SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate

EC No 219-207-4

CAS No 2386-87-0

Evaluating Member State(s): Ireland

Dated: 12 January 2018

Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2013

Before concluding the substance evaluation a Decision to request further information was issued on: 19 December 2014.

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

7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate was originally selected for substance evaluation in order to clarify concerns about:

- Skin sensitisation
- Mutagenicity
- Developmental toxicity
- High risk characterisation ratios for workers

During the evaluation, an additional concern was identified relating to effects in the nasal tissue observed in an oral repeated dose toxicity study.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Not applicable.

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 exposure estimates presented in the registration data. A number of exposure modification factors were applied to generate the dermal exposure estimates. It is noted that these have not always been applied in line with the relevant exposure model guidance or ECHA Guidance R.14[2]. Therefore, the evaluating MSCA is of the opinion that the dermal exposure estimates presented in the registration data may underestimate the potential for worker exposure.

[2] Guidance on information requirements and chemical safety assessment. Chapter R.14: Occupational exposure estimation

The evaluating MSCA has calculated dermal exposure estimates using ECETOC TRA v3.0 and Riskofderm v2.1 and applying modification factors in line with the relevant guidance, which when compared with the long-term systemic DNELs for the dermal route result in risk characterisation ratio (RCR) values greater than 1. Therefore, the evaluating MSCA concluded that based on the available information, dermal exposure may not be adequately controlled.

The evaluating MSCA also considers that the registered substance should be classified as skin sensitisation category 1, rather than the self-classification of skin sensitisation category 1B. In accordance with Table E3-1 of ECHA Guidance Part E[3], where a substance is classified as skin sensitisation category 1, i.e. where the available data does not allow potency categorisation, the risk management measures and operational conditions applicable to the "high hazard" band should be applied. These measures aim to avoid exposure. The evaluating MSCA considers that further review and refinement of the implemented operational conditions and risk management measures is required by the registrants to ensure exposure is avoided.

Therefore, the registrants are advised to review their exposure estimates and update as appropriate.

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 CLP for 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate. The registrants have self-classified the substance as skin sensitisation category 1B (skin sens. 1B; H317).

The available *in vitro* mutagenicity studies carried out with the registered substance indicate a concern for gene mutation. Positive results in the presence of metabolic activation were observed in the key Ames study in *S. typhimurium* strains TA 100, TA 1535 and *E. coli* WP2 strain, which all detect base pair substitutions. In a mammalian cell gene mutation assay in mouse lymphoma cells, positive responses in the presence and absence of metabolic activation were observed. The positive response in the absence of metabolic activation indicates a possible concern for a direct action of the substance as a mutagen at initial sites of contact. In a follow up *in vivo* oral transgenic rodent somatic and germ cell mutation assay, an increase in mutant frequency was observed in the forestomach, as site of first contact, at the high dose group (1000 mg/kg bw/day). The evaluating MSCA considers that the increase in mutant frequency in the forestomach at 1000 mg/kg bw/day in this assay to be indicative of a possible direct action of the registered substance as a mutagen at initial sites of contact and concludes that classification as mutagen category 2 (muta. 2; H341) is warranted. A harmonised classification and labelling in accordance with Article 36 of CLP is justified.

The critical effect observed in the available 90-day oral repeated dose toxicity study with the registered substance was degeneration of the olfactory epithelium in the nasal tissue in both sexes at ≥ 50 mg/kg bw/day. The degeneration was characterised by loss of sustentacular cells, vacuolation and desquamation of neuroepithelial cells which resulted in decreased height of the olfactory epithelium. The effects were not fully reversible following a twenty-eight day recovery period. Such effects could be an indication of functional impairment. The evaluating MSCA considers this finding to be a treatment-

[3] Guidance on information requirements and chemical safety assessment. Part E – Risk Characterisation.

related systemic effect as there was no indication of difficulties in administration of the test material or clinical signs of reflux. Moreover, it is considered unlikely that the animals were exposed to toxic or caustic vapours given the low vapour pressure of the registered substance and the choice of vehicle (corn oil). The evaluating MSCA concludes that classification as specific target organ toxicity – repeated exposure, category 2 (STOT RE 2: H373) is warranted.

It is noted that less than 5% of the notifications to the C&L Inventory for this substance apply a classification as STOT RE 2; H373. Also effects on nasal tissue following oral administration are unusual and therefore the evaluating MSCA considers that there is a need to communicate this specific hazard via harmonised classification and labelling.

With respect to skin sensitisation the evaluating MSCA considers that there is insufficient data currently available to allow sub-categorisation for skin sensitisation. Therefore, the evaluating MSCA considers that the substance should be classified as skin sensitisation category 1 (skin sens. 1; H317).

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)

Indication of a tentative plan is not a formal commitment by the evaluating Member State. A commitment to prepare a REACH Annex XV dossier (SVHC, restrictions) and/or CLP Annex VI dossier will be made via the Registry of Intentions.

Table 2

FOLLOW-UP		
Follow-up action	**Date for intention**	**Actor**
Preparation of Annex VI CLH proposal	2018	Ireland

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate was originally selected for substance evaluation in order to clarify concerns about:

- Skin sensitisation
- Mutagenicity
- Developmental toxicity
- High risk characterisation ratios for workers

During the evaluation, an additional concern was identified relating to effects in the nasal tissue observed in an oral repeated dose toxicity study.

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Skin Sensitisation	The evaluating MSCA concluded that the concern for skin sensitisation is verified. The evaluating MSCA considers that classification as skin sensitiser category 1 is appropriate.
Mutagenicity	Based on positive results in *in vitro* gene mutation studies in bacterial and mammalian cells in the presence and absence of metabolic activation and the increase in mutant frequency observed in the forestomach in an *in vivo* oral transgenic rodent somatic and germ cell mutation assay, the evaluating MSCA concluded that the concern for gene mutation is verified. The evaluating MSCA considers that classification as mutagen category 2 is appropriate. Based on the negative results in the germ cell sample in the TGR and the lack of effects on male reproductive organs in the repeated dose toxicity study, the evaluating MSCA concluded that classification as mutagen category 1B for effects on germ cells is not appropriate.
Developmental toxicity	Based on the available information, the evaluating MSCA concluded that the concern for developmental toxicity is not substantiated.
Specific target organ toxicity – repeated exposure	In a 90-day oral repeated dose toxicity study in rats with the registered substance, degeneration of the olfactory epithelium in the nasal tissue in both sexes was observed at the end of the treatment period. At the end of the 28-day recovery period, while there was some evidence of regenerative changes, the effect was not fully reversible. Based on the available information, the evaluating MSCA concluded that the effect was a treatment related systemic effect and therefore the concern is verified. A NOAEL of 5 mg/kg bw/day was selected based on this finding and used for DNEL derivation. The evaluating MSCA concluded that classification as STOT-RE category 2 is appropriate.
Human health (worker) exposure	The evaluating MSCA concluded that the potential dermal exposure to workers may be underestimated in the registration data and therefore the potential concern for dermal exposure remains. Further refinement by the registrants of the dermal exposure estimates and the operational conditions and risk management measures are recommended.

7.2. Procedure

Pursuant to Article 44(2) of the REACH Regulation, 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate was included in the Community Rolling Action Plan (CoRAP) for evaluation in 2013. The Competent Authority of Ireland was appointed to carry out the evaluation. The substance evaluation commenced on 1 March 2013.

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

Based on the evaluation of the available data, the evaluating MSCA concluded that there was a need to request further information to clarify the concerns relating to mutagenicity and worker exposure and therefore pursuant to Article 46(1) of the REACH Regulation prepared a draft decision to request further information. The draft decision was submitted to ECHA on 6 March 2014. The decision was agreed by the Member State Committee and the final decision was issued to the registrants on the 19 December 2014.

On 21 October 2016 the lead registrants 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.

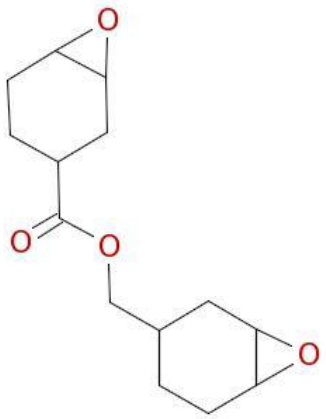
7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate
EC number:	219-207-4
CAS number:	2386-87-0
Index number in Annex VI of the CLP Regulation:	Not listed in Annex VI of CLP
Molecular formula:	C14H20O4
Molecular weight range:	252 g/mol
Synonyms:	Celloxide 2021P Cycloaliphatic Epoxy Resin ERL-4221 ERL-4221 Uvi-Cure S105 Uvi-Cure S105E Uvi-Cure S110LV

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	Colourless, odourless liquid
Vapour pressure	0.002 Pa at 25 ^{0}C
Water solubility	13850 mg/L at 20 ^{0}C
Partition coefficient n-octanol/water (Log Kow)	Log Pow 1.34 at 20 ^{0}C
Flammability	Not applicable
Explosive properties	Not applicable
Oxidising properties	Not considered to have oxidising properties
Granulometry	Not applicable
Stability in organic solvents and identity of relevant degradation products	Not applicable
Dissociation constant	Not applicable
Viscosity	241m.Pa s at 25 ^{0}C

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

7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate is a cycloaliphatic liquid epoxy resin used in a number of industrial sectors including inks and coatings, electricity and electronics. It also has applications in additives and composites.

Table 7

USES	Use(s)
Uses as intermediate	Not applicable
Formulation	Formulation of end use products
Uses at industrial sites	Use in coating agents Use as an additive in polycarbonate, polyvinyl chloride and adhesives Use as an antioxidant in insulators Use as a reactive agent Use in electric and other applications Use in LED materials
Uses by professional workers	Not applicable
Consumer Uses	Not applicable
Article service life	-

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate is not listed on Annex VI of CLP.

7.6.2. Self-classification

In the registration(s):

- Skin Sens. 1B; H317: May cause an allergic skin reaction

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

- Skin Sens. 1; H317: May cause an allergic skin reaction
- Aquatic Chronic 3; H412: Harmful to aquatic life with long lasting effects
- STOT RE 2; H373: May cause damage to organs (liver, sense organs) through prolonged or repeated exposure
- Skin Irrit. 2; H315: Causes skin irritation
- Eye Irrit. 2; H319: Causes serious eye irritation
- STOT SE 3; H335: May cause respiratory irritation
- Muta. 2; H341: Suspected of causing genetic defects

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 is presented in the registration data.

7.9.2. Acute toxicity and Corrosion/Irritation

The registration data identifies an LD_{50} (oral) of 5000 mg/kg bw, an LC_{50} (inhalation, 4 hr.) of >5.19 mg/L air and LD_{50} (dermal) of >2000 mg/kg bw. The registration data concludes that no classification for acute toxicity is required for 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate. Based on the available information, the evaluating MSCA can support this conclusion.

The registrants concluded 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 this conclusion.

7.9.3. Sensitisation

A Guinea Pig Maximisation Test (reliable with restrictions) using the Magnusson-Kligman method, with the registered substance is reported in the registration data. This study is GLP compliant and was conducted prior to the availability of OECD 406. Ten male and ten female Hartley Albino guinea pigs were intradermally injected with 5% w/v 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate in propylene glycol, followed by topical application of the undiluted test substance. One of the ten test group animals died on day 11, the cause of death was not established and all other animals survived throughout the study. Positive reactions were observed in the test group in 12/19 after 24 hours and 8/19 after 48 hours. The registration data concludes that based on the

results of this study, the registered substance exhibits the potential to induce skin sensitisation in guinea pigs and is self-classified as Skin Sens. 1B H317: May cause an allergic skin reaction.

Based on the available information, the evaluating MSCA agrees that the registered substance meets the criteria for classification as a skin sensitiser but considers that the available data does not allow a decision on sub-categorisation into category 1A or 1B. The choice of intradermal induction dose and the relatively high response rate, while meeting the criteria for subcategorisation into category 1B, does not allow a definitive conclusion that category 1A is not appropriate. In addition, a number of deviations from the test guideline were noted, such as the number of test animals used and the absence of individual animal grading data which further hamper the assessment. No further data was identified which could assist in the sub-categorisation. Therefore the evaluating MSCA concludes that classification as skin sensitisation category 1 (skin sens. 1) is appropriate.

7.9.4. Repeated dose toxicity

A 90-day oral repeated dose toxicity study with the registered substance is reported in the registration data. This study is GLP compliant and conducted in accordance with OECD 408.

In the 14-day range finding study, the test substance was administered by oral gavage once daily for 14 days to groups of 20 (10/sex/dose) rats at dose levels of 0, 100, 500, 750 and 1000 mg/kg bw/day. No mortalities were reported. A dose related decrease in body weight and body weight gain was observed from 500 mg/kg bw/day in males and at 1000 mg/kg bw/day in females. An increase in absolute and relative liver weight was observed from 100 mg/kg bw/day in males and from 500 mg/kg bw/day in females. The liver weight changes were accompanied by an increase in incidence and/or severity of periportal hepatocyte vacuolation. Based on hepatic effects observed at all doses, no NOAEL was identified and the doses selected for the main study were 5, 50 and 500 mg/kg bw/day.

In the main study, the test substance was administered once daily by oral gavage to three groups of rats at dose levels of 5, 50 and 500 mg/kg bw/day for 90 days. A vehicle control group was administered corn oil on a comparable treatment schedule. The control and 500 mg/kg bw/day groups each consisted of 25 males and 25 females, of which 10/sex/dose were assigned to the 28-day recovery group. 5 and 50 mg/kg bw/day groups each consisted of 20 males and 20 females, of which 5/sex/dose were assigned to the 28-day recovery group.

No mortalities were reported. Body weights in males at 500 mg/kg bw/day were decreased over the study period, and did not return to control levels by the end of the recovery period. No treatment related changes in food consumption, haematology, ophthalmological, oestrus cycle or spermatogenic parameters were observed. At the end of the 13-week treatment period, an increase in absolute and relative kidney weights in both sexes at 500 mg/kg bw/day was observed. There were accompanying alterations in serum chemistry and urinalysis parameters at both 50 and 500 mg/kg bw/day: increase in serum urea nitrogen and phosphorous levels and a decrease in urine pH and creatinine, the latter in males only. No histopathological changes in the kidney were observed in any treatment group and no kidney related effects were evident at the end of the recovery period. Serum cholesterol levels in females at 50 mg/kg bw/day and in both sexes at 500 mg/kg bw/day were decreased and direct bilirubin and sorbitol dehydrogenase levels were increased in both sexes at 500 mg/kg bw/day. At necropsy, pale livers were observed in 3/15 males at 500 mg/kg bw/day. An increase in absolute and relative liver weight was observed at 50 and 500 mg/kg bw day in both sexes, accompanied by fine periportal hepatocellular vacuolation. The incidence was reported as 4/15, 5/15, 14/15 and 15/15 for males and 2/15, 2/15, 12/15 and 15/15 for females, for the 0, 5, 50 and 500 mg/kg bw/day treatment groups, respectively. For the high dose group, the study report indicates the effect was

mild in severity, and for all other groups the effect was reported as minimal. At the end of the recovery period, no evidence of hepatocellular vacuolation was observed in either sex indicating reversal of the lesion.

Degeneration of the olfactory epithelium in nasal tissue was observed at 50 and 500 mg/kg bw/day in both sexes. The study report states that the degeneration was characterised by the loss of sustentacular cells, vacuolation and desquamation of neuroepithelial cells which resulted in decreased height of the olfactory epithelium but there appeared not to be an effect on the underlying structures or connective tissue. The incidence was reported as 0/15, 0/15, 2/15 and 12/15 in males and 0/15, 0/15, 3/15 and 13/15 in females for the 0, 5, 50 and 500 mg/kg bw/day treatment groups, respectively. At the end of the twenty-eight day recovery period, olfactory epithelium degeneration was observed in both sexes at 50 and 500 mg/kg bw/day but at a lower incidence. There was some evidence of regenerative changes: basal cell proliferation and regeneration of sustentacular and neuroepithelial cells. Foci of replacement of olfactory epithelium by ciliated columnar epithelium was observed in 6/15 males and 9/15 females at 500 mg/kg bw/day and the study director considered this change to be part of the repair process, suggesting that local damage to basal cells prevented repair to olfactory epithelium. A NOAEL of 5 mg/kg bw/day was identified based on nasal epithelial degeneration observed at 50 and 500 mg/kg bw/day, in addition to increased liver and kidney weights, reduced bodyweight gains and lower food consumption at these doses.

The evaluating MSCA notes that no difficulties with administration of the dose via gavage cannula or any clinical signs after dosing which would indicate reflux of the test material were reported during the study period. Moreover, given the low vapour pressure of the registered substance (-2 x 10^{-3} Pa) and the choice of vehicle (corn oil) in the study, it is considered highly unlikely that the high dose animals were exposed to toxic or caustic vapours from the oral preparation. Therefore, while effects on nasal tissue following oral administration are relatively rare, the evaluating MSCA considers that based on the available information it cannot be excluded that the effect on nasal tissues observed was due to systemic exposure of the test substance.

Although no mechanism of action was identified in this case, the evaluating MSCA notes that the target tissue, sustentacular cells, contain high levels of metabolising enzymes including cytochrome P450 and flavin mono-oxygenases (Harkema *et. al.,* 2006). Other chemicals causing degeneration and/or atrophy of the olfactory epithelium following administration by routes other than inhalation include methacrylonitrile, benzyl acetate, dipropylene glycol, o-nitrotoluene, cyclohexanone oxime, butanal oxime and methyl ethyl ketoxime. Metabolic predilection could explain regional distribution of lesions in the nasal cavity following non-inhalation exposure. For example, nasal cell cytochrome P-450 2E1 is thought to play a role in the metabolism of methacrylonitrile resulting in degeneration of nasal epithelial cells (Sells *et. al.,* 2007).

Therefore, based on the available information the evaluating MSCA supports the selection of nasal epithelial degeneration as the critical effect observed in this study and the choice of NOAEL of 5 mg/kg bw/day for DNEL derivation. Moreover, as the effect on nasal epithelium may be an indication of functional impairment which was not fully reversible during the 28-day 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 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate 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 four *S. typhimurium* strains (TA1535, TA 1537, TA 98 and TA 100)

and *E. coli* WP2 uvrA strain were exposed to concentrations of the test material at 156, 313, 625, 1250, 2500 and 5000 µg/plate. Positive results were obtained in the presence of microsomal metabolic activation for TA 100, TA 1535 and *E. coli* WP2 uvrA and in the absence of metabolic activation for E. Coli WP2 uvrA. A brief summary of a second bacterial reverse mutation assay available only in Japanese is also reported in the registration data. Due to the limited details available, it is not possible to independently assess the result. However it is noted that positive results with metabolic activation were reported in *S. typhimurium* strains TA 1535 and TA 100, and *E. coli WP2* treated with 100, 200, 500, 1000, 2000 and 5000 µg/plate of test material.

In a GLP compliant, non-guideline mammalian gene mutation assay, mouse lymphoma L5178Y cells (TK+/-) were exposed to concentrations of the test material for four hours up to 250 µg/ml in the presence and absence of microsomal metabolic activation. The expression time was reported as 3 days, and the selection time was 14 days for mutant selection and 11-12 days for viability. For mutant selection, 4 x 10^5 cells/tube were evaluated and for viability control, 200 cells/tube. No information is reported on the number of replicates assessed or the purity of the test material. Positive results in the presence of metabolic activation were obtained at concentrations ≥ 150 µg/ml and in the absence of metabolic activation at ≥ 100 µg/ml. In a second non-GLP compliant, non-guideline mammalian cell mutation assay, Chinese Hamster Ovary (CHO) cells were exposed to five concentrations of the test material (purity not reported) between 100 x 10^{-4} % and 6.25 x 10^{-4} % by volume in the absence of, and 200 x 10^{-4} % and 12.5 x 10^{-4} % by volume in the presence of, metabolic activation. No information is provided on the exact concentrations tested. It is reported that the test was conducted in duplicate. Following an exposure period of 5 and 16 hours with and without metabolic activation respectively, 100 cells per dish were evaluated. No increase in the frequency of mutants was observed.

In a non-GLP compliant, non-guideline sister chromatid exchange (SCE) assay, CHO cells were exposed in the absence of metabolic activation to six concentrations of test material (purity not reported) between 100 x 10^{-4} % and 3.125 x 10^{-4} % by volume. Although the test was conducted in triplicate, due to cytotoxicity, results from only one assay are reported which showed a dose-related increase in SCE in the absence of metabolic activation.

In a non-GLP compliant, non-guideline Unscheduled DNA Synthesis (UDS) assay, primary rat liver hepatocytes were treated with six concentrations of test material (purity not reported) at concentrations between 1 x 10^{-4} % and 0.1 % by volume. No information is available on the exact concentrations or number of replicates tested. Increased UDS activity was observed at the three lowest concentrations, although the study summary indicates that since the results were not consistently statistically significant when compared with solvent control, the result was considered to be ambiguous.

In a GLP compliant, *in vivo* bone marrow micronucleus study comparable to EU Method B.12 (OECD 474, 1997), 500, 1000 and 2250 mg/kg bw of the test material was administered in peanut oil by intraperitoneal injection to groups of 5 male and 5 female Swiss Albino mice. Bone marrow was sampled at 24, 48 and 72 hours post dosing. 1000 polychromatic erythrocytes (PCEs) per animal were scored for the presence of micronuclei. Decreased motor activity, collapse, weakness, ataxia and laboured breathing were observed in both sexes at 2250 mg/kg bw. Cytotoxicity was noted in females at 500 and 2500 mg/kg bw at 48 hours only. A statistically significant increase in micronucleated PCEs was observed in males at 1000 mg/kg bw at 48 hours only. However, in the absence of a dose-response this was not considered to be biologically significant. The evaluating MSCA notes that a lower number of PCEs (1000 PCEs) was evaluated in the study than the 4000 PCEs recommended in the current version of OECD 474 (2016). It is noted in the registration data that while the number of PCEs evaluated in this study are lower than those required by the test guideline, the very low incidence of micronucleated PCEs (< 2 micronuclei per 1000 PCE) was statistically validated and the low PCE:NCE did not invalidate the study.

In a GLP compliant *in vivo* UDS assay conducted in accordance with OECD 486, groups of 10 male Sprague-Dawley rats were administered a single dose by oral gavage of the test substance in water at doses of 500, 1000 and 2000 mg/kg bw. No increase in net nuclear grain counts in hepatocytes isolated following exposures of either 2 - 4 hours or 12 - 16 hours was observed and it was concluded that the test substance did not induce unscheduled DNA synthesis in this assay.

A GLP compliant transgenic rodent somatic and germ cell gene mutation (TGR) assay conducted in accordance with OECD 488 is available with the registered substance. Male transgenic mice (MutaMouse – CD2-LacZ80/HazfBR) were treated for 28 days with 0, 250, 500 or 1000 mg/kg bw/day of test material in corn oil via oral gavage. A concurrent positive control substance, ethylnitrosurea, was administered intraperitoneally at 100 mg/kg bw for two consecutive days. Following a 3 day sampling period the mutation frequency was determined in the liver, forestomach, nasal epithelium and germ cells (testes and vas deferens/cauda epididymis). Due to the small amount of nasal tissue extracted from each animal, nasal tissue was pooled in each test group and the genomic DNA was extracted from the pooled sample. For the remainder of the tissues, genomic DNA samples were extracted from each animal.

A statistically significant increase in mutant frequency was observed in the forestomach and liver at 1000 mg/kg bw/day when compared to the concurrent negative control. The mean mutant frequencies ($x10^{-6}$) in the forestomach were reported to be 49.1 ± 11.7, 52.2 ± 15.4, 54.9 ± 5 and 78.5 ± 10.7 at 0, 250, 500 and 1000 mg/kg bw/day, respectively. The mean mutant frequencies in the liver were reported to be 48.2 ± 14.1, 62 ± 12.5, 61.2 ± 13.8 and 78.2 ± 18.1 at 0, 250, 500 and 1000 mg/kg bw/day, respectively. No increase in mutant frequency was observed in nasal tissue or germ cells at any dose. The positive control substance elicited a statistically significant increase in mutant frequency in the four tissue samples when compared with the concurrent negative control.

The study author noted that the increase observed in the forestomach at 1000 mg/kg bw/day exceeded the "acceptable range" of the test laboratory which was defined as the historical control mean value ± 3 standard deviations (SD), suggesting the result may be biologically relevant. However, the study author also noted that the increase in mutant frequency in liver at the same dose was within the laboratory's "acceptable range". Therefore, this increase was considered by the study author to be marginal and not biologically relevant. Overall, it was concluded that the test substance induced gene mutation in the forestomach of transgenic mice under the conditions of the study.

The registrants considered that the increase in mutant frequency observed in the forestomach at 1000 mg/kg bw/day to be ambiguous and not biologically significant as it was observed only at the highest dose level. In addition they noted that the mutant frequency observed in the 1000 mg/kg bw/day group ($78.5 \pm 10.7 \times 10^{-6}$) is only marginally outside the acceptable range identified by the test laboratory for the stomach (78.0×10^{-6}) and within the historical control range of the test laboratory for the stomach (31.1 x 10-6 to 84.7×10^{-6}). The registrants also commented that the forestomach is a tissue with a highly acidic pH and so the relevance to other potential site of contact tissues such as skin or respiratory tract is unclear. The registrants did not consider the increase in mutant frequency observed in the liver to be biologically significant as the result was within the acceptable range of the laboratory and within the historical control range of the test laboratory.

Overall, the registrants concluded that the available *in vivo* data is not sufficient to trigger classification of 7-oxabicyclo [4.1.0] hept-3-ylmethyl-7-oxabicyclo [4.1.0] heptane-3-carboxylate for mutagenicity according to CLP.

The evaluating MSCA considers that the available *in vitro* data indicates a concern for gene mutation. Positive results in the presence of metabolic activation were observed in the key Ames study in *S. typhimurium* strains TA 100, TA 1535 and WP2, which all detect base

pair substitutions. In the mammalian cell gene mutation assay in mouse lymphoma cells, positive responses in the presence and absence of metabolic activation were observed. The positive response in the absence of metabolic activation indicates a possible concern for a direct action of the substance as a mutagen at initial sites of contact. The remaining supporting *in vitro* data showed equivocal results with respect to DNA damage.

No increase in unscheduled DNA synthesis was observed in an *in vivo* oral UDS study in rats. The evaluating MSCA notes that the UDS study is an indicator assay which can detect presumed DNA lesions in cells of the liver but not in other tissues. Therefore, the concern of direct action of the registered substance as a mutagen at the initial site of contact is not completely addressed by this study. The available *in vivo* mouse micronucleus assay is not relevant for the investigation of gene mutation.

The oral TGR assay in mice evaluated tissues at the site of first contact (forestomach) as well as the main site of metabolism (liver), the target tissue identified in the 90-day oral repeated dose toxicity study (nasal tissue) and germ cells. The evaluating MSCA agrees with the conclusion of the study author that the increase in mutant frequency in the forestomach at 1000 mg/kg bw/day is biologically and statistically significant. The evaluating MSCA notes that OECD 488 recommends the glandular stomach rather than the forestomach as a site of first contact tissue following oral administration. In this case, the evaluating MSCA considers that the positive response seen in the forestomach in the high dose group is indicative of potential gene mutation at the site of initial contact. In accordance with OECD 488, the stomach is considered an appropriate site of first contact tissue to sample following oral administration and therefore the evaluating MSCA does not agree with the conclusion of the registrants that this tissue is not relevant for assessing potential site of initial contact effects.

With respect to the statistically significant increase in mutant frequency in the liver, the evaluating MSCA agrees with the conclusion of the study author that as the increase is marginal and within the acceptable limits of the test laboratory, that the result is not biologically relevant.

It is noted that due to the small amount of nasal tissue available, pooled rather than individual samples were prepared. While no increase in mutant frequency were observed in any of the pooled samples of 0, 250, 500 or 1000 mg/kg bw/day groups, a statistically significant increase in mutant frequency was observed in the pooled sample of the positive control. The evaluating MSCA notes that this supports the validity of the negative response in this tissue in the test item treated groups.

The evaluating MSCA notes that the sampling of seminiferous tubules and vas deferens/cauda epididymis following 28 + 3 day regime as used in this study results in a mixed population of cells at all stages germ cell development. In accordance with paragraph 33 of OECD 488, such a sampling regime does not provide complete coverage of germ cell development. However, it provides some coverage of cells exposed across the majority of phases of germ cell development, and can be useful for detecting some germ cell mutagens. No increase in mutant frequency was observed at any dose level in the study. The evaluating MSCA notes that no changes to the male reproductive organ weights, sperm motility, sperm morphology, sperm count and sperm production rate were observed in the available oral repeated dose toxicity study with the registered substance.

Overall, the evaluating MSCA considers the increase in mutant frequency in the forestomach at 1000 mg/kg bw/day in the TGR assay to be indicative of a possible direct action of the registered substance as a mutagen at initial sites of contact and concludes that classification as mutagen category 2 is appropriate. Based on the negative results in the germ cell sample in the TGR and the lack of effects on male reproductive organs in the repeated dose toxicity study, the evaluating MSCA concludes that classification as mutagen category 1B for effects on germ cells is not appropriate.

7.9.6. Carcinogenicity

A non-guideline, non-GLP dermal carcinogenicity study is reported in the registration data. Groups of 40 male mice were dermally administered undiluted EP-221 (reported to be composed of pure 7-oxabicyclo(4.1.0)heptane-3-carboxylic acid, 7-oxabicyclo(4.1.0)hept-3-ylmethyl ester) at 4000 – 8000 mg/kg bw, acetone (vehicle control) or 0.2% methyl cholanthrene in acetone (positive control) to clipped intact skin three times per week for up to 29 months. It is noted that there was limited reporting of effects other than tumour incidences. After 23 months of exposure, 1 tumour was observed in the test group compared with 2 in the vehicle control group. At study termination, the survival rate was higher in the test group compared with the vehicle control. Under the conditions of this study, no increase in tumour incidence following administration of the test substance was observed.

A number of predictions for carcinogenicity of the registered substance were obtained from QSAR models (ECHA 2013). The OECD Toolbox returned the following predictions: Toolbox Profiler Mutagenicity/Carcinogenicity alerts and Micronucleus alerts by Bengini/Bossa, DNA binding by OASIS and DNA binding by OECD. In all cases the structural alerts were related to the epoxide moiety, which can react with DNA. DEREK (Derek Nexus: 3.0.1) predicts carcinogenicity as "plausible", based on the epoxide moiety of the registered substance and its potential to react with DNA. TOPKAT (Discovery Studio v9.04) predicts the substance as a carcinogen with high reliability and the prediction is considered to be within the domain of the model. In all cases, the alerts do not take into account the influence of the rest of the structure. Very few structures with the epoxy group attached to a cyclic ring were found and they gave conflicting predictions.

The degenerative and regenerative changes in nasal tissue were observed in the available repeated dose toxicity study. However no concern for hyperplasia or pre-neoplastic lesions was identified. The available dermal carcinogenicity study does identify a concern for (pre-)neoplastic lesions.

The evaluating MSCA concluded that based on the available hazard and use information there is currently no concern for carcinogenicity. The evaluating MSCA recommends that further assessment of carcinogenicity be undertaken in the event of a change in registered uses or a change in exposure potential from existing uses.

7.9.7. Toxicity to reproduction

Effects on fertility

No data available.

Developmental toxicity

In an oral pre-natal developmental toxicity (PNDT) study conducted in accordance with OECD 414, groups of 25 female Sprague Dawley rats were administered the registered substance once daily via oral gavage at doses of 0, 5, 25 125 and 500 mg/kg bw/day, from gestation days (GD) 6 to 19. All females survived to scheduled necropsy and no clinical signs of toxicity were observed.

At 500 mg/kg bw/day, there was a statistically significant decrease in mean body weight gain and food consumption during GD 6-9 and 18-20. When the whole gestation period was evaluated (GD 6-20), the reduction in body weight gain was statistically significant. No significant effects on body weight gain or food consumption were observed at ≤ 125 mg/kg bw/day. A statistically significant increase in mean kidney weights was observed at

125 and 500 mg/kg bw/day. At necropsy, 1 female at 125 mg/kg bw/day and 2 females at 500 mg/kg bw/day had depressed areas of the renal cortex of either left or right kidney. Given the effect was not observed bilaterally and also the low numbers affected, the relationship to treatment is unclear.

Foetal effects observed in the high-dose group included statistically significant decreases in body weight, and in mean litter proportions of ossified cervical centrum number 1 (11.7% versus 25.7% in control group). An increase in the mean litter proportions of unossified sternebrae was observed in the high-dose group. However, this was not statistically significant when compared with the concurrent controls. It is noted that all variations reported are common in this strain of rat: published incidences of ossified cervical centrum number 1, unossified sternebrae numbers 5 and/or 6 and unossified sternebrae numbers 1, 2, 3 and/or 4 are 6.6 to 35.8 % per litter (3004 litters), 0.3 to 26.1% per litter (1415 litters) and 0 to 1.3% per litter (106 litters), respectively (Hood, 2012).

Based on the available data, the registrants identified a NOAEL of 25 mg/kg bw/day for maternal toxicity and a NOAEL of 125 mg/kg bw/day for developmental toxicity, concluding that as the skeletal variations observed at 500 mg/kg bw/day were observed at a maternally toxic dose, no classification for developmental toxicity is warranted.

The evaluating MSCA does not support the conclusion in the registration data that the skeletal effects in the foetal animals of the high-dose group were observed at maternally toxic doses. The registered substance does not appear to cause overt maternal toxicity to the extent that would affect offspring. With respect to the decrease in foetal body weight observed at 500 mg/kg bw/day, the evaluating MSCA notes that the decrease was only marginally outside the historical control range of the laboratory and therefore the effect could be considered slight. Moreover, the incidences of skeletal variation observed only slightly above or within the historical control ranges, are common in this strain of rat and were not accompanied by other biologically significant findings, other than decreased foetal body weight.

The evaluating MSCA identified a NOAEL of 25 mg/kg bw/day for maternal toxicity based on the reduced body weight gain and food consumption, in addition to the significant increase in kidney weight observed at ≥125 mg/kg bw/day and a NOAEL of 125 mg/kg bw/day for developmental toxicity based on significant decreases in foetal body weight and mean litter proportions of ossified cervical centrum No. 1. 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.

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

Based on the available data, the following long-term systemic DNELs for workers were identified by the registrants, which are summarised in table 8.

Table 8

CRITICAL DNELS/DMELS - WORKERS					
Endpoint of concern	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)**	**DNEL/ DMEL**	**Justification/ Remarks**
Repeated dose toxicity (inhalation)	Systemic effects - Long-term	90-day oral repeated dose toxicity study	NOEC: 4.4 mg/m^3 (applying AF of 25)	DNEL: 0.18 mg/m^3	
Repeated dose toxicity (dermal)	Systemic effects – Long-term	90-day oral repeated dose toxicity study	NOAEL: 5 mg/kg bw/day (applying AF of 100)	DNEL: 0.05 mg/kg bw/day	

The NOAEL from the 90-day oral repeated dose toxicity study was selected as the point of departure for the calculation of long-term systemic DNELs for the dermal and inhalation routes. In accordance with ECHA Guidance R.8[4], default absorption values were applied for route-to-route extrapolation in the derivation of inhalation and dermal DNELs. In the absence of route-specific information, a factor of 2 was applied for oral to inhalation extrapolation and a factor of 1 was applied for oral to dermal extrapolation. The evaluating MSCA agrees with the assessment factors (AFs) applied and thus supports the DNEL derived by the registrants.

No DNELs were derived for systemic effects after short term (acute) dermal or inhalation exposure since 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate is not classified for acute toxicity.

No DNELs were derived for local effects after short or long term dermal exposure since no quantitative hazard data is available to address these exposure patterns. A qualitative assessment is reported in the registration data, noting that the substance is classified for skin sensitisation and is thus categorised in the "moderate hazard" band in accordance ECHA Guidance Part E[5]. Based on the available information, the evaluating MSCA agrees that skin sensitisation is the critical effect for this exposure pattern.

For local effects following long term inhalation exposure, no long-term inhalation study is available in the registration dossier. The registrants consider that the long-term systemic inhalation DNEL is protective for long-term local effects. The evaluating MSCA considers that based on the current registered uses and the available data indicating that the critical effects observed are as a result of systemic exposure to the registered substance, a DNEL for local effects following long term inhalation exposure is not required.

No DNELs were derived for the general population since 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate is used only in industrial settings.

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

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

Based on the available information, the registered substance is not acutely toxic by the oral, dermal or inhalation routes and is not irritating to skin or eyes.

There is sufficient information available to determine that the registered substance is a skin sensitiser. However, the evaluating MSCA does not agree with the conclusion in the registration data that this data supports sub-categorisation into category 1B and instead the evaluating MSCA concludes that classification as skin sensitisation category 1 is appropriate.

The critical effect observed in the available oral 90-day repeated dose toxicity study was nasal epithelial degeneration observed at ≥ 50 mg/kg bw day, which was not fully reversible during the 28-day recovery period. While effects on nasal tissue following oral administration are relatively rare, there is no information available which would indicate the effects observed in this study were as a result of dosing error or exposure to toxic or caustic vapours of the registered substance. Therefore, the evaluating MSCA considers that the effect on nasal tissues observed was due to systemic exposure of the test substance and a NOAEL of 5 mg/kg bw/day is identified for risk characterisation. The evaluating MSCA also considers that classification as specific target organ toxicity – repeated exposure category 2 (STOT-RE 2) is appropriate.

A concern for gene mutation was identified from the available *in vitro* data where positive results were observed in bacterial and mammalian cell gene mutation assays in the presence and absence of metabolic activation. The positive response in the absence of metabolic activation indicates a possible concern for a direct action of the substance as a mutagen at initial sites of contact. In a follow up *in vivo* oral TGR assay, an increase in mutant frequency in the forestomach was observed at the high dose (1000 mg/kg bw/day). The evaluating MSCA considers that the available data is indicative of a possible direct action of the registered substance as a mutagen at initial sites of contact and concludes that classification as mutagen category 2 is appropriate.

The evaluating MSCA concludes that based on the available hazard and use information there is currently no concern for carcinogenicity. The evaluating MSCA recommends that further assessment of carcinogenicity be undertaken in the event of a change in registered uses or change in exposure potential from existing uses.

No data is available for the evaluation of reproductive toxicity (fertility).

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 warranted.

7.10. Assessment of endocrine disrupting (ED) properties

Not evaluated.

7.11. PBT and VPVB assessment

Not evaluated.

7.12. Exposure assessment

7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate is a cycloaliphatic epoxy resin. It is used in a wide range of industrial applications including use

in inks, coatings, surface treatments and adhesives and in the production of synthetic polymers, light emitting diode (LED) and insulating materials. The substance is registered for industrial use only.

The following exposure scenarios were addressed in the registration dossiers and these were assessed as part of the substance evaluation.

Industrial:

- Formulation of end use products
- Use in coating agents
- Use as an additive in polycarbonate, polyvinyl chloride, adhesives and as an antioxidant in insulators
- Use as a reactive agent
- Use in electric and other applications
- End use in LED materials.

7.12.1. Human health

7.12.1.1. Worker

The exposure assessment in the registration dossiers covers both dermal and inhalation exposure to workers from industrial uses. There are no registered professional uses. For all exposure scenarios, exposure was considered to be direct exposure to the registered substance.

No exposure monitoring data is reported in the registration dossiers. The dermal exposure estimates reported in the registration dossiers were generated using ECETOC TRA v3.0 or Riskofderm v2.1. Inhalation exposure estimates were generated using ECETOC TRA v3.0, except for activities where there is potential for aerosol generation, e.g. PROC 7 and 10, where the Advanced REACH Tool (ART) v1.5 was used. For each exposure scenario, exposure estimates were generated for local and systemic effects following long term inhalation exposure and systemic effects following long term dermal exposure. A qualitative assessment was undertaken for local effects following long term dermal exposure.

As part of the evaluation, the evaluating MSCA considered the description of the activities and technical processes covered by each exposure scenario, including the control measures employed. The evaluating MSCA attempted to replicate the exposure estimates using the information provided in the registration data and where this was not possible, a reasonable "worst case" exposure estimate was generated. The justifications provided for the choice of model input parameters and any modifications made outside the model estimates were also assessed.

The registration data states that the formulation and industrial uses covered by the exposure scenarios presented are generally carried out in closed, automated or semi-automated processes where there is no or limited potential for worker exposure. The evaluating MSCA notes that closed or fully automated conditions are described for some activities (PROCs 1, 2 and 3). However, there are some activities which are covered by PROC codes for which worker exposure is anticipated (PROCs 4, 5, 7, 9, 10 and 15). Also, it is acknowledged in the registration data that there may be sites where activities are not carried out under completely enclosed processes. Therefore, the evaluating MSCA considered there was a need to assess the potential for worker exposure.

The evaluating MSCA notes there is a high reliance on local exhaust ventilation (LEV) and gloves in the exposure scenarios. LEV is specified for all worker exposure scenarios where activities are not carried out under completely enclosed systems. In order to address "worst case" conditions, it is stated in the registration data that exposure estimates were generated assuming LEV is in place. The evaluating MSCA notes that while use of LEV is

reasonable for many industrial processes, it may be difficult to implement in practice for certain activities, in particular cleaning and maintenance activities.

The use of chemically resistant gloves conforming to European Union Standard E374 with specific activity training is specified for every activity and the recommended glove material type, thickness and breakthrough time is also specified. Respiratory protective equipment is not specified for any activity.

A number of exposure modification factors have been applied to generate the exposure estimates presented in the registration data. In particular, modification factors for the use of LEV, gloves, task durations and concentration of the substance in a mixture have been used. The evaluating MSCA notes that these have not always been applied correctly which may potentially lead to an underestimation of exposure, in particular for dermal exposure estimates, as discussed below.

An exposure modification factor to take account of the use of LEV has been applied for dermal exposure estimates. The evaluating MSCA notes that the use of such a modification factor for LEV is usually not justifiable for low volatility substances such as the registered substance where surface contamination rates are largely not affected by the rate of evaporation (ECHA Guidance R.14)[6]. It is noted that no specific justification has been provided in the registration data to justify the use of this modification. The evaluating MSCA generated dermal exposure estimates using ECETOC TRA v3.0 without applying the exposure modification factor for LEV and found that the estimates were significantly higher than those reported in the registration data.

The dermal exposure estimates reported in the registration data also applied modification factors to take account of the concentration of the substance in a mixture, where it is not used as a neat substance. The evaluating MSCA notes that ECETOC TRA v3.0 only allows application of a modification factor for concentrations in a mixture of up to 25%. However, in the registration data, concentration modification factors above 25% have been applied. For example, for the dermal exposure estimate for one cleaning and maintenance activity (covered by PROC 5), a concentration modification factor of greater than 25% was applied. ECHA Guidance R.14 states that deviation from the ECETOC TRA default values should not be made without a justification and evidence e.g. a linear relationship between the exposure output and the concentration. No such justification or evidence is provided in the registration data for the deviation from the default approach. The evaluating MSCA notes that where the default model parameters are used, a significantly higher dermal exposure estimate is obtained.

In some of the exposure scenarios, the choice of PROC code used to describe a particular worker activity, or the combination of PROC codes used in the exposure scenario, are not adequately justified. In particular, PROC 5 ("mixing or blending in batch processes") is used to generate exposure estimates for equipment cleaning activities. Based on the description of the cleaning tasks performed by workers, the evaluating MSCA considers this PROC code may not be appropriate and may significantly underestimate the potential dermal exposure. According to ECHA Guidance R.12[7] PROC 10 ("roller application and brushing") covers activities such as application of cleaning agents and cleaning of surfaces and so may be more appropriate to estimate worker exposure for equipment cleaning activities. The evaluating MSCA generated dermal exposure estimates using PROC 10 in ECETOC TRA v3.0 and Riskofderm v2.1, which were both significantly higher than those reported in the registration data.

In the registration data, PROC 2 is used to generate exposure estimates for filtering and filling activities at "non-dedicated sites". While the registration data indicates that this is a

[6] Guidance on information requirements and chemical safety assessment. Chapter R.14: Occupational exposure estimation

[7] Guidance on information requirements and chemical safety assessment. Chapter R.12: Use description

closed automated process, it also states that LEV is used on sites where the substance is not completely contained or enclosed. The evaluating MSCA considers that the use of PROC 2 may not cover all possible activities, in particular at sites where complete containment or enclosure is not achieved and that PROC 8a ("transfer of substance or mixture (charging and discharging) at non-dedicated facilities") may be more appropriate. The evaluating MSCA generated a dermal exposure estimate using PROC 8a in ECETOC TRA v3.0 which was again significantly higher than that reported in the registration data.

The potential for aerosol generation was identified for two activities in the exposure scenario covering end use of the registered substance in coating agents (PROC 7 and PROC 10). The registration data indicates that such spray activities are automated and conducted in closed systems and thus the exposure estimates represent incidental contact with contaminated surfaces during, for example, maintenance or trouble shooting tasks. The evaluating MSCA notes that this modelling scenario is unlikely to reflect such maintenance or trouble shooting tasks since spraying and aerosol release are not expected during maintenance activities. In addition, workers would not be segregated from the source (i.e. contaminated surfaces) during maintenance activities. The evaluating MSCA calculated dermal exposure estimates for PROC 7 and PROC 10 using ECETOC TRA v3.0 and Riskofderm v2.1 to reflect maintenance tasks which were again significantly higher than those reported in the registration data.

The evaluating MSCA has calculated dermal exposure estimates for a number of activities. For ECETOC TRA v3.0, the evaluating MSCA assumed no LEV use, the use of gloves and application of concentration modification factor (i.e. up to 25%) in accordance with ECHA Guidance R.14, where appropriate. For Riskofderm v2.1, not all model input parameters were documented in the registration data, in particular for those activities for which ECETOC TRA v3.0 instead of Riskofderm v2.1 was to generate the exposure estimate. For these PROCs the evaluating MSCA assumed reasonable worst case model input parameters based on the description of the activity in the registration data and the typical use conditions for the activity. The exposure estimates generated using both models are summarised in table 9 below.

Further details on the exposure assessment conducted by the evaluating MSCA are included in a confidential annex to this report.

Table 9

DERMAL EXPOSURE ESTIMATES GENERATED BY THE EVALUATING MSCA		
PROC code	**ECETOC TRA v3.0 (mg/kg bw/day)**	**Riskofderm v2.1 (mg/kg bw/day)**
PROC 2	0.07	-
PROC 4	0.34	0.8
PROC 5	0.69	0.8
PROC 7	2.14	1.1
PROC 8a	0.69	0.8
PROC 8b	0.69	0.8
PROC 9	0.34	0.8
PROC 10	1.37	1.1

The dermal exposure estimates calculated by the evaluating MSCA, as reported in table 9, are significantly higher than those reported in the registration data. The evaluating MSCA therefore considers that the potential for dermal exposure may be underestimated in the registration data.

As discussed above, the evaluating MSCA made a number of assumptions in generating the Riskofderm v2.1 exposure estimates and therefore there is some uncertainty regarding the reliability of these exposure estimates. Therefore, for the purpose of risk characterisation the evaluating MSCA used the ECETOC TRA v3.0 exposure estimates reported in table 9 and compared these with those reported in the registration data.

A qualitative assessment for local effects following dermal exposure is reported in the registration data. This is based on the conclusion that the substance is self-classified as skin sensitisation category 1B and in accordance with ECHA Guidance Part E the substance is assigned to the "moderate hazard" band. The operational conditions (OC) and risk management measures (RMM) recommended for the "moderate hazard" band in Table E3-1 of ECHA Guidance Part E to minimise dermal exposure are documented in the registration data. The evaluating MSCA notes that these are the same OC and RMM applied for the quantitative assessment of exposure for systemic effects following dermal exposure. Given the uncertainty in the dermal exposure estimates discussed above, the evaluating MSCA considers that there is some uncertainty regarding whether dermal exposure is adequately controlled.

With respect to inhalation exposure, the potential for aerosol generation was identified for two activities covered by PROC 7 and PROC 10. In both cases, the modelled inhalation exposure estimates were generated using "spraying" model parameters in ART with a short activity duration and were reported to be low (less than 1 x 10^{-3} mg/m^3). It is indicated in the registration data that such spray activities are automated and conducted in closed systems and thus the exposure estimates represent incidental contact with contaminated surfaces during, for example, maintenance or trouble shooting tasks. Similarly for the dermal exposure estimate discussed above, the evaluating MSCA notes

that this modelling scenario is unlikely to reflect such maintenance or trouble shooting tasks. The evaluating MSCA calculated inhalation exposure estimates for PROC 7 and PROC 10 to reflect maintenance tasks using ART, using the modelling scenario "handling of contaminated objects" and using reasonable worst case input parameters. Based on these model estimates, no concern for inhalation exposure from such tasks was identified.

Based on the information provided in the registration data, no concern for inhalation exposure was identified by the evaluating MSCA for the remaining worker activities reported in the registration data.

Overall, the evaluating MSCA concluded that the dermal exposure estimates presented in the registration data may underestimate the potential for exposure and therefore a potential concern for dermal exposure remains.

The registrants are recommended to consider further refinement of the dermal exposure estimates.

7.12.1.2. Consumer

No consumer uses identified in the registration data.

7.12.2. Environment

Not evaluated.

7.13. Risk characterisation

7.13.1. Human health

7.13.1.1. Worker

The leading health effects which are relevant for risk characterisation were degeneration of nasal epithelium observed in oral 90-day repeated dose toxicity study, skin sensitisation and mutagenicity.

The registration data identified DNELs for long-term systemic dermal and inhalation exposure of 0.05 mg/kg bw/day and 0.18 mg/m^3, respectively, based on nasal tissue degeneration observed in an oral 90-day repeated dose toxicity study. These values have been used to conduct a quantitative risk characterisation for long term systemic dermal and inhalation exposures. Based on the data available, the evaluating MSCA supports the DNELs derived.

The registration data has concluded that the risk characterisation ratios for both dermal and inhalation exposure for all exposure scenarios are below 1.

The evaluating MSCA can support the conclusion of the registrants that there is no concern for inhalation exposure.

With respect to dermal exposure, the evaluating MSCA considers that the exposure estimates reported in the registration data may underestimate the potential dermal exposure. Table 10 summarises the risk characterisation ratio (RCR) values obtained when the dermal exposure estimates generated by the evaluating MSCA using ECETOC TRA v3.0 are compared with the long-term systemic DNELs for the dermal route.

Table 10

RCRS FOR LONG TERM DERMAL EXPOSURE, SYSTEMIC EFFECTS		
PROC code	**ECETOC TRA v3.0 (mg/kg bw/day)**	**RCR**
PROC 2	0.07	1
PROC 4	0.34	7
PROC 5	0.69	14
PROC 7	2.14	43
PROC 8a	0.69	14
PROC 8b	0.69	14
PROC 9	0.34	7
PROC 10	1.37	27

The evaluating MSCA concluded that based on the available information, dermal exposure may not be adequately controlled.

A qualitative assessment for local dermal exposure is also reported in the registration data. The registered substance is self-classified as skin sensitisation category 1B and in accordance with ECHA Guidance Part E the registration data assigns the substance to the "moderate hazard" band. The registration data documents the OC and RMM which are recommended for "moderate hazard" band in Table E3-1 of ECHA Guidance Part E. However, given the uncertainty in the dermal exposure estimates presented in the registration data for systemic effects, the evaluating MSCA considers that there is some uncertainty regarding whether the existing OC and RMM are adequate.

The evaluating MSCA agrees that the registered substance meets the criteria for classification as a skin sensitiser and that a qualitative assessment is appropriate for skin sensitisation. However, the evaluating MSCA does not agree that the available data allows a decision on sub-categorisation into category 1A or 1B. The choice of intradermal induction dose and the relatively high response rate in the available guinea pig maximisation test while meeting the criteria for sub-categorisation into category 1B does not allow a definitive conclusion that category 1A is not appropriate. No further data was identified which could assist the potency assessment. Therefore, as sub-categorisation into category 1A cannot be excluded, the evaluating MSCA concludes that classification as skin sensitisation category 1 is appropriate. In accordance with Table E3-1 of ECHA Guidance Part E, where a substance is classified as skin sensitisation category 1, i.e. where the available data does not allow potency categorisation, the RMM and OCs applicable to the "high hazard" band should be applied. These measures aim to avoid exposure. The evaluating MSCA considers that further review and refinement of the implemented OC and RMM is required by the registrants, in line with the requirements for the "high hazard" band, to ensure exposure is avoided.

The evaluating MSCA concludes that based on the available data the registered substance should be classified as mutagen category 2. According to ECHA Guidance Part E, this

classification indicates a "high hazard" band. In this case the available data is indicative of a possible direct action of the registered substance as a mutagen at initial sites of contact and there is currently no data which indicates a concern for germ cell mutagenicity. Therefore, the evaluating MSCA considers that the control measures which will be implemented for skin sensitisation will be sufficient to cover the concern for mutagenicity.

7.13.2. Environment

Not evaluated.

7.14. References

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7.15. Abbreviations

AF	Assessment factor
BW	Body weight
CAS	Chemical abstracts service
CHO	Chinese hamster ovary
CLP	Classification, labelling and packaging (Regulation (EC) No 1272/2008)
DNEL	Derived no effect level
GD	Gestation day
LD50	Median lethal dose. The dose causing 50 % lethality
LED	Light emitting diode
LEV	Local exhaust ventilation
MSCA	Member State Competent Authority
NOAEC	No observed adverse effect concentration
NOAEL	No observed adverse effect level
NOEL	No observed effect level
OECD	Organisation for Economic Co-operation and Development
OC	Operational conditions
PCE	Polychromatic erythrocytes
PBT	Persistent, Bioaccumulative, Toxic
PNDT	Pre-natal developmental toxicity
PROC	Process category
RCR	Risk characterisation ratio
RMM	Risk management measures
SCE	Sister chromatid exchange
TGR	Transgenic rodent somatic and germ cell mutation
TPA	Tonnes per annum
UDS	Unscheduled DNA synthesis
vPvB	Very Persistent and very Bioaccumulative