Hellenic Democracy
Ministry of Finance
General Secretariat of
Public Revenue
General Directorate of
General Chemical State Laboratory

SUBSTANCE EVALUATION CONCLUSION
as required by REACH Article 48
and
EVALUATION REPORT

for

(-)-Pin-2(10)-ene
EC No 242-060-2
CAS No 18172-67-3

Evaluating Member State: Greece

Dated: 9th October 2015

Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2014

Following a compliance check targeted to the substance identity and carried out by ECHA, the identifiers of the substance have been changed, in agreement with the registrants, as presented below.

Previous Substance name: pin-2(10)-ene

Previous EC Number submitted: 204-872-5

Previous CAS Number submitted: 127-91-3

Current Substance name: (-)-pin-2(10)-ene

Current EC Number: 242-060-2

Current CAS Number: 18172-67-3

Greece concluded the evaluation in March 2015 without any request for information from the Registrants under Article 46(1) decision.

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

Contents

Part A. Conclusion

1. CONCERNS SUBJECT TO EVALUATION

(-)-Pin-2(10)-ene was originally selected for substance evaluation in order to clarify the following suspected risks:

- Suspected sensitizer
- Lack of data on respiratory sensitisation
- Lack of scenarios on consumers' exposure especially through inhalation
- Wide-spread and dispersive use both for consumers and workers (high aggregated tonnage and various consumer uses)

During the evaluation other concerns were also identified. The additional concerns were:

- The acute and chronic hazards to the aquatic environment that were not adequately addressed in the registration dossier
- Systemic inhalation and local dermal exposure of workers and professionals under certain scenarios appeared high in the CSR presented

In addition the eMSCA realized that in case new hazards are identified (i.e. respiratory sensitisation), new risk assessment should be performed for workers and consumers.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

There are no other ongoing processes and no relevant legislation for the specific substance.

The evaluating Member State has also performed a Risk Management Option analysis (RMOA), which has been submitted to ECHA. The conclusions thereof will be presented in a different document.

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State 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	X*
Other EU-wide measures	

No need for regulatory follow-up action	

**Depending on the outcome of the CLH process*

4. FOLLOW-UP AT EU LEVEL

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

During the SEv process the Registrants decided to endorse the majority of the suggestions made by the eMSCA in the informal communication during the evaluation and updated the REACH registration dossier accordingly by the end of the SEv process.

Clarification of the hazard properties regarding skin and respiratory sensitisation has now been made available in the updated registration dossier, including an extensive literature review especially for respiratory sensitisation. The eMSCA concluded that the extra data provided by the registrant were enough for evaluation.

More specifically, the registrants considered all available data provided in the registration dossier on potential effects of (-)-pin-2(10)-ene to the respiratory system and applied according to their expert judgment the criteria set by Reg. 1272/2008/EC. The registrants concluded that classification for any inhalation hazard (respiratory tract irritation or respiratory sensitisation) is not warranted. Nevertheless, the eMSCA is of the opinion that the evaluation of the data available on respiratory sensitisation, both from human epidemiological studies and from supporting animal data, is worth being performed through a CLH process, which is the legally appropriate regulatory process to assess the hazard of a substance and reach an opinion through Risk Assessment Committee (RAC). It is noted that classification for the human health hazard of respiratory sensitisation is based only on human data, according to the Reg. 1272/2008/EC and human data can be ambiguous and lead to different conclusions. It should be noted that the lack of animal studies to substantiate the respiratory sensitisation classification renders it a challenging human health endpoint.

In addition, (-)-pin-2(10)-ene is currently self-classified as **Skin Sens. 1B (H317)** and is supported both by animal and human data. Verifying skin sensitisation, which is attributed by the industry on a self-classification basis, by a regulatory CLH process is also worth-doing.

Furthermore, the acute and chronic hazards of (-)-pin-2(10)-ene to the aquatic environment have been addressed by the registrants by introducing new data and properly evaluating both new and existing data. It should be noted that these data are based on acute toxicity studies available. The substance is now adequately self-classified as **very toxic to aquatic life (H400)** and **very toxic to aquatic life with long-lasting effects (H410)**. Nevertheless, QSAR calculated NOECs for fish and daphnia could even lead to a less severe classification, if verified by experimental data, too. Therefore, environmental hazards could also be a part of a regulatory CLH process.

A reduction in the aggregated tonnage has now been introduced in the registration dossiers, after relevant documented responses (questionnaires) provided by all co-registrants concerning the uses of (-)-pin-2(10)-ene. The current aggregated tonnage does not exceed **15000 T/y,** while the tonnage for consumer uses remains under **1000** T/y. However (-)-pin-2(10)-ene is still considered a substance with a wide dispersive use.

A thorough consumer risk assessment, which minimises concerns for relevant risks, has been performed and included in the updated registration dossier and was additionally reviewed and verified during the evaluation process. A more precise description of the

processes (temperatures, ventilation type, duration of operations etc), more realistic considerations regarding exposure duration and better knowledge of the tonnages among the different uses have led to a reduced number of worse case assumptions for workers and professional users. **Therefore, in addition to the low risks for the consumers, inhalation and local dermal exposure of workers and professionals appear reasonably controlled now. On the other hand, if harmonised classification on respiratory sensitisation for (-)-pin-2(10)-ene is decided in a CLH regulatory process, a new risk assessment should be performed for workers, professional users and consumers. Since (-)-pin-2(10)-ene is a constituent of various products that are inhaled or can be inhaled through their normally expected uses, a possible restriction proposal could also be identified as an appropriate risk management measure.**

4.1.1. Harmonised Classification and Labelling

(-)-Pin-2(10)-ene does not have a harmonised classification but is self-classified as Skin Sens. 1B (H317) and could potentially be a respiratory sensitizer, based on the available literature data, as explained above. Although the registrants in the updated dossier examined the available literature data and concluded that there was no indisputable evidence for the respiratory sensitizing properties of (-)-pin-2(10)-ene, the eMSCA believes that the specific hazard class is of the greatest concern and should be thoroughly examined through the harmonised classification and labelling process (submission of a CLH dossier for inclusion of the substance in Annex VI of the CLP). It is important to stress the fact that the endpoint of respiratory sensitisation lacks validated animal tests for classification purposes and is based on human data which can be ambiguous and difficult to interpret.

Furthermore, the environmental hazards of (-)-pin-2(10)-ene are also recognised in the updated dossier and the relevant self-classification as very toxic to aquatic life (H400, M=1) and very toxic to aquatic life with long-lasting effects (H410, M=1) is now proposed. The eMSCA believes, after having discussed it with the registrants and based on the NOECs for fish and daphnia calculated by QSAR, that even a less severe classification for environmental hazards could be discussed through a harmonised classification and labelling process (CLH dossier), if available experimental studies could support this conclusion (read-across included).

Finally, harmonized classification for the skin sensitisation properties of (-)-pin-2(10)-ene, which is currently self-classified as **Skin Sens. 1B (H317)**, in a CLH dossier is also warranted.

Thus, a CLH dossier should be prepared proposing a new entry in Annex VI of the CLP.

Depending on the outcome of the harmonised classification and labelling process on the respiratory sensitisation endpoint, and following an updated risk assessment, a restriction process on specific uses that include inhalation of (-)-pin-2(10)-ene as part of the normally expected conditions and applications could be a viable solution for addressing and adequately controlling the risk associated with the use of (-)-pin-2(10)-ene on a EU wide basis. It is noted that end uses of (-)-pin-2(10)-ene include consumer products, such as washing and cleaning products, air care products, insect repellants and cosmetics.

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

Not applicable.

4.1.3. Restriction

Based on current information, a proposal for restriction is not fully justified. The risks associated with the use of (-)-pin-2(10)-ene for both consumers and workers/professionals seem to be adequately controlled, taking into consideration the current recognised health hazards. Nevertheless, if the respiratory hazard is verified through the CLH process and if the updated risk assessment shows high consumer risks then:

- a maximum concentration of (-)-pin-2(10)-ene could be introduced in final consumer products
- a restriction in the use of (-)-pin-2(10)-ene in air care products could be justified as an appropriate risk management option, if the respiratory sensitisation hazard is proven and substantiated

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
CLH dossier for inclusion of the substance in Annex VI of the CLP *Hazard classes to be dealt with* • *Skin sensitisation* • *Respiratory sensitisation* • *Hazardous to aquatic environment (acute and long-lasting effects)*	*March 2017*	*The Registrants could possibly act as dossier submitter. The eMSCA cannot undertake the responsibility of preparing a CLH dossier and is not legally obliged to do so, as (-)-pin-2(10)-ene is not a biocidal active substance (art. 36 and 37 Reg. 1272/2008/EC).*

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

(-)-Pin-2(10)-ene was originally selected for substance evaluation in order to clarify the concerns associated with the:

- Suspected skin sensitizing properties
- Lack of data on respiratory sensitisation
- Lack of scenarios on consumers' exposure through inhalation
- Wide-spread and dispersive use both for consumers and workers

During the evaluation also other concerns were identified. The additional concerns were:

- The acute and chronic hazards to the aquatic environment were not addressed.
- Systemic inhalation and local dermal exposure of workers and professionals under certain scenarios appeared rather high.

Table 3

EVALUATED ENDPOINTS **Endpoint evaluated**	**Outcome/conclusion**
Skin Sens 1B *May cause an allergic skin reaction*	*Skin Sensitisation properties confirmed* *Self-classification applied* *C & L process to be initiated*
Respiratory Sensitisation	*A thorough literature search provided the necessary data that enables the evaluation of the specific endpoint.* *Concern not substantiated by the registrant through application of the Reg. 1272/2008/EC criteria.* *A detailed and thorough reassessment of the available data should be initiated through the Classification and Labelling Process, which is the legally appropriate regulatory process to assess the respiratory hazard endpoint. Eventually, an opinion should be agreed through the Risk Assessment Committee (RAC).*
Aquatic Acute 1 *H400: Very toxic to aquatic life, M=1*	*Environmental hazard confirmed* *Self-classification applied*

	C & L process to be initiated.
Aquatic Chronic 1 *H410: Very toxic to aquatic life with long lasting effects, M=1*	*Environmental hazard confirmed* *Self-classification applied* *C & L process to be initiated.*
Exposure scenarios and risk characterisation for workers, professionals and consumers	*Adequately controlled* *No additional risk management measures required for the moment. Nevertheless, depending on the outcome of the harmonised classification and labelling process and if the respiratory sensitisation hazard is justified, an updated risk assessment should be performed for respiratory sensitisation. If the risk is proven not to be adequately controlled, a restriction process could be initiated.*

7.2. Procedure

The areas of concern were evaluated based on the original registration dossier, the Chemical Safety Report (CSR), documents submitted during the substance evaluation process, the updated registration dossier and on literature data shared with the registrants. The eMSCA focused on the hazard endpoints mentioned in Table 3, as well as on the exposure scenarios and the risk associated with the use of (-)-pin-2(10)-ene both for consumers and for workers/professionals.

Summary of substance evaluation procedural history with some important dates (only main steps):

1. April 2014: A substance identity (SID) issue was identified during the targeted compliance check of the substance. The SID issue was whether the substance registered was a racemic mixture or a specific isolated enantiomer. After the registrants provided clarifications, it was concluded that the substance undergoing the evaluation is (-)-pin-2(10)-ene with identifiers CAS 18172-67-3 and EC 242-060-2.
2. May 2014: The eMSCA informed the registrants about the areas of concern regarding the SEv of (-)-pin-2(10)-ene. In summary, the points raised during the communication with the registrants were:
    - The endpoint of respiratory sensitisation was not dealt in the registration dossier despite the fact that there are published data in the literature dealing with potentially respiratory sensitisation caused by (-)-pin-2(10)-ene and other structurally and toxicologically similar substances (both in humans and animal studies).
    - Although the registrant(s) recognized that (-)-pin-2(10)-ene is used in consumer products, which are designed to be directly inhaled by the general

population (e.g. air fresheners), no exposure scenarios for consumers for inhalation/ respiratory hazards were available. Furthermore, although (-)-pin-2(10)-ene is extensively used in consumer products, such as washing and cleaning products, the exposure scenarios for skin sensitisation for consumers were not exploited in detail and were rather vague.

- There was an initial concern about the wide-spread and dispersive use both for consumers and for workers/professional users. In addition, the exposure scenarios and risks associated with certain uses for workers and professionals seemed not to be adequately controlled, as the RCRs were rather high. Some parameters crucial for the exposure assessment appeared poorly estimated (even over-estimated in some cases).
- The eMSCA asked the registrants to provide a detailed study for the derivation of DNELs, dose descriptors and the use of assessment factors (some assessment factors needed revision), regarding worker and consumer exposure.
- The two environmental hazard endpoints, Aquatic Acute 1, H400 and Aquatic Chronic 1, H410, were addressed in the original registration dossier by the registrants with studies and concluded with no classification. Nevertheless, more than 250 notifiers in the C&L inventory had already classified the substance with the aforementioned endpoints. The eMSCA asked the registrants to re-evaluate the specific endpoints.

3. July 2014: The eMSCA and the registrants had a meeting discussing the issues, which had been raised during the course of the SEv process so far. The key points discussed were:
   - Uses of (-)-pin-2(10)-ene: Distribution of (-)-pin-2(10)-ene tonnages between industrial and professional/consumer uses. Data on (-)-pin-2(10)-ene concentrations in final products
   - Ecotoxicological studies: New data and classification of (-)-pin-2(10)-ene for environmental hazards
   - Inhalation/respiratory endpoints: Discussion on the information required, literature review and subsequent agreement on the set of data to be used.
   - Agreement on deadlines for the SEv procedure and re-submission of the updated dossier.
4. September 2014: The registrants supplied the eMSCA the confidential position document regarding the ecotoxicological results, environmental classification and derived PNECs, of (-)-pin-2(10)-ene.
5. September 2014: The registrants supplied the eMSCA with the confidential position document regarding the respiratory sensitisation endpoint of (-)-pin-2(10)-ene.
6. October 2014: The registrants supplied the eMSCA with the confidential document regarding the tonnages, uses and concentrations of (-)-pin-2(10)-ene in final products.
7. October 2014: The registrants supplied the eMSCA with the confidential document regarding the calculation of DNELs for (-)-pin-2(10)-ene.

8. October 2014: The registrants supplied the eMSCA with the confidential position document regarding the exposure scenarios and risk characterisation measurements of (-)-pin-2(10)-ene with all the improvements summarized.
9. November 2014: The eMSCA started thoroughly evaluating the confidential information and all documents provided by the registrants. The registrants, after agreeing with the eMSCA on the new information and data, proceeded with updating the registration dossier by including data on respiratory sensitisation, by evaluating the above-mentioned endpoint, by changing the classification for the environmental endpoints (self-classification as H400, M=1 and H410, M=1) and by rewriting Chapters 9 and 10 of the CSR. Furthermore, after careful evaluation of the confidential data provided by the registrants on tonnage bands, the eMSCA came to the conclusion that although there is wide dispersive use for the (-)-pin-2(10)-ene, the risk is substantially controlled for workers, professional users and consumers for the hazard endpoints identified.
10. December 2014: The General Chemical State Laboratory of Greece, as the evaluating CA, has come to the conclusion that no request for further information according to Article 46 (1) is required for (-)-pin-2(10)-ene.

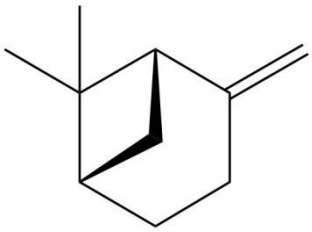
7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	(-)-Pin-2(10)-ene
EC number:	242-060-2
CAS number:	18172-67-3
Index number in Annex VI of the CLP Regulation:	
Molecular formula:	$C_{10}H_{16}$
Molecular weight range:	136.24
Synonyms:	(1S,5S)-6,6-dimethyl-2-methylenebicyclo[3.1.1]heptanes **(-)-pin-2(10)-ene** **(1*S*)-(−)-β-Pinene** **(1*S*,5*S*)-2(10)-Pinene**

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	690 Pa at 20°C 851 Pa at 25°C
Water solubility	≤ 0.02 mg/L at 20°C, **initial dossier** = 6.95 mg/L at 20°C, **updated dossier***
Partition coefficient n-octanol/water (Log Kow)	log Kow of 4.425 ± 0.005 at 25 °C
Flammability	
Flash Point	39°C at ca. 1 atm The flash point was determined with a closed cup tester by the Setaflash method. The flash point of (-)-pin-2(10)-ene is 39°C. The substance is classified as flammable liquid category 3 (H226) according to CLP Regulation (EC) No 1272/2008.
Explosive properties	*Not applicable*
Oxidising properties	*Not applicable*
Granulometry	*Not applicable*
Stability in organic solvents and identity of relevant degradation products	*Not applicable*
Dissociation constant	*Not applicable*
Viscosity	2.2 mPa s (dynamic) at 20°C 1.4 mPa s (dynamic) at 40°C The dynamic viscosity was determined with a rotational viscometer. The substance can be considered as a Newtonian fluid. The dynamic viscosity of (-)-pin-2(10)-ene at a shear rate of 583 s-1 is 2.2 mPa.s at 20°C and 1.4 mPas.s at 40°C. (-)-pin-2(10)-ene is classified for

	aspiration toxicity Category 1 according to Regulation (EC) No 1272/2008 (CLP) criteria (hydrocarbon with a kinematic viscosity of less than 20.5 mm2/s at 40°C): H304: May be fatal if swallowed and enters airways.

* A recent study was performed in order to determine the water solubility of (-)-pin-2(10)-ene. In this study, the water solubility of (-)-pin-2(10)-ene was determined to be 6.95 mg/L using the slow-stirring method (at 20°C and pH 4-7), which is the preferred method for this kind of substances. This value is retained to be used as key value for the chemical safety assessment. This result is supported by literature data on (-)-pin-2(10)-ene: 8.06 mg/L (Copolovici, 2005: geometric mean of three literature values), 11.03 mg/L (Fichan, 1999: two liquid phase contact methods giving an emulsion treated in 2 ways, settling and centrifugation); 12.7 mg/L (Tamura, 2005: close to the flask method not suitable for low solubility substances). These latter values are slightly overestimated due to the methods used for calculation. It must be noted that the study performed in 2010 to determine the water solubility of (-)-pin-2(10)-ene using the elution method, that was originally included in the registration dossier, led to a water solubility value ≤ 0,02 mg/L at 20ºC and pH 8. After re-examination, this study is considered as not reliable and is disregarded for the following reasons:

- ✓ The water solubility measured at 20°C (≤ 0.02mg/L) in this study, is not consistent with previously reported values for (-)-pin-2(10)-ene: 11.03 mg/L (Fichan, 1999); 12.7 mg/L (Tamura, 2005) and 8.06 mg/L (Copolovici, 2005) and with the result of the Madru's recent study on (-)-pin-2(10)-ene (slow-stirring, 6.95 mg/L at 20°C).
- ✓ The mean values obtained from the three consecutive tests conducted with different flow rates differed by more than 30%. Therefore, according to the OECD 105 guideline criteria, the study is not valid. The water solubility decreased, when the water flow rate decreased. This can be explained by an insufficient quantity of the test item loaded on the support material, leading to erroneous results.

Therefore, the water solubility value of (-)-pin-2(10)-ene found in the more recent study (**6.95 mg/L**) is considered as the most accurate and is selected to be used as key value for the chemical safety assessment of this substance.

7.5. Manufacture and uses

7.5.1. Quantities

Table 6: Aggregated tonnage (per year)

Tonnage range to be ticked only.

☐ 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

Table 7

Uses (EU wide)	% Tonnage/year	Aggregated tonnage/ year
Manufacture	73%	10,000 - 50,000 t

Importation	27%	
Isolated intermediate	41%	
Polymers	49%	
Fragrances	10%	

7.5.2. Overview of uses

The following applications/uses for (-)-pin-2(10)-ene have been identified (relevant quantitative data are provided in Table 7):

1. Manufacturing of substances
2. Formulation of preparations containing the substance
3. Uses at industrial sites
   - 3.1. Use of the substance as an intermediate to be transformed to another substance
   - 3.2. Industrial use of the substance as a monomer for polymerisation
   - 3.3. Industrial end-use of washing and cleaning products, polished and wax blends, cosmetics, air-care products and biocides (< 4% of the aggregated tonnage per year)
4. Use of products containing the substance by professional workers (< 5% of the aggregated tonnage per year, products similar to the ones mentioned above)
5. Consumer uses of commercial products such as washing and cleaning products, polished and wax blends, cosmetics, personal care products, perfumes, fragrances, air-care products/ air fresheners/ odour agents and biocides (< 5% of the aggregated tonnage per year, with air care products and air fresheners being the main source of the substance)

During these applications/uses several use descriptors have been identified and used for exposure assessment. Namely, in manufacturing of substances and formulation of preparations, uses in closed processes have been described with either no likelihood of exposure, or occasional controlled exposure, and processes where the possibility of exposure may arise under certain reasonably expected conditions which could be prevented or monitored. Furthermore, transferring/pouring of the substance or preparation from and to vessels/containers of various sizes at dedicated or non-dedicated facilities has been identified and had to be explicitly studied from an exposure point of view. Uses of (-)-pin-2(10)-ene as laboratory reagent or for preparation of articles by processes such as tabletting, compression, extrusion and pelletisation had minor contribution to exposure.

In uses at industrial sites, apart from the above, industrial spraying has been recognised as an important contributor to exposure, which was also the case for uses by professional workers. In the latter case, roller application or brushing has also been identified.

Consumer uses revealed low but frequent exposure of humans with a variety of products and everyday processes.

Table 8

USES	Use(s)
Uses as intermediate	Manufacture of bulk, large scale chemicals (manufacture of fine chemicals
Formulation	Formulation of preparations, compounding of fragranced products
Uses at industrial sites	Substance used as intermediate (Manufacture of bulk, large scale chemicals, manufacture of fine chemicals), Substance use as monomer for polymerisation, Use of fragranced products
Uses by professional workers	Formulation and use of fragranced products
Consumer Uses	**Use of Fragranced products**: Air care products, biocidal products (e.g. disinfectants, pest control), perfumes, fragrances, polishes and wax blends, washing and cleaning products (including solvent based products), cosmetics, personal care products

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

Not applicable

7.6.2. Self-classification

- ***In the registration dossier at the beginning of the SEv process***

Table 9

International Chemical Identification	EC No	CAS No	Classification	
			Hazard Class and Category Code(s)	Hazard statement code(s)
(-)-pin-2(10)-ene	242-060-2	18172-67-3	Flam. Liquid 3	H226: Flammable liquid and vapour.
			Asp.Tox. 1	H304: May be fatal if swallowed and enters airways.
			Skin Irrit. 2	H315: Causes skin irritation
			Skin Sens 1B	H317: May cause an allergic skin reaction

- ***In the updated registration dossier at the end of the SEv process***

Table 10

International Chemical Identification	EC No	CAS No	Classification	
			Hazard Class and Category Code(s)	Hazard statement code(s)
(-)-pin-2(10)-ene	242-060-2	18172-67-3	Flam. Liquid 3	H226: Flammable liquid and vapour.
			Asp.Tox. 1	H304: May be fatal if swallowed and enters airways.
			Skin Irrit. 2	H315: Causes skin irritation
			Skin Sens 1B	H317: May cause an allergic skin reaction
			Aquatic Acute 1	H400: Very toxic to aquatic life. M=1
			Aquatic Chronic 1	H410: Very toxic to aquatic life with long lasting effects. M=1

The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory (last updated March 2015)*:*

Table 11

HAZARD CLASS	No of NOTIFIERS
Aquatic Acute 1*	**1074**
Aquatic Chronic 1*	**1033**
Eye Irrit. 2	917
Aquatic Chronic 4	49
Resp Sens 1	1
Eye Irrit	1
STOT SE	1

*These hazard classes were added in the updated dossier as a result of the SEv process.

7.7. Environmental fate properties (Updated Dossier)

7.7.1. Degradation

(-)-Pin-2(10)-ene was found to be **readily biodegradable** in water and sediment (biodegradation by activated sludge > 60% ThOD) in an OECD 301D closed bottle test.

The pass level for ready biodegradability was reached in the required time window within the 28-d period of the test: 76% biodegradation on Day 28. Alpha pinene and delta 3 carene, which are structurally similar compounds, were also found to be readily biodegradable according to OECD 301 criteria. Therefore, it is concluded that (-)-pin-2(10)-ene, is readily biodegradable according to the criteria of the OECD 301 guideline.

Environmental distribution

7.7.2. Bioaccumulation

No experimental fish BCF is available for (-)-pin-2(10)-ene. In the absence of an experimental BCF, a log Kow of 4.4 is considered. Using QSAR models, the bioconcentration factor was estimated, giving a geometric mean of 838 L/Kg. Therefore, bioaccumulation potential is expected for (-)-pin-2(10)-ene.

7.8. Environmental hazard assessment

The hazards endpoints for aquatic compartments were thoroughly evaluated. Although originally the specific endpoints were not identified as a concern (manual screening), during the evaluation the eMSCA observed that there were not adequately addressed in the registration dossier, while the majority of the C & L notifiers self-classified (-)-pin-2(10)-ene for its acute and chronic hazard properties. The eMSCA evaluated all the data, calculated all the numbers shown below and confirmed the results regarding the environmental hazard endpoints presented by the registrants in the updated registration dossier

7.8.1. Aquatic compartment (including sediment)

(-)-Pin-2(10)-ene is a substance "difficult to test" for the purposes of determining its aquatic toxicity (according to OECD Guidance No 23 (2000) on aquatic toxicity testing of difficult substances and mixtures).

Table 12

Property	Value used for CSA and discussion
Physical state	liquid at 20°C and 101.3 kPa
Vapour pressure	519 Pa at 20°C
Partition coefficient n-octanol/water (log value)	4.4 at 25°C
Water solubility	6.95 mg/L at 20°C

Table 13

Indicator values of difficulty (OECD GD No 23)	Properties of (-)-pin-2(10)-ene
log Kow > 4	log Kow = 4.4
Water solubility < 100 mg/L	Water solubility = 6.95 mg/L
Henry's law constant > 0.1 Pa.m3/mol	Henry's law constant* = 10173 Pa·m3/mol

The Henry's law constant (HLC) for a substance is a measure of its equilibrium between an ideal solution phase and the vapour phase. As such it is a measure of the potential for a substance to be lost from solution by evaporation (OECD GD No 23).

As an approximation, if HLC is greater than 100 Pa.m3/mol, more than 50% of the substance could be lost from the water phase in 3-4 hours (Mackay 1992 cited by OECD GD No 23).

Data from Tables 12 and 13 shown above provide evidence that (-)-pin-2(10)-ene is difficult to test for aquatic toxicity. The highest concerns are media preparation and maintaining required exposure concentrations, due to low water solubility (high log Kow) and volatilisation from the test solutions (high HLC).

In the study conducted in 2010, not enough precautions were taken to reduce losses of the test substance during the water solubility determination and an erroneous value was obtained (< 0.02 mg/L). This led to the false conclusion that (-)-pin-2(10)-ene was not acutely toxic at the limit of its water solubility and was therefore not classified. A new water solubility study was conducted in 2013 and it appeared that the substance had to be classified for aquatic toxicity. In addition, as the 2010 submitted dossier included algae and daphnid acute data on structurally related substances but not on (-)-pin-2(10)-ene itself, new tests were carried out for these two species in 2014.

The substance is an organic substance. It is slightly soluble in water (ca. 6.95 mg/L according to a slow-stirring method adapted from OECD Guideline 123) and stable to hydrolysis. The following toxicity values are available:

Short-term toxicity to fish

Pimephales promelas: 96h-LC50= 0.502 mg/L (measured concentrations)

Cyprinus carpio: 96h-LC50= 0.557 mg/L (measured concentrations)

QSAR estimation: 96h-LC50= 0.68 mg/L

Short-term toxicity to aquatic invertebrates

Daphnia magna: 48h-EC50= 1.250 mg/L (measured concentrations)

Daphnia magna: 48h-EC50= 1.345 mg/L (measured concentrations)

QSAR estimation: 48h-EC50= 0.86 mg/L

Geometric mean of the three values: 1.13 mg/L

Short-term toxicity to algae

Pseudokirchneriella subcapitata: 48h-EC50= 0.826 mg/L (measured concentrations)

QSAR estimation: 72h-EC50= 0.70 mg/L

The lowest acute aquatic toxicity values based on the available data, range between 0.1 and 1.0 mg/L. The long-term toxicity of the substance to aquatic organisms was not investigated. Thus, there are no adequate chronic toxicity data available.

Biodegradation

(-)-Pin-2(10)-ene was found to be readily biodegradable (biodegradation by activated sludge > 60% ThOD) in an OECD 301D closed bottle test.

Information on bioaccumulation potential

No experimental fish BCF is available for (-)-beta (-)-pin-2(10)-ene. In the absence of an experimental BCF, a log Kow of 4.4 is considered. Using QSAR models, the bioconcentration factor was estimated, giving a geometric mean of 838 L/Kg. Therefore, bioaccumulation potential is expected for (-)-pin-2(10)-ene.

CLP self-classification for environment

Based on the results above, the eMSCA concluded that (-)-pin-2(10)-ene should be classified as follows:

- Acute aquatic hazard: Category 1. M-Factor: 1.

  Reasoning: lowest E(L)C50 between 0.1 and 1.0 mg/L.

- Chronic aquatic hazard: Category 1. M-Factor: 1.

  Reasoning: adequate chronic toxicity data are not available, lowest acute E(L)C50 value range between 0.1 and 1.0 mg/L, readily degradable substance with log Kow > 4.

The registrants shared and applied the same conclusion as the eMSCA in the updated registration dossier and support this conclusion.

7.8.2. Terrestrial compartment

Not evaluated

7.8.3. Microbiological activity in sewage treatment systems

Not evaluated

7.8.4. PNEC derivation and other hazard conclusions

The PNEC values were determined for the substance itself by application of methods provided in ECHA Guidance Chapter R.10 (May 2008) and RIVM report (2004).

a. PNEC water

The proposed approach to derive PNEC values is the assessment factor method where a toxicity value is divided by an assessment factor. The size of the assessment factor accounts for a number of uncertainties:

- intra- and inter-laboratory variation of toxicity data
- intra- and inter-species variations (biological variance)
- short-term to long-term toxicity extrapolation
- laboratory data to field impact extrapolation.

When acute data are available for three trophic levels, the standard approach to PNEC determination is to apply an assessment factor of 1000 to the lowest lethal or effect concentration (E(L)C50). However, the assessment factors presented in Table R.10-4 from ECHA Guidance R.10 should be considered as general factors that under certain circumstances may be changed according to justification including one or more of the following:

- evidence from structurally similar compounds (evidence established by read across from closely related compounds may demonstrate that a higher or lower factor may be appropriate);
- knowledge of the mode of action including endocrine disrupting effects (some substances, by virtue of their structure, may be known to act in a non-specific manner);
- the availability of test data from a variety of species covering the taxonomic groups of the base-set species across at least three trophic levels. In such a case the assessment factors may only be lowered if these multiple data points are available for the most sensitive taxonomic group.

The assessment factor used for determination of the PNEC water is based on the following rationale.

Measured acute data

Reliable short-term toxicity data are provided for (-)-pin-2(10)-ene covering three trophic levels (fish, invertebrates, algae). The relevant values are:

Fish

96h-LC50= 0.502 mg/L (*Pimephales promelas,* measured concentrations)

96h-LC50= 0.557 mg/L (*Cyprinus carpio*, measured concentrations)

Daphnia magna

48h-EC50= 1.250 mg/L (measured concentrations)

48h-EC50= 1.345 mg/L (measured concentrations)

Algae

48h-EC50= 0.826 mg/L (*Pseudokirchneriella subcapitata,* measured concentrations)

The ratio between the lowest acute toxicity and the highest acute toxicity is 2.7, suggesting a low inter-species variation for aquatic toxicity.

Mode of Action

(-)-Pin-2(10)-ene is a bicyclic monoterpene and is structurally similar to alpha-pinene and delta-3-carene. These substances exhibit aquatic toxicity data in the same range as (-)-pin-2(10)-ene.

According to toxtree v.2.5.1, when applying Verhaar *et al*. (1992) schedule or Enoch *et al*. (2008) modifying Verhaar's schedule, alpha-pinene, delta-3-carene, and (-)-pin-2(10)-ene have all a narcotic Mode of Action (MoA), Mode of Action 1, which is considered to be the baseline toxicity MoA, the least toxic MoA.

Predicted acute data

Fish: 96h-LC50= 0.68 mg/L

Daphnia: 48h-EC50= 0.86 mg/L

Algae: 72h-EC50= 0.70 mg/L

The predictions are obtained with QSAR for Mode of Action 1, based on validated data derived from standard toxicity tests, for which the concentrations of the test item had been determined by chemical analyses over the test periods. The predictions are sufficiently robust and are appropriate for the purposes of chemical safety assessment.

Acute to Chronic ratios

It is generally assumed that for MoA 1 substances the Acute to Chronic Ratio (ACR) is below 100 and ranges from 1 to 10. In the case of substance (-)-pin-2(10)-ene, an algae-NOEC is not available. Instead of a NOEC, an EC10 is available. Considering the EC50 (0.826 mg/L) and the EC10 (0.378 mg/L) from the algae study, ACR for (-)-pin-2(10)-ene is calculated to be 2.19. This is an expected ACR value for MoA 1. Therefore, even without any other chronic data, it is assumed that the interspecies uncertainty is low and indicative of MoA 1.

The standard AF of 1000 for the freshwater PNEC derivation enables to cover all types of substances, the narcotic mode of action and the other modes considered more toxic. According to the MoA and the ACR value for algae, it is assumed that AF for determination of PNEC water can be lowered from 1000 to 500.

The selected value for PNEC freshwater is based on experimental short-term data of 0.502 mg/L.

b. PNEC STP

One respiration inhibition test carried according to OECD Guideline No 209 is available. The 3h-EC50 was determined to be 326 mg/L. The 3h-EC10 was 38 mg/L. The standard approach for the calculation of PNEC STP is to apply an assessment factor of 100 on the EC50 value or an assessment factor of 10 on the EC10 value. The lowest value is accepted which is derived from the EC50 and is equal to **3.26 mg/L**.

c. PNEC sediment

In the absence of ecotoxicological data on sediment, a provisional PNEC sediment (freshwater) is calculated using the equilibrium partitioning method. The calculation is based on the following equations and parameters:

Equations:

$$PNEC_{sediment} = (K_{susp\text{-}water} \cdot PNEC_{water} \cdot 1000)/RHO_{susp}$$

and

$$K_{susp\text{-}water} = F_{air\text{-}susp} \cdot K_{air\text{-}water} + F_{water\text{-}susp} + F_{solid\text{-}susp} \cdot (K_p/1000) \cdot RHO_{solid}$$

and

$$K_p = K_{oc} \cdot F_{oc}$$

where

$K_{susp\text{-}water}$ is the partition coefficient of the suspended matter to water

K_p is the solid to water partition coefficient

$K_{air\text{-}water}$ is the air to water partition coefficient

K_{oc} is the partition coefficient of organic carbon to water

RHO_{susp} is the bulk density of the suspended matter

RHO_{solid} is the bulk density of the solid phase

$F_{air\text{-}susp}$ is the volume fraction of air in the suspended matter

$F_{water\text{-}susp}$ is the volume fraction of water in the suspended matter

$F_{solid\text{-}susp}$ is the volume fraction of the solid in the suspended matter

F_{oc} is the fraction of the organic carbon in water

Parameters:*

RHO_{susp} = 1150 Kg·m^{-3}

RHO_{solid} = 2500 Kg·m^{-3}

$K_{air-water}$ = 1

K_{oc} = 3317 L/Kg

$F_{air-susp}$ = 0

$F_{water-susp}$ = 0.9 m^3·m^{-3}

$F_{solid-susp}$ = 0.1 m^3·m^{-3}

F_{oc} = 0.1 Kg·Kg^{-1}

* Default values are taken from TGD, part II, paragraph 2.3.4, table 5, page 43 and the ECHA Guidance Chapter R. 10 (May 2008)

Results:

K_p = 331.7 L/Kg

$K_{susp-water}$ = 83.8 m^3·m^{-3}

$PNEC_{sediment}$ = 72.87 µg/Kg sediment wet weight

$PNEC_{sediment}$ = 335 µg/Kg sediment dry weight

where the conversion from wet to dry weight is based on the assumption that the wet sediment consists of 90% v/v water (density 1 Kg/L) and 10% v/v solids (density 2,5 Kg/L). This results in a multiplication factor of 4.6 which is used for the calculation of $PNEC_{sediment}$ on a dry weight basis.

d. PNEC soil

In the absence of ecotoxicological data, a provisional PNEC soil is calculated using the equilibrium partitioning method. The calculation is the following:

Equations:

$$PNEC_{soil} = (K_{soil-water} \cdot PNEC_{water} \cdot 1000)/RHO_{solid}$$

and

$$K_{soil-water} = F_{air-soil} \cdot K_{air-water} + F_{water-soil} + F_{solid-soil} \cdot (K_p/1000) \cdot RHO_{solid}$$

and

$$K_p = K_{oc} \cdot F_{oc}$$

where

$K_{soil-water}$ is the partition coefficient of soil to water

K_p is the solid to water partition coefficient

$K_{air-water}$ is the air to water partition coefficient

K_{oc} is the partition coefficient organic carbon - water

RHO_{soil} is the bulk density of wet soil

RHO_{solid} is the bulk density of the solid phase

$F_{air-soil}$ is the volume fraction of air in soil

$F_{water-soil}$ is the volume fraction of water in soil

$F_{solid-soil}$ is the volume fraction of solids in soil

F_{oc} is the fraction of the organic carbon in water

Parameters:*

RHO_{soil} = 1700 Kg·m^{-3}

RHO_{solid} = 2500 Kg·m^{-3}

$K_{air-water}$ = 1

K_{oc} = 3317 L/Kg

$F_{air-soil}$ = 0.2

$F_{water-soil}$ = 0.2 m^3·m^{-3}

$F_{solid-soil}$ = 0.6 m^3·m^{-3}

F_{oc} = 0.02 Kg·Kg^{-1}

* Default values are taken from TGD, part II, paragraph 2.3.4, table 5, page 43 and the ECHA Guidance Chapter R. 10 (May 2008)

Results:

K_p = 66.34 L/Kg

$K_{susp-water}$ = 99.9 m^3·m^{-3}

$PNEC_{sediment}$ = 58.8 µg/Kg sediment wet weight

$PNEC_{sediment}$ = 66.4 µg/Kg sediment dry weight

where the conversion from wet to dry weight is based on the assumption that the wet soil consists of 60% v/v solids (density 2.5 Kg/L) and 20% v/v water (density 1.0 Kg/L) and 20% v/v air by volume. This results in a multiplication factor of 1.13 which is used for the calculation of the $PNEC_{soil}$ on a dry weight basis.

Table 14

PNEC DERIVATION AND OTHER HAZARD CONCLUSIONS		
Hazard assessment conclusion for the environment compartment	**Hazard conclusion**	**Remarks/Justification**
Freshwater	$1.0 \cdot 10^{-3}$ mg/L	Assessment factor: 500
Marine water	$1.0 \cdot 10^{-4}$ mg/L	Assessment factor: 5000 An additional assessment factor of 10 is applicable for extrapolation from freshwater to marine species.
Intermittent releases to water	$1.0 \cdot 10^{-2}$ mg/L	Assessment factor: 50 The assessment factor for PNEC freshwater is reduced by a factor of 10, when releases are intermittent.

Sediments (freshwater)	335 µg/kg sediment dw	PNEC freshwater using the equilibrium partitioning method
Sediments (marine water)	33.5 µg/kg sediment dw	PNEC marine water using the equilibrium partitioning method
Sewage treatment plant	3.26 mg/L	Assessment factor: 100 The standard approach the calculation of PNEC STP is to apply an assessment factor of 100 on the EC50 value
Soil	66,4 µg/kg soil dw	PNEC freshwater using the equilibrium partitioning method

7.8.5. Conclusions for classification and labelling

Ecotoxicological profile of (-)-pin-2(10)-ene

Classification and PNECs derived from all the information presented in this section are based on acute toxicity studies available and are given below.

CLP Classification

(-)-Pin-2(10)-ene is classified very toxic to aquatic life:

Aquatic acute 1 H400 Very toxic to aquatic life

Aquatic chronic 1 H410 Very toxic to aquatic life with long lasting effects

M factor = 1

Table 14

PNECs

PNEC	Value
Freshwater	$1.0 \cdot 10^{-3}$ mg/L
Marine water	$1.0 \cdot 10^{-4}$ mg/L
Water – intermittent releases	$1.0 \cdot 10^{-2}$ mg/L
STP	3.26 mg/L
Sediment – fresh water	335 µg/kg sediment dw
Sediment – marine water	33.5 µg/kg sediment dw
Soil	66,4 µg/kg soil dw

7.9. Human Health hazard assessment

Discussion:

Several hazard endpoints were evaluated but the focus was on the skin and respiratory sensitization, since the eMSCA is of the opinion that the specific endpoints were not adequately addressed in the original registration dossier.

An extensive literature review based on occupational/epidemiological studies, patient case studies and on animal studies was performed in order to re-evaluate the specific hazard endpoints.

In conclusion the self-classification of (-)-pin-2(10)-ene as **Skin Sens. 1B (H317)** was confirmed. Positive LLNA results in mice justify classification as a Skin Sensitiser 1B for (-)-pin-2(10)-ene. Skin sensitisation in humans, on the other hand, showed that, contrary to turpentine oil and alpha-pinene, beta-pinene did not elicit positive dermal reaction up to 10% in petrolatum although the 2 patients tested were already sensitised to many essential oils (Dharmagunawardena, 2002). Older case reports (Keil, 1947) have demonstrated positive patch test results for both alpha-pinene and beta-pinene.

Concerning classification for respiratory sensitisation, it is important to note that according to the Reg. 1272/2008/EC classification criteria, there are no formally recognised and validated animal tests for respiratory sensitisation. Data from human observations indicating respiratory sensitisation (specific respiratory hypersensitivity and /or asthma, other hypersensitivity reactions such as rhinitis/conjunctivitis and alveolitis) in exposed populations can be used for classification purposes. Relevant information with respect to respiratory sensitisation may be available from case reports, epidemiological studies, medical surveillance, reporting schemes. However, data from some animal studies may be indicative of the potential of a substance to cause respiratory sensitisation in humans (CLP Annex I, 3.4.2.1.3) and may provide supportive evidence in case human evidence is available. Respiratory sensitisation is considered a condition with the clinical character of an allergic reaction. However, immunological mechanisms do not have to be demonstrated.

There seems to be evidence for potential human respiratory sensitization by beta-pinene. Available studies are either using (-)-pin-2(10)-ene, as the test material or pinene isomers (e.g. alpha-pinene), racemic mixture thereof or structurally related substances, such as delta-carene. Indicatively, plywood mill workers in New Zealand exposed to pinene, among others, appear to have an increased risk of developing work-related respiratory symptoms, with asthma symptoms being more common than the general population and associated with duration of employment and were reported to lessen or disappear during holidays (Fransman et al., 2003). Results from lung function tests in Swedish workers indicate chronic rather than acute reactions in the airways (Eriksson et al., 1997). In Finnish sawmill workers, work-related respiratory symptoms appeared to correlate with monoterpene exposure during processing of pine and with wood dust exposure during processing of spruce (Rosenberg et al., 2002). Recently, it has been suggested that human lung function may be negatively associated with the presence of alpha-pinene indoors in the Canadian population (Cakmak et al., 2014). Moreover, animal studies in BALB/c mice suggest that (+/-)-alpha-pinene/ozone reaction products may have moderate-lasting adverse effects on both the upper airways and pulmonary regions, important in the context of the etiology or exacerbation of lower airway symptoms in office workers, or of occupational asthma in workers involved in industrial cleaning operations (Rohr et al., 2002, Nielsen et al., 2005). Results from in vitro studies suggest synergistic antitumor activity of paclitaxel applied together with alpha- or beta-pinene in tumor lung cells (Zhang et al., 2015). The effects of alpha- and beta-pinene

were also studied on rat trachea in vitro and it was found that in tracheal rings they both potentiated the contractions induced by acetylcholine (ACh) (Lima et al., 2010).

The registrants in the updated dossier included enough new studies and claimed that occupational studies report respiratory parameters of workers, who were co-exposed to monoterpenes, but also to wood dust and potentially many other irritant substances, which is true. The toxicological effect of the other cofactors was not taken into account in those studies. The registrants reasoned that changes in the respiratory parameters showed chronic rather than acute reaction in the airways, which would probably be due to wood dust exposure rather than terpenes exposure (Eriksson, 1997). These results were confirmed, according to the registrants, by studies in human volunteers exposed for 2h to alpha-pinene, where no significant changes in respiratory parameters could be identified (Falk, 1990). Also, exposure of healthy volunteers to Oriented Strand Boards emissions did not elicit sensory irritations or pulmonary effects. More particularly, 2 h exposures to mixed emissions with terpenes concentrations up to 4.6 mg/m3 (including up to 0.7 mg/m3 beta-pinene) did not induce acute respiratory health effects in humans (Gminski, 2010). Based on the above, the registrants and concluded that classification for any inhalation hazard (respiratory tract irritation or respiratory sensitisation) is not warranted.

Based on the above, the eMSCA is of the opinion that the evaluation of human data for (-)-pin-2(10)-ene, which can be ambiguous and lead to different conclusions, along with supporting animal data, has to be assessed through a regulatory process of an Annex VI CLH dossier after the conclusion of the SEv process. In this CLH dossier development process, the issue of substance identity of the test material which causes the respiratory sensitisation effects (i.e. (-)-pin-2(10)-ene, pinene isomers (e.g. alpha-pinene), racemic mixture thereof or structurally related substances, such as delta-carene) would also be clarified.

7.9.1. Toxicokinetics

Not relevant for this evaluation.

7.9.2. Acute toxicity and Corrosion/Irritation

Summary and discussion on Acute Toxicity

Acute oral toxicity studies are available for the following structurally related substances: alpha-pinene, beta-pinene, delta-3-carene, turpentine oil and camphene. They show LD50 of 3700, > 5000, 4800, 3956 and > 5000 mg/kg bw, respectively. Although these studies are old and briefly described, they all show consistent results about all these structure-related substances.

Acute dermal toxicity studies are also available for each of the following substances: alpha-pinene, (-)-pin-2(10)-ene, delta-3-carene, turpentine oil and camphene. They show LD50 > 5000, > 5000, > 5000, > 2000 and > 2500 mg/kg bw, respectively. Although these studies are old and briefly described, they all show consistent results about all these structurally related substances. Moreover, the low dermal toxicity of these substances is consistent with and confirmed by the low oral toxicity.

The following information is taken into account for any hazard / risk assessment: All studies available show oral LD50 equal to or higher than 3700 mg/kg bw in rats.

All studies available show dermal LD50 equal to or higher than 2000 mg/kg bw in rabbits.

Value used for CSA (values for the registered substance, studies reliability 4)**:**

Acute oral toxicity: (LD50: 3700 mg/kg bw)

Acute dermal toxicity: (LD50: 2000 mg/kg bw)

Justification for classification or non classification

Oral and dermal LD50 are higher than 2000 mg/kg bw in rats and rabbits, respectively, therefore (-)-pin-2(10)-ene does not need to be classified for acute toxicity according to the Annex VI of the CLP Regulation (EC) No 1272/2008.

However, based on its viscosity, (-)-pin-2(10)-ene is classified for aspiration hazard Category 1 according to Regulation (EC) No 1272/2008 (hydrocarbon with a kinematic viscosity of less than 20.5 mm2/s at 40°C) and as harmful "R65: may cause lung damage if swallowed" according to Directive 67/548/EEC.

Summary and discussion on irritation

In GLP *in vitro* studies on Episkin model, (-)-pin-2(10)-ene was applied topically to reconstructed human epidermis model (3 epidermis units/dose) for 15 min at room temperature. The mean relative cell viability was 38.5 ± 3.5. When alpha pinene and delta-3-carene were used as test materials the mean relative cell viability was 39.6 ± 5.6, and 29.8 ± 1.3%, respectively.

The results were therefore positive for (-)-pin-2(10)-ene and the substance is proven irritating to skin. Information on structurally related substance support this conclusion.

In an eye irritation study conducted according to OECD 405 Guideline and GLP, 3 male New Zealand White rabbits were exposed to 0.1 mL of undiluted (-)-pin-2(10)-ene in one eye. The calculated mean scores for each individual lesions for all animals at three scoring times (24, 48 and 72 h) were as follows: 0, 0, 0 for cornea score; 0, 0, 0 for iris score; 1, 1, 2 for conjunctivae score and 1.3, 1, 1 for chemosis score. All the signs were resolved within 7 days after treatment. The substance is therefore not irritating to eyes.

Similar results were obtained for the structurally similar substance delta-3-carene, that support the conclusion on no classification. In an *in vivo* eye irritation study conducted according to OECD 405 Guideline and GLP, 3 female New Zealand White rabbits were exposed to 0.1 mL of undiluted delta-3-carene in one eye. The calculated mean scores for each individual lesions for all animals at three scoring times (24, 48 and 72 h) were as follows: 0, 0, 0 for cornea score; 0, 0, 0 for iris score; 2, 1.33, 1.33 for conjunctivae score and 2, 1.33, 1 for chemosis score. All the signs were resolved within 7 days after treatment.

The information presented above is taken into account for any hazard / risk assessment.

Value used for CSA:

Skin irritation / corrosion: Adverse effect observed (irritating)

Eye irritation / corrosion: No adverse effect observed (not irritating)

Justification for classification or non classification

In an *in vitro* skin irritation study performed on reconstructed human epidermis, cell viability was ≤ 50 %. Therefore, (-)-pin-2(10)-ene is classified as skin irritant category 2 according to CLP Regulation (EC) No 1272/2008.

In an *in vivo* eye irritation study performed according to OECD 405 Guideline, reversible slight irritating effects were observed on rabbit eyes with irritation scores not high enough to lead to classification. Therefore, (-)-pin-2(10)-ene is not classified for eye irritation according CLP Regulation (EC) No 1272/2008.

7.9.3. Sensitisation

Skin sensitization

In a LLNA performed according to OECD 429 Guideline and in compliance with GLP, groups of CBA/J mice (4 females/dose) were exposed to 0.25 µL of (-)-pin-2(10)-ene in Acetone/olive oil (4/1, v/v) at concentrations of 0 (vehicle control), 5, 10, 25, 50 and 100% (v/v) to the dorsal surface of both ears for three consecutive days.

No clinical signs and no mortality were observed during the main test. No local reactions and no notable increase in ear thickness were observed at any of the tested concentrations. Stimulation Index (SI) for 5, 10, 25, 50 and 100 % were 2.29, 1.16, 2.23, 7.17 and 6.47, respectively. The threshold positive value of SI=3 was exceeded at the concentration > 50%. At such concentrations local irritation was not recorded. The calculated effective concentration inducing a SI of 3 (EC3) was 29%. Therefore, the significant lymphoproliferative responses observed were attributed to delayed contact hypersensitivity. As a result, (-)-pin-2(10)-ene is classified as skin sensitising.

When considering human data on skin sensitisation properties of (-)-pin-2(10)-ene, patients sensitised to essential oils, whose one of the most common components was (-)-pin-2(10)-ene, did not show skin reactions when patch tested with (-)-pin-2(10)-ene.

Animal data on structurally similar substances support classification, where as human data are difficult to conclude upon. More specifically, in maximisation tests on guinea pigs conducted with delta-3-carene and turpentine oil, 15/22 and 16/25 animals showed positive responses, respectively. In a clinical trial, turpentine oil was identified as a strong sensitiser, with 16/25 human volunteers showing positive response to turpentine oil.

In conclusion, (-)-pin-2(10)-ene was classified as Skin Senitiser 1B based on the positive LLNA, with EC3 = 29%.

The above information is taken into account for any hazard / risk assessment.

Value used for CSA: Adverse effect observed (sensitising).

Justification for classification or non classification

(-)-Pin-2(10)-ene) induced positive response in a LLNA with an EC3 = 29%. Therefore it is classified as skin sensitizer Category 1B according to CLP Regulation (EC) No 1272/2008.

Respiratory sensitisation[2]

Among human data evaluating monoterpenes exposure and occurrence of respiratory hypersensitivity, occupational signs of respiratory hypersensitivity were found in workers from joinery shops or plywood mill. These data were introduced in the registration

[2] For a complete listing of the references used for the evaluation of the skin and respiratory sensitization endpoints look at the references section of the document.

dossier as a result of the SEv process. However, as it is usually the case with many epidemiological human data, these workers were co-exposed to many other substances, especially wood dusts that are well known to cause asthma. This point has been raised by the registrants, while evaluating the human data on respiratory sensitisation according to the Reg. 1272/2008/EC criteria. Therefore, the registrants claimed that no direct correlation between exposure to (-)-pin-2(10)-ene and signs of respiratory hypersensitivity like occupational asthma could be evidenced. The absence of direct evidence of respiratory hypersensitivity in humans due to (-)-pin-2(10)-ene) exposure is a sufficient indication, according to the registrants, that there is no need to classify (-)-pin-2(10)-ene) as respiratory sensitiser in the registration dossier.

The registrants have developed a scientific reasoning to support the above conclusion, when requested so by the eMSCA. Many respiratory sensitisers were found positive in the Local Lymph Node Assay (LLNA), a test validated for the detection of skin sensitisers. According to the toxicological data relevant to assess (-)-pin-2(10)-ene) toxicity by inhalation, (-)-pin-2(10)-ene) is irritating to skin but is considered as non-irritating to eyes. (-)-Pin-2(10)-ene) was found positive in one recent LLNA, with EC3 = 29% which corresponds to a weak skin sensitiser. Patients sensitised to essential oils, whose one of the most common components was (-)-pin-2(10)-ene), did not show skin reactions when patch tested with (-)-pin-2(10)-ene. Moreover, in a new study by Wei et al. 2010 provided by the registrants that is not part of the registration dossier, (-)-pin-2(10)-ene was found negative in another LLNA with (-)-pin-2(10)-ene concentrations up to 100%. Additionally, (-)-pin-2(10)-ene did not induce skin reactions in a Guinea-Pig Maximisation Test.

To strengthen their conclusion, the registrants reviewed animal data related to effects of (-)-pin-2(10)-ene or of the structurally related substance α-pinene on the respiratory system. Partial read-across data from α-pinene are available in repeated dose toxicity studies by inhalation. Both rats and mice were exposed to α-pinene in 90-day repeated dose toxicity studies (National Toxicology Program, 2006). According to the data available, no clinical signs related to impaired respiratory system such as dyspnoea or rhinitis were recorded in both species. Moreover, no toxicologically significant histopathological effects due to exposure to α-pinene were observed at histopathological examination of the respiratory system in both species.

In addition, the sensory irritant properties of β-pinene enantiomers were studied in mice. These properties cannot be related to cytotoxic irritating effects relevant for classification as respiratory irritant because sensory irritation consists of interaction with nerve receptors not leading to tissue lesions.

The eMSCA believes that there seems to be evidence for potential human respiratory sensitization by beta-pinene. Available studies are either using (-)-pin-2(10)-ene, as the test material or pinene isomers (e.g. alpha-pinene), racemic mixture thereof or structurally related substances, such as delta-carene. Indicatively, plywood mill workers in New Zealand exposed to pinene, among others, appear to have an increased risk of developing work-related respiratory symptoms, with asthma symptoms being more common than the general population and associated with duration of employment and were reported to lessen or disappear during holidays (Fransman et al., 2003). Results from lung function tests in Swedish workers indicate chronic rather than acute reactions in the airways (Eriksson et al., 1997). In Finnish sawmill workers, work-related respiratory symptoms appeared to correlate with monoterpene exposure during processing of pine and with wood dust exposure during processing of spruce (Rosenberg et al., 2002). Recently, it has been suggested that human lung function may be negatively associated with the presence of alpha-pinene indoors in the Canadian

population (Cakmak et al., 2014). Moreover, animal studies in BALB/c mice suggest that (+/-)-alpha-pinene/ozone reaction products may have moderate-lasting adverse effects on both the upper airways and pulmonary regions, important in the context of the etiology or exacerbation of lower airway symptoms in office workers, or of occupational asthma in workers involved in industrial cleaning operations (Rohr et al., 2002; Nielsen et al., 2005)., Results from in vitro studies suggest synergistic antitumor activity of paclitaxel applied together with alpha- or beta-pinene in tumor lung cells (Zhang et al., 2015). The effects of alpha- and beta-pinene were also studied on rat trachea in vitro and it was found that iIn tracheal rings they both potentiated the contractions induced by acetylcholine (ACh) (Lima et al., 2010).

Therefore, the eMSCA had indicated the need to address the respiratory sensitisation endpoint in the registration dossier, since there is evidence in the literature that (-)-pin-2(10)-ene) exposure can cause occupational asthma symptoms in humans. On the other hand, the line of evidence supporting respiratory sensitisation provided by the new data introduced, is scientifically challenged by the registrants, as presented above.

In conclusion, the eMSCA is of the opinion that the evaluation of the data available on respiratory sensitisation is worth being performed through a CLH process, which is the legally appropriate regulatory process to assess the hazard of a substance based on a satisfactory data set, and reach an opinion through RAC. Classification for the human health hazard of respiratory sensitisation is based only on human data, according to the Reg. 1272/2008/EC and human data can be ambiguous and lead to different conclusions. It should be noted that the lack of animal studies to substantiate the respiratory sensitisation classification renders it a challenging human health endpoint.

7.9.4. Repeated dose toxicity

Not evaluated.

7.9.5. Mutagenicity

Not evaluated.

7.9.6. Carcinogenicity

Not evaluated.

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

Not evaluated.

7.9.8. Hazard assessment of physico-chemical properties

Viscosity:

2.2 mPa s (dynamic) at 20°C

1.4 mPa s (dynamic) at 40°C

The dynamic viscosity was determined with a rotational viscometer. The substance can be considered as a Newtonian fluid. The dynamic viscosity of (-)-pin-2(10)-ene at a shear rate of 583 s-1 is 2.2 mPa.s at 20°C and **1.4 mPas.s at 40°C**. (-)-Pin-2(10)-ene should be classified for aspiration toxicity Category 1 according to Regulation (EC) No 1272/2008 (CLP) criteria (hydrocarbon with a kinematic viscosity of less than 20.5 mm^2/s at 40°C):

H304: May be fatal if swallowed and enters airways.

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

The Greek eMSCA brought to the attention of the registrants the need to re-evaluate the DNELs of the original registration dossier for local long-term effects by dermal route and for systemic long-term effect by inhalation, since some of the corresponding assessment and uncertainty factors needed minor adjustments. For the new calculations the following assessment and uncertainty factors were used:

Table 15

Uncertainty /Assessment Factors	
Uncertainty factors	
Differences in absorption depending on route of exposure (route to route extrapolation, human/animal)	➢ 1 inhalation to oral/dermal routes
Modification of exposure (experiment and human)	➢ 6/8 Mouse exposure condition (6 h)/Worker exposure condition (8 h) ➢ (6/24) x (5/7) (Mouse exposure condition (6 h - 5/7 days)/General population exposure condition (24 h - 7/7 days)
Modification for respiratory volume	➢ Standard respiratory volume for mice: Standard respiratory volume for humans x allometric scaling x duration of exposure = 0.2 L/min/kg x 7 x 60 min x 8 h = 0.672 m^3/kg (workers) ➢ Standard respiratory volume for mice: Standard respiratory volume for humans x allometric scaling x duration of exposure = 0.2 L/min/kg x 7 x 60 min x 24 h = 2.02 m^3/kg
Assessment Factors	
Interspecies differences - Differences in metabolic rate per b.w. (allometric scaling) - Remaining differences	➢ None for inhalation route ➢ **7** (default factor for mice) for dermal and oral route ➢ **3** (Among all animal studies assessing skin sensitisation, the lowest concentration inducing a positive response was found in a LLNA with EC_3 = 29%. Among all available clinical studies, the highest concentration without positive response found in a reliable study (Dharmagunawardena et al, 2002) was 10%; therefore, an assessment factor of 3 is selected, corresponding to the demonstrated difference of concentration without effect between animals and humans). ➢ **2.5** (Toxicodynamic and toxicokinetic remaining differences)

Intraspecies differences	➢ **5** (Default factor for workers) ➢ **10** (Default factor for general population)
Duration extrapolation (sub-acute/sub-chronic/chronic)	**2** (Sub-chronic to chronic extrapolation)
Issues related to dose-response for systemic effects	None
Dose-response for local effects	**1** (EC_3 value obtained from LLNA with appropriate dose-response relationship)
Vehicle or matrix effect	**3** (The vehicle used in the study was lipophilic)
Exposure considerations	**3** (Taking into account the state of the skin and repeated exposure)
Quality of whole database	**1**

No systemic or local acute hazard has been identified. In humans no skin irritation effect was observed at 10 mg/m^3 (Falk et al., 1990).

The need for the registrants to revise their initial DNELs especially for local long-term effects by dermal route and for systemic long-term effect by inhalation was identified by the eMSCA and was brought in conformity by the registrants. The resulting values are shown in Table 16.

Table 16

CRITICAL DNELS/DMELS					
Endpoint of concern	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptors (e.g. NOAEL, NOAEC)**	**DNEL/ DMEL**	**Justification/ Remarks**
Inhalation	Systemic long-term	Repeated dose toxicity 90-day inhalation studies (2) conducted by NTP (National Toxicological Program), 2006	NOAEC mouse 283.24 mg/m^3	5.69 mg/m^3 (workers)	Read across study on alpha-pinene Two 90-day inhalation studies were conducted by NTP (National Toxicological Program) with alpha-pinene, one in rats, the other in mice. Mortality was observed in female rats in the high dose group. As no specific target organ was sufficiently impaired by the treatment to cause mortality, it may be concluded that these deaths have a general systemic toxicity origin (NOAEL 200 ppm). The lowest NOAEL was found in male and female mice (50 ppm) based on minimal to moderate hyperplasia in the transitional epithelium of the urinary bladder from 100 ppm. Although the relevance of this
				1 mg/m^3 (general population)	
Dermal	Systemic long-term			0.8 mg/Kg bw/day (worker)	
Oral and dermal	Systemic long-term			0.3 mg/Kg bw/day (general population)	

					effect for humans is uncertain, this study is selected for calculating the systemic long-term DNELs for (-)-pin-2(10)-ene, in a conservative approach.
Dermal	Local long-term	2010 – GLP study; Dharmaguna wardena et al., 2002	EC3=7250 µg/cm^2	54 µg/cm^2 (worker)	Skin sensitisation LLNA studies. Skin sensitisation is the most critical local effect of (-)-pin-2(10)-ene.
				27 µg/cm^2 (general population)	

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

Toxicological profile of (-)-pin-2(10)-ene

Classification derived from all the information presented in this section is given below.

Table 17

International Chemical Identification	EC No	CAS No	Classification	
			Hazard Class and Category Code(s)	Hazard statement code(s)
(-)-pin-2(10)-ene	242-060-2	18172-67-3	Asp.Tox. 1	H304: May be fatal if swallowed and enters airways.
			Skin Irrit. 2	H315: Causes skin irritation
			Skin Sens 1B	H317: May cause an allergic skin reaction

Concerning the respiratory sensitisation endpoint, the eMSCA believes that it is a difficult endpoint to evaluate, since, according to the Reg. 1272/2008/EC, it is based exclusively on human data that are difficult to assess and can lead to different conclusions. Based on registrants' evaluation of the human data, now provided in the registration dossier, there is no concrete conclusion that exposure to (-)-pin-2(10)-ene exclusively can cause occupational asthma symptoms in humans. The registrants believe that the subjects of the epidemiological studies provided were **co-exposed** to many other substances, especially wood dusts that are well known to cause asthma. Therefore, the registrants could not substantiate a correlation between exposure to **pure** (-)-pin-2(10)-ene and signs of respiratory hypersensitivity like occupational asthma. Therefore, and based only on co-exposure, classification of (-)-pin-2(10)-ene as a respiratory sensitiser is not proposed according to the registrants' data evaluation.

7.10. Assessment of endocrine disrupting (ED) properties

Not evaluated.

7.10.1. Endocrine disruption – Environment

Not evaluated.

7.10.2. Endocrine disruption - Human health

Not evaluated.

7.10.3. Conclusion on endocrine disrupting properties (combined/separate)

Not evaluated.

7.11. PBT and VPVB assessment

Not evaluated.

7.12. Exposure assessment

One of the main concerns during the SEv process had been the exposure of consumers to (-)-pin-2(10)-ene, which had been poorly dealt with in the original CSR.

Exposure of workers during industrial application of (-)-pin-2(10)-ene for manufacture of the substance or use of the substance as an intermediate (to be transformed to another substance) or even during polymerisation or formulation of mixtures and fragrance products in various processes (distillation, general batch production process, holding/ mixing tanks, drum/ container filling, discharging of vessels, sampling, equipment cleaning, waste management etc) seemed to have been overestimated, especially regarding the duration of exposure (i.e. use of operation duration rather than exposure duration), but also some other technical operational details. In consequence, the RCRs both for dermal exposure and for systemic inhalation for workers exposure had appeared elevated (well above 0.5, but in all cases below 1). On the contrary and interestingly enough, quality control procedures and respective laboratory analyses had not shown elevated exposure of workers through inhalation.

Regarding sensitive populations (pregnant women, elder people, children etc.) the eMSCA believes that they are not expected to constitute specific target groups for the uses of the substance. Thus, although exposure to (-)-pin-2(10)-ene is expected through the normal uses thereof, particularly elevated exposure for such sensitive groups compared to the general population or workers is not anticipated.

The eMSCA communicated all these concerns and thoughts to the registrants. All the above led to the update of Sections 9 & 10 of the CSR by the registrants.

As a result, several improvements were introduced in the updated dossier. Combined exposure due to aggregated tonnages and combined uses from different registrants has been taken into account.

Namely, for industrial uses:

- ✓ More precise description of the processes was introduced (e.g. temperatures, ventilation type, duration of operations, indoor process with or without open windows, outdoor process, frequency of process repetition, concentration of the substance, daily use at site, spraying or aerosol conditions, emission rate, discharge rate etc). Therefore, the number of worse case assumptions was reduced. The eMSCA checked the revised conditions of exposure and found them more realistic and representative of everyday practice. As a result, the worst case scenarios seem now reasonable.

- ✓ Improvement of the risk assessment tools used (ECETOC TRA v1 in 2010 / v3 in 2014), where the ECPA model of exposure developed by BfR was introduced in the new version.
- ✓ Revised estimates of exposure for some PROC; more flexibility on exposure duration and concentration of the product for dermal risk assessment.
- ✓ Extended use of Tier 2 tools: ART 1.0 for inhalation exposure and Riskofderm 2.0 for dermal exposure.

For fragrance/consumer uses:

- ✓ 26 new consumer scenarios were introduced.
- ✓ New version of the IFRA guidance for REACH Exposure Scenarios (version 2.1, December 2012) was applied with more detailed information on consumer uses, on concentrations in final products etc.
- ✓ Use of Tier 2 tools ConsExpo v.5 beta and AISE REACT dedicated to consumer risk assessment.
- ✓ Parameters used in Tier 2 tools (based on Practices and Habits for consumer from Western Europe - HERA project, amended by AISE in 2009) led to introduction of more realistic values than those obtained with Tier 1 tools.

Due to the revision of the environmental hazards, the registrants also provided a revised environmental exposure and risk assessment that included:

- ✓ Availability of data on waste water (actual measurements of (-)-pin-2(10)-ene concentration).
- ✓ Availability of mass balance data.
- ✓ Better knowledge on the distribution of the tonnages between the different uses (specific figures instead of maximal tonnages applied for each use).
- ✓ Use of new version of the IFRA guidance for REACH Exposure Scenarios (version 2.1, December 2012.
- ✓ Grouping of specific ERCs (spERCs) as proposed by IFRA: grouping of spERCs from AISE and Cosmetics Europe, based on release fraction to water and site scale.
- ✓ Use of typical volume percentage ranges of fragrance substance EU tonnage per spERC group, as proposed by IFRA when no specific data is available.

The eMSCA did not perform evaluation of the environmental exposure and risk assessment, as this had not been one of the original concerns that triggered the SEv process.

Some general editorial comments/recommendations on the output of the revised exposure and risk assessment for (-)-pin-2(10)-ene provided by the registrants that do not affect the conclusion of the evaluation, are the following:

- ✓ The detailed calculations performed for worker exposure scenarios using the ECETOC Targeted Risk Assessment (TRA) 3.0, the ART and the RISKOFDERM models should be included as an Appendix to the CSR.
- ✓ The detailed calculations performed for consumer exposure scenarios using both the ECETOC Targeted Risk Assessment (TRA) 3.1 and the ConsExpo 5.0 models should be included as an Appendix to the CSR.
- ✓ An Overview table of the "Quantitative Risk Assessment for Exposure to Humans (Workers & Consumers)" would be useful in order to provide ECHA and other

reviewers of the CSR with a convenient summary of the key elements of the assessment.

7.12.1. Human health

7.12.1.1. Worker

It is important to note that personal protective measures for dermal exposure (i.e. chemical resistant gloves) are included in the scenarios but no protective measures for inhalation are proposed. This is consistent with the fact that the registrants have not identified any hazard related to the respiratory track, even after the evaluation of the new data set on respiratory sensitisation, as explained above. In case a respiratory related hazard was identified, new risk assessment would be performed. Depending on the possible risk, new personal protective measures could be introduced. Therefore, the need for assessment of potential classification for respiratory sensitisation through a CLH dossier becomes decisive.

Exposure for workers in all tested representative scenarios always remained well below the respective DNEL values.

The following types of workers/professional users contributing scenarios are identified and presented:

Table 18

Type of working contributing scenario	Number	Exposure concentration
Manufacture of substance	13	➢ Long-term systemic through inhalation: 6 scenarios <2 mg/m^3, 7 scenarios <0.5 mg/m^3 (DNEL=5.69 mg/m^3) ➢ Long-term systemic dermal: 3 scenarios < 0.25 mg/Kg bw/day 10 scenarios <0.015 mg/Kg bw/day (DNEL=0.8 mg/Kg bw/day) ➢ Long-term local dermal: 3 scenarios <10 µg/cm^2, 10 scenarios <2 µg/cm^2 (DNEL=54 µg/cm^2)
Intermediate use	5	➢ Long-term systemic through inhalation: 5 scenarios <0.25 mg/m^3 (DNEL=5.69 mg/m^3) ➢ Long-term systemic dermal: 5 scenarios < 0.02 mg/Kg bw/day (DNEL=0.8 mg/Kg bw/day) ➢ Long-term local dermal: 5 scenarios <2 µg/cm^2 (DNEL=54 µg/cm^2)
Use at industrial site	23	➢ Long-term systemic through inhalation: 10 scenarios involving mixing, spraying, use of laundry detergents and pharmaceutical (disinfection) products <2.4 and >1 mg/m^3, 13 scenarios <0.3 mg/m^3 (DNEL=5.69 mg/m^3) ➢ Long-term systemic dermal: 6 scenarios involving sampling and transfer < 0.16 mg/Kg bw/day, 17 scenarios < 0.05 mg/Kg bw/day (DNEL=0.8 mg/Kg bw/day) ➢ Long-term local dermal: 13 scenarios <2 µg/cm^2, 10 scenarios involving sampling and transfer < 12 and >

		6 µg/cm^2 (DNEL=54 µg/cm^2)
Formulation	15	➢ Long-term systemic through inhalation: 4 scenarios <2.5 mg/m^3, 11 scenarios <0.5 mg/m^3 (DNEL=5.69 mg/m^3) ➢ Long-term systemic dermal: 6 scenarios < 0.18 mg/Kg bw/day, 9 scenarios < 0.03 mg/Kg bw/day, (DNEL=0.8 mg/Kg bw/day) ➢ Long-term local dermal: 6 scenarios including various mixing and transfer processes <20 µg/cm^2 , 9 scenarios < 5 µg/cm^2 (DNEL=54 µg/cm^2)
Industrial end-use of washing and cleaning products	18	➢ Long-term systemic through inhalation: 9 scenarios <2.4 and > 1 mg/m^3, 9 scenarios < 0.2 mg/m^3 (DNEL=5.69 mg/m^3) ➢ Long-term systemic dermal: 4 scenarios < 0.17 mg/Kg bw/day, 14 scenarios < 0.05 mg/Kg bw/day (DNEL=0.8 mg/Kg bw/day) ➢ Long-term local dermal: 17 scenarios <6 µg/cm^2 and > 1 µg/cm^2 , 1 scenario (DNEL=54 µg/cm^2)
Professional workers	26	➢ Long-term systemic through inhalation: 15 scenarios including dish wash and laundry products, metal descaling agent, rinse products, floor care products, sanitary cleaners etc <2.4 and > 0.6 mg/m^3 , 11 scenarios <0.3 mg/m^3 (DNEL=5.69 mg/m^3) ➢ Long-term systemic dermal: 10 scenarios < 0.23 and > 0.1 mg/Kg bw/day, 16 scenarios < 0.08 mg/Kg bw/day (DNEL=0.8 mg/Kg bw/day) ➢ Long-term local dermal: 13 scenarios including dewaxing products, metal descaling agent, rinse products, floor care products, sanitary cleaners etc <12 µg/cm^2 (DNEL=54 µg/cm^2)
Professional workers using end-use polishes and wax blends	6	➢ Long-term systemic through inhalation: 2 scenarios including treatment of leather, wood and furniture products <2.3 mg/m^3, 4 scenarios <0.92 mg/m^3 (DNEL=5.69 mg/m^3) ➢ Long-term systemic dermal: 4 scenarios including wood, furniture and floor products < 0.22 mg/Kg bw/day, 2 scenarios < 0.03 mg/Kg bw/day (DNEL=0.8 mg/Kg bw/day) ➢ Long-term local dermal: 4 scenarios including wood, furniture and floor products <12 µg/cm^2 , 2 scenarios < 2 µg/cm^2 (DNEL=54 µg/cm^2)

7.12.1.2. **Consumer**

In the 24 new exposure scenarios for consumers that have been developed and evaluated, all consumer products containing (-)-pin-2(10)-ene have been included. Various types of dispersing/applying/using the commercial product have been taken into consideration, such as sprays, impregnated products (wipes, tablets etc), liquid products in normal packaging or soluble packaging, dusts, solids etc. Several parameters important for the calculation of exposure, such as the amount of product typically used in everyday life, the frequency and duration of use that results to different levels of exposure via different routes that can be reasonably expected (inhalation, dermal, oral), the repetition of use, the skin contact area, the inhalation volume, the room volume etc

were evaluated by the eMSCA after the provision of the new scenarios by the registrants in the updated registration dossier.

The following types of consumers' contributing scenarios are identified and presented:

Table 19

Type of consumer contributing scenarios	Number of scenarios	Exposure concentration
Consumer end use of washing and cleaning products (conc. 0.01-1%)	18	➢ Long-term systemic through inhalation: 3 scenarios <0.35 mg/m^3, 15 scenarios <0.05 mg/m^3 (DNEL=1 mg/m^3) ➢ Long-term systemic dermal: 3 scenarios < 0.15 mg/Kg bw/day, 15 scenarios <0.04 mg/Kg bw/day (DNEL=0.3 mg/Kg bw/day) ➢ Long-term local dermal: 1 scenario including cleaning products of all types for indoor use and respective wipes <10 µg/cm^2, 2 scenarios <7 µg/cm^2 , 10 scenarios < 0.05 µg/cm^2 (DNEL=27 µg/cm^2) ➢ Oral exposure remains negligible in all scenarios
Consumer end use of air care products (concentration 0.25-5%)	3	➢ Long-term systemic through inhalation: all scenarios <0.04 mg/m^3 (DNEL=1 mg/m^3) ➢ Long-term systemic dermal: all scenarios < 0.005 mg/Kg bw/day (DNEL=0.3 mg/Kg bw/day) ➢ Long-term local dermal: all scenarios <0.2 µg/cm^2 (DNEL=27 µg/cm^2) ➢ Oral exposure remains negligible in all scenarios
Consumer end use of polishes and wax blend (conc.~ 0.1%)	2	➢ Long-term systemic through inhalation: all scenarios <0.2 mg/m^3 (DNEL=1 mg/m^3) ➢ Long-term systemic dermal: all scenarios < 0.02 mg/Kg bw/day (DNEL=0.3 mg/Kg bw/day) ➢ Long-term local dermal: all scenarios <1 µg/cm^2 (DNEL=27 µg/cm^2) ➢ Oral exposure remains negligible in all scenarios
Consumer end use of biocides (conc. ~ 1%)	3	➢ Long-term systemic through inhalation: all scenarios <0.002 mg/m^3 (DNEL=1 mg/m^3) ➢ Long-term systemic dermal: all scenarios < 0.2 mg/Kg bw/day (DNEL=0.3 mg/Kg bw/day) ➢ Long-term local dermal: all scenarios <0.5 µg/cm^2 (DNEL=27 µg/cm^2) ➢ Oral exposure remains < 0.005 mg/Kg

		bw/day in all scenarios

7.12.2. Environment

7.12.2.1. Aquatic compartment (incl. sediment)

Not evaluated

7.12.2.2. Terrestrial compartment

Not evaluated

7.12.2.3. Atmospheric compartment

Not evaluated

7.12.3. Combined exposure assessment

Combinations of exposure scenarios for workers and professionals, as those described above, is not likely to happen, as in the vast majority of scenarios exposure is based on 6-8 hours shifts. Nevertheless, workers and professional users are also consumers and consumers may be involved in more than one exposure scenarios for consumers, as those described above.

Exposure of workers and professionals in worst case scenarios through inhalation remains well below the 50% of the DNEL for long-term systemic effects and any additive contribution from the scenarios for the consumers exposure through inhalation will never exceed 10% of the said DNEL. Consequently, combined exposure for workers and professionals through inhalation is expected to be well controlled.

Exposure of workers and professionals in worst case scenarios via the dermal route remains well below the 50% of the DNEL for long-term systemic effects and any additive contribution from the scenarios for the consumers exposure via the dermal route will never exceed 35% of the mentioned DNEL. For local effects, dermal exposure for workers and professionals in worst case scenarios does not exceed 40% of the respective DNEL. Additive contribution from consumers' exposure scenarios to the workers/professional exposure scenarios could raise the overall exposure in the worst case scenario up to 30%. In all cases, combined exposure for workers and professionals via the dermal route is expected to be well controlled.

For consumers, additive exposure through inhalation when all consumers' contributing scenarios are taken into account, remain less than 30% of the respective DNEL for long-term systemic effects, while for local effects relevant combined dermal exposure remains less than 40% of the respective DNEL. Finally, dermal exposure of consumers by adding all contributing scenarios studied for systemic effects still remains lower than the respective DNEL but only by 10%.

In conclusion, exposure both for workers/professional users and for consumers appears well controlled. Nevertheless, restriction regulatory measures for consumers could reduce further consumers' exposure.

7.13. Risk characterisation

RCRs appear well below 1 for all exposure scenarios and for all routes of exposure and combined exposure through inhalation and dermal route for systemic effects, as it can seen in Table 20 below:

Table 20

Type of contributing scenario	Population	RCRs
Manufacture of substance	Workers	➢ RCRs < 0.08 for all routes and combined exposure in 5 scenarios ➢ RCRs < 0.5 for inhalation and combined exposure in 5 scenarios ➢ RCRs < 0.5 for dermal route (systemic effects) and combined exposure in 3 scenarios
Intermediate use		All RCRs < 0.04 for all routes and combined exposure for all scenarios
Use at industrial site		All RCRs < 0.05 for all routes and combined exposure for all scenarios
Formulation		➢ RCRs < 0.25 for all routes and combined exposure in 10 scenarios ➢ RCRs < 0.45 for inhalation and combined exposure in 5 scenarios and for dermal exposure (local effects) in 1 scenario
Industrial end-use of washing and cleaning products		➢ RCRs < 0.05 for all routes and combined exposure in 4 scenarios ➢ RCRs < 0.45 for inhalation and combined exposure in 8 scenarios ➢ RCRs < 0.2 for dermal route (systemic effects) and combined exposure ➢ RCRs < 0.2 for dermal route (local effects) in 8 scenarios
Professional workers		➢ RCRs < 0.25 for local dermal exposure in 1 scenarios ➢ RCRs < 0.45 for inhalation and combined exposure in 15 scenarios (9 of this scenarios also have RCRs for local dermal exposure < 0.25) ➢ RCRs < 0.1 for all routes and combined exposure in 10 scenarios
Professional workers Professional workers using end-use polishes and wax blends		➢ RCRs < 0.3 for dermal exposure in 2 scenarios ➢ RCRs < 0.5 for inhalation and combined exposure in 3 scenarios (2 of this scenarios also have RCRs for dermal exposure < 0.3) ➢ RCRs < 0.1 for all routes and combined exposure in 1 scenarios
Use of washing and cleaning products (conc. 0.01-1%)	Consumers	➢ RCRs < 0.5 for inhalation, dermal (all effects) and combined exposure in 4 scenarios ➢ All RCRs < 0.15 for all routes and combined exposure for 14 scenarios
Use of air care products (conc. 0.25-5%)		➢ RCRs < 0.2 for dermal (local effects) exposure in 1 scenario

		➢ All RCRs < 0.05 for all routes and combined exposure for 2 scenarios
Use of polishes and wax blend and biocides (conc ~0.1%)		All RCRs < 0.04 for all routes and combined exposure for all scenarios

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* *A list of the main additional information sources not present in the registration dossiers.*

7.15. Abbreviations

ACR	Acute Chronic Ratio
AF	Assessment Factor
BCF	Bio - Concentration Factor
CLH	Harmonised Classification & Labelling
CLP	Regulation 1272/2008/EC for Classification Labeling & Packaging
CoRAP	Community Rolling Action Plan
CSA	Chemical Safety Assessment
CSR	Chemical Safety Report

DNEL	Derived No Effect Level
ECHA	European Chemicals Agency
eMSCA	evaluating Member State Competent Authority
ERC	Environmental Release Category
GES	Generic Exposure Scenario
GLP	Good Laboratory Practice
HLC	Henry's Law Constant
IFRA	International Fragrance Association
IW	Industrial Workers
LLNA	Local Lymph Node Assay
MoA	Mode of Action
OECD	Organisation for Economic and Co-operational Development
PC	Product Category
PNEC	Predicted No Effect Concentration
PROC	Process Category
PW	Professional Workers
QSAR	Quantitative Structure-Activity Relationship
RCR	Risk Characterisation Ratio
RMOA	Risk Management Option Analysis
SEv	Substance Evaluation
STP	Sewage Treatment Plant
SU	Sector for end Use
SVHC	Substances of Very High Concern
ThOD	Theoretical Oxygen Demand