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FranceAgriMer
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DES PRODUITS DE L'AGRICULTURE ET DE LA MER

Perfume, aromatic and medicinal plants

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Inventory of available knowledge on the assessment of identified hazards and study of the technical and economic impacts of the evolution of the REACH and CLP regulations on the French essential oil industry

Summary Note

Your Specialties, Our Expertise

Inventory of available knowledge on the assessment of identified hazards and study of the technical and economic impacts of the evolution of the REACH and CLP regulations on the French essential oil industry

SUMMARY NOTE

FranceAgriMer

Project No.	Report No.	Date
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Contents

Foreword

This document is an English translation made by FranceAgriMer of a document written by CEHTRA in French.

Although this study was monitored by a steering committee and although a certain number of comments made during meetings by the members of this committee were considered, the content of this report if offered by its authors and is intended to be neutral.

The inventory of available data was carried out as exhaustively as possible, but in an incomplete and non-definitive manner due to the project's timeline (entry into force of the planned regulatory changes and evolution in the classification of hazardous substances) and due to the very large quantity of information that the authors had to review.

As a result, the study makes it possible to illustrate the issues raised and to assess certain potential impacts related to the revision of the REACH and CLP regulations, without, however, making it possible to measure all of the actual impacts for the industry and its players.

Summary/Abstract

The 10 Essential Oils (EO) included in this study were selected to best illustrate the impact of the revision of the REACH and CLP regulations (including the new assessment of the Endocrine Disrupting Potential (ED) of substances) may have for all French producers in the French EO sector. Therefore, these Essential oils include:

- EOs from medicinal and aromatic plants (MAPs) produced in large volumes in France and for which a significant number of distilleries having submitted a REACH registration dossier: lavender and lavandin EO (about 140 t/year and 2000 t/year, respectively).
- EOs from MAPs with large production volumes in France and for which the number of distilleries having submitted a registration dossier is smaller: EOs from clary sage, coriander seed, Scotch pine and peppermint (about 5 t/year, except sage with production volumes of 30 t/year)
- 4 other EOs from MAPs produced in French overseas territories and/or exclusively registered by industrial producers; the inclusion of these EOs allows to better highlight the economic challenges the industry may face as well as the specificity of EOs compared to substances of less complex composition.

No EOs, and only three components of the selected 10 EOs (benzyl salicylate, geraniol, thymol) are listed in the public databases of substances having a potential endocrine disruption effect.

To date, none of these three components have been identified as having endocrine disruption properties.

The papers we selected for their relevance in investigating the endocrine disruption properties of the EOs included in this study show no evidence of the endocrine disruption effects for any of the 10 EOs we have studied.

Data on potential endocrine disruption effects (mostly *in vitro*) have been identified for a number of EO components, but no systematic correlation has been clearly demonstrated with the endocrine activity of EOs containing these constituents.

The proposals to update the REACH regulation with regard to the data required for the study of the endocrine disruption properties will involve numerous tests that will not always allow a definitive and safe conclusion as to whether such or such substance has endocrine disruption properties or not. This study shows that several technical difficulties are expected in performing and interpreting these tests

and in applying the MOCS (More than One Constituent Substance) principle to EOs. Depending on the proposals, having different financial impacts, the number of new tests to be conducted and associated workload for CRO (Contract Research Organizations) laboratories could increase significantly.

If Annexes VII and VIII of REACH (data required for registration dossiers at tonnage bands of 1 to 10 t/year and 10 to 100 t/year, respectively) are merged, which is being considered, in order to assess the risks for all substances above the production and/or import threshold of 1 t/year in the European Union, this will also have a major financial impact. The specificities of natural complex substances (NCS) and the complexity of their chemical composition entail additional costs, due to the increased volume of data to be compiled, in particular for the environmental risk assessment. Industrial companies have very often registered EOs or other NCS with only few participants included in their joint submission and most of the time, their registration only covered the 1 to 10 t/year tonnage band.

For lavender and lavandin, the estimated extra cost for updating the REACH registration dossiers in the most plausible scenario (merging of Annexes VII and VIII and endocrine disruption potential tests required only by *in vitro* method*)* has been estimated to vary from 0 € (lavandin or lavender EO dossiers already submitted for the over 10 t/year tonnage band) to 5,700 € (lavender EO dossiers already submitted for the 1 to 10 t/year tonnage band); in this scenario, which is not the worst in budget terms, the companies in the lowest tonnage band will bear a higher cost than those with a registration for a higher tonnage band.

Other EOs from MAPs produced in France, for which the 1 to 10 t/year is the only tonnage band , we estimate that additional costs will vary from about 20,000 € (for clary sage and coriander seed EO) to about 118,000 € (Scotch pine EO).

These direct costs linked to updating registration dossiers are proportional to the turnover of the companies in question. These extra costs will also have an impact on the other players in the industry, whose business indirectly depends on the business of producers, such as the manufacturers and distributors of finished products, consumers, or other companies, such as those linked to the tourism industry.

The other main economic issue related to the revision of the REACH and CLP regulations is the implementation of the MOCS principle to determine the hazard classification of a substance based on certain properties: in case data is obtained on EOs, the final classification would be determined from this data, only if it is more stringent than the one obtained by applying the CLP mixture classification rule.

Considering the available knowledge at the time of this study, the hazard properties of EOs that could be impacted by this new MOCS approach are as follows:

- PBT[i] : no direct consequence currently anticipated because EOs do not meet criterion T (its inclusion in the MOCS approach is not envisaged) and all 3 criteria must be met for a substance to be considered Persistent, Bioaccumulative and Toxic (PBT).
- vPvB[i] : currently, data obtained on EOs themselves are used to demonstrate that most EOs are readily biodegradable; if the presence of non-biodegradable constituents at levels as low as 0.1% were to be taken into account, by default, to conclude that an EO is a vPvB substance, then many EOs could be classified as vPvB substances;
- ED, PMT, vPvM[i] EO: lack of sufficient data to derive preliminary conclusions, but as EO are composed of multiple components, the probability of their classification being impacted is greater than for single substances.
- CMR[i].

[i] PBT (Persistent, Bioaccumulative and Toxic), ED (Endocrine Disruptor), PMT (Persistent, Mobile, and Toxic), vPvM (very Persistent, very Mobile), vPvB (very Persistent, very Bioaccumulative), CMR (Carcinogenic, Mutagenic and Reprotoxic)

Among the 10 EOs included in this study, the classification of only one EO would have to be modified according to the MOCS approach, i.e. the ylang-ylang EO which should be classified in the reprotoxic category 2 because it contains constituents classified as reprotoxic 2 at a level above 3% although it is not currently classified as reprotoxic based on the "results on the substance itself" approach. If the intention to change the classification of paracymene from reprotoxic 2 to 1B became effective, the MOCS principle would result in half of the EOs included in this study ending in the reprotoxic 1B category (EOs of lavender, coriander, Scotch pine, peppermint, and thyme, since they contain more than 0.3% of paracymene). Paracymene is an extremely common compound found in natural complex substances, and it is present in 153 out of 365 EOs listed by the European Federation of Essential Oils (EFEO), and this is therefore particularly critical. Even if we do not take the MOCS principle into account, this study demonstrates that classifying EOs based on the presence of multiple compounds at low concentrations and on the fact that little data is available as compared to other less complex substances, will most likely result in classification being impacted by the individual classification of one of the EO's components. The MOCS approach would make it impossible to use the results obtained for the substance itself even when these results could result in lighter constraints with regard to classification (case encountered in the few available studies), and this not only for the CMR properties, but also for several other properties, which are presented above.

The indirect costs (loss of market opportunities) linked to the "worst-case" classification which would take MOCS provisions into account, cannot be quantified since they vary according to the classification level of each EO. Indeed, the classification of EOs according to their hazard potential as defined by the MOCS provisions could involve limitations in the use of the EOs, in particular in the perfumery and cosmetic industries, to the benefit of other substances of simpler composition, or could even lead to production prohibition (a consequence which is not highlighted according to the current classification of the components found in the 10 EOs included in this study). The economic impact for the industry could therefore be huge and much greater than the direct impact linked to the costs of updating the registration dossiers which, depending on the case and the turnover of the companies, can however range from very low to very high.

1. Introduction

This report is a summary of the work conducted in the context of a technical and economic impact study of the implementation of the current and forecasted revisions of the REACH and CLP regulations.

This work was carried out in 3 phases, as described in the specifications provided by FranceAgriMer[1] :

1. Phase 1: Identify all known hazard classifications of the components of essential oils (EOs) produced in France for the hazard classes impacted by the MOCS approach. Identify the data that could point to the potential endocrine disruption (ED) nature of EOs and of some of their components in the scientific literature, in the opinions of health agencies or expert reports and in data provided by industry.
2. Phase 2: Identify all the analytical and test methods that could be used to meet the future requirements of the REACH and CLP regulations regarding the endocrine disruption hazard; this inventory will point out the limitations of these methods in order to highlight the possible need to implement or develop specific methods.
3. Phase 3: Assess the economic impacts on the French EO industry, according to various regulatory evolution scenarii, and more specifically, the impact for small production volumes (1-10 tons/year).

2. State of current knowledge relevant to this study

The review of the current knowledge was conducted at a time when the final regulatory updates had not yet been adopted. Thus, several discussions were underway at the time when the authors of this study were gathering existing information on the issues addressed of this study. Therefore, the information included in this study is uncertain and information interpretation is subject to potential evolutions, including, but not limited to:

- Modifications in the potential evolutions of the REACH and CLP regulations, their implementation probability, and their impact on the industry.
- The proposed hazard classifications of substances are discussed and reviewed on a regular basis; they are therefore not finally decided upon.

Moreover, due to the timeline of this study and given the very large amount the wealth of information available which is more or less directly related to this wide-ranging study, this research cannot be considered as being completed and exhaustive since other data/regulatory measures may or might be available/implemented in the future.

Finally, **the objective of this study was:**

- **to provide a review of knowledge available regarding the hazard classification of the selected EOs and of their components for the hazard classes impacted by the MOCS approach.**
- **Identify the limitations of test methods that can be used to meet future REACH and CLP requirements regarding the endocrine disruption hazard.**
- **To assess the potential financial consequences of any potential changes to the REACH and CLP regulations, based on currently available knowledge and to the best of our ability.**

The purpose of this study was not to assess the hazard nature of EOs.

With these objectives in mind, this review was intended to better understand the issues at stake for the industry. Therefore, the authors carried out the following actions:

- We assessed the relevance of the EO screening process and looked at the way this process could be refined.
- We hypothesized the most plausible and impactful assumptions regarding changes in the REACH and CLP regulations for the EO industry.
- We identified strategies, methods, and potential technical and financial issues to meet potential new REACH requirements and to assess the consequences of implementing potential changes to the CLP regulations.
- We reviewed the data in the REACH dossiers for EOs and their components and we identified the critical data that would be missing in case the REACH and CLP regulations were to be modified.
- We reviewed data related to the assessment of the ED potential of EOs and their components.

2.1 Industrial and regulatory context

2.1.1 Selection of the 10 EOs

The following 6 EOs were selected on the basis of their registration dossier submitted by at least one French distillery:

1 - Lavandin
2 - Lavender
3 - Clary sage
4 - Coriander seed
5 - Scotch pine
6 - Peppermint

Although no French distillery was identified among the companies that registered these substances, the following 4 EOs were also included:

7 - Ylang Ylang
8 - Vetiver
9 - Geranium Rosat / Bourbon
10 - Thyme[ii]

[ii] As no REACH registration dossier was found for one of the thyme EOs, it has been decided to cover thyme EO (MAP produced in France) in this study through the carvacrol-rich Origanum EO (registration dossier submitted by a French company) because of constituents of interest for the study commonly present in the 2 types of EOs: para-cymene, gamma-terpinene and thymol

These 4 EOs were selected according to the following criteria:

- They are produced in French overseas territories, and/or,
- A registration dossier was submitted by French industrial producers (importer and/or French non-agricultural manufacturer, see paragraph 4.2) and/or,
- The composition of a registered EO quality is of particular interest to illustrate the economic issues linked to the proposed modifications of the REACH and CLP regulations.

2.1.2 Potential updates to the REACH and CLP regulations

The following issues were selected as the most impactful for the industry if changes to the regulations were to be implemented:

- The systematic implementation of the assessment of the ED potential: the aim of this strategy is to acquire data which, depending on results and tonnage, will allow to investigate further and prioritize the assessments. For this assessment, additional tests (potentially on vertebrates depending on the proposals and tonnages) may be required as part of the REACH registration dossiers, in order to determine the ED potential[2] . The ED potential of a substance is an issue of concern for both human health and the environment; the implementation of an assessment strategy and the definition of a new hazard according to CLP provisions will allow a better understanding of the hazard.

- The implementation of a chemical safety assessment for the REACH registration, applicable as of a production level of 1 ton/year (Annex VII): this would lead to the calculation of DNELs (Derived No Effect Levels) and PNECs (Predicted No Effect Concentrations), i.e., the exposure doses or concentrations above which human populations and environmental organisms should not be exposed. Currently the calculation of DNELs and PNECs would not be possible from the information requested when registering a substance for a production level included in the 1 to 10 tons band (Annex VII). Current discussions are focused on a merging of Annex VII and Annex VIII[iii] , or on a complete overhaul of the requirements, based on a pre-assessment. In the context of this study, the merging of Annex VII and Annex VIII was chosen as it is the option most frequently mentioned in the discussions[3] .

- The introduction of MOCS requirements (More than One Constituent Substances): UVCB substances (Substances of Unknown or Variable Composition, Complex Reaction Products and Biological Materials) as well as other substances with more than one constituent (i.e. mono-component substances containing impurities, and multi-component substances) will be defined as MOCS. The main impact of this measure could be that certain effects (CMR properties, biodegradation, and bioaccumulation) will be assessed based on data available on the components impacted by the MOCS requirements and not on the whole substance. The MOCS approach has also been proposed for the new ED hazard class[4] . The aim of introducing

[iii] Annexes VII and VIII of the REACH Regulation list the physicochemical, (eco)toxicological, and environmental fate information requirements applicable to registration dossiers for production levels of 1 to 10 t/year, and 10 to 100 t/year, respectively (for dossiers for a production level of 10 to 100 t/year, the data required in Annex VIII are to be added to the data required in Annex VII)

this concept is to harmonize the classification rules by favoring the by default mixture approach (CLP amendment). The consequences for the REACH assessment process and for the generation of associated data and test strategies are also envisaged in relation to this new concept[5] .

The dates of entry into force of the revised regulations are not yet known, but they should take place sometime in 2023. It is expected that the revision of the CLP Regulation will happen before that of the REACH regulation.

2.2 Data available for the 10 EOs included in the study and for their components

2.2.1 Methodology

For each EO and for each of their component, all the data submitted in the registration dossier, as listed on the European Chemicals Agency website, were inventoried.

Concerning the endocrine disruption potential (ED), as these data are not yet required when filing a REACH registration dossier, our approach was as follows:

- For each EO and each of their components, we identified those which are identified as likely to have a potential ED potential and we identified their concern level according to the number of list(s) they appeared on and according to the nature of the list(s) on which the substance appears among the 18 following lists:

Table 1 - List of 18 databases listing substances with potential ED effects

REACH - ANNEX XIV (authorization)[6]	REACH - SVHC list (article 59)[7]	ECHA - PACT - RMOA[8]	ECHA - CoRAP[9]	ANSES[10]	Danish EPA List of EDC[11]
UN Environment Program (WHO)[12]	BKH List (2000)[13]	BKH - RPS List (2002)[14]	DHI List (2007)[15]	EdList.org List I[16]	EdList.org List II
EdList.org List III	EU Commission Impact Assessment[17]	DeDUCT Database 2.0[18]	TEDX List[19]	SIN List[20]	ETUC List[21]

- We reviewed existing studies conducted on EO and/or their components, as available in the scientific literature (data from regulatory dossiers not considered) or via knowledge of existing information belonging to private companies and interviews with relevant persons.

2.2.2 Summary of the information we reviewed :

The following table summarizes the information collected for each EO, namely

- Identifiers used for the REACH registration of the EO.
- Agricultural production level in France.
- Registration by French agricultural distillers (number) or by French industrial companies and maximum tonnage band covered by the joint submission of REACH registrations for any given natural substance.
- Hazard classification of the natural substance.
- Composition complexity level of the registered EO, especially in terms of number of components.
- Presence of CMR components and/or components requiring further investigation for the determination of their ED potential.

Table 2 – Information summary regarding the 10 EOs included in the study

Plant	EC name (REACH registration)	EC NUMBER (REACH)	Agri. production	French registration. Max. tonnage	Classification	Composition	Specific components
Lavandin	Lavender, Lavandula hybrida, ext.	294-470-6	2000 t/year	100 French distilleries out of 135 - 100 t/year	Skin Sens 1B, H317 Eye Irr 2, H319 Aquatic chronic 3, H412	Complex	Para-cymene and gamma-terpinene reprotoxic cat. 2 (< 1%) Traces of Geraniol ED lists
Lavender	Lavender, Lavandula angustifolia, ext.	289-995-2	140 t/year	35 French distilleries out of 150 - 100 t/year	Asp. Tox. 1, H304 Eye Irr 2, H319 Skin Sens 1B, H317 Aquatic Chronic 3, H412	Complex	Gamma-terpinene reprotoxic cat. 2 (< 1 %) Traces of Geraniol ED lists
Clary sage	Sage, Salvia sclarea, ext.	283-911-8	30 t/year	15 French distilleries out of 30 - 10 t/year	Skin Sens 1B, H317 Aquatic Chronic 3, H412	Complex	Traces of Geraniol ED lists
Coriander	Coriander, ext.	283-880-0	4 t/year	4 French distilleries out of 20 - 10 t/year	Asp. Tox. 1, H304 Skin Irr 2, H319 Eye Irr 2, H319 Skin Sens 1B, H317 Aquatic Chronic 2, H411	Complex	Para-cymene reprotoxic cat. 2 (< 4 %) Traces of Geraniol ED lists

Plant	EC name (REACH registration)	EC NUMBER (REACH)	Agri. production	French registration. Max. tonnage	Classification	Composition	Specific components
Scotch Pine	Pine, Pinus sylvestris, ext.	281-679-2	5 t/year	1 French distillery out of 5 - 10 t/year	Flam. Liq. 3, H226 Asp. Tox. 1, H304 Skin Irr 2, H315 Eye Irr 2, H319 Skin Sens 1B, H317 Aquatic Chronic 2, H411	Complex	Para-cymene reprotoxic cat. 2 (potentially > 1%)
Peppermint	Peppermint, ext.	282-015-4	8 t/year	2 French distilleries out of 50 - 100 t/year	Skin Irr 2, H315 Eye Irr 2, H319 Skin Sens 1B, H317 Aquatic Chronic 3, H412	Complex	Para-cymene reprotoxic cat. 2 (potentially >1%)
Ylang-ylang (2 EOs with dossier)	Ylang-ylang, ext. / Essential oil of Ylang Ylang III obtained from the flowers of Cananga odorata (Annonaceae) by steam distillation	281-092-1/947-049-2 (New)	Overseas territory	No French distillery, but French industrial companies	Asp. Tox. 1, H304 Skin Irr 2, H315 Skin Sens 1B, H317 Aquatic Chronic 3, H412	Complex	Methyl-anisole reprotoxic cat. 2 (>5%) Benzyl Salicylate and Geraniol detected ED lists
Vetiver	Vetiveria zizanioides, ext.	282-490-8	Overseas territory	No French distillery, but French industrial companies	Skin Irr 2, H315 Skin Sens 1, H317 Eye Irr 2, H319 Aquatic Chronic 2, H411	Particularly complex	-
Rose Geranium	Pelargonium graveolens, ext.	290-140-0	Ultra-marine territory	French Indus.	Flam. Liq. 4 : H227 Skin Irrit. 2 : H315 Eye Irrit. 2A : H319 Skin Sens. 1B : H317 Aquatic Acute 3; H402	Complex	Traces of Geraniol ED lists

Plant	EC name (REACH registration)	EC NUMBER (REACH)	Agri. production	French registration. Max. tonnage	Classification	Composition	Specific components
Thyme	Carvacrol-rich essential oil obtained from the leaves of Origanum spp, Labiatae, by distillation	New EC number: 947-697-6	1.5 t/year	French Indus.	Acute Tox. 4, H302 Asp. Tox. 1, H304 Skin Irr 2, H315 Eye Dam 1, H318 Skin Sens 1B, H317 Repr. 2, H361 Aquatic Chronic 2, H411	Complex	Para-cymene and gamma-terpinene reprotoxic cat. 2 (>5%) Traces of thymol ED lists

3. Assessment of the ED potential of EOs in the context of the evolutions of the REACH and CLP regulations

The objectives of this part of the study were to:

- Analyze available bibliographic references[iv] focusing more specifically on the methodology used by their authors to rule on the ED nature of the studied EOs.
- To inventory the potential future information requirements on endocrine disruption potential imposed by the REACH and CLP regulations.
- Identify the available test methods (OECD and other official guidelines) to meet these requirements according to the 2 scenarii currently developed for the updating of the REACH regulation.
- To offer a critical analysis of these methods and point out their limits with regard to the specificities of the EOs, more specifically with regard to their physicochemical specificities.

3.1 ED data on EOs and their components

3.1.1 Components which appear on the list of substances of interest for their ED nature

The EOs themselves were not detected on the lists.
Only 3 components are present on these lists:

- Geraniol:
  - Specific data: interaction with estrogen receptor (ED) shown in *in vitro* studies, and at high concentrations, the ED potential has not been confirmed *in vivo.*

[iv] The specific references used for this section are available in the consolidated report prepared for this impact assessment.

- Lists :
  - Non-ED-related regulatory process (OECD 414/443) for the validation of the proposed tests required for each production level registered under REACH; standard non-ED process.
  - regulatory process for the assessment of the endocrine disruption potential of a substance. Assessment is carried out by ANSES in the framework of the biocides regulation; standard process, regardless of the substance.

- Benzyl salicylate:
  - Specific data: The estrogen receptor activity which was observed *in vitro* was extremely low, at concentrations close to cytotoxicity, and the potency was seven orders of magnitude less than the effect of estradiol. Regardless of the absorption route, once absorbed, benzyl salicylate is rapidly and extensively hydrolyzed *in vivo* by esterase, thus only salicylic acid and benzyl alcohol are available in the system. No *in vivo* adverse effects of benzyl salicylate are expected that could be attributed to an endocrine mechanism of action.
  - Lists: appears in several regulatory lists for its endocrine disruption potential. However, since this substance was included in the CoRAP list, the generation of information on the endocrine disruption properties of the substance became mandatory as part of the compliance check. In addition, new information is expected for the assessment of the ED properties of salicylic acid (EC 200-712-3), which is a metabolite of this substance, and which could influence the ED assessment of the substance. Based on the information that was generated, the German authority does not currently consider the environmental risk assessment of the substance to be a priority.

- Thymol:

  Specific data: Several works show an anti-androgenic effect of thymol, in *in vitro* studies (weak activity). No *in vivo* data is available to confirm the relevance of these effects
  - List: inclusion in the Deduct list based on meta-thymol data: not relevant since thymol and meta-thymol are different substances.

In conclusion, in the **current state of knowledge**, no component of the studied EOs has been identified as having proven ED properties. However, it will be necessary to monitor whether an ED 2 classification (suspected) is proposed by a Member State.

Data on potential endocrine effects (mainly *in vitro*) have been identified for a number of EO components, but no systematic correlation with endocrine activity of EOs containing these components has been clearly demonstrated.

3.1.2 Data on EOs

A comprehensive search of all potentially relevant references available in the literature for the assessment of the ED potential was conducted for each of the 10 selected EOs.

For the EOs of Coriander seed, Peppermint, Vetiver, Thyme (rich in carvacrol), Scotch Pine and Clary Sage, no data was found on this matter.

For rose geranium / bourbon and ylang-ylang EOs, a small number of data was found. An *in vitro* study of the estrogenic activity, an improvement of the health status in postmenopausal women with vaginal atrophy and an increase in the level of salivary estrogens after inhalation for 20 min were reported for rose geranium / bourbon EO. For ylang-ylang EO, no effect on the level of salivary estrogens was reported after inhalation for 20 min. An increase of human placental lactogen (hPL) *in vitro* (placental cells) and the non-activation of the P2X7 gene were reported.

Several studies related to the ED potential were found for lavender EO (when investigation for studies on lavandin EO, the same studies as those conducted on lavender EO were found).
Contradictions between *in vitro* and *in vivo* results have been observed but no effect was finally proven. More specifically, the cases of premature gynecomastia/thelarche associated with the use of hygiene products potentially containing lavender EO have been challenged as numerous weaknesses were found in the studies and the publication of a larger cross-sectional study showed no link between the use of products containing lavender EO and the incidence of premature gynecomastia/thelarche

In conclusion, in the **current state of knowledge,** no EO has been identified as having proven ED properties.

3.2 Testing for ED potential in case of an update of the REACH regulation – assessment of the implications for the EOs

3.2.1 Classification of EDs according to CLP

According to the CLP classification proposal[v] , category 1 corresponds to the hazard class for a substance that is a "known or suspected endocrine disruptor for the human health / the environment".

Category 1 classification is based primarily on evidence from human and/or animal data. These data must provide evidence that the substance meets the 3 criteria listed below:

a) Have an adverse effect on an intact organism or its progeny; and
b) Have endocrine activity; and
c) Have an endocrine disruption mode of action (biologically plausible link between the endocrine activity and the adverse effect).

However, in cases in which information is available that casts doubt on the relevance of the mode of action of the endocrine disruptor for humans/the environment, a classification of the substance in category 2 "Suspected endocrine disruptor" may be more appropriate.

Regarding the classification criteria for mixtures, the mixture must be classified as:

- Category 1 ED when it contains at least one ingredient classified as Category 1 ED at a concentration ≥ 0.1%.
- Category 2 ED when it contains at least one ingredient classified as Category 2 ED at a concentration ≥ 1%.

[v] at the time of the study, discussions were still ongoing regarding the ED criteria, as the final delegated act had not been published and its final content was not known.

3.2.2 Presentation of potential study requirements and related costs

The assessment of the ED potential of a substance is not yet part of the information requirements for the registration of a REACH dossier. However, many discussions are underway since 2020, and in particular within the CARACAL expert group, aimed at including this requirement to the registration process. Currently, information requirements have a limited capacity to provide data on ED properties. Indeed, these can only be observed/suspected from study data related to the endocrine system (e.g. reproductive and developmental toxicity studies (OECD 421, 422, 414, 443, 234), or toxicity studies repeated after 28 and 90 days (OECD 407, 408).

As a result, two proposals are currently under discussion (report of the 4th CARACAL working group meeting (CASG-ED/2021/03)) to incorporate criteria for information requirements in the REACH registration dossiers, that would allow assessing the ED potential based on the quantity of substance either manufactured or imported. These proposals and their related costs are presented below.

The proposals considered in the study for the cost scenarios are as follows:

- Proposal 1: ED effects to be assessed by *in vitro* methods under Annex VII,
- Proposal 2: same requirements as in proposal 1 under Annex VII, plus ED effects to be assessed by *in vivo* methods under Annex VIII.

The prospective experimental costs presented here are for the new maximum potential data requirements under Annexes VII to VIII, in order to fill in the gaps with experimental studies (maximum rate found between two European CRO laboratories (Contract Research Organization), without resorting to alternative methods).

Table 3 - Costs involved to meet data requirements under Annex VII (common to both proposals)

Estrogen receptor transactivation assay (OECD 455)	**Androgen receptor transactivation assay (OECD 458)**	***In vitro* steroidogenesis (OECD 456)**	**Aromatase assay (US EPA TG OPPTS 890.1200)**
23 700 €	23 700 €	48 800 €	34 900 €

Thyroid Disruption Tests			
***In vitro* determination of thyroid peroxidase (TPO) inhibition**	**Determination of transthyretin binding**	**Thyroid receptor transcriptional activation test**	**Symport sodium iodide interaction assay (NIS)**
26 800 €	15 900 €	16 800 €	13 800 €

Considering a maximalist approach, if we add up the estimated costs of the experimental studies, the implementation of the new REACH requirements for the assessment of the ED potential of a substance for the update of a registration dossier for a production level ranging from 1 to 10 t/year would result in an additional cost of around €157,900 (assuming only the most expensive thyroid disruption test would be performed).

Table 4 - Costs of Data Requirements for Annex VIII (Second Proposal Only)

Preliminary study "endocrine disruptor screening program" in rats	Uterotrophic test in rodents (OECD 440)	Hershberger test in rats (OECD 441)	Short-term fish reproduction test (OECD 229)	Amphibian metamorphosis test (OECD 231)
32 270 €	62 200 €	124 500 €	138 300 €	126 000 €

Merging of Annexes VII and VIII/update of a dossier under Annex VIII

Among the current discussions (CARACAL, 2022), the most frequently anticipated avenue is the merging of Annex VII (tonnage band between 1 and 10 tons/year) and Annex VIII (tonnage band between 10 and 100 tons/year). The requirements of Annex VIII would then apply to Annex VII.

In this case, the *in vivo* studies required under Annex VIII would need to be performed and the study requirements exemptions that exist under Annex VII could apply. This would result in *in vivo* testing being performed to assess modalities A and E (Androgen and Estrogen), and using the results of an OECD 422 study (Combined Repeated Dose Toxicity and Reproductive and Developmental Toxicity Screening Study) to assess modality T (Thyroid), instead of the *in vitro* studies required under Annex VII to assess modalities A, E and T.

As a consequence, and in the event of a merging of Annexes VII and VIII or of the updating of a dossier under Annex VIII, the specific studies for the assessment of the ED potential of a substance would represent a budget of 532,070 € and would be as follows

- OECD 456 (*In vitro* steroidogenesis test H295R*),*
- OECD 440 (Uterotrophic bioassay in rodents),
- OECD 441 (Hershberger rat bioassay),
- OECD 231 (Amphibian metamorphosis test),
- OECD 229 (Short-term fish reproduction test).

3.2.3 Limitations of the EOs' ED assessment

In general, there are several technical and scientific limitations regarding *in vitro* ED assessment tests (metabolic capacities, solubility of the tested substance...), as well as *in vivo* tests (stress depending on the administration route, reproducibility/consistency of the results...). Furthermore, the question remains as to whether it is relevant to extrapolate results obtained *in vitro* to an *in vivo* situation, and to extrapolate the results of these tests to humans.

Tests used to assess endocrine disruption have not been specifically validated for substances of complex composition. However, there are several critical limitations specifically related to the complex composition of EOs that may call into question the relevance of using these tests, including:

- Solubility in water,
- Presence of contaminants (pesticides, herbicides, plastics, and dissolution of the substances they contain...),
- Extrapolation between the ED properties of the components (when known) and of the EO is difficult or impossible depending on the possible interactions between components (inhibition, addition... depending on the mechanism of action),
- Bioavailability of the components,
- Chirality of the components,
- Composition variability for a given EO.

4. Estimation of the Costs potentially associated to the update of REACH and CLP for the French EO's sector

We assessed the direct costs linked to the potential update of the REACH and CLP regulations for 6 EOs produced in France.
We worked on different options based on the various regulatory scenarii and we identified practical cases to illustrate the potential financial impact of updating the REACH registration dossiers for French growers or industrial companies.
We also worked on the economic challenges for the industry, in relation to the updating of the REACH and CLP regulations.

4.1 Cost assessment of adapting the REACH registration dossiers to comply with new expected requirements

4.1.1 Anticipated scenarii

In order to assess the potential incremental costs (costs in addition to those costs to meet the current requirements for registration) involved in updating the registration dossiers for the 6 selected Eos, we first assessed the increase in costs for all participants involved in joint submissions, according to the following scenario:

1. Merging of Annexes VII and VIII and low budget scenario for the new required studies (ED assessment tests, as required in Proposal 1),
2. Merging of Annexes VII and VIII and high budget scenario for the new required studies (ED assessment tests, as required in Proposal 2 + *in vitro* bioaccumulation study),
3. Annexes VII and VIII kept separate and low budget scenario for the new required studies (ED assessment tests, as required in Proposal 1),
4. Annexes VII and VIII kept separate, and high budget scenario for the new required studies (ED assessment tests, as required in Proposal 2 + *in vitro* bioaccumulation study),

4.1.2 Direct costs for joint submissions

Different categories of costs – which will add to the costs already in place for the joint submission of a REACH submission[22] - had to be assessed and included into the direct costs supported by the companies. This assessment was conducted based on the information we collected and/or on our past experience regarding the various potential scenarios. This approach allowed us to apply some rules for assessing the potential future costs in a standardized manner:

A. Additional study costs:
    a. Depending on the 2 different potential financial scenarii, specific number of new studies will be required.
    b. In case Annexes VII and VIII are merged, when the registration dossier does not already cover the 10 to 100 t/year tonnage band.
B. Additional cost linked to the use of an external service provider:
    a. Technical overheads (monitoring of studies and compilation of data to be included in

the dossiers) must be factored in, regardless of the anticipated scenario, since all scenarii anticipate additional requirements regarding the assessment of the ED nature of the substances.

b. Additional technical costs linked to the drafting of the Chemical Safety Report (CSR), should the new requirements demand it be modified or entirely created. Additional administrative costs are to be anticipated (management of joint submissions in order to comply with new REACH requirements).

- **Joint submission for the maximum 1 to 10 t/year tonnage band:**

In the case of dossiers for which a joint submission has been submitted, covering the 1 to 10 t/year tonnage band, the following table illustrates the estimated additional costs for the 3 scenarii which are developed:

1. Annexes VII and VIII are kept separate: proposal 1 for the study requirement because the requirement in Annex VIII (specific to proposal 2) does not apply to this tonnage band.
2. Merging of Annexes VII and VIII and Proposal 1 for study requirements.
3. Merging of Annexes VII and VIII and Proposal 2 for study requirements.

Table 5 - Estimated direct costs for each developed scenario, for submissions in the 1-10 t/y. production bracket

	Annexes kept separate	Annexes merged (P1 studies)	Annexes merged (P2 studies)
Total for all studies (ED potential, as per Proposal 1)	157 900 €	157 900 €	-
Total for all studies (ED potential according to Proposal 2) + Bioaccumulation	-	-	580 870 €
Total for all studies to meet requirement of Annex VIII + CSR	-	291 000 €	291 000 €
Monitoring of the studies	16 000 €	39 000 €	60 000 €
IUCLID dossier (abstracts + adaptations)	9 000 €	25 000 €	40 000 €
Drafting of the Chemical Safety Report	0 € (not required)	40 000 €	40 000 €
TOTAL (estimated, including technical studies and preparation of the dossier)	183 000 €	553 000 €	1 010 000 €

This table does not include any administrative costs, as these costs are proportional to the number of parties involved in the joint submission and may therefore vary from one substance to another.

This table is generic and has been applied by default for cost calculations related to EOs in the joint submission category. It does not consider the 2 following specific cases which were identified thanks to the work conducted in phase 1 and for which the costs are different, for both Annex merging scenarii. These 2 specific cases are:

- Coriander seed EO: we considered an already available study which is currently required under Annex VIII requirements, i.e.: the OECD 422 study.

- Vetiver EO: this EO has a particularly complex composition (more than 100 constituents), which results in additional costs linked to data collection and to the drafting of the Chemical Safety Report.

- **Joint submission for the maximum tonnage band of 10 to 100 t/year:**

Unlike what can be done for joint submissions for the 1-10 tonnage band, it is not possible to present the incremental costs involved for joint submissions for the 10 to 100 tonnage band in one single generic table as the number of specific cases and scenario is quite large. However, it is possible to extrapolate what these costs might be, using a comparison with the costs involved for joint submissions for the 1 to 10. tonnage band:

- Annexes are kept separated: cost sharing system based on the number of joint registrants, as currently used.
- Annexes are merged: joint submissions costs would be lower in both merger scenarii, since the studies needed to meet Annex VIII requirements and for the drafting of the Chemical Safety Report are already in the dossiers. A redistribution of all the costs paid to meet the requirements under Annex VIII from those companies which submitted for the 1 to 10 t/year tonnage band to those which submitted for the 10 to 100 t/year tonnage band, and a sharing of all the costs among all the joint registrants should be anticipated in this situation.
- In all cases, the Chemical Safety Report will have to be updated in order to include all the additional studies and to reflect the Mixture Assessment Factor (MAF) if the revised version of the REACH regulation requires it.

4.1.3 Direct filing costs for the players in the industry

For each of the 6 EOs produced in France, we used available information in order to assess the submission costs. Such assessment of the costs considers whether the company has already sent a submission or not, and the results we obtained are for:

- A registration submission for a production volume of 1 to 10 t/year or 10 to 100 t/year, when the joint submission covers this latest tonnage band (EO of lavandin , lavender, peppermint),
- a registration dossier from 1 to 10 t/year, when the joint submission covers only this tonnage band (EO of clary sage, coriander seed, Scotch pine).

Based on the many scenarii we developed, the involved costs (additional costs, in addition to the already paid registration costs) are presented below:

- **Joint submission for the maximum tonnage band of 10 to 100 t/year:**
    - Lavandin

Table 6 - Number of companies and tonnage bands – Joint submission for Lavandin essential oil:

REACH registration	1-10 t/year	10-100 t/year	Total
Number of French distilleries	50	50	100
Total number of companies in the joint submission	65	70	135

Table 7 - Estimated additional costs for a company filing a submission for lavender OE, taking into consideration the various potential scenario as well as the relevant tonnage band.

ED requirement	Merging of Annex VII and VIII	Registered tonnage	Updated cost
Most likely scenario: new study requirements under P1 and merging of the Annexes			
Proposition 1	Yes	> 10 t/year	- 400 € (restitution)
		1 to 10 t/year	3 800 €
Most impactful scenarii based on registered tonnage			
Proposition 2	No	> 10 t/year	10 000 €
Proposition 2	Yes	1 to 10 t/year	8 000 €

- Lavender

Table 8 - Number of companies and tonnage bands in the joint submission for lavender EO:

REACH registration	1-10 t/year	10-100 t/year	Total
Number of French distilleries	32	3	35
Total number of companies in the joint submission	137	13	150

Table 9 - Estimated incremental cost for a company and its lavender EO dossier based on several scenarii and its registration tonnage band:

PE requirement	Merging of Annex VII and VIII	Registration tonnage	Update cost
Most likely scenario: new study requirements in P1 and merging of annexes			
Proposition 1	Yes	> 10 t/year	- 2200 € (restitution)
		1 to 10 t/year	5 700 €
Most impactful scenarios based on registration tonnage			
Proposal 2	No	> 10 t/year	46 800 €
Proposal 2	Yes	1 to 10 t/year	5 700 €

- **Joint submission of less than 10 t/year (rounded estimates for one company) :**
  - Clary sage: 30 members
    - Most plausible scenario (P1 and Merging): 20,000 euros
    - Most impacting scenario (P2 and Merging): 37,000 euros
    - Least impacting scenario (P1 and Maintenance): 7,000 euros

- Coriander seed: 20 members
  - Most plausible scenario (P1 and Merging): 19,000 euros
  - Most impacting scenario (P2 and Merging): 44,000 euros
  - Least impacting scenario (P1 and Maintenance): 10,000 euros
- Scotch pine: 4 members only
  - Most plausible scenario (P1 and Merging): approximately 118,000 euros
  - Most impacting scenario (P2 and Merging): about 214,000 euros
  - Least impacting scenario (P1 and Maintenance): 39,000 euros

The additional costs for the other dossiers are not presented because we had no access to some of the data (cost of dossiers to date and number of joint registrants per tonnage band) necessary for an accurate assessment of the costs.

- **Illustration of direct costs for companies**

The elements that have the greatest impact on direct costs for a company are:

1. The number of companies participating in the joint submission:
   a. If no merging of the annexes, the number of companies per tonnage band,
2. Whether or not testing is required to assess the endocrine disruption potential:
   a. If required, the level of requirement that will be applied,
3. Whether or not Annexes VII and VIII are merged:
   a. In case the Annexes are merged, the tonnage band covered so far in the joint submission,
4. The price of the tests conducted by the CRO laboratories,
5. The cost of compiling the associated data.

It should be noted that administrative costs are not considered to impact the direct costs for a company. Indeed, although these costs represent a significant part of the overall extra cost for a joint submission, these extra costs are shared by the joint registrants, and this has a much greater budget impact when the analysis is conducted at company level.

Based on all the calculations made according to the REACH and CLP update scenarii, we now show possible budgetary consequences for companies in the EO sector (agricultural or industrial) on the basis of different theoretical practical cases, by comparing the registration dossiers submitted to one or the other of the tonnage bands in relation to the theoretical turnover of the company concerned.

To illustrate the potential impact for one of the distilleries, we have developed 4 distillery hypotheses with different combinations of registration dossiers:

Table 10 - Illustration of the potential additional cost of REACH updates for a distillery:

Example of distillery dossier(s)	Cost estimates for the various scenarii	Minimum share of sales, depending on the scenario [vi]
Lavandin, between 1 and 10 t/year	1 200 € to 7 800 €	Between 1% and 16%
Lavandin, between 10 and 100 t/year + lavender, between 1 and 10 t/year	1 800 € to 10 660 €	Between 2% and 22%
Lavandin between 10 and 100 t/year Clary sage between 1 and 10 t/year	8 350 € to 40 600 €	Between 8% and 85%
Scotch pine between 1 and 10 t/year	39 000 € to 214 000 €	Between 35% and 446%

To assess the impact for industrial producers, we used the example of a company specialized in Natural Complex Substances ("NCS", i.e. EO and other plant extracts with a composition that can be extremely complex (large number of constituents) and/or largely unknown) of significant size in the industry; this example has been developed on the basis of a plausible theoretical company case, i.e.:

- 70 dossiers submitted,
- Half are non-EO plant extracts (mostly submitted individually or with one other company),
- 1 out of 10 dossiers (7) was submitted for volumes above 10 t/year.

In the case of this company, and if we consider the merging of Annexes VII and VIII and proposal 1 for the assessment of the endocrine disruption hazard, the total cost of updating all the dossiers submitted by this company would amount to 15,000,000 €, which would represent about 68% of its turnover for the natural substances it has registered[vii] .

4.1.4 Direct costs of updating REACH registration dossiers in connection with the revision of the CLP regulation

We anticipate that the revision of the REACH regulation will be linked to the revision of the CLP regulation. Indeed, the revision of the CLP regulation, if it includes the consideration of the MOCS concept, should introduce various adaptations to the testing requirements as listed in the REACH regulation[5].

However, and to the best of our knowledge, the details of these adaptations, and more specifically the impact on the relevant hazard classes, had not yet been decided upon at the date of this study. In addition, the proposals for the classification of the hazards linked to the substances are being discussed and reviewed on a regular basis and these proposals are therefore not fixed.

Thus, the elements presented in this section should only be understood as potential scenarii and the possible consequences for the sector should be read as assumptions **for the time being**.

[vi] In 2018, among French distilleries, 25% had an annual turnover below €48,000 and 50% had an annual turnover of €110,000
[vii] For the company used as an illustration, the annual turnover of 22 million euros was assessed to be directly related to natural substances registered under REACH

- **<u>Principle and adaptation of REACH requirements</u>:**

Although MOCS are substances, they are similar to mixtures since they contain more than one component/constituent. Based on this assumption, it can be argued that an approach similar to the one used for the classification of mixtures and substances should apply. The hazard classes potentially affected by this MOCS approach under the CLP regulation are as follows:

- Carcinogenic, Mutagenic, or Reprotoxic (CMR),
- Persistent bioaccumulative and toxic (PBT) and very persistent, very bioaccumulative (vPvB),
- Persistent, mobile, and toxic (PMT) and very persistent very mobile (vPvM),
- Endocrine disruptor (ED).

For MOCS that contain CMR-classified components (harmonized classification or self-classification) above the limits set out in Article 11 of the CLP regulation this information on the classified constituents prevails over the test data obtained on the MOCS itself, with the exception of test data on a MOCS that indicates CMR properties that have not been identified on the components.

Thus, in terms of testing for compliance with the REACH regulation, this would result in:

- A test exemption for MOCS containing CMR category 1 components (in concentrations above that resulting in a CMR category 1 classification of the MOCS according to the CLP rule for the classification of mixtures) for tests related to these respective properties.
- An obligation to test, if lacking when compared to the requirements set out in the annexes for mutagenicity and reprotoxicity properties, for MOCS containing no components classified as CMR or containing components classified as CMR category 2 or containing components classified as CMR category 1, below the classification limits applicable to mixtures (i.e. 0.1 %, for hazard classes C and M, and 0.3 % for classification R)

Having due consideration to the fact that the revision of the CLP regulation is not yet effective, this approach would also be followed for MOCS that would contain components classified as ED (classification not yet applicable). The classification limits for mixtures (which would be applied to MOCS) would be: 0.1% for the classification of mixtures containing components classified as ED category 1 and 1% for those classified as category 2.

Information on the components regarding the bioaccumulation and biodegradation properties used to assign "dangerous for the aquatic environment" classification predominates. It is anticipated (revision of CLP not yet effective) that it would also predominate for PBT, vPvB, PMT, vPvM classifications, in the test data obtained on the tested MOCS itself, with the exception of test data on a MOCS that indicate bioaccumulation and biodegradation properties that have not been identified on the components.

Thus, in terms of testing for compliance with the REACH regulation, this would result in the following situation:

- For biodegradability, bioaccumulation, and mobility: data based on relevant components.
- For toxicity: data based preferably on the MOCS themselves, while considering relevant data on components, according to a "*weight-of-evidence*" approach.

- **Possible consequences for the industry:**

According to the current analysis of CMR critical constituents (according to the "IFRA labelling Manual"[23]) which was provided to us by the EFEO (European Federation of Essential Oils) as we were conducting this study, only one constituent is classified in category 1 for one of the hazardous C, M or R properties. This component is safrol (classified as carcinogenic category 1), which is not found in the EOs covered in this study.

However, the proposals for CMR classification of components present in EOs are likely to evolve. In the event a component present in 1 of the 10 EOs included in the study at a concentration of more than 0.3%, becomes classified as Reprotoxic 1, then the testing requirements to assess this property would disappear. This could then mean that for an EO with a maximum tonnage band covering 1 to 10 t/year, and in a scenario in which Annexes VII and VIII would be merged, the OECD 422 study (combined repeated and reproductive toxicity study) could be replaced by an OECD 408 study (90-day repeated toxicity study) with a decrease of about 75,000 € of the joint submission costs. However, the anticipated impact in terms of indirect costs (see chapter 4.2) could then be so significant that the production/marketing of the material (and therefore the associated registration dossier) could be suspended.

With respect to the impact of MOCS on costs to assess biodegradability, mobility (test requirements to assess mobility are not yet known) and bioaccumulation (the possibility that bioaccumulation test requirements are only partially covered in the current P2 scenarios), the actual impact of the MOCS concept is difficult to assess.

Most of the EOs included in this study[viii] are currently considered readily biodegradable by the joint-registrants, considering the information they submitted in their dossier, i.e. data on the EO itself and/or on the components representing the majority of the composition. If the strategy (invalidation of the result obtained on the EO and lack of data for several components potentially considered as being relevant for the analysis of this hazard property) was considered unsatisfactory by ECHA, and in case studies had to be paid to a private owner so that obtained results can be used , then this could result in very high costs. In a by-default assessment, if we consider that about 30 components (for which data would be available) must be considered for the EO of the study and considering an estimated cost of 5,000 € per component, the additional cost could amount to 150,000 € for the joint submission.

In conclusion, at the date of the study - but more significant consequences cannot be ruled out in the future - and considering the difficulties in quantifying such consequences in a concrete manner, the consequences envisaged by the submission of the MOCS concept should not have a high direct financial impact on the dossiers when compared to the other elements considered for this study.

4.2 Estimated indirect costs potentially related to the update of the REACH and CLP regulations

The indirect costs (or more generally the economic stakes) linked to the implementation of the REACH and CLP amendments are likely to affect all the players in the sector:

- The "agricultural producers": farmers and distillation cooperatives,
- Industrial producers": industrial manufacturers/importers of raw materials,

[viii] The content of the registration dossier for geranium EO is not available, and the exhaustive detail of the content of some other dossiers is unknown to us, such as peppermint or Ylang-Ylang

- Downstream users": manufacturers of finished products and distributors,
- The "end users": consumers and companies whose business indirectly depends on other players in the industry.

The indirect costs were addressed using the description of the following economic issue: *"the potential loss of market for French actors in the EO industry (producers and downstream users, in particular the cosmetics and perfumery industry), either in the event of restrictions on use or sectoral regulations prohibiting certain classes of hazards (regulatory measure), or by a desire on the part of the profession not to use classified substances in formulated products (non-regulatory measure)".*

4.2.1 Potential indirect economic impact of the revision of the CLP regulation (and associated classification system) for the EO industry

- **<u>The MOCS principle used for classification purpose</u>:**

The inclusion of the MOCS concept is intended to standardize the assessment of substances to determine their hazardous classification with respect to their properties. Indeed, in case of different classifications between the ones that can be determined from tests on the substance itself and the ones that can be determined according to the rule of classification of mixtures, depending on the composition of components classified as hazardous, the MOCS approach would impose the use of the most unfavorable inferable classification; this measure intends to implement the "precautionary principle"[ix] . To date, a flexible approach to classification is used:

- when good toxicological data is available on a natural complex substance (NCS) this data is used to infer the classification,
- on the other hand, in the absence of quality data, we use a calculation based on the rules applicable to mixtures in order to determine the classification (% of components classified according to the classification thresholds present in the composition).

Regarding the 10 EOs included in this study, we were only able to compare one study which provides a result on the EO itself with results about to the presence of a classified compound, which would result in a classification for one of the items potentially impacted by the MOCS approach. This EO is ylang-ylang.

The results obtained in an OECD 422 study on ylang-ylang EO, which contains from 6 to 10% of p-methyl anisole (a component classified as Reprotoxic category 2[23]), did not show effects that could lead to a category 1 or 2 R classification. According to the MOCS approach, ylang-ylang EO should be classified as category 2; it is not currently classified as such, based on the "result-based" approach used for the substance itself.

Of the 9 other EOs included in the study, only one includes components classified as CMR above the limits of classification of mixtures: the Origanum EO which is rich in carvacrol; if we use the MOCS rule, this EO should be classified as R2 because it contains para-cymene and gamma-terpinene at levels

[ix] According to the European Parliament: "The precautionary principle aims to allow decision-makers to take protective measures when scientific evidence of a danger to the environment or human health is uncertain and the stakes are high. <u>The precautionary principle (europa.eu)</u>

above 3% of its composition. If Annexes VII and VIII are merged and the MOCS rule is applied, it should be the subject of an OECD 422 study, which could potentially highlight reprotoxicity effects and therefore classify the EO as R2 or even R1. On the other hand, if no effects are observed as for Ylang-Ylang, this EO could not be downgraded and should remain classified as R2.

If we broaden the analysis to all the EOs produced by the French industry, we must then consider the industrial producers who each have a range of registered NCS (of which the EOs are part) which is much wider than that of agricultural producers, resulting in the fact that the vast majority of NCS registered under the REACH regulation have an impact on at least 1 French industrial stakeholder.

A total of 13 natural complex substance (NCS)) were tested, of which 3 (including ylang-ylang EO) contained R2 components above the 3% mixture classification limit, 1 was just below this level and none of the results obtained showed effects that could mandate a category 1 or 2 R classification.

Para-cymene is an extremely common compound among NCSs (present in 153 NCSs out of 365). This component is the subject of a request for harmonized classification as R1B (CLH register of intent by Sweden 15 August 2022[x]). If the intention to modify the classification of para-cymene from R2 to 1B became effective, the MOCS principle would lead to the classification as Reprotoxic category 1B of half of the EO included in this study, namely the EOs of lavandin, coriander, Scotch pine, peppermint, and thyme, since they contain more than 0.3% of para-cymene.

For the ED hazard property, the same considerations should apply if the MOCS approach is adopted. At present, as ED classification criteria are not adopted yet, it is not possible to conduct an analysis of the potential impact on the 10 EOs included in this study, nor on any other.

Regarding bioaccumulation and persistence properties, for the 10 EOs for which we know the elements included in their dossiers, a precautionary approach has been considered for the aquatic environmental classification, applying the long-term risk on a by-default basis (considering that the substance is non-biodegradable, or if it is biodegradable, that it contains components with a *log Kow* >3, i.e. it has bioaccumulation potential).

To date, the elements required to assess the impact of the amendments to the REACH and CLP regulations are not available for hazard classes P and B. But we anticipate that, in the absence of the flexibility that would be introduced by the MOCS approach for the assessment of these properties, the proportion of NCSs, including potentially one/some among the 10 EOs in the study, to be classified as vPvB or vPvM could be significant (NCSs generally do not meet the T-criterion).

So far when tested as such for reprotoxicity properties (and for other properties not impacted by the MOCS approach and therefore not covered in this study - such as aquatic ecotoxicity), NCSs have not generated effects that are directly correlated to the presence of components above the classification thresholds retained by the MOCS approach. If the MOCS approach was applied for CMR and/or vPvB classifications (or even ED and/or vPvM later on), this would mean that the specificity of NCSs (complex composition with potential synergistic or inhibitory effects) would not be considered.

- **<u>Potential consequences of the MOCS approach on indirect costs and related issues for the industry</u>:**

It is difficult to conduct a holistic assessment of the impact on indirect costs on the entire French industry.

[x] https://www.echa.europa.eu/web/guest/registry-of-clh-intentions-until-outcome/-/dislist/details/0b0236e1878e49bc

It is reminded that this analysis was carried out to date and to the best of our knowledge.

EOs are used in a wide variety of sectors: as flavoring agents in the food industry (34.6%), as perfumes and active ingredients in cosmetics and in the aromatherapy industry (29.3%), as fragrances in detergents and washing powder (16.6%), as active pharmaceutical ingredients (16.1%), and also, to a lesser extent, as biocides or phytosanitary products.

The REACH regulation only requires registration for about 45% of these uses, namely when EOs are used as perfumes and active components in cosmetics and aromatherapy products (29.3%), as fragrances for detergents and laundry (16.6%). CLP labelling is not applicable for uses as flavoring agents (34.6 %[xi]).

Currently, a public consultation (*call for evidence*) is opened by ECHA for the use of skin sensitizing substances in mixtures intended for the general public, but the use of EOs in finished cosmetic products is excluded from the scope of this consultation. Indeed, cosmetic products are covered in a separate regulation.

The use of fragrances in detergents and laundry (16.6%) is not covered in the regulation for cosmetic products and therefore could eventually be impacted by a possible measure aimed at restricting the use of complex natural materials having a sensitizing effect on the skin. Furthermore, the conclusions regarding the classification of some EOs for this property could be rediscussed[24], for example because of the data obtained from artificially oxidized linalool (a component classified as “skin sensitizer category 1B”, which is one of the most abundant compounds in the EOs included in this study and which can make up 50% of the composition of lavender and lavandin EOs)[25] . Of the 10 EOs included in this study (some of them containing linalool), all of them are classified as "skin sensitizers”: some were classified by default, according to the mixture calculation rule, not because of positive results, but because the *in vitro* methods required for this hazard property are not all suitable, and this approach is common to most of the registered NCSs. However, recent toxicovigilance data collected by the French poison control centers show a very low frequency of adverse effects (1 case per 304,500 units sold, all effects combined, including the possible phenomenon of sensitization or skin allergy)[26] .

Even if the % of outlets in the various segments of the industry would need to be refined for each EO, this example illustrates one of the possible consequences of the implementation of the MOCS concept, and shows the potential impact of automatic classification in terms of prohibition or restriction for such or such type of submission and user.

The actual impact of implementing the MOCS approach cannot be quantified. Classifications are likely to evolve over time: proposals are discussed before they are adopted, data used to infer the classification levels are generated incrementally, and are not available for all EOs or their constituents at the time of EO assessment.

Among the sectoral measures likely to have a negative impact on EOs in terms of market losses, we can mention the ban on substances classified as CMR[xii] category 1A, 1B or 2 for use in cosmetic products. Regarding similar substances, more specifically those classified as category 1 CMR hazards (and potentially regarding new hazard categories that would be introduced by the CLP regulation, such as ED), the REACH regulation anticipates they could be included under Annex XIV, i.e. "substances subject to authorization", which would mean that they could no longer be produced in France or in French overseas territories. This would create a risk of market loss as well risks of production relocation. Annex XVII of the REACH regulation, which sets out the restrictions applicable to substances, mixtures and/or articles, prohibits the placing on the market of CMR 1A and 1B substances

[xi] Figure mentioned for the food industry, although this is not the only outlet in the food sector
[xii] Hazard categories for substances classified as PE, PBT, vPvB, vPvM category 1 or 2 are not included, as CLP has not yet incorporated them

as such or in mixtures at concentrations above generic or specific concentration limits.

In addition to the regulatory consequences related to the classifications of EO, we cannot rule out a willingness of the industry to stop using classified substances in formulated products.

While real and fully presented in the joint report, the indirect cost challenges for the industry listed below could not be quantified and therefore were not addressed. These challenges are primarily as follows:

- potential loss of jobs
- potential loss of biodiversity,
- difficulties in hiring the large number of expert human resources required to prepare the registration dossiers or rto work in the laboratories,
- multiplicity of laboratory tests, possibly including *in vivo* tests[xiii] : many of the 10 EOs included in the study are mainly used in cosmetics, an industry for which regulations prohibit testing ingredients and finished products on vertebrates; animal testing considerations for cosmetics industry stakeholders, NGOs and consumers must also be considered,
- EO use in consumer products will depend on consumers' perception of the risks associated with the use of products that would be perceived as having particularly hazardous properties.

[xiii] ECHA's Board of Appeal issued two decisions on August 18, 2020 regarding two UV filters used in sunscreens, and exclusively for cosmetic use: homosalate and ethylhexyl salicylate, the latter being suspected of being endocrine disruptors. The Board of Appeal considers that the REACH Regulation requires registrants to perform vertebrate animal studies even if the substance is used exclusively as an ingredient in cosmetic products, and that this is in line with the Cosmetics Regulation.

5. Conclusion

EOs are not exempt from registration obligations under the REACH regulation, because although they are of natural origin, they are classified as hazardous (which is the case of the 10 EOs included in this study, which were selected to best illustrate the subject at the level of the entire industry). However, incident rates as recorded by the poison control centers show that the use of EOs is well under control in France as confirmed by the very limited number of cases of misuse and by the very low level of reported adverse effects.

To ensure better safety for workers, the environment, and consumers, it is anticipated that:

- In the future, the REACH regulation will require registered substances to be tested for their ED potential and that a chemical risk assessment will be carried out as of the 1 t/year tonnage band instead of 10 t/year.
- The MOCS concept will be applied according to the precautionary principle: in case of different classifications between the one inferred from tests on the substance itself and the one inferred from the classification rule for mixtures which takes into account the composition in constituents classified as hazardous, the MOCS approach would require using the worst-case inferred classification.

The evaluation of the ED character of a substance is likely to generate enormous difficulties at European level because of the number of tests potentially involved, because of the difficulty involved in having these tests performed in CRO laboratories and because of the challenges involved in organizing and monitoring these tests. Difficulties in interpreting the cause-and-effect relationships due to the scientific complexity of the matter are also to be anticipated for each of the substances individually, including those substances present in the composition of EOs.

Data reviewed for this study did not make it possible to evidence proven ED properties for any of the studied EOs, nor for any of their components. However, this study allowed to address the specific difficulties linked to EOs, namely the large number of components and the multitude of data to be analyzed, grouped, and correlated to try to determine the existence of potential cause-and-effect relationships between the results obtained for the components and those obtained for the EOs themselves.

The specificities of EOs, their physicochemical characteristics, and the difficulty in implementing the required tests to meet the requirements set out under the REACH regulation, are already known by the producer companies in the industry which started compiling the data, despite the challenges they face, such as:

- Lack of data on the molecular weight of an EO: in such a situation, all the required *in vitro* test methods cannot be implemented to assess the skin sensitizing properties of the EO.
- Solubility in test medium: *log Kow* test not applicable on EO itself.
- Bioavailability of different components for ecotoxicology tests.
- Compositional variability of an EO and representativeness of the tested sample.

These specificities will have to be considered for the new tests proposed for the assessment of the ED character of an EO. No test has been performed on an EO itself for the purpose of validating the testing methods for ED characterization.

Although each EO dossier contains its own specificities, this study has identified 3 broad categories of EO dossiers, based on their estimated update cost (developed under different REACH and CLP update scenarii and cost assumptions):

1. EOs from MAPs produced in large volumes in France (> 100 t/year) and registered by a large number of companies in Europe (> 100): lavandin and lavender.
2. EOs from MAPs produced in smaller volumes in France (< 30 t/year) or in overseas territories (small quantities) and registered by a moderate number of companies in Europe (between 10 and 50): clary sage, coriander, peppermint, ylang-ylang, vetiver, geranium.
3. EOs from MAPs produced in small volumes in France (< 10 t/year) or in overseas territories (small quantities) and registered by a very limited number of companies in Europe (between 1 and 5): Scotch pine.

These direct costs, i.e. costs supported by producers in order to update their dossiers, must be analyzed in the light of the companies' annual Turnover (TO). Although each player has its specific TO model, some broad categories of producers can be identified:

1. Agricultural producers:
    a. Large distilleries: distilleries which have registered lavandin EO (10-100 t/year) plus potentially 1 or more other EOs and which report an estimated TO over 100,000 €.
    b. Small distilleries: can be considered representative of this category those who have registered only one EO in the tonnage band of 1 to 10 t/year and having an estimated TO below 50,000 €.
2. Industrial producers:
    a. Large industrial producers: companies which have registered about fifty NCSs with a TO associated with their registered natural materials assessed at 20,000,000 €.
    b. Small industrial producers: importers and distributors which have registered 5 NCSs at most, with a TO associated with their registered natural materials assessed at 5,000,000 € maximum.

These costs will also have an impact on other players in the sector, whose business depends indirectly on the business of producers, i.e.: manufacturers and distributors of finished products, consumers, and other companies, such as those operating in the tourist industry in the south-east of France.

The table in the following page shows cost estimates for representative EOs in the 3 main categories of EOs, according to the estimated cost companies concerned by the registration of concerned EO will have to support in order to update their dossiers, depending on the different REACH and CLP update scenarii.

Table 11 - Estimated costs for representative EOs of the 3 main categories of EOs according to their estimated updating costs, depending on the REACH and CLP regulation update scenarii

Essential oil	Scenario for the annexes	Scenario considered in the study (proposition	Tonnage submitted by the company	Overall additional technical costs for updates and revisions	Current cost of existingdossier Annex VIII	Current cost under Annex VIII – Per company	Current compensated cost under Annex VIII – Per company	Additional updating cost per company
Lavandin	Annexes 7 and 8 merged	P2	10 - 100	*648 500 €*	*295 000,00 €*	*2 000,00 €*		3 544 €
			1-10	*648 500 €*	*295 000,00 €*		*2 200,00 €*	7 744 €
		P1	10 – 100	*190 000 €*	*295 000,00 €*	*2 000,00 €*		-367 €
			1-10	*190 000 €*	*295 000,00 €*		*2 200,00 €*	3 833 €
	Annexes 7 and 8 kept separate	P2	10 - 100	*648 500 €*				9 634 €
			1-10	*54 000 €*				1 141 €
		P1	10 - 100	*190 000 €*				1 671 €
			1-10	*183 000 €*				1 572 €
Coriander		P1	1-10	*182 690 €*				10 048 €
		P1	1-10	*347 500 €*				19 113 €
		P1	1-10	*797 884 €*				43 884 €
Scotch pine		P1	1-10	*182 690 €*				39 096 €
		P1	1-10	*347 500 €*				118 278 €
		P1	1-10	*797 884 €*				214 660 €

Substances classified as category 1A and 1B CMR substances are prohibited from being placed on the market as such or in mixtures at concentrations above generic or specific concentration limits, and could be prohibited from production in Europe. Restrictions on use may also apply to substances classified as category 2 CMR substances.

The issue linked to the classification of certain components and the resulting possible classification of the EO has already been experienced by the industry:

- In the absence of quality data, a classification for CMR properties using a calculation method (% in the composition of components classified according to the classification thresholds) compliant with the CLP classification rule for mixtures is implemented as the various players in the industry comply with the classifications listed in the "IFRA Labelling Manual».

- For registration dossiers with a known content, the aquatic environmental classification is inferred by applying the default long-term risk for biodegradable substances, which considers the presence of at least one component with a bioaccumulation potential.

The MOCS principle (if applied, as the final CLP delegated act has not yet been published and its final content is still unknown) would introduce an obligation to use the worse classification between that inferred from the CLP mixture rule and that obtained from tests on the EO itself. This requirement would apply for CMR properties, but also for many other hazards, including potential human and environmental ED properties, and other environmental hazards such as vPvB.

EOs are not produced in large quantities by each company (joint submission dossier): 10 t/year for 4 of the 10 selected EOs included in the study. We assessed that this production level represents between 10 and 15% of all the natural complex substance (NCS) registered in Europe. Para-cymene, which is potentially present in lavandin EO at a level above 0.3% (and the same is true for 4 other EOs included in the study), and which is present in almost half of the natural complex substance (“NCS” ": EOs and other plant extracts) inventoried in Europe by the EFEO), is currently self-classified as a category 2 Reprotoxic substance, but could become classified in category 1B, in case a proposal for a harmonized classification similar to the one submitted by Sweden in August 2022 is adopted.

This study was carried out with a prospective purpose: no definitive conclusion can be drawn from it given the constant evolutions in the components’ classification criteria and given the fact that the REACH and CLP regulations have not yet been officially modified. The scope of the study being so wide, it was impossible to be completely exhaustive.

Nevertheless, the revision of the REACH and CLP regulations could have considerable technical and economic impacts for the sector because of its specificities which involve low production volumes and complex compositions. The new tests to be carried out to assess the ED nature of components will collide with the difficulties of assessing the possible interactions between components. The industrial companies, which, due to their low tonnage, often have access to a limited data set, will probably have to resort to animal testing (despite the fact that these EOs are frequently used in cosmetics), the results of which could not be used to infer the classification of substances if the MOCS principle is applied. These costs will potentially be much higher for the smaller players in case of a merging of Annexes VII and VIII of the REACH regulation. Because of the multiplicity of components to be assessed (and taking into account the fact that the industry does not always have access to data or

does not have the necessary resources to assess their relevance), and because of the presence of such components in EOs, even at low concentration levels, and due to the fact that new properties will have to be assessed according to the MOCS concept, market opportunity losses for EOs to the benefit of other substances having a less complex composition could be a consequence in the medium to long term.

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Inventory of available knowledge on the assessment of identified hazards and study of the technical and economic impacts of the evolution of the REACH and CLP regulations on the French essential oil industry - Summary Note

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Director of publication: Christine Avelin
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FranceAgriMer
ÉTABLISSEMENT NATIONAL
DES PRODUITS DE L'AGRICULTURE ET DE LA MER

12 rue Henri Rol-Tanguy - TSA 20002 / 93555 MONTREUIL Cedex
Tél. : 01 73 30 30 00 **www.franceagrimer.fr**

FranceAgriMer
@FranceAgriMerFR