalinisation of nasal tissue. The evaluating MSCA concluded that classification as STOT-RE category 2 is appropriate.
Mutagenicity	Based on the results of an *in vivo* mammalian alkaline comet assay (OECD 489), in which no increase in the incidence of DNA strand breaks was reported in the nasal epithelium, lungs or liver of rats following inhalation exposure of an aerosolised atmosphere of the registered substance, the evaluating MSCA concluded that the concern for clastogenicity is not substantiated.

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome / conclusion**
Reproductive toxicity	No data to address the fertility endpoint are currently available. A testing proposal decision has been issued by ECHA for the registered substance requesting an extended one generation reproductive toxicity study (EOGRTS, OECD 443), with a decision deadline of 10 September 2020. Based on the available pre-natal developmental toxicity (PNDT) study in rats, no concern for developmental toxicity was identified. A testing proposal decision has been issued by ECHA for the registered substance requesting a pre-natal developmental toxicity study (OECD 414) in a second species (rabbits), with a decision deadline of 15 November 2021.
Worker Exposure	The evaluating MSCA concluded that the potential for aerosol inhalation exposure to workers may be underestimated in the registration data for certain activities. Therefore, a potential concern for aerosol inhalation exposure for certain aerosol generating activities remains. Further refinement by the registrants of the aerosol inhalation exposure estimates and the operational conditions and risk management measures are recommended.
Consumer Exposure	The evaluating MSCA concluded that the potential for aerosol inhalation exposure to consumers from the use of spray paints may be underestimated in the registration data and therefore the concern for consumer exposure remains for this registered use.

7.2. Procedure

Pursuant to Article 44(2) of the REACH Regulation, 3-trimethoxysilylpropyl methacrylate was included on the Community rolling action plan (CoRAP) for evaluation in 2015. The Competent Authority of Ireland was appointed to carry out the evaluation. The substance evaluation commenced on 1 March 2015.

The evaluation was targeted to human health hazards and exposure. Although not the focus of the evaluation, a preliminary assessment of the environmental hazards was also undertaken and no concerns were identified. The main source of information for the evaluation was the registration dossiers.

Based on the evaluation of the available data, the evaluating MSCA concluded there was a need to request further information to clarify the concerns relating to skin sensitisation, mutagenicity (clastogenicity) and exposure to workers and consumers. Therefore, pursuant to Article 46(1) of the REACH Regulation, a draft decision was prepared to request further information. The draft decision was submitted to ECHA on 8 March 2016. The decision was agreed at the Member State Committee meeting in February 2017 and issued to the registrants on 29 March 2017.

On 4 July 2018 the lead registrant updated their registration dossier to comply with the final decision. The substance evaluation conclusion and evaluation report was prepared taking into account the updated registration data and chemical safety report.

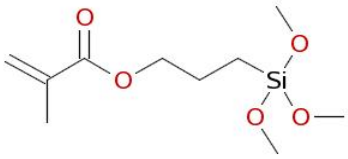
7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	3-trimethoxysilylpropyl methacrylate
EC number:	219-785-8
CAS number:	2530-85-0
Index number in Annex VI of the CLP Regulation:	Not listed in Annex VI
Molecular formula:	$C_{10}H_{20}O_5Si_1$
Molecular weight range:	248.4 g/mol
Synonyms:	1-Propanol, 3-(trimethoxysilyl)-, methacrylate 2-Methyl-2-propenoic acid 3-(trimethoxysilyl)propyl ester 2-Propenoic acid, 2-methyl-, 3-(trimethoxysilyl)propyl ester 3-Methacryloxypropyltrimethoxysilane Methacrylic acid, 3- (trimethoxysilyl)propyl ester Methacryloxypropyltrimethoxysilane Silane A174 Trimethoxy(3-methacryloxypropyl)silane α-Methacryloxypropyltrimethoxysilane γ-Methacryloxypropyltrimethoxysilane

Type of substance ☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:



7.4. Physico-chemical properties

Table 5

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	Liquid
Vapour pressure	2.3 Pa at 25 °C (OECD 104)
Water solubility	2200 mg/L at 20 ^{0}C (QSAR)
Partition coefficient n-octanol/water (Log Kow)	2.1 at 21 ± 1 °C (OECD 107)
Flammability	Not flammable
Explosive properties	Not explosive
Self-ignition temperature	275 °C at 101.35 - 103.07 kPa (EU Method A.15)
Oxidising properties	Not oxidising
Granulometry	Not applicable
Stability in organic solvents and identity of relevant degradation products	No data available
Dissociation constant	Not relevant
Relative density	1.04 g/cm^{3} at 20 ^{0}C
Viscosity	3.2 mm^{2}/s at 20 °C (QSAR)

7.5. Manufacture and uses

7.5.1. Quantities

Table 6

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t	☐ 10 – 100 t	☐ 100 – 1000 t	☒ 1000- 10,000 t	☐ 10,000-50,000 t
☐ 50,000 – 100,000 t	☐ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☐ > 1000,000 t	☐ Confidential

7.5.2. Overview of uses

3-trimethoxysilylpropyl methacrylate is an organofunctional silane. It has a number of technical functions including adhesion promotor, cross-linking agent, binder, film former, surface modifier, dispersing agent, intermediate (precursor) and monomer. A number of industrial, professional and consumer uses are reported in the registration dossiers.

Table 7

USES	Use(s)
Uses as intermediate	Use as a chemical intermediate
Formulation	Formulation of end use products
Uses at industrial sites	Manufacture of the registered substance Use as a monomer Use in non-metal surface treatments Use in coatings and inks Use in adhesives and sealants Use as a laboratory reagent
Uses by professional workers	Use of coatings and inks Use of adhesives and sealants Use in dental applications Use of cosmetic and personal care products
Consumer Uses	Use of coatings Use of adhesives and sealants Use of cosmetic and personal care products
Article service life	None indicated

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

3-trimethoxysilylpropyl methacrylate is not listed in Annex VI of CLP.

7.6.2. Self-classification

In the registration(s), 3-trimethoxysilylpropyl methacrylate is not self-classified.

The following hazard classes are notified among the aggregated self-classifications in the C&L Inventory:

- Acute Toxicity 4; H302: Harmful if swallowed
- Skin Irritation 2; H315: Causes skin irritation
- Eye Irritation 2; H319: Causes serious eye irritation

- Specific target organ toxicity single exposure (STOT SE) 1; H370: Causes damage to organs
- Specific target organ toxicity single exposure (STOT SE) 3; H335: May cause respiratory irritation
- Specific target organ toxicity repeated exposure (STOT RE) 1; H372: Causes damage to organs through prolonged or repeated exposure
- Specific target organ toxicity repeated exposure (STOT RE) 2; H373: May cause damage to organs through prolonged or repeated exposure.

7.7. Environmental fate properties

Not evaluated.

7.8. Environmental hazard assessment

Not evaluated.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

No toxicokinetic data are available for 3-trimethoxysilylpropyl methacrylate.

The registered substance is of low volatility (2.3 Pa at 25 ^{0}C) and has a moderate log kow value (log Kow of 2.1 at 21 ^{0}C). An estimated blood: air partition coefficient of 4500:1 is reported in the registration data. Based on these physico-chemical parameters, absorption of the registered substance following oral, dermal or inhalation exposure is expected.

Modelling information reported in the registration data indicates that distribution would be mainly to fatty tissues and elimination via the urine is expected.

The available hydrolysis data indicate that 3-trimethoxysilylpropyl methacrylate rapidly hydrolyses in contact with water, with a half-life of less than 2 hours (0.018, 1.87 and 0.068 hours at pHs 4, 7 and 9, respectively) resulting in the hydrolysis products methanol and 3-(trihydroxysilyl)propyl methacrylate. 3-(trihydroxysilyl)propyl methacrylate has a low volatility (1.2 x 10^{-5} Pa at 20 °C), high water solubility (1,000,000 mg/l at 20°C) and a moderate log P value (log Kow of -0.9 at 20 ^{0}C).

7.9.2. Acute toxicity and Corrosion / Irritation

The registration data identified an LD_{50} (oral) of > 2000 mg/kg bw, an LC_{50} (inhalation, aerosol, 4 hour) of >2280 mg/m^3 and LD_{50} (dermal) of > 2000 mg/kg bw. The registration data concludes that no classification for acute toxicity is required for 3-trimethoxysilylpropyl methacrylate.

The registration data concludes that the registered substance does not meet the criteria for classification as irritating to the skin or eyes.

Based on the available information, the evaluating MSCA can support these conclusions.

7.9.3. Sensitisation

In a local lymph node assay (LLNA) conducted in accordance with OECD 429 (guideline study, assigned Klimisch score 1), 3-trimethoxysilylpropyl methacrylate in an acetone: olive oil vehicle (4:1 v/v) was applied topically to the dorsal surface of the ears of groups of 5 female CBA:J mice at 0 %, 2 %, 5 % or 10 % w/w (unpublished study report, 2018b). The dose selection was determined based on the results of a pre-screen test. No concurrent positive control group was included. However, the results of periodic testing of the positive control were included in the study report demonstrating the reliability of the test system. No mortality or clinical signs of systemic toxicity were observed. There was no treatment related effect on body weight or body weight gain. The study authors considered the majority of auricular lymph nodes to be normal in size, with the exception of an enlarged node in one low-dose animal. However, no associated macroscopic abnormalities of the surrounding area were noted for any animal. The stimulation index (S.I.) for 2 %, 5 % and 10 % w/w groups were reported as 0.9, 1.2, and 0.9, respectively. The EC3 value was estimated to be > 10 %. Under the conditions of the study, 3-trimethoxysilylpropyl methacrylate was not sensitising to skin.

In a non-guideline Guinea Pig Maximisation Test (GPMT) with the registered substance, 10/sex Hartley guinea pigs were intradermally induced with a 5 % w/v solution of 3-trimethoxysilylpropyl methacrylate in cottonseed oil and topically induced with undiluted 3-trimethoxysilylpropyl methacrylate (unpublished study report, 1994b). The positive control group were treated with dinitrochlorobenzene and the negative control group with cottonseed oil. Animals of the test and negative control groups were challenged with 50 % w/v 3-trimethoxysilylpropyl methacrylate in cottonseed oil. Negative control animals were also challenged with 100 % cottonseed oil, and positive control animals with 0.1 % dinitrobenzene in 80 % ethanol. Positive reactions were observed in the test group: 6/20 (mild) and 14/20 (moderate) at 24 hours and 15/20 (mild) and 5/20 (moderate) at 48 hours. Positive reactions were also observed in negative control animals challenged with either 3-trimethoxysilylpropyl methacrylate in cottonseed oil or cottonseed oil alone, demonstrating a possible reactivity in response to the cottonseed oil vehicle. All positive control animals were reported to have had moderate skin reactions at 24 hours and moderate to severe skin reactions at 48 hours. The registration data concluded that the result was ambiguous and the evaluating MSCA supports this conclusion.

The registration data also reports the results of two GPMT studies conducted in accordance with EU Method B.6 with the structural analogues, 3[dimethoxy(methyl)silyl]methyl methacrylate (CAS No. 121177-93-3) and 2-Propenoic acid,2-(trimethoxysilyl)methyl methacrylate (CAS No. 54586-78-6) as supporting information (unpublished study report, 2003a and unpublished study report, 2003b). Both substances are alkoxysilanes with methacrylate groups in the side chain. In both studies, no skin reactions were observed following the challenge exposure. Thus, both substances were considered to be not sensitising under the conditions of the studies. The evaluating MSCA notes no robust read-across justification is provided in the registration dossier to support the use of this data.

The registrants concluded that 3-trimethoxysilylpropyl methacrylate is not a skin sensitiser. Based on the negative LLNA with the registered substance, the evaluating MSCA can support this conclusion.

7.9.4. Repeated dose toxicity

The repeated dose toxicity of 3-trimethoxysilylproply methacrylate was investigated in eight inhalation repeated dose toxicity studies of varying duration. Seven of these studies exposed test animals to aerosolised atmospheres and one to a vapour atmosphere of 3-trimethoxysilylpropryl methacrylate.

In a non-guideline 9 day inhalation repeated dose toxicity study, groups of 20 (10/sex/group) Fischer-344 rats were exposed to 3-trimethoxysilylpropyl methacrylate vapour for 6 hours/day at target concentrations of 0, 8, 20 and 40 ppm (approx. 0, 81, 204 and 407 mg/m^3) (unpublished study report, 1982). Body weight, food, and water consumption were monitored. Serum chemistry analysis and urinalysis were performed. At study termination, animals were subject to gross pathology, organ weights were recorded and a histopathological examination was performed. The measured chamber concentrations were 7.5 ± 1.4, 23.0 ± 2.0 and 42.0 ± 2.0 ppm for the low, mid and high concentration groups, respectively. Food and water consumption were increased in males in the high concentration group. There was a trend of decreased relative kidney weight in treated males, which was statistically significant in the low and high concentration groups. Absolute heart weights were decreased in females in the mid and high concentration groups and relative heart weight was decreased in males in the high concentration group. No laryngeal granulomas were observed. The study report did not include tables of individual animal or group histopathological findings other than those for the larynx but noted that no other histological lesions were observed. The registration data identified a LOAEC of 8 ppm.

In a non-guideline 9 day inhalation repeated dose toxicity study, groups of 20 (10/sex/group) Fischer-344 rats were exposed to aerosolised atmospheres of 0, 50, 100 and 300 mg/m^3 of a 15 % w/w starting solution of 3-trimethoxysilylpropyl methacrylate in distilled water (pH 4) for 6 hours/day (unpublished study report, 1983). Body weight, food and water consumption were monitored. Serum chemistry analysis and urinalysis were performed. At study termination, all animals were subject to gross pathology and the following organ weights recorded: liver, heart, brain, lung, kidney and testes. Selected tissues, including larynx, trachea, nasal turbinates, lungs, liver, kidneys and spleen were subject to histological evaluation. The calculated chamber concentrations were 49.6 ± 4.3, 98.8 ± 10.7 and 302.0 ± 16 mg/m^3 for the low, mid and high concentration groups, respectively. The mass median aerodynamic diameter (MMAD) in the treatment groups was between 1.04 ± 2.16 µm and 1.40 ± 2.40 µm. Body weights were decreased in animals of the high concentration group. Serum albumin and total serum globulin levels were increased in all treated males. A first histopathological analysis reported no treatment related effects. However, a subsequent re-evaluation of the larynxes found granulomatous laryngitis in a significant number of treated animals, approximately 77 % of males and 64 % of females (the incidences per group were not reported). The registration data identified a LOAEC of 50 mg/m^3.

In a 4 week non-guideline inhalation repeated dose toxicity study, five groups of between 20 to 40 male Fischer F-344 rats were exposed to aerosolised atmospheres generated

using different starting concentrations of 3-trimethoxysilylpropyl methacrylate and pHs for 6 hours/day, 5 days/week (unpublished study report, 1986). The target concentrations were 0, 10 and 50 mg/m^3 (using a 1 % w/w aqueous starting solution at pH 5) and 50 mg/m^3 (using a 15 % w/w aqueous starting solution at pH 3) and using two different methods of aerosol generation, recirculated and non-recirculated solutions. Body weights were recorded weekly. Ten (10) males from the 0, 50 mg/m^3 (1 % w/w aqueous starting solution at pH 5, non-recirculated) and 50 mg/m^3 (15 % w/w aqueous starting solution at pH 3, recirculated) groups were subject to an interim sacrifice following 2 weeks exposure and subject to histopathological examination of the larynx. At study termination, all animals were subject to histopathological examination of lungs, nasal turbinates, larynx and trachea. The calculated chamber concentrations were 13.5 ± 1.02, 68.2 ± 3.29, 68.8 ± 5.76 and 69.0 ± 3.19 mg/m^3 for the 10, 50 (1 % w/w starting solution, non-recirculated), 50 (15 % w/w starting solution, recirculated) and 50 (15 % w/w starting solution, non-recirculated) mg/m^3 groups, respectively. The MMAD in the treatment groups was between 2.92 ± 1.91 µm and 5.2 ± 2.19 µm. The study report indicates that the characterisation of the aerosol atmospheres by scanning electron microscopy/energy dispersive X-ray analysis (SEM/EDX) analysis indicated that 3-trimethoxysilylpropyl methacrylate was not present as a solid particulate in the chamber atmospheres. At the interim sacrifice the incidence of laryngeal granulomas was 0/10, 5/10 and 10/10 in the 0, 50 (1 % w/w starting solution at pH 5, non-recirculated) and 50 (15 % w/w starting solution at pH 3, recirculated) mg/m^3 groups, respectively. At study termination, the incidence of laryngeal granulomas was 0/20, 0/20, 17/20, 20/20 and 20/20 in the 0, 10, 50 (1 % w/w starting solution at pH 5, non-recirculated), 50 (15 % w/w starting solution at pH 3, recirculated) and 50 (15 % w/w starting solution at pH 3, non-recirculated) mg/m^3 groups, respectively. The study report noted that the granulomas were located in the posterior epiglottis and appeared as bulges in the mucosal layer. The study report also noted that the laryngeal granulomas observed at 50 mg/m^3 generated using a 1 % w/w starting solution were smaller than those observed at 50 mg/m^3 generated using 15 % w/w starting solution. There was an increased incidence of hyaline body formation in the cytoplasm of the nasal turbinates. The reported incidences were 4/20, 13/20, 18/20, 11/20 and 7/20 in the 0, 10, 50 (1 % w/w starting solution at pH 5, non-recirculated), 50 (15 % w/w starting solution at pH 3, recirculated) and 50 (15 % w/w starting solution at pH 3, non-recirculated) mg/m^3 groups, respectively. The study authors noted that this effect was observed in the absence of inflammation, cellular degeneration or metaplasia and noted that the biological significance was unclear. The registration data identified a NOAEC of 15 mg/m^3 based on the formation of laryngeal granulomas at higher concentrations. The evaluating MSCA notes that this concentration resulted in a significant increase in the incidence of cytoplasmic hyalinisation of nasal turbinates and therefore the evaluating MSCA considers 15 mg/m^3 to be a LOAEC.

In a second non-guideline 4 week inhalation repeated dose toxicity study, six groups of 24 male Fischer 344/CDF rats were exposed to aerosolised atmospheres of 0, 15, 50, 70 or 100 mg/m^3 of a 1 % w/w starting solution (pH 3) or 100 mg/m^3 of a 15 % w/w starting solution (pH 5) of 3-trimethoxysilylpropyl methacrylate in distilled water for 6 hours/day, 5 days/week (unpublished study report, 1989b). An additional 4 males per group were exposed to aerosolised atmospheres of 50 (1 % w/w starting solution, pH 5), 100 (1 % w/w starting solution, pH 5) or 100 (15 % w/w starting solution pH 3) mg/m^3, sacrificed following two or four exposures and the larynxes examined by transmission electron microscopy (TEM). At study termination, 20 males/group were subject to histopathological examination of lungs, nasal turbinates, larynx, trachea and any tissues with gross lesions. For the remaining 4 males/group, larynxes were removed and prepared for analysis by

TEM. The calculated chamber concentrations were 14.0 ± 1.42, 48.9 ± 2.77, 70.2 ± 2.88, 97.0 ± 2.46 and 100.9 ± 11.3 mg/m^3 for the 15, 50, 70 or 100 (1% w/w starting solution, pH 5) and 100 (15 % w/w starting solution, pH 3) mg/m^3 groups, respectively. The MMAD in the treatment groups was between 2.09 ± 2.62 µm and 2.54 ± 2.65 µm. Analysis of larynxes after two exposures at 100 mg/m^3 (15 % w/w starting solution, pH 3) by TEM showed a marked degree of cellular degeneration of the laryngeal epithelium. No information is included in the study report on the TEM analysis from the other groups following 2 or 4 exposures. At study termination, the incidence of laryngeal granulomas was 0/20, 0/20, 0/20, 0/20, 17/20 and 20/20 at 0, 5, 50, 70 or 100 (1% w/w starting solution, pH 5) and 100 (15 % w/w starting solution, pH 3) mg/m^3 groups, respectively. The study report notes that the granulomas were located on the ventral floor of the larynx and were larger in animals exposed to 15 % w/w starting solution compared to those exposed to a 1 % w/w starting solution. The incidence of squamous metaplasia of the mucosa overlying the laryngeal granulomas was statistically significantly increased from 70 mg/m^3: the incidences were reported as 1/20, 3/20, 4/20, 14/20, 19/20 and 20/20 in the 0, 15, 50, 70 or 100 (1% w/w starting solution, pH 5) and 100 (15 % w/w starting solution, pH 3) mg/m^3 groups, respectively. TEM examination of larynxes showed regeneration of the epithelium, with cuboidal and/or columnar cells replaced with squamous cells. The incidence of cytoplasmic hyalinisation in the nasal cavity was statistically significantly increased at 100 mg/m^3 (15 % w/w starting solution, pH 3). The incidence of goblet cell hyperplasia in the nasal mucosa was statistically significantly increased in all treatment groups when compared with the control; the incidences were 2/20, 20/20, 19/20, 20/20, 19/20 and 20/20 in the 0, 15, 50, 70 or 100 (1% w/w solution, pH 5) and 100 (15 % w/w starting solution, pH 3) mg/m^3 groups, respectively. An increased incidence of granulomatous rhinitis was also observed in the treatment groups, statistically significant at 50, 100 (1% w/w starting solution, pH 5) and 100 (15 % w/w starting solution, pH 3) mg/m^3. The registration data identified a LOAEC of 15 mg/m^3.

In a 4 week non-guideline inhalation repeated dose toxicity study, groups of 10 male Fischer 344 rats were exposed for 6 hours/day, 5 days/week to aerosolised atmospheres of 150 mg/m^3 of a 2 % w/w starting solution of 3-trimethoxysilylpropyl methacrylate (pH 5) in distilled water (unpublished study report, 1991). Control animals were exposed to air only. Body weights were recorded. At study termination, animals were subject to histopathological examination of lungs, nasal turbinates, larynx, trachea, kidney and any tissues with gross lesions. The calculated chamber concentration was 143.0 ± 10.4 mg/m^3 and the MMAD was 2.65 ± 1.74 µm. The incidence of laryngeal granulomas (9/10) and squamous metaplasia in the larynx (10/10) was statistically significantly increased in the treated group compared with the control (0/10 for both lesions). The granulomas were observed on the ventral floor of the larynx and were associated with mild squamous metaplasia of the overlying laryngeal mucosa. The incidence of cytoplasmic hyalinisation in the olfactory mucosa of the nasal cavity was also statistically significantly increased in the treated group (9/10) when compared with the control (0/10). A LOAEC of 143 mg/m^3 was identified in the registration data.

In a 13 week inhalation repeated dose toxicity study conducted according to GLP, 40/sex/group Fisher 344 rats were exposed for 6 hours/day, 5 days/week to aerosolised atmospheres of 0 or 100 mg/m^3 of a 2 % w/w starting solution of 3-trimethoxysilylpropyl methacrylate (pH 5) in distilled water (unpublished study report, 1994). Following the last exposure and at 1, 4, 8 and 12 months post exposure, 8/sex/group were subject to histopathological evaluation. The measured chamber concentration was 102.0 ± 5.76 mg/m^3 and the MMAD was 1.7 ± 1.5 µm. At the end of the exposure period, absolute lung

weights were increased in females and relative lung weights were increased in both sexes. Laryngeal granulomas, located on the floor of the larynx in the ventral region and graded as moderate to marked, and squamous metaplasia of the mucosal epithelium overlying the granulomas were observed in 15/16 animals in the 100 mg/m^3 group (compared with 0/16 in the control). Hyaline epithelial inclusions within the epithelial lining of the nasal cavity, graded as mild to moderate, were observed in all animals in the 100 mg/m^3 group (compared with 0/15 in the control). In the lung, alveolar histiocytosis was observed in 11/16 animals in the 100 mg/m^3 group (compared with 0/16 in the control). During the recovery period, two females in the 100 mg/m^3 group died but the deaths were not attributed to treatment. At the end of the 12 month recovery period, the incidences in the treated group of laryngeal granulomas (13/15 versus 0/16 in the control), hyalinisation of the nasal epithelium (15/16 versus 1/16 in the control) and alveolar histiocytosis (15/15 versus 0/16 in the control) remained increased, indicating no or limited recovery of these lesions during this period. Laryngeal squamous metaplasia was observed in 2/30 females (1 each in the 1 and 12 months post exposure recovery groups) and 1/32 males (in the 12 months post exposure recovery group) at 100 mg/m^3. There was no evidence of atypia or dysplasia in association with the squamous metaplasia observed. The study report notes that at 12 months post exposure, the squamous epithelia had reverted to the transitional epithelia normally found in this area of the larynx, indicating recovery of this lesion. Granulomatous lymphadentitis of the mediastinal lymph nodes was observed in animals in the 100 mg/m^3 from 1 month post exposure, with an increased incidence at the end of the 12 month recovery period (10/14 compared with 0/11 in the control). A LOAEC of 100 mg/m^3 was identified by the registrants.

In a 14 week inhalation repeated dose toxicity study, 18/sex/group Fischer 344 rats were exposed for 6 hour/day, 5 days/week to aerosolised atmospheres of 0, 50, 100 or 250 mg/m^3 of a 15 % w/w starting solution of 3-trimethoxysilylpropyl methacrylate (pH 4) in distilled water (unpublished study report, 1984). The study design was similar to OECD 413 but did not include the measurement of bronchoalveolar lavage fluid or lung burden and the study report did not include tables of individual animal or group data. At study termination, 10/sex/group were subject to necropsy and the remaining 8/sex/group held for a recovery period of 91 days. The calculated chamber concentrations were 49.6 ± 2.4, 99.5 ± 5.9 and 244 ± 8.7 mg/m^3 for the low, mid and high concentration groups, respectively. The MMAD ranged from 1.55 ± 0.43 µm to 1.62 ± 0.65 µm. A decrease in body weight and liver weight in males was observed in the high concentration group at study termination, both of which were comparable to controls at the end of the recovery period. Laryngeal granulomas, described as focal in nature and located in the ventral portion of the larynx, were reported in all treatment groups. The study report noted that in many cases, the granulomas were accompanied by polyp formation although no further details are provided. Cytoplasmic hyalinisation of cells in the olfactory mucosa of the nasal cavity was observed in all treatment groups, graded as moderate in the mid and high concentration groups and slight in the low concentration group. The study report noted that there was no evidence of cellular degeneration or necrosis associated with these lesions. At the end of the recovery period, there was no reported difference in number or size of laryngeal granulomas and no indication of resolution of cytoplasmic hyalinisation. However, the study report noted that at the end of the recovery period, slight cytoplasmic hyalinisation was also observed in half of the males in the control group. A LOAEC of 50 mg/m^3 was identified in the registration data.

In a second non-guideline 14 week inhalation repeated dose toxicity study, four groups of Fischer 344 rats were exposed to aerosolised atmospheres of 0, 5, 15 or 50 mg/m^3 of a

1% w/w starting solution of 3-trimethoxysilylpropyl methacrylate in distilled water (pH 5) (unpublished study report, 1989a). After 46 days of exposure, 10 males exposed to 50 mg/m^3 were sacrificed and the larynxes examined microscopically. At week 13, 10/sex/group were sacrificed and blood and urine were analysed, and organs weighed. Histopathological examination was completed on a number of organs including lungs, nasal turbinates, larynx and trachea. The calculated chamber concentrations were 4.9, 14.7 and 50.1 mg/m^3 for the low, mid and high concentration groups, respectively. The MMAD was between 2.3 µm and 2.9 µm. There was a statistically significant decrease in serum globulin levels in males at 50 mg/m^3, and a non-statistically significant decrease in females exposed to ≥ 15 mg/m^3. There was a statistically significant increase in absolute brain weight in females in all treatment groups and in absolute and relative kidney weight in females exposed to 50 mg/m^3. In males, the heart to body weight ratio was statistically significantly increased in males exposed to ≥ 15 mg/m^3. No histopathological findings were reported in these organs. Cytoplasmic hyalinisation of the olfactory mucosa was observed in all treated animals, the incidences were 0/20, 19/20, 20/20 and 20/20 for the control, low, mid and high concentration groups, respectively. The study report notes that while the observed cytoplasmic hyalinisation occurred in the absence of cellular degeneration or necrosis, there was an increase in severity of this lesion with increasing exposure concentrations. There was a statistically significant increase in alveolar histiocytosis in the high concentration group (12/20) when compared with the control (0/20). The low and mid concentration groups were not assessed for this effect. Laryngeal granulomas, described as “mineralised” in the study report, were observed in 8/10 animals sacrificed at day 46. At study termination, the same mineralised laryngeal granulomas were observed in the control and all treatment groups, the incidences were 8/20, 5/20, 8/20 and 8/20 for the control, low, mid and high concentration groups, respectively. The study report describes the observed laryngeal granulomas as consisting of small foci of degeneration and mineralisation, notes that they were histopathologically different to those seen in other studies and concludes that in this case, the observed laryngeal granulomas represent a spontaneous change in both control and treated rats and are thus not treatment related. The registration data identified a NOAEC of 50 mg/m^3 on the basis that no laryngeal granulomas were observed. The evaluating MSCA notes there was a statistically significant increase in cytoplasmic hyalinisation of the olfactory mucosa at all concentrations and therefore considers that no NOAEC can be identified from this study. Instead, the evaluating MSCA considers that 5 mg/m^3 should be considered as a LOAEC.

A summary of incidences of laryngeal granulomas and cytoplasmic hyalinisation in nasal tissue in the available aerosol inhalation repeated dose toxicity studies with 3-trimethoxysilylpropyl methacrylate is presented in table 8 below.

Table 8

SUMMARY OF INCIDENCES OF LARYNGEAL GRANULOMAS AND CYTOPLASMIC HYALINISATION IN NASAL TISSUE IN AEROSOL INHALATION REPEATED DOSE TOXICITY STUDIES WITH 3-TRIMETHOXYSILYLPROPYL METHACRYLATE					
Study duration	**Dose groups/ conditions**	**Laryngeal granulomas**	**Cytoplasmic hyalinisation of nasal tissue**	**Recovery period**	**Reference**
9 days	0, 50, 100, 300 mg/m^3. 15 % starting solution pH 4	Observed in all treatment groups (incidences not reported)	No	No	unpublished study report 1983
4 weeks	0, 10, 50 mg/m^3 1 % starting solution pH 5 Non-recirculated aerosol generation	2 week interim evaluation: 0 mg/m^3: 0/10 50 mg/m^3 (1 %): 5/10 50 mg/m^3 (15 %): 10/10 Study termination: 0 mg/m^3: 0/20 10 mg/m^3: 0/20 50 mg/m^3 (1 % non-recirculated solutions): 17/20 50 mg/m^3 (15 % recirculated solutions): 20/20 50 mg/m^3 (15% non-recirculated solutions): 20/20	Study termination: 0 mg/m^3: 4/20 10 mg/m^3: 13/20 50 mg/m^3 (1 % non-recirculated solutions): 18/20 50 mg/m^3: (15 % recirculated solutions): 11/20 50 mg/m^3: (15% non-recirculated solutions): 7/20	No	unpublished study report 1986
	50 mg/m^3 15 % starting solution pH 3 Recirculated and non-recirculated aerosol generation				
4 weeks	0, 15, 50, 70, 100 mg/m^3 1 % starting solution pH 5	0 mg/m^3 : 0/20 15 mg/m^3: 0/20 50 mg/m^3: 0/20 70 mg/m^3: 0/20 100 mg/m^3 (1%): 17/20 100 mg/m^3 (15 %) 20/20	0 mg/m^3: 0/20 15 mg/m^3: 0/20 50 mg/m^3: 0/20 70 mg/m^3: 1/20 100 mg/m^3 (1 %): 1/20 100 mg/m^3 (15 %): 7/20	No	unpublished study report 1989b
	100 mg/m^3 15 % starting solution pH 3				
4 weeks	0, 150 mg/m^3 2 % starting solution pH 5	0 mg/m^3: 0/10 150 mg/m^3: 9/10	0 mg/m^3: 0/10 150 mg/m^3: 9/10	No	unpublished study report 1991

SUMMARY OF INCIDENCES OF LARYNGEAL GRANULOMAS AND CYTOPLASMIC HYALINISATION IN NASAL TISSUE IN AEROSOL INHALATION REPEATED DOSE TOXICITY STUDIES WITH 3-TRIMETHOXYSILYLPROPYL METHACRYLATE					
Study duration	**Dose groups / conditions**	**Laryngeal granulomas**	**Cytoplasmic hyalinisation of nasal tissue**	**Recovery period**	**Reference**
13 weeks	0, 100 mg/m^3 2 % starting solution pH 5	0 mg/m^3:0/16 100 mg/m^3: 15/16	0 mg/m^3: 0/15 100 mg/m^3: 16/16	Yes- 1 year recovery period. At 12 months post exposure: Laryngeal granulomas: 0 mg/m^3: 0/16 100 mg/m^3: 13/15 Cytoplasmic hyalinisation: 0 mg/m^3: 1/16 100 mg/m^3: 15/16	unpublished study report 1994a
14 weeks	0, 50, 100, 250 mg/m^3 15 % starting solution pH 4	Observed in all treatment groups (incidences not reported)	Observed in all treatment groups (incidences not reported)	Yes – 90 days recovery period. No evidence of recovery (incidences not reported)	unpublished study report 1984
14 weeks	0, 5, 15, 50 mg/m^3 1 % starting solution pH 5	None reported	0 mg/m^3: 0/20 5 mg/m^3: 19/20 15 mg/m^3: 20/20 50 mg/m^3: 20/20	No	unpublished study report 1989a

As discussed in section 7.9.1, 3-trimethoxysilylpropyl methacrylate rapidly hydrolyses in contact with water ($t_{1/2}$ of < 2 hours at pH 4-7) resulting in the hydrolysis products methanol and 3-(trihydroxysilyl)propyl methacrylate. The test atmospheres in the aerosol inhalation repeated dose toxicity studies were generated using aqueous starting solutions of 3-trimethoxysilylpropyl methacrylate and it is therefore expected that some hydrolysis would have occurred prior to exposure of the animals. The registration data notes that due to the relatively high concentrations of the starting solutions of 3-trimethoxysilylpropyl methacrylate used to generate the aerosol atmospheres, some condensation or polymerisation of the silanol hydrolysis product is expected. Although in most of the available studies the test atmospheres were not analysed for the presence of condensate, in one study SEM/EDX analysis showed that 3-trimethoxysilylpropyl methacrylate was not present as a solid particulate in the chamber atmospheres generated using a 1 % and 15 % w/w starting solution of 3-trimethoxysilylpropyl methacrylate (unpublished study report , 1986). Therefore, the test animals in the aerosol inhalation repeated dose toxicity studies

were likely exposed to a combination of the parent substance, the hydrolysis products and possibly the polymerisation product.

The evaluating MSCA notes that there are a number of limitations with the available inhalation repeated dose toxicity studies. In general, the studies were not conducted in accordance with the relevant OECD test guidelines and some were conducted with the specific aim of investigating the formation of laryngeal granulomas. Therefore, the test designs may not be optimal for investigating systemic toxicity or deriving a point of departure for risk assessment for systemic effects. The studies vary in the type of analysis performed and the level of detail reported. In addition, the test atmospheres were generated using starting solutions of 3-trimethoxysilylpropyl methacrylate at varying concentrations and pH, making comparison between studies difficult. As discussed above, as the test animals in the aerosol studies were likely exposed to a combination of the parent substance, the hydrolysis product and possibly the polymerisation product, there is some uncertainty regarding which portion of the test atmosphere is responsible for the effects seen.

The evaluating MSCA assessed the available data using a weight of evidence approach, taking into account the above limitations in the data. The evaluating MSCA considers that the available data is sufficient to identify a concern for local effects in the respiratory tract following inhalation exposure to aerosolised atmospheres of 3-trimethoxysilylpropyl methacrylate. The formation of laryngeal granulomas and cytoplasmic hyalinisation of nasal epithelium were consistently observed in the aerosol inhalation studies, regardless of the concentration or pH of the starting solutions or the duration of exposure.

With respect to laryngeal granulomas, these were observed after only two exposures and persisted up to 12 months following a 13 week exposure (unpublished study report, 1989b, unpublished study report, 1994). Although the laryngeal granulomas were histopathologically similar across studies, the starting solutions with higher concentrations of 3-trimethoxysilylpropyl methacrylate (e.g. 15 % w/w) resulted in larger laryngeal granulomas compared to starting solutions of lower concentrations of 3-trimethoxysilylpropyl methacrylate (e.g. 1 % w/w). The reason for this is unclear. The study authors postulated that the laryngeal granulomas developed following degeneration of susceptible cells in the larynx and the subsequent movement of the test material into the submucosa, where it then polymerised and formed the granuloma (unpublished study report, 1989b). However, the exact mechanism of formation of the observed laryngeal granulomas was not identified. Squamous metaplasia of the mucosal epithelium overlying the granulomas was also reported in some studies, which appeared to be as a result of regeneration of the epithelium following exposure. A significant reduction in the incidence of squamous metaplasia of the larynx following a 12 month recovery period after a 13 week exposure to aerosolised atmospheres of 100 mg/m^3 3-trimethoxysilylpropyl methacrylate was reported indicating recovery of this lesion (unpublished study report, 1994). In addition, no evidence of dysplasia or atypia associated with the squamous metaplasia was observed. It is reported that for non-genotoxic substances, squamous metaplasia of the larynx that occurs in the absence of atypia or dysplasia is not considered to be a pre-cancerous lesion (Kaufmann *et. al.,* 2009). The evaluating MSCA therefore considers the squamous metaplasia observed to be an adaptive effect rather than a pre-cancerous effect. The evaluating MSCA considers the NOAEC for the formation of laryngeal granulomas is 15 mg/m^3 (unpublished study report, 1986).

An increased incidence of cytoplasmic hyalinisation in the olfactory mucosa of the nasal tissue was consistently observed across the aerosol inhalation repeated dose toxicity

studies at exposure concentrations ≥ 5 mg/m^3 3-trimethoxysilylpropyl methacrylate (unpublished study report, 1989a). This effect had not resolved 12 months following a 13 week exposure to aerosolised atmospheres of 100 mg/m^3 (unpublished study report, 1994). The study authors suggested that the cytoplasmic hyalinisation observed in the nasal tissue could represent a non-specific irritant response and it was postulated that it is a result of the synthesis of either structural or secretory proteins by these cells (unpublished study report, 1991). However, in general the study reports noted the uncertain biological significance of this effect, noting the cytoplasmic hyalinisation occurred in the absence of inflammation or evidence of cellular degeneration. The registration data did not identify cytoplasmic hyalinisation in the nasal tissue as a critical effect.

The evaluating MSCA notes that cytoplasmic hyalinisation of tissues of the respiratory tract can occur following exposure to chemical irritants (Harkema, *et. al*., 2018). The available aerosol inhalation repeated dose toxicity studies with the registered substance had a number of variables in the test system design, including different pH and different starting concentrations of 3-trimethoxysilylpropyl methacrylate. These parameters may have impacted on the hydrolysis rate and thus the formation of particulate material consisting of the hydrolysis and/or the polymerisation products that could lead to such an irritant effect. However, the evaluating MSCA notes that cytoplasmic hyalinisation of the nasal tissue was observed in studies using different starting concentrations of 3-trimethoxysilylpropyl methacrylate and different pH, at exposure concentrations from 5 to 250 mg/m^3 and following 4 week and 13 week exposures. Therefore, no specific study parameters could be identified which could be linked to the effects observed. The evaluating MSCA also notes that there was no evidence of recovery of this effect following a 12 month recovery period after a 13 week exposure to 100 mg/m^3 3-trimethoxysilylpropyl methacrylate (unpublished study report, 1994). Therefore, based on the available information, the evaluating MSCA considers that it cannot be excluded that the observed cytoplasmic hyalinisation of the nasal tissue was due to exposure to the registered substance. The evaluating MSCA considers 5 mg/m^3 to be the LOAEC for this effect (unpublished study report, 1989a).

With respect to the derivation of a DNEL for local effects in the respiratory tract, the evaluating MSCA considers the critical effects to be the formation of laryngeal granulomas and cytoplasmic hyalinisation of nasal tissue. It is noted that there was no evidence of laryngeal granuloma formation or cytoplasmic hyalinisation of the nasal tissue in the 9-day vapour inhalation repeated dose toxicity study with 3-trimethoxysilylpropyl methacrylate (unpublished study report, 1982). The duration of this study is not sufficient to conclude with certainty that such effects would not occur following vapour exposure, although it provides some evidence that the effects are linked to aerosol exposure. The evaluating MSCA acknowledges that there is some uncertainty regarding the adversity of the cytoplasmic hyalinisation observed in nasal tissue. However, it is noted that this effect was observed at concentrations ≥ 5 mg/m^3 and did not resolve during a 12 month recovery period following a 13 week exposure to 100 mg/m^3 of 3-trimethoxysilylpropyl methacrylate. Therefore, applying the precautionary principle, a LOAEC of 5 mg/m^3 is selected as the point of departure for DNEL derivation for long term local effects in the respiratory tract.

Regarding systemic effects, the evaluating MSCA notes that organ weight changes in liver, brain, spleen and kidneys were observed in some studies. However, these changes did not generally demonstrate dose-dependent trends, were found in only one sex and/or study, and did not have any corresponding histopathological finding. A decrease in body weight gain appeared to be the most consistent finding from the available studies, which occurred

from 15 mg/m^3. However, as discussed above, the evaluating MSCA notes that the design of the studies may not be optimal to investigate systemic toxicity.

Based on the formation of laryngeal granulomas which were observed at concentrations ≥ 50 mg/m^3 following 4-week and 13 week exposures to aerosolised atmospheres of 3-trimethoxysilylpropyl methacrylate and which may be an indication of functional impairment which was not reversible during a 12 month recovery period, the evaluating MSCA concludes that classification as specific target organ toxicity – repeated exposure, category 2 is appropriate.

7.9.5. Mutagenicity

The genotoxicity of 3-trimethoxysilylpropyl methacrylate has been investigated *in vitro* and *in vivo*.

In a GLP compliant bacterial reverse mutation assay conducted in accordance with OECD 471, triplicate plates of *S. typhimurium* strains TA98, TA100, TA1535 and TA1587 and *E. coli* WP2 uvrA strain were exposed to concentrations of between 15 µg/plate and 5000 µg/plate of 3-trimethoxysilylpropyl methacrylate in DMSO using the pre-incubation method (ECHA, 2019). Evidence of cytotoxicity was observed at ≥ 1500 µg/plate. No increase in revertant frequency was observed in any of the tested strains, either in the presence or absence of metabolic activation. A number of supporting bacterial reverse mutation assays with 3-trimethoxysilypropyl methacrylate are also reported in the registration data, all of which report no increase in revertant frequency in either the presence or absence of metabolic activation.

In an *in vitro* mammalian gene mutation assay, similar to OECD 476 and conducted in accordance with GLP, Chinese hamster ovary (CHO) cells were exposed to concentrations of 3-trimethoxysilylpropyl methacrylate in methanol at concentrations of between 0.1 mg/ml and 0.8 mg/l for 5 hours in the presence and absence of metabolic activation (ECHA, 2019). The expression time was 2-3 days, and the selection time was 9-12 days. The test was performed in duplicate. No increase in mutation frequency was observed with or without metabolic activation. The study summary notes that cytotoxicity was observed at > 1 mg/ml in the preliminary study.

In a GLP compliant *in vitro* chromosome aberration assay, similar to OECD 473, CHO cells were exposed to 3-trimethoxysilylpropyl methacrylate in methanol at concentrations of between 0.1 mg/ml and 0.6 mg/ml in the presence and absence of metabolic activation (ECHA, 2019). Cells were exposed for 2 hours in the presence of metabolic activation and 8 hours in the absence of metabolic activation. Expression times were 6 hours and 12 hours and fixation times were 8 hours and 14 hours. One hundred cells were evaluated for aberrations. A statistically significant increase in the incidence of chromosome aberrations was observed in both the presence and absence of metabolic activation. In a GLP compliant non-guideline sister chromatid exchange (SCE) assay, CHO cells were exposed to 3-trimethoxysilylpropyl methacrylate in methanol at concentrations of between 0.1 mg/ml and 0.6 mg/ml without metabolic activation for 5 hours and between 0.06 mg/ml and 0.35 mg/ml with metabolic activation for 2 hours (ECHA, 2019). Twenty five cells/concentration were evaluated for SCE and test was performed in duplicate. No increase in the incidence of SCE was observed with or without metabolic activation.

In a GLP compliant *in vivo* mammalian erythrocyte micronucleus study conducted according to OECD 474, 5/sex/dose Swiss Webster mice were administered 3-trimethoxysilylpropyl methacrylate in corn oil at 0, 2500, 4000 and 5000 mg/kg bw/day by intraperitoneal injection (ECHA, 2019). Peripheral blood was collected at 30, 48 and 72 hours post administration. One thousand polychromatic erythrocytes (PCEs) were scored for the presence of micronuclei and the PCE/NCE (normochromatic erythrocyte) ratio was calculated for 1000 cells. A slight decrease in the PCE/NCE ratio was observed at 5000 mg/kg bw/day at 72 hours post treatment indicating exposure to the bone marrow. No increase in the number of micronuclei in PCEs were observed. The evaluating MSCA notes that the most recent version of OECD 474 (adopted July 2016) requires 4000 PCEs per animal to be scored for the presence of micronuclei and the thus the lower number of PCEs scored in this study could indicate a possible lower sensitivity of the study to detect micronuclei.

In an *in vivo* mammalian alkaline comet assay conducted in accordance with OECD 489 and GLP, aerosol atmospheres of hydrolysed 3-trimethoxysilylpropyl methacrylate (unknown purity) at pH 3 were administered nose only to 6/sex/group Sprague Dawley rats at concentrations of 0, 250, 500 and 1000 mg/m^3 for 6 hours/day for 2 days (unpublished study report, 2018a). A concurrent positive control group was administered ethyl methanesulfonate via oral gavage. Animals were sacrificed between 2 and 4 hours following the final exposure and nasal, lung and liver tissue samples were prepared for analysis. A total of 150 cells per animal were scored and assessed for cytotoxicity, % tail DNA, comet tail migration and comet tail moment. In the lung tissue, a statistically significant increase in % tail DNA was observed in males at 500 mg/m^3 when compared with the concurrent negative control. However, the result was within the historical control range of the test laboratory and lacked a dose response relationship, and was therefore not considered treatment related. No increase in % tail DNA in the nasal tissue or the liver was reported. A statistically significant increase in % tail DNA was observed in all tissues in the positive control group. There was an increased incidence of hedgehogs in the lung of males at 1000 mg/m^3, in the liver of all treated females and in the nasal tissue in males at 250 and 1000 mg/m^3 and in females at 250 and 500 mg/m^3. OECD 474 notes that the etiology of hedgehogs is unclear but they may be an indication of cytotoxicity.

Overall the registration data concluded that 3-trimethoxysilylpropyl methacrylate is not genotoxic based on the available data.

The evaluating MSCA considers that the available *in vitro* data indicates a concern for clastogenicity. Positive results in the presence and absence of metabolic activation were observed in an *in vitro* chromosome aberration assay in CHO cells. In particular, the positive result in the absence of metabolic activation indicates a possible concern for a direct action of the substance as a DNA damaging agent at sites of direct contact. No concern for gene mutation was identified from the available *in vitro* data.

A negative *in vivo* mammalian erythrocyte micronucleus study is available with the registered substance. However, the study was conducted by the intraperitoneal route and thus is not appropriate to address the concern for clastogenicity at sites of direct contact. The available *in vivo* mammalian Comet assay was conducted via the inhalation route and evaluated site of contact tissues (nasal tissue and lung) as well as the liver as the primary site of metabolism. In addition, the study was conducted with aerosolised atmospheres of the registered substance in water at pH 3 in order to mimic the conditions of the aerosol inhalation repeated dose toxicity studies which identified a concern for local effects in the respiratory tract, specifically the formation of laryngeal granulomas and cytoplasmic

hyalinisation in nasal tissue (see section 7.9.4 for further details). No increase in DNA damage was observed in any tissue examined in this study.

The evaluating MSCA notes that OECD 489 indicates that positive control substances should be administered via the same route as the test substances when measuring site of contact effects. In the *in vivo* mammalian Comet assay with the registered substance, the positive control substance was administered via oral gavage and therefore deviated from OECD 489 in this regard. The registrants justified the choice of route of administration of the positive control by noting that the test laboratories they contacted to perform the study did not have historical positive control data generated via the inhalation route to validate the study in accordance with acceptability criteria in OECD 489 and indicated they were unable to administer positive controls via inhalation due to concerns for worker safety. The registrants also noted that there are no examples of positive controls for the inhalation route of exposure for this assay in the literature. The evaluating MSCA notes that OECD 489 does not provide any recommendation on the type of substance which would be suitable to be used as a positive control via the inhalation route. In addition, the evaluating MSCA acknowledges that there may be practical difficulties in administering a known genotoxic substance via the inhalation route as a positive control as it could pose a risk to laboratory staff. Taking the above points into account, the evaluating MSCA considers that the study is sufficient to conclude that there is no concern for clastogenicity of the registered substance.

Based on the available information, the evaluating MSCA considers that there is no concern for genotoxicity for 3-trimethoxysilylpropyl methacrylate.

7.9.6. Carcinogenicity

No carcinogenicity data are reported in the registration data.

As discussed in section 7.9.4, a number of inhalation repeated dose toxicity studies with aerosolised atmospheres of the registered substance are available. From these studies, a concern for local effects in the respiratory tract was identified. Laryngeal granulomas were consistently observed in the available studies, occurring after only two exposures and persisted up to 12 months following a 13 week exposure (unpublished study report, 1989b, unpublished study report, 1994). The study authors postulated that the laryngeal granulomas developed following degeneration of susceptible cells in the larynx and the subsequent movement of the test material into the submucosa, where it then polymerised and formed the granuloma (unpublished study report, 1989b). However, the exact mechanism of formation of the observed laryngeal granulomas was not identified. Squamous metaplasia of the mucosal epithelium overlying the granulomas was also reported in some studies, which appeared to be a result of regeneration of the epithelium following exposure. The incidences of squamous metaplasia of the larynx during a 12 month recovery period following 13 week exposure to aerosolised atmospheres of 3-trimethoxysilylpropyl methacrylate was significantly reduced indicating recovery of this lesion and no evidence of dysplasia or atypia associated with the squamous metaplasia observed (unpublished study report, 1994).

As discussed in section 7.9.5, no concern for genotoxicity was identified for 3-trimethoxysilylpropyl methacrylate. It is noted that for non-genotoxic substances, squamous metaplasia of the larynx that occurs in the absence of atypia or dysplasia is not

considered a pre-cancerous lesion (Kaufmann *et. al.,* 2009). The evaluating MSCA therefore considers the squamous metaplasia observed to be an adaptive effect rather than a pre-cancerous effect.

The evaluating MSCA concluded that based on the available hazard and use information there is currently no concern for carcinogenicity for 3-trimethoxysilylpropyl methacrylate.

7.9.7. Toxicity to reproduction

Effects on Fertility

There is currently no study available to address the fertility endpoint.

The registration data reports that no effects on reproductive organs were observed in two 13/14 week inhalation repeated dose toxicity studies with aerosolised atmospheres of 3-trimethoxysilylpropyl methacrylate at concentrations up to 100 mg/m^3 (unpublished study report, 1989a and unpublished study report, 1994a). Further details of these studies can be found in section 7.9.4. The evaluating MSCA notes that these studies were not specifically designed to investigate effects on fertility. The registration data also reports that in a pre-natal developmental toxicity in rats conducted in accordance with OECD 414 with 3-trimethoxysilylpropyl methacrylate, no adverse effects on fertility were observed (ECHA, 2019). Limited examination of reproductive parameters was undertaken in this study.

The evaluating MSCA considers that the available data is not sufficient to address the fertility endpoint.

The evaluating MSCA notes that a testing proposal decision has been issued by ECHA for the registered substance requesting an extended one-generation reproductive toxicity study (EOGRTS) (OECD 443), with a decision deadline of 10 September 2020.

Developmental toxicity

In pre-natal developmental toxicity study, conducted in accordance with OECD 414, 25 pregnant female CD(R) rats per group were administered 3-trimethoxysilylpropyl methacrylate by oral gavage at doses of 0, 520, 2080, 5200 mg/kg bw/day (0.5, 2 and 5 ml/kg bw/day) daily from gestation days 6 to 15 (ECHA, 2019). Clinical signs of maternal toxicity were observed in the mid and high-dose groups, including unkempt appearance, staining of the urogenital area and red vaginal discharge. A decrease in gestational body weight, body weight gain and food consumption was reported in high dose females. A decrease in body weight gain and food consumption was also observed in females at the mid dose group for the first 3 days of treatment only. Absolute and relative liver and kidney weights were increased in high dose females, with a non-statistically significant decrease observed in mid dose females. Two females of the high dose group bore litters with only non-viable implantations at scheduled sacrifice. No effects on the number of corpora lutea, number of implantations per litter or pre-implantation loss were reported. There was a decrease in foetal body weight/litter in the high dose group. Evidence of developmental delay was observed in foetuses of the mid- and high-dose groups. No increase in individual types of malformations were noted although an increase in soft tissue malformations per category and total malformations was observed in the mid and high dose groups. Due to the low frequency of occurrence of the individual anomalies observed, the biological significance of the increase in soft tissue malformations is unknown. The incidence of skeletal alterations observed in the high dose group included the presence of rudimentary

ribs on cervical arch number 7, increased incidence of unossified arch of the atlas, poorly ossified or unossified squamosal, metacarpals, metatarsals and sternebrae.

The registration data identified a NOAEL for maternal toxicity of 520 mg/kg bw/day. With respect to developmental toxicity, the evaluating MSCA notes that the registration data indicates that the study author concluded that the NOAEL for developmental toxicity was 520 mg/kg bw/day, based on the evidence of delayed development observed in the high dose group and soft tissue malformations in the mid and high dose groups. However, the registration data identified a NOAEL for developmental effects of 5200 mg/kg bw/day, concluding instead that the observed foetal effects were secondary to maternal toxicity.

The evaluating MSCA notes that the registration data includes limited details of the results of this study, and in particular does not include details of the incidences of effects observed per dose group. Therefore, it is difficult to assess the significance of the effects reported. Based on the available information, the evaluating MSCA can support the selection of a NOAEL for maternal toxicity of 520 mg/kg bw/day. However, the evaluating MSCA does not agree with the selection of NOAEL for developmental toxicity of 5200 mg/kg bw/day. As minimal maternal toxicity was reported in the mid dose group, the effects observed in foetuses at this dose cannot be attributed solely to maternal toxicity. The evaluating MSCA therefore considers that the NOAEL for developmental toxicity should be 520 mg/kg bw/day.

The evaluating MSCA notes that the mid and high doses in this study (equivalent to 2000 mg/kg bw/day and 5000 mg/kg bw/day) were set well above the limit dose of 1000 mg/kg bw/day specified in OECD 414. Therefore, the biological significance of the soft tissue and skeletal alterations observed at these doses is difficult to interpret. Overall based on the available data, the evaluating MSCA concludes that there is no concern for developmental toxicity and classification for reproductive toxicity (development) is not appropriate based on the results of this study.

The evaluating MSCA notes that a testing proposal decision has been issued by ECHA for the registered substance requesting a pre-natal developmental toxicity study (OECD 414) in a second species (rabbits), with a decision deadline of 15 November 2021.

7.9.8. Hazard assessment of physico-chemical properties

Not evaluated.

7.9.9. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

A number of DNELs for different exposure patterns were reported in the registration data. The evaluating MSCA has focused the evaluation on the derivation of DNELs for long-term local effects following aerosol inhalation exposure.

The DNELs for long-term local effects following aerosol inhalation exposure identified by the registrants are summarised in table 9.

Table 9

CRITICAL DNELS REPORTED IN REGISTRATION DATA					
Endpoint of concern	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)**	**DNEL**	**Justification / Remarks**
Inhalation	Local effects – long-term	WoE inhalation repeated dose toxicity studies selected NOAEC 15 mg/m^3	Corrected NOAEC: 7.5 mg/m^3 (applying AF of 12.5)	DNEL: 0.6 mg/m^3	Workers – formation of laryngeal granulomas
Inhalation	Local effects – long-term	WoE inhalation repeated dose toxicity studies selected NOAEC 15 mg/m^3	Corrected NOAEC: 2.7 (applying AF of 25)	DNEL: 0.1 mg/m^3	General population – formation of laryngeal granulomas

For the derivation of DNELs for long-term local effects for the inhalation route, the evaluating MSCA agrees with the registrants that the formation of laryngeal granulomas was one of the critical effects observed in the available inhalation repeated dose toxicity studies. However, the evaluating MSCA does not agree with the assessment factors (AFs) applied by the registrants for this critical effect to derive the DNELs for workers and the general population. The registrants applied the default AFs in accordance with ECHA Guidance R.8[2], including an AF of 1 for "quality of the whole database". Given the limitations in the available repeated dose toxicity studies as discussed in section 7.9.4, the evaluating MSCA considers that a higher factor of 2 for "quality of the whole database" should be applied. Therefore, the evaluating MSCA considers that the AF applied should be 25 for workers and 50 for the general population, resulting in DNELs for long-term local effects following aerosol inhalation exposure of 0.3 mg/m^3 for workers and 0.05 mg/m^3 for the general population.

The evaluating MSCA also identified cytoplasmic hyalinisation of nasal tissue as a second critical effect from the available inhalation repeated dose toxicity studies, which was observed at concentrations ≥ 5 mg/m^3. The evaluating MSCA acknowledges that there is some uncertainty regarding the adversity of this effect. However, it is noted that cytoplasmic hyalinisation was consistently observed in the studies at concentrations lower than those resulting in laryngeal granulomas and that this effect did not resolve during a 12 month recovery period following a 13 week exposure to 100 mg/m^3 of 3-trimethoxysilylpropyl methacrylate. Applying the precautionary principle, the evaluating MSCA has selected this effect as the point of departure for DNEL derivation for long-term local effects following aerosol inhalation exposure.

[2] Guidance on information requirements and chemical safety assessment. Chapter R.8: Characterisation of dose [concentration]-response for human health

With respect to DNELs for the general population, given the use profile for consumer use of spray paints discussed in section 7.12.1.2, the evaluating MSCA calculated a DNEL for infrequent use.

DNELs for long-term local effects following aerosol inhalation exposure identified by the evaluating MSCA are summarised in table 10.

Table 10

CRITICAL DNELS IDENTIFIED BY THE EVALUATING MSCA					
Endpoint of concern	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)**	**DNEL**	**Justification / Remarks**
Inhalation	Local effects – long-term	WoE inhalation repeated dose toxicity studies selected NOAEC 15 mg/m^3	Corrected NOAEC: 7.5 mg/m^3 (applying AF of 25)	DNEL: 0.3 mg/m^3	Workers – formation of laryngeal granulomas
Inhalation	Local effects – long-term	WoE inhalation repeated dose toxicity studies: selected LOAEC 5 mg/m^3	Corrected LOAEC: 2.5 mg/m^3 (applying AF of 75)	DNEL: 0.034 mg/m^3	Workers – cytoplasmic hyalinisation of nasal tissue
Inhalation	Local effects – long-term	WoE inhalation repeated dose toxicity studies selected NOAEC 15 mg/m^3	Corrected NOAEC: 2.7 (applying AF of 50)	DNEL: 0.05 mg/m^3	General population – formation of laryngeal granulomas. Infrequent use
Inhalation	Local effects – long-term	WoE inhalation repeated dose toxicity studies selected LOAEC 5 mg/m^3	Corrected LOAEC: 0.9 mg/m^3 (applying AF of 150)	DNEL: 0.006 mg/m^3	General population - cytoplasmic hyalinisation of nasal tissue. Infrequent use

7.9.10. Conclusions of the human health hazard assessment and related classification and labelling

Based on the available information, 3-trimethoxysilylpropyl methacrylate is not acutely toxic by the oral, dermal or inhalation routes, is not irritating to skin or eyes and is not a skin sensitiser.

From the available inhalation repeated dose toxicity studies with aerosolised atmospheres of 3-trimethoxysilylpropyl methacrylate, a concern for local effects in the respiratory tract was identified. Laryngeal granulomas were observed at concentrations of ≥ 50 mg/m^3 and

cytoplasmic hyalinisation of the nasal tissue was observed at concentrations ≥ 5 mg/m^3. These effects were not reversible during a 12 month recovery period following a 13 week exposure to a concentration of 100 mg/m^3. The evaluating MSCA considers that the formation of laryngeal granulomas may be an indication of functional impairment and concludes that classification as specific target organ toxicity – repeated exposure, category 2 (STOT-RE 2) is appropriate.

Based on the available information, the evaluating MSCA considers that there is no concern for genotoxicity for 3-trimethoxysilylpropyl methacrylate.

There is currently no study available addressing the fertility endpoint. A testing proposal decision has been issued by ECHA for the registered substance requesting an extended one-generation reproductive toxicity study (EOGRTS) (OECD 443), with a decision deadline of 10 September 2020.

Based on the available data, the evaluating MSCA concludes that there is no concern for developmental toxicity. The evaluating MSCA notes that a testing proposal decision has been issued by ECHA for the registered substance requesting a pre-natal developmental toxicity study (OECD 414) in a second species (rabbits), with a decision deadline of 11 November 2021.

7.10. Assessment of endocrine disrupting (ED) properties

No concern for endocrine disruption for human health was identified from the available information.

No assessment of endocrine disrupting properties for the environment was undertaken.

7.11. PBT and VPVB assessment

Not evaluated.

7.12. Exposure assessment

3-trimethoxysilylpropyl methacrylate is used in a number of industrial applications including as a chemical intermediate and monomer, and in the formulation and use of non-metal surface treatments, coatings, sealants and adhesives. It is also used in coatings, inks, sealants, adhesives and dental applications for professional use and in coatings, adhesives and sealants, and cosmetic and personal care products for consumer use.

The following exposure scenarios were addressed in the registration data:

- Manufacture of the registered substance
- Industrial manufacture/formulation of end use products
- Use as a chemical intermediate
- Use as a monomer
- Use in non-metal surface treatments

- Use in coatings and inks
- Use in adhesives and sealants
- Use as a laboratory reagent
- Use in dental applications
- Use in cosmetics and personal care products

7.12.1. Human health

The exposure assessment in the registration data covers both dermal and inhalation exposure to vapours and aerosols of 3-trimethoxysilylpropyl methacrylate. The registration data states that 3-trimethoxysilylpropyl methacrylate rapidly hydrolyses in contact with water ($t_{1/2}$ of < 2 hours at pH 4-7), resulting in 3-(trihydroxysilyl)propyl methacrylate (hydrolysis product) and methanol. Therefore, for activities where hydrolysis of the registered substance is expected, the exposure assessment in the registration data also considered dermal and inhalation exposure to vapours and aerosols of the hydrolysis product. Based on the reported hydrolysis rate, the evaluating MSCA agrees that exposure to both the registered substance and the hydrolysis product is possible. The evaluating MSCA notes that as no monitoring data is available to allow a reliable estimate of the fraction of the registered substance or hydrolysis product available for exposure per use or activity, the registration data applied a worst-case approach assuming 100 % of either the parent or hydrolysis product was available.

As discussed in section 7.9.4, the critical effects observed in the available inhalation repeated dose toxicity studies with aerosolised atmospheres of aqueous solutions of 3-trimethoxysilylpropyl methacrylate were the formation of laryngeal granulomas and cytoplasmic hyalinisation of the nasal tissue. As these effects were observed following aerosol exposure, the evaluating MSCA focused the exposure assessment on the potential for inhalation exposure from activities where aerosol generation is likely. The evaluating MSCA notes that modelling for aerosol inhalation exposure for 100 % registered substance or 100 % hydrolysis product will result in the same exposure estimate, as they both have low volatility and all other modelling input parameters are the same.

As part of the evaluation, the evaluating MSCA considered the description of the activities and technical processes covered by each activity with the potential for aerosol generation, including any control measures specified in the registration data. The justifications provided for the choice of model input parameters and any modifications made outside the model estimates were assessed.

7.12.1.1. Worker

As discussed above, the evaluating MSCA focused the exposure assessment on those activities leading to the potential for aerosol inhalation exposure to industrial and professional workers.

The registration data referenced sector-specific worker exposure descriptions (SWEDs) from FEICA (Association of European Adhesives and Sealants Manufacturers)[3] in exposure scenarios covering industrial and professional application of sealants and adhesives. The registration data also referenced SWEDs from CEPE (The European Council of the Paint, Printing Ink and Artists' Colours Industry) in exposure scenarios covering industrial and professional application of coatings and inks. At the time of finalising the substance evaluation, the SWEDs developed by CEPE were not publically available. Therefore, it was not possible for the evaluating MSCA to assess whether the input parameters used for exposure modelling in the registration data were representative of the typical use conditions for such coating and ink products.

No exposure monitoring data is reported in the registration data. The aerosol inhalation exposure estimates reported in the registration data were generated using ECETOC TRA v3.0 and the Advanced REACH Tool (ART) v1.5. The evaluating MSCA notes that exposure to powder aerosols is within the domain of reliable application of ECETOC TRA. However, according to ECHA Guidance R.14[4], exposure to liquid aerosol mists is not within the domain of reliable application of ECETOC TRA unless "representative measured exposure data" on aerosol mists are available to "calibrate" the model by assessing whether medium dustiness values reported by the model represent a conservative exposure estimate for aerosols. The evaluating MSCA notes that no measured exposure data is presented in the registration data to justify the use of ECETOC TRA to generate exposure estimates for liquid aerosol mists. Therefore, the evaluating MSCA considers that the use of ECETOC TRA to generate exposure estimates for liquid aerosols in this case has not been justified and thus these exposure estimates reported in the registration data may be unreliable. It is noted that exposure from aerosols generated from liquids or powders are within the applicability domain of ART. For this reason, the evaluating MSCA considers that ART is a more appropriate model to generate liquid aerosol exposure estimates and therefore the evaluating MSCA used ART v1.5 to generate inhalation exposure estimates for liquid aerosols. The evaluating MSCA also used ART v1.5 to generate inhalation exposure estimates for powder aerosols. Where no representative scenario could be identified in ART for a particular activity associated with powder formulations, the evaluating MSCA used ECETOC TRA v3.1 to generate the exposure estimate.

The evaluating MSCA notes that for some exposure scenarios, insufficient information was provided in the registration data on the activities covered to fully evaluate the potential for aerosol exposure. In addition, for some exposure scenarios, there were inconsistencies in the registration data between the description of the task and the stated control measures, and the model input parameters used to generate the exposure estimates. In particular, the form (i.e. liquid or powder) of the product produced or used was not always clear. The evaluating MSCA notes that the physical form of the product will have a significant impact on the potential for aerosol inhalation exposure. In addition, aspects such as the use of respiratory protective equipment (RPE), the duration of the task, the type and effectiveness of local exhaust ventilation (LEV) and the emission source distance for automated processes were in some cases inconsistent within an exposure scenario or were considered by the evaluating MSCA to be unrealistic for the type of activity described. For example, for some industrial and professional activities, the registration data specifies the use of

[3] https://echa.europa.eu/csr-es-roadmap/use-maps/use-maps-library

[4] Guidance on information requirements and chemical safety assessment. Chapter R.14: Occupational Exposure Assessment

moveable LEV as a control measure. Based on the information provided in the registration data, the evaluating MSCA notes that such a control measure may be unrealistic for some activities described, where higher levels of control would be expected. The evaluating MSCA also notes that the percentage effectiveness of such moveable LEV systems is typically lower than the LEV model input parameter specified in the registration data, leading to uncertainty regarding the control measures in place.

Due to the choice of exposure model, the lack of clarity regarding the activities covered by the exposure scenarios and the inconsistencies between the activities described and the model input parameters, the evaluating MSCA considers that there is uncertainty regarding whether some of the aerosol inhalation exposure estimates reported in the registration data are representative of the potential for inhalation exposure from aerosol generating activities. Therefore, based on the exposure estimates reported in the registration data, the evaluating MSCA could not conclude on the potential for aerosol inhalation exposure.

The evaluating MSCA attempted to generate aerosol inhalation exposure estimates using ART v1.5 and, where no representative scenario in ART for an activity using powder formulations was available, ECETOC TRA v3.1. The evaluating MSCA applied a reasonable worst-case approach, taking into account the information provided in the registration data and the operational conditions and risk management measures reported in the referenced FEICA SWEDs for the relevant exposure scenarios. It is noted that ART has additional exposure determinants (input parameters) compared with ECETOC TRA. Therefore, where ECETOC TRA was used to generate exposure estimates in the registration data, the specific ART exposure determinants were not always specified. In such cases when using ART, the evaluating MSCA selected typical exposure determinants for the activity, but it is acknowledged that these may overestimate the potential for exposure.

The outcome of the exposure assessment performed by the evaluating MSCA is further discussed in sections 7.12.1.1.1 and 7.12.1.1.2, below. Further information on the exposure modelling performed by the evaluating MSCA is presented in a confidential annex to this report.

7.12.1.1.1. Industrial workers

Industrial spraying activities (PROC 7), which have the potential for aerosol generation, are reported in the exposure scenarios covering industrial application of coatings and inks. Two types of spraying activity are broadly described in the registration data: automated processes with (semi) closed systems and non-automated spraying. For both types of spraying activity, application of both liquid and powder formulations containing the registered substance are described. With respect to non-automated spraying, the evaluating MSCA notes that there are some inconsistencies in the registration data regarding the description of the activity and the model input parameters selected, in particular regarding the effectiveness of the LEV specified. The registration data specifies the use of moveable LEV but based on the description of the activity in the registration data, the evaluating MSCA considers that this type of LEV may not be realistic for such industrial activities where higher levels of control would be expected. In addition, the evaluating MSCA notes that a higher effectiveness value than that achieved with moveable LEV systems is used to generate the exposure estimates reported in the registration data. Based on the exposure modelling performed by the evaluating MSCA, it was concluded that where LEV with an effectiveness of at least 90 % is assumed, the potential for aerosol inhalation exposure from non-automated spraying of liquid formulations is reduced; however a concern remains for non-automated spraying of powder formulations. The

evaluating MSCA also identified the potential for aerosol inhalation exposure from automated spraying of powder formulations. With respect to the scenario of automated spraying of liquid formulations, the evaluating MSCA concluded that the potential for aerosol inhalation exposure is low.

The potential for aerosol generation was also identified during activities related to transfer and packaging (PROC 8b or 9), mixing and blending (PROC 5), roller application, brushing, dipping, immersion or pouring of products (PROC 10 and/or 13) and cleaning and maintenance (different combinations of PROC 5, 8a, 8b and 28). These activities were reported in exposure scenarios relating to the formulation of end use products, use as a chemical intermediate and monomer, use of coatings, inks and sealants, and use in non-metal surface treatments.

For transfer activities (covered by PROC 8b or 9) for liquid and powder formulations, a number of different scenarios are covered in the registration data which specify different combinations of transfer rates, task durations and substance concentrations, and with or without the use of LEV. From the transfer activities described, and based on the exposure modelling performed by the evaluating MSCA, the potential for aerosol inhalation exposure from transfer of neat liquids and transfer of powders where no LEV is specified were identified. For the transfer of neat liquid, the evaluating MSCA notes that the task duration specified in the registration data may not be realistic for such a task and that a shorter task duration could reduce the potential for aerosol inhalation exposure. With respect to the transfer of powder formulations where no LEV is specified, the evaluating MSCA notes that for similar liquid transfer activities described in the registration data where LEV is specified, the potential for aerosol inhalation exposure is low. Therefore, the potential for aerosol inhalation exposure could be reduced for powder transfer activities with the use of appropriate control measures. For the remaining transfer activities, the evaluating MSCA concluded that the potential for aerosol inhalation exposure is low.

With respect to mixing and blending activities (covered by PROC 5) with liquid and powder formulations, a number of scenarios are presented in the registration data covering different combinations of substance concentrations, task durations, and with or without the use of LEV. The evaluating MSCA identified the potential for aerosol inhalation exposure from mixing and blending of powder formulations. However, based on the description of the activity in the registration data, the evaluating MSCA considers that there is some uncertainty regarding whether mixing and blending of powder formulations is a relevant activity, since the model input parameters selected in the registration data are more reflective of liquid formulations. For the remaining mixing and blending activities with liquid formulations, the evaluating MSCA concluded that the potential for aerosol inhalation exposure is low.

Application of liquid formulations containing the registered substance by rolling, brushing, dipping, immersion or pouring (PROC 10 and/or 13) are reported in the exposure scenarios covering industrial application of coatings and inks, sealants and adhesives, and non-metal surface treatments. Application of powder formulations containing the registered substance is also reported in the exposure scenario covering industrial application of coatings and inks. For application of both liquid and powder formulations, two types of activity are broadly described in the registration data: automated processes with (semi) closed systems and manual processes. With respect to application of coatings and inks, the evaluating MSCA notes that there are some inconsistencies in the registration data regarding the description of the activities and the model input parameters selected, for example the extent to which the worker is segregated from the activities for automated processes and the type and effectiveness of control measures for manual processes. Based

on the exposure modelling performed by the evaluating MSCA, it was concluded that for manual processes with liquid formulations of coatings and inks where LEV with an effectiveness of 90 % or above is assumed, the potential for aerosol inhalation exposure is reduced. However, where LEV with an effectiveness of less than 90 % is assumed, the evaluating MSCA identified a concern for aerosol inhalation exposure for this activity. With respect to application of powder formulations of coatings and inks by either automated or manual processes, the evaluating MSCA notes there is no representative scenario in ART for these activities. Therefore, the evaluating MSCA used ECETOC TRA to generate the exposure estimates and concluded from this exposure modelling that a potential for aerosol inhalation exposure exists for these activities. The evaluating MSCA also identified the potential for aerosol inhalation exposure for manual application of sealants and adhesives where no LEV is specified. However, the evaluating MSCA notes that for similar activities associated with manual application of sealants and adhesives described in the registration data where appropriate control measures are specified, the potential for aerosol inhalation is low. Therefore, the potential for aerosol inhalation exposure could be reduced for such manual application of sealants and adhesives by specifying appropriate operating conditions and risk management measures. For the remaining rolling, brushing, dipping, immersion or pouring activities described in the registration data, the evaluating MSCA concluded that the potential for aerosol inhalation exposure is low.

A number of the exposure scenarios in the registration data include activities associated with cleaning, maintenance, loading and waste management with liquid and powder formulations. These activities are described using PROC 5, 8a, 8b and 28, or combinations of these PROCs. For the majority of these activities, an exposure modification factor has been applied in the registration data for the use of LEV or draining and flushing of the system before commencing the activities. The evaluating MSCA notes that the use of LEV may be difficult to implement in practice for such activities but considers that the use of an exposure modification factor may be appropriate where draining and flushing of a system is specified in the operational conditions and risk management measures. Based on the information provided in the registration data, the evaluating MSCA considers that there is some uncertainty regarding which activity class in ART is most appropriate to model the various cleaning and maintenance activities described in the registration data, in particular for activities associated with powder formulations. Therefore, although the exposure estimates generated by the evaluating MSCA using ART for these activities indicate a potential concern for aerosol inhalation exposure, it is acknowledged that these estimates may not accurately reflect the potential for exposure from the various cleaning and maintenance activities covered by the registration data. Therefore, the evaluating MSCA also generated exposure estimates for cleaning and maintenance activities associated with powder formulations using ECETOC TRA and also concluded that a potential for aerosol inhalation exposure exists. The evaluating MSCA concluded that the potential for aerosol inhalation exposure was low for cleaning, maintenance, loading and waste management activities associated with liquid formulations.

The industrial worker activities for which the evaluating MSCA concluded that a potential for aerosol inhalation exposure exists are summarised in table 11 below

Table 11

ACTIVITES FOR WHICH THE EVALUATING MSCA CONCLUDED THAT A POTENTIAL FOR AEROSOL INHALATION EXPOSURE EXISTS – INDUSTRIAL WORKERS	
Activity	**PROC code**
Application of coatings and inks by spraying: automated processes with (semi) closed systems– powder formulations	7
Application of coatings and inks by spraying: non-automated spraying– powder formulations	7
Transfer activities with LEV– neat liquid	8b, 9
Transfer activities without LEV – powder formulations	8b
Mixing and blending activities with LEV – powder formulations	5
Application of coatings and inks by roller application, brushing, dipping or pouring: automated processes with (semi) closed systems– powder formulations	10, 13
Application of coatings and inks by roller application, brushing, dipping or pouring: manual processes with LEV – powder formulations	10,13
Application of sealants and adhesives by roller application, brushing, dipping or pouring: manual application without LEV – liquid formulations	10
Cleaning, loading, maintenance, waste management: with and without draining and flushing of system – powder formulations	5, 8a, 8b

The evaluating MSCA notes that some further refinement of the exposure estimates by the registrants may be possible. For example, further clarification of the exposure determinants required for ART would allow refinement of the exposure estimates. In addition, clarifying the type of LEV, or where RPE or LEV are already specified, LEV and/or RPE with a higher effectiveness may also reduce the potential for exposure.

The registrants are recommended to consider further refinement of the aerosol inhalation exposure estimates for those scenarios reflected in table 11.

7.12.1.1.2. Professional workers

Non-industrial spraying activities (PROC 11), which have the potential for aerosol generation, are reported in the exposure scenario covering professional application of coatings and inks. Two types of spray activity are described in the registration data: indoor spraying where the use of both LEV and RPE is specified, and indoor or outdoor spraying where only RPE is specified. The potential for aerosol generation was also identified during activities related to roller application, brushing or dipping (PROC 10), which are reported in exposure scenarios covering professional application of coatings and inks and application of sealants and adhesives. In these exposure scenarios two types of activities are broadly

described: indoor application where the use of both LEV and RPE is specified (relevant for coatings and inks) and indoor or outdoor application where only general ventilation is specified. For both application types, the registration data describes the use of liquid formulations only.

In general, the evaluating MSCA considers that the use of LEV is unlikely for many professional activities. With respect to the professional application of coatings and inks described in the registration data, the evaluating MSCA notes that a number of product types, including paints, primers and varnishes, and uses, including those in vehicle refinishing, are covered by the exposure scenario. It is noted that the registration data does not include information to allow a conclusion as to whether the use of LEV is reasonable, and for which activities. The evaluating MSCA also notes that where the use of LEV is specified for application of coatings and inks, there is some inconsistency in the registration data regarding the type of LEV specified and corresponding effectiveness assumed in the modelling input parameters. Therefore, the evaluating MSCA notes that while the potential for aerosol inhalation exposure is considered to be low where the use of LEV (and RPE, where relevant) is specified, the evaluating MSCA was unable to conclude whether such control measures are realistic for all product types described in the registration data. However, the evaluating MSCA accepts that the use of appropriate LEV is expected for professional spray application of coatings and inks in vehicle refinishing, where higher levels of control are generally employed (HSE, 2011). For such uses in vehicle refinishing, the evaluating MSCA concluded that the potential for aerosol inhalation exposure is low, where LEV with an effectiveness of at least 80 % is assumed.

Based on the exposure modelling performed by the evaluating MSCA, the potential for aerosol inhalation exposure for professional spray application of coatings and inks where only RPE is specified was identified.

For activities related to roller application, brushing or dipping of coatings and inks or sealants and adhesives where neither LEV nor RPE is specified, the evaluating MSCA notes that parameters such as whether the use is small or large scale (as referenced in the FEICA SWEDs for use of sealants and adhesives), the number of air changes per hour and the size of the room will impact on the exposure estimate. Based on the description of these activities in the registration data, the evaluating MSCA could only generate a range of exposure estimates which was too broad to allow a conclusion on the potential for aerosol inhalation exposure. Therefore, the evaluating MSCA concluded that there is the potential for aerosol inhalation exposure from certain roller application, brushing or dipping activities.

The professional worker activities for which the evaluating MSCA concluded that a potential for aerosol inhalation exposure exists are summarised in table 12 below.

Table 12

ACTIVITES FOR WHICH THE EVALUATING MSCA CONCLUDED THAT A POTENTIAL FOR AEROSOL INHALATION EXPOSURE EXISTS – PROFESSIONAL WORKERS	
Activity	**PROC code**
Application of coatings and inks by spraying: indoor or outdoor application with RPE– liquid formulations	11
Application of coatings and inks by roller application, brushing or dipping: indoor or outdoor application – liquid formations	10
Application of sealants and adhesives by roller application, brushing or dipping: indoor or outdoor application – liquid formulations	10

The evaluating MSCA notes that some further refinement of the exposure estimates by the registrants may be possible. For example, further clarification of the exposure determinants required for ART would allow refinement of the exposure estimates. In addition, clarifying more precisely the use conditions (e.g. large or small scale applications, room size, etc.) would also allow a more accurate exposure estimate.

The registrants are recommended to consider further refinement of the aerosol inhalation exposure estimates for those scenarios reflected in table 12.

7.12.1.2. Consumer

As discussed in section 7.12.1, the evaluating MSCA focused the exposure assessment on those activities leading to the potential for aerosol inhalation exposure. For consumers, the potential for aerosol inhalation exposure was identified from the use of spray paints (PC 9a), for which an exposure scenario is included in the registration data.

The activity described is indoor or outdoor application of paints supplied in aerosol cans. According to the registration data, such products are used infrequently and for short periods of time. The evaluating MSCA notes there is some uncertainty regarding whether such spray paints are actually supplied for use by consumers, since the registration data also states that paints (and coatings) containing the registered substance are not supplied to consumers for spray applications. However, as an exposure scenario for this use is included in the registration data, and since consumer use of spray paints is not a use advised against in the registration data, the evaluating MSCA assessed it.

The exposure scenario in the registration data referenced specific consumer exposure determinants (SCEDs) from CEPE. At the time of finalising the evaluation, the SCEDs developed by CEPE were not publically available. Therefore, it was not possible for the evaluating MSCA to assess whether the input parameters used for exposure modelling in the registration data were representative of the typical use conditions for such products by consumers.

No exposure monitoring data are reported in the registration data. The aerosol inhalation exposure estimates reported in the registration data for consumer use of spray paints were generated using ART v1.5, using model input parameters that were stated to be more conservative than those reported in the relevant ConsExpo fact sheet, and assuming the use of no risk management measures. Harber's Law was used to correct the exposure estimate to take account of a shorter duration of exposure for consumers compared with workers.

The evaluating MSCA acknowledges that in certain scenarios it may be appropriate to use ART, with appropriate modifications, to generate consumer exposure estimates. However, as ART was developed for the estimation of worker exposure and the variability of estimates generated by the model are based on worker shift measurements, the applicability of any exposure estimate to consumers should be treated with caution. In addition, the evaluating MSCA considers that the application of Harber's Law to correct for differences in duration of exposure from workers to consumers is not justified, as an exposure modifier to correct for duration of exposure is already included in the model input parameters. Table R.15-1 in ECHA Guidance R.15[5] states that for infrequent uses, the recommended approach is to generate an event exposure estimation and compare it to an infrequent use DNEL. ConsExpo Web is a higher tier model developed for the estimation of consumer exposure. It contains a specific model for spray products, which allows the estimation of an event exposure. Therefore, the evaluating MSCA considers that in this case, ConsExpo Web is a more appropriate model to generate aerosol inhalation exposure estimates for consumers.

The evaluating MSCA generated an aerosol inhalation exposure estimate for an event exposure using the spray model in ConsExpo Web 1.0.6. The default ConsExpo Web input parameters were used with the exception of the spray duration, which was as per the registration data. The inhalation exposure estimate calculated by the evaluating MSCA is significantly higher than that reported in the registration data. Therefore, the evaluating MSCA considers that the potential for aerosol inhalation exposure from spray application of paints by consumers may be significantly underestimated in the registration data.

The evaluating MSCA concluded that a potential for aerosol inhalation exposure from spray application of paints by consumers exists.

7.12.2. Environment

Not evaluated.

7.12.3. Combined exposure assessment

Not evaluated.

[5] Guidance on information requirements and chemical safety assessment. Chapter R.15: Consumer Exposure Assessment

7.13. Risk characterisation

7.13.1. Human health

The evaluating MSCA focused the risk characterisation on inhalation exposure from activities or uses which have the potential for aerosol generation.

The leading health effects which are relevant for risk characterisation were the formation of laryngeal granulomas and cytoplasmic hyalinisation of nasal tissue observed in the available aerosol inhalation repeated dose toxicity studies.

7.13.1.1. Worker

The registration data concluded that the risk characterisation ratios (RCRs) for long term local effects from aerosol inhalation exposure for all relevant exposure scenarios are below 1.

As discussed in section 7.9.9, the evaluating MSCA derived different DNELs for workers to those reported in the registration data for long term local effects following aerosol inhalation exposure: 0.3 mg/m^3 (laryngeal granulomas) and 0.034 mg/m^3 (cytoplasmic hyalinisation). The evaluating MSCA applied a precautionary approach and used the lower DNEL of 0.034 mg/m^3, based on cytoplasmic hyalinisation of nasal tissue, for risk characterisation.

As outlined in section 7.12.1.1, the evaluating MSCA considers that there is some uncertainty regarding whether the exposure estimates reported in the registration data are representative of the potential for inhalation exposure from aerosol generating activities. Therefore, based on those estimates, the evaluating MSCA could not conclude on whether there was a potential for aerosol inhalation exposure.

The evaluating MSCA generated aerosol inhalation exposure estimates for those activities for which aerosol generation is expected and compared them with the DNEL for long term local effects following aerosol inhalation exposure (cytoplasmic hyalinisation of nasal tissue) derived by the evaluating MSCA.

Table 13 summarises the industrial worker activities for which the evaluating MSCA concluded that the RCR values for long term local effects from aerosol inhalation exposure are 1 or above.

Table 13

RCR VALUES DERIVED BY THE EVALUATING MSCA FOR LONG TERM LOCAL EFFECTS FROM AEROSOL INHALATION EXPOSURE – INDUSTRIAL WORKERS		
Activity	**PROC code**	**RCR**
Application of coatings and inks by spraying: automated processes with (semi) closed systems – powder formulations	7	> 1
Application of coatings and inks by spraying: non-automated spraying – powder formulations	7	> 1
Transfer activities with LEV– neat liquid	8b, 9	> 1
Transfer activities without LEV – powder formulations	8b	> 1
Mixing and blending activities with LEV – powder formulations	5	> 1
Application of coatings and inks by roller application, brushing, dipping or pouring: automated processes with (semi) closed systems with LEV – powder formulations	10, 13	> 1
Application of coatings and inks by roller application, brushing, dipping or pouring: manual processes with LEV – powder formulations	10, 13	> 1
Application of sealants and adhesives by roller application, brushing, dipping or pouring: manual application without LEV – liquid formulations	10	= 1
Cleaning, loading, maintenance, waste management: with and without draining and flushing of system – powder formulations	5, 8a, 8b	> 1

As discussed in section 7.12.1.1.1, for some exposure scenarios the description of the activity, the physical form (i.e. liquid or powder) of the product used or the stated control measures were not always clear or did not always correlate with the selected model input parameters. For this reason, a number of assumptions were made by the evaluating MSCA in generating the exposure estimates. These are further discussed in a confidential annex to this report. While this uncertainty is acknowledged, the evaluating MSCA concluded that based on the available information, aerosol inhalation exposure may not be adequately controlled for the industrial activities reported in table 13.

It is noted that a number of the activities in table 13 relate to powder formulations. The evaluating MSCA notes that further refinement of the operational conditions or risk management measures may be needed to reduce the potential for aerosol inhalation exposure for these activities, for example by specifying LEV with a higher effectiveness which is appropriate for the work activity or additional control measures to limit the exposure to powder formulations. In addition, the evaluating MSCA notes that there is some uncertainty in the registration data regarding the physical form of the product used

for some activities, for example whether mixing and blending of powder formulations is a relevant activity.

With respect to activities in table 13 which do not specify the use of LEV (i.e. manual application of sealants and adhesives and transfer activities of powder formulations), the evaluating MSCA notes that for similar activities reported in the registration data where additional operating conditions and risk management measures are specified, the RCRs are below 1. Therefore, some further refinement of the exposure estimates by the registrants may be possible by specifying appropriate operational conditions and risk management measures.

Table 14 summarises the professional worker activities for which the evaluating MSCA concluded that the RCR values for long term local effects from aerosol inhalation exposure are above 1. For those activities which the evaluating MSCA could only generate a range of exposure estimates based on the information provided in the registration dossier, the RCRs are indicated as a range.

Table 14

RCR VALUES DERIVED BY THE EVALUATING MSCA FOR LONG TERM LOCAL EFFECTS FROM AEROSOL INHALATION EXPOSURE – PROFESSIONAL WORKERS		
Activity	**PROC code**	**RCR**
Application of coatings and inks by spraying: indoor or outdoor application with RPE– liquid formulations	11	> 1
Application of coatings and inks by roller application, brushing or dipping: indoor or outdoor application – liquid formations	10	1 < and >1
Application of sealants and adhesives by roller application, brushing or dipping: indoor or outdoor application – liquid formulations	10	1 < and >1

As discussed in section 7.12.1.1.2, based on the description of activities in the registration data, the evaluating MSCA could only generate a range of exposure estimates for some activities leading to RCRs above and below 1, depending on the model input parameters selected (which are further discussed in a confidential annex to this report). While this uncertainty is acknowledged, the evaluating MSCA concluded that based on the available information, aerosol inhalation exposure may not be adequately controlled for the professional activities reported in table 14.

The evaluating MSCA notes that some further refinement of the exposure estimates may be possible by, for example, clarifying more precisely the use conditions (e.g. large or small scale applications, room size, etc.) in order to allow for a more accurate exposure estimate.

As discussed in section, 7.12.1.1.2, the evaluating MSCA considers that in general the use of LEV is unlikely for many professional activities. With respect to professional use of coatings and inks, the registration data specifies the use of LEV (and RPE) for some activities. While the potential for aerosol inhalation exposure is considered to be low where use of LEV (and RPE) is specified, the evaluating MSCA was unable to conclude whether such control measures are realistic for all product types described in the registration data. However, the evaluating MSCA accepts that the use of LEV is expected for professional

spray application of coatings and inks in vehicle refinishing, where higher levels of control are generally employed.

7.13.1.2. Consumer

The registration data concluded that the risk characterisation ratio for long term local effects via aerosol inhalation exposure for consumer use of spray paints is below 1.

As discussed in section 7.9.9, the evaluating MSCA derived different DNELs for the general population to those reported in the registration data for long term local effects following aerosol inhalation exposure following infrequent use: 0.05 mg/m^3 (laryngeal granulomas) and 0.006 mg/m^3 (cytoplasmic hyalinisation). The evaluating MSCA applied a precautionary approach and used the lower DNEL of 0.006 mg/m^3, based on cytoplasmic hyalinisation of nasal tissue, for risk characterisation.

As outlined in section 7.12.1.2, the evaluating MSCA considers that the potential for aerosol inhalation exposure from spray application of paints by consumers may be underestimated in the registration data. Therefore, the evaluating MSCA generated an exposure estimate for this use and compared it with the DNEL for infrequent use for long term local effects following aerosol inhalation exposure (cytoplasmic hyalinisation of nasal tissue) derived by the evaluating MSCA. The RCR derived by the evaluating MSCA for this use is significantly > 1.

The evaluating MSCA notes that there is some uncertainty in the registration data regarding whether paints containing the registered substance are actually supplied for spray application by consumers. However, as this is a registered use of the substance and is not a use advised against in the registration data, the evaluating MSCA assessed the use and concluded that aerosol inhalation exposure of consumers may not be adequately controlled.

7.13.2. Environment

Not evaluated.

7.14. References

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7.15. Abbreviations

AF	Assessment factor
ART	Advanced REACH Tool
Bw	Body weight
CAS	Chemical abstracts service
C&L	Classification and labelling
CHO	Chinese hamster ovary
CLP	Classification, labelling and packaging (Regulation (EC) No 1272/2008)
CMR	Carcinogenicity, mutagenicity and toxicity to reproduction
CoRAP	Community rolling action plan
DEO	Dermal Exposure Operation
DNEL	Derived no effect level
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
EDX	Energy dispersive X-ray analysis
EOGRTS	Extended one-generation reproductive toxicity study
FEICA	Association of European Adhesives and Sealants Manufacturers
GLP	Good laboratory practice
GPMT	Guinea pig maximisation test
LEV	Local exhaust ventilation
LLNA	Local lymph node assay
LD50	Median lethal dose. The dose causing 50 % lethality
LOAEC	Lowest observed adverse effect level
MMAD	Mass median aerodynamic diameter
MSCA	Member state competent authority
NOAEC	No observed adverse effect concentration
NOAEL	No observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
PBT	Persistent, Bioaccumulative, Toxic
PND	Post-natal day
PROC	Process category
RCR	Risk characterization ratio
RPE	Respiratory protective equipment
SCE	Sister chromatid exchange
SCED	Specific consumer exposure determinants
SEM	Scanning electron microscopy
SWED	Sector-specific worker exposure descriptions
TEM	Transmission electron microscopy
TPA	Tonnes per annum
TRA	Targeted risk assessment
vPvB	Very Persistent and very Bioaccumulative
Wk	Week
WoE	Weight of evidence