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Phytotherapy and aromatherapy in food-producing animals

Proposed human health risk assessment methodology

Anses opinion
Collective expert appraisal report

December 2021

ANSES Opinion
Request No 2020-SA-0083
Related Request Nos 2014-SA-0081 and 2013-SA-0122

The Director General

Maisons-Alfort, 8 December 2021

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety

on the state of knowledge on essential oils and plants of interest for phytotherapy and aromatherapy in food-producing animals and proposed human health risk assessment methodology

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Its opinions are published on its website. This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 8 December 2021 shall prevail.

On 29 June 2020, ANSES issued an internal request to conduct the following expert appraisal: state of knowledge on essential oils and plants of interest for phytotherapy and aromatherapy in food-producing animals and proposed human health risk assessment methodology.

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1. BACKGROUND AND PURPOSE OF THE REQUEST

This internal request followed on from the report on the “Inventory of alternatives to antibiotics aimed at reducing their use in animal husbandry” (Request No 2013-SA-0122) and from one of the conclusions of the report on the “Assessment of marketing authorisation applications for herbal veterinary medicinal products” (Request No 2014-SA-0081) concerning the primary challenge for MA applications for these substances: the lack of an appropriate maximum residue limit (MRL) status for the large majority of plants of interest in veterinary medicine.

The issue of the MRL status of plants and herbal preparations, including essential oils (EOs), is fundamental for the preventive and curative phytotherapy and aromatherapy treatment of food-producing animals, both when assessing MA application dossiers and when prescribing a product for off-label use, for example an extemporaneous herbal preparation (principle of the “therapeutic cascade”, Art. L5143-4 of the French Public Health Code). In addition, the use of phyto/aromatherapy is becoming more and more widespread on farms, in response to the development of organic agriculture and the need to reduce the use of antibiotics (One Health, Ecoantibio plan), and also due to the development of xenobiotic resistance in all pathogens.

The development of phyto/aromatherapy in food-producing animals requires a prior MRL assessment of plants and herbal preparations, including EOs, in order to guarantee a safe consumer exposure level. This assessment is the responsibility of the European Medicines Agency (EMA). In a context where efforts are being made to control resistance to antibiotics and other classes of xenobiotics and to find therapeutic alternatives, and in response to the development of organic agriculture, possibilities for assessing hazards and risks to consumers need to be studied, to meet the expectations of farmers, veterinarians and consumers.

It is important to note that in phyto/aromatherapy, the definition and quality of products are essential. Strict botanical identification of the plant used is a prerequisite, as is the knowledge of its origin. Differences in varieties, cultivars or chemotypes, geographic locations and harvest periods are likely to induce widely varying compositions. Plant parts have to be defined. In addition, it is necessary to clearly define preparations. For extracts, the method used to treat the plant raw material, the extraction solvent and process (extraction temperature, duration, etc.), and the drug/extract ratio need to be defined. These factors influence the qualitative and quantitative chemical composition of preparations as well as their therapeutic potential and even their toxicity. Any purification processes implemented have to be defined. For aromatherapy, the recognised methods for extracting EOs for therapeutic purposes are defined in pharmacopoeias. These products generally have complex compositions and can sometimes contain more than 100 compounds. EOs can be rectified (crystallisation, distillation, fractioning, etc.), which adds another determining factor. As a result, the MRL approach (according to Regulation (EC) No 470/2009) appears to be unsuitable.

Therefore, an internal request on plants and herbal preparations, including EOs, of interest in veterinary medicine seemed necessary to assess the risks to consumer health. The objective was to propose a consumer risk assessment approach taking into account the specific characteristics of these herbal products.

The work carried out involved a preliminary review of the state of knowledge on plants and EOs of interest for phyto/aromatherapy in food-producing animals, in order to establish human health risk profiles using:

- available data from the development of monographs for herbal medicinal products for human use;
- available data from assessments of plants in other regulations, in particular those on animal feed and plant protection products;
- the identification of plants and herbal preparations, including EOs, similar to those considered by EMA as not posing any risks to consumer health (listed in Table 1 of Regulation (EU) No 37/2010);
- the identification of plants and herbal preparations, including EOs, whose toxicity is known in humans and that are also likely to pose a risk to consumers if used in veterinary phyto/aromatherapy.

In conclusion, this work aimed to provide insights for the adoption of a tailored approach for granting an MRL status for plants and herbal preparations, including EOs.

This work did not examine the efficacy or the benefit/risk ratio of plants used in veterinary medicine. It was a first step before a comprehensive assessment of the consumer health risks associated with the plants and herbal preparations, including EOs, used in phyto/aromatherapy for food-producing animals.

2. ORGANISATION OF THE EXPERT APPRAISAL

ANSES entrusted examination of this request to the Expert Committee on Assessment of physico-chemical risks in food (CES ERCA). The Agency also mandated the Working Group on Phytotherapy and aromatherapy veterinary medicinal products (MV PHYTO AROMA WG) for this expert appraisal.

The methodological and scientific aspects of this group's work were regularly submitted to the CES. The report produced by the Working Group takes account of the observations and additional information provided by the CES members.

This expert appraisal work was therefore conducted by a group of experts with complementary skills. It was carried out in accordance with the French Standard NF X 50-110 "Quality in Expertise Activities".

ANSES analyses interests declared by experts before they are appointed and throughout their work in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals. The experts' declarations of interests are made public on website: https://dpi.sante.gouv.fr

The CES ERCA adopted the collective expert appraisal work and its conclusions and recommendations, which are covered in the accompanying report, at its meeting of 19 October 2021 and informed ANSES's General Directorate.

3. ANALYSIS AND CONCLUSIONS OF THE CES AND WG

Previous work on the possible submission of simplified MA application dossiers for herbal veterinary medicinal products (request No 2014-SA-0081) had recommended determining the MRL status of plants, herbal preparations and EOs by using the available data in regulations other than those on veterinary medicinal products.

A three-step approach was used:

1. The first step inventoried uses of phytotherapy and aromatherapy in animal husbandry, based on data provided by users, prescribers and trainers. Based on the hearings conducted, a list of the main plants and EOs used in animal husbandry was drawn up (80 plants and 60 EOs were identified). The aim of this first stage was not to produce an exhaustive list of uses but rather to select **significant and relevant cases** for the identification stage (third stage).
2. The second stage consisted in **surveying risk assessment methodologies** focusing on the use of plants and EOs as presented in regulations other than those on veterinary medicinal products. Numerous assessments have already been published dealing with plants and EOs as part of their authorisations for use in human medicine, as food ingredients, or in the form of feed supplements and additives, for example. This stage resulted in the production of a list of data to be processed, obtained primarily from European agencies such as the European Food Safety Authority (EFSA) and EMA, to be able to work on the identification stage.
3. The third stage involved conducting a **preliminary assessment of consumer risks** for the plants and EOs most frequently mentioned during the hearings (10 plants, five EOs). This assessment also focused on widespread and majority substances in EOs (eight compounds). The assessment was carried out based on data available in opinions published by health agencies, supplemented by a literature search when necessary.

   At the end of the assessment, each plant or EO was classified in one of the following categories:

   - No concern for consumers of food derived from treated animals,
   - Insufficient data to conclude as to whether there is any concern for consumers of food derived from treated animals.

   There was another possible category, but it did not apply to any of the examples studied during this work:

   - Preparation of concern for consumers of food derived from treated animals , based on the available data.

Based on this work, in particular the preliminary consumer risk assessments, a methodology for the consumer risk assessment for herbal veterinary medicinal products is being proposed with a supporting two-step decision tree that can guide assessors throughout their assessments.

3.1. Methodology

The approach takes into account the available data on plants, herbal preparations and EOs as used in food-producing animals. Defining the plant part with its corresponding preparations, as well as their methods and routes of administration and doses, is important. This methodology

only applies to traditionally used plants, herbal preparations and/or EOs for which this information is known.

The term “herbal preparation”, usually used for products obtained using methods such as extraction, distillation, expression, fractioning, purification, concentration or fermentation, will be used in the text and the decision tree for easier reading, instead of “plants, herbal preparations and/or EOs”.

In light of the specific nature of their components, EOs have to undergo assessments separate from those of the plants used to **obtain them**.

- **Data search**

The data used come from various national (ANSM, ANSES, etc.), European (EMA, EFSA, REACH, Pharmacopoeia, etc.) and international (JECFA, JMPR, WHO, etc.) organisations. To supplement and/or update these data, it may be necessary to carry out a literature search.

- **General data, uses and composition**

It is necessary to ensure that the herbal preparation considered is indeed a traditional-use preparation, as defined by Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, with regard to traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use (Article 16c 1(c)). The data and conclusions cannot be systematically extrapolated to other preparations obtained from the same plant.

A number of European regulations should be consulted. Firstly, if the herbal preparation is listed in Table 1 of Regulation (EU) No 37/2010, its use is authorised in food-producing animals according to the provisions of this text. The information given in the “Other Provisions (according to Article 14(7) of Regulation (EC) No 470/2009)” column should be examined. It must limit use of the preparation in veterinary medicine (route of administration, homoeopathic use restrictions, etc.). If these provisions are restrictive, further assessment is necessary. For example, when Table 1 of Regulation (EU) No 37/2010 states “For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding to the mother tincture and dilutions thereof only”, the herbal preparation cannot be used in veterinary medicine as part of phytotherapy. It can be noted that inclusion in Table 2 of Regulation (EU) No 37/2010, which strictly prohibits any use of a substance in food-producing animals, according to Regulation (EC) No 470/2009, currently only concerns, when it comes to plants, the genus *Aristolochia* and all preparations thereof.

Secondly, it is necessary to check whether the herbal preparation is one of the “essential nutrients or normal constituents of the diet in man and animals” with no known restrictions (see Regulation (EU) 2018/782). A list of the plants included in the normal human diet (Annex I of Regulation (EC) No 396/2005) is available and used for the assessment of plant protection products. However, there is no official list that can be referred to in order to find out whether a herbal preparation is part of the normal diet of animals. The presence of a plant during grazing, or obvious dietary uses for animals not grazing, and the list of feed additives, are sources of

information that can be used. If a herbal preparation is authorised in food or feed without restrictions, its veterinary use appears possible. It should be noted that EOs are not directly considered as being part of the normal human diet, as they are only used for flavouring.

Similarly, authorisation of a herbal preparation as an additive for use in animal nutrition (Regulation (EC) No 1831/2003) or as a flavouring agent (Regulation (EU) No 872/2012) in food or feed without restriction enables it to be used in veterinary medicine, provided that there is no genotoxic concern for flavouring agents in particular, as food and feed additives have no genotoxic potential. If the risk is confirmed by *in vivo* genotoxicity data, the preparation is of concern for consumers and cannot be used in veterinary medicine. If any doubt remains as to the genotoxic potential, the preparation should be considered as potentially of concern for consumers and in this case, no conclusion can be drawn. A case-by-case assessment is necessary with the possibility of generating additional data in order to deal with the issue of the possible use of the MRL approach.

All restrictions and provisions shall have the meanings assigned to them in the regulations, according to recommendations of use by route of administration, sub-population, acceptable daily intake (ADI), content in food/feed, etc. It is necessary to ensure that they are compatible with the use of the herbal preparation in veterinary medicine. Otherwise, the assessment should continue.

The assessment can continue when the herbal preparation has a traditional use. Otherwise, the preparation should be considered as potentially of concern for consumers and no conclusion can be drawn. A case-by-case assessment is necessary with the possibility of generating additional data in order to deal with the issue of the possible use of the MRL approach.

The presence of a plant, herbal preparation or EO in food supplements for human use is not taken into account in the first steps of the assessment: in fact, these are only authorised following a limited assessment of consumer risk. Similarly, authorisation in human medicine is not taken into account in the first steps of the assessment, since this authorisation is based on a positive benefit/risk ratio. Moreover, drug exposure tends to be occasional and does not fit with the consumer risk approach, which is based on “lifelong” exposure.

- **ADI, TRV and consumer exposure**

There are very few relevant Toxicological Reference Values (TRVs) for plants, herbal preparations and EOs as a whole. That is why it may be necessary to take into consideration substances considered as potentially of concern that are contained in herbal preparations. These components should be identified and quantified. This approach is used for plant protection products (OECD 2017).

Substances of concern are substances that are of major toxicological concern, that are potentially genotoxic (*e.g*. methyl eugenol) or that have a structural alert known to have genotoxic properties. The notion of structure-activity relationship can therefore be used for substances for which few toxicological data are available.

To identify these components, the pharmacopoeial standards are used as a priority, followed by AFNOR standards, when available. Otherwise, the compositions described in the literature (for example, in books such as “Essential Oil Safety” by Tisserand and Young and “Pharmacognosy – Phytochemistry, Medicinal Plants” by Bruneton) are considered.

Doses of human medicinal products can serve as TRVs as a last resort. Vigilance data (pharmacovigilance, nutrivigilance, etc.) should also be taken into account when available.

Exposure should be estimated according to a worst-case scenario. The ingested quantity of substances is estimated in relation to the dose of the preparation in animals. Bioavailability in animals is assumed to be 100%. Taking the standard food basket of 500 g meat, 1.5 L milk and 100 g eggs for a human with a body weight of 60 kg (Regulation (EU) 2018/782), it is then possible to estimate a theoretical consumer exposure level and compare it with the ADI (*e.g.* methyl eugenol for tea tree EO).

If consumer exposure is below the TRV, the preparation can be used in traditional conditions. Otherwise, the preparation should be considered as potentially of concern for consumers and no conclusion can be drawn. A case-by-case assessment is necessary with the possibility of generating additional data in order to solve the issue or the possibility of using the MRL approach.

If components are identified as posing a risk (genotoxic, for example), it will not be possible to use the herbal preparation in a veterinary medicinal product without a more comprehensive assessment or even an MRL approach.

- **Approach by substance**

If TRVs are not available for the herbal preparation and/or for any of the substances of concern contained in the plant, a substance-by-substance approach should be used.

- Absorption, distribution, metabolism and excretion (ADME) data for the target animals, or for laboratory animals, are needed. If data are available for humans, they should be used as well.

Absorption data should be taken into account initially for the target animals. If absorption according to the route of administration of the herbal preparation is negligible, consumer exposure will also be negligible. In this case, the herbal preparation may be used in animals by this route of administration. Use of the herbal preparation will have to be limited to this sole route of administration. If oral absorption of the substance is negligible in consumers and is not known as having local effects on the digestive tract, the herbal preparation may be used in a veterinary medicinal product for food-producing animals.

The metabolic profile of the substance and its elimination should be taken into account.

As with an assessment using the MRL approach, *in vitro* to *in vivo* extrapolation (laboratory animals/food-producing animals) is possible, with the application of uncertainty factors (see

Regulation (EU) 2018/782). In addition, pharmacokinetic approaches such as physiologically based pharmacokinetic modelling (PBPK) can be used when these are available and have been validated for food-producing animals.

Extensive and rapid metabolisation into metabolites with no identified risks to humans or animals also enables a herbal preparation to be used. Data on metabolism in hepatocytes or microsomes can also be used.

Unfortunately, few ADME data are available for herbal preparations. Predictive models for pesticide metabolism are currently being developed by the OECD. These tools, which should be able to predict the fate of substances and provide information about their toxicokinetics, could potentially be used for veterinary medicinal products. It should also be noted that EMA has published opinions on the transformation products of certain EO components. Tools for predicting toxicity have also been developed at European level and include Toxtree and Toolbox.

- At this point of the approach, it is necessary to determine the toxicological profile of the substance or of its metabolites that are potentially of concern.

If metabolites are identified as being of concern (of genotoxic concern, for example), it will not be possible to use the herbal preparation in veterinary medicine without a more comprehensive assessment or even an MRL approach.

If the available toxicological data are not sufficient for one of the substances of concern, use of the preparation cannot be authorised, due to uncertainty surrounding the existence of risk.

- **Determining an ADI**

If there are sufficient toxicological data for the studied substance or the metabolite that poses a risk, a TRV should be defined by a competent authority; this should be the ADI as a priority or, failing that, another relevant TRV. Such information is seldom available for the components of plants or EOs.

If there are no toxicological data, the Threshold of Toxicological Concern (TTC) approach can be used for each substance of concern. EFSA uses this method for plants. This approach may only be used on a case-by-case basis for minority substances in the preparation (*e.g*. low-exposure metabolites).

- **Exposure limits in cases of traditional use in humans**

If an ADI cannot be defined, all the available data concerning observed effects in humans should be taken into account (use in human medicine, nutrivigilance, epidemiology, etc.). Exposure benchmarks can be used, for example doses in human medicine.

If there are no exposure limits in cases of traditional use in humans, studies will need to be undertaken. The MRL approach is required.

- **Consumer exposure**

If an ADI is available, the last step involves checking that consumer exposure does not exceed it, or ensuring that there is no toxicological concern.

If residue data are available, *i.e*. concentrations of substances or metabolites potentially of concern in food (muscle, liver, kidneys, fat, milk, eggs) derived from animals having received the herbal preparation or substance, then these can be used to assess consumer exposure.

If consumer exposure is above the ADI, the preparation or substance cannot be used in veterinary medicinal products for food-producing animals. The MRL approach should be implemented to refine the consumer risk.

If consumer exposure is below the ADI, the herbal preparation containing this substance can be used in traditional conditions. The analysis will need to be repeated for the other substances of concern in the herbal preparation.

Veterinary use of the herbal preparation will be authorised in food-producing animals when this analysis is favourable for all of the substances identified as being of concern.

3.2. Decision tree

The approach presented in the previous section has been organised in the form of a two-step decision tree.

The first step in the tree applies to plants and herbal preparations. This step can lead to a preparation being considered as potentially of concern for consumers. In this case, additional data will be needed to conclude as to the consumer risk, or else the MRL approach should be used.

If it cannot be concluded in the first step that there is no risk or concern for consumers, a substance-by-substance assessment should be carried out (step 2).

When there is doubt regarding a response, the assessment should follow the decision tree to the most unfavourable situation, in order to protect consumers.

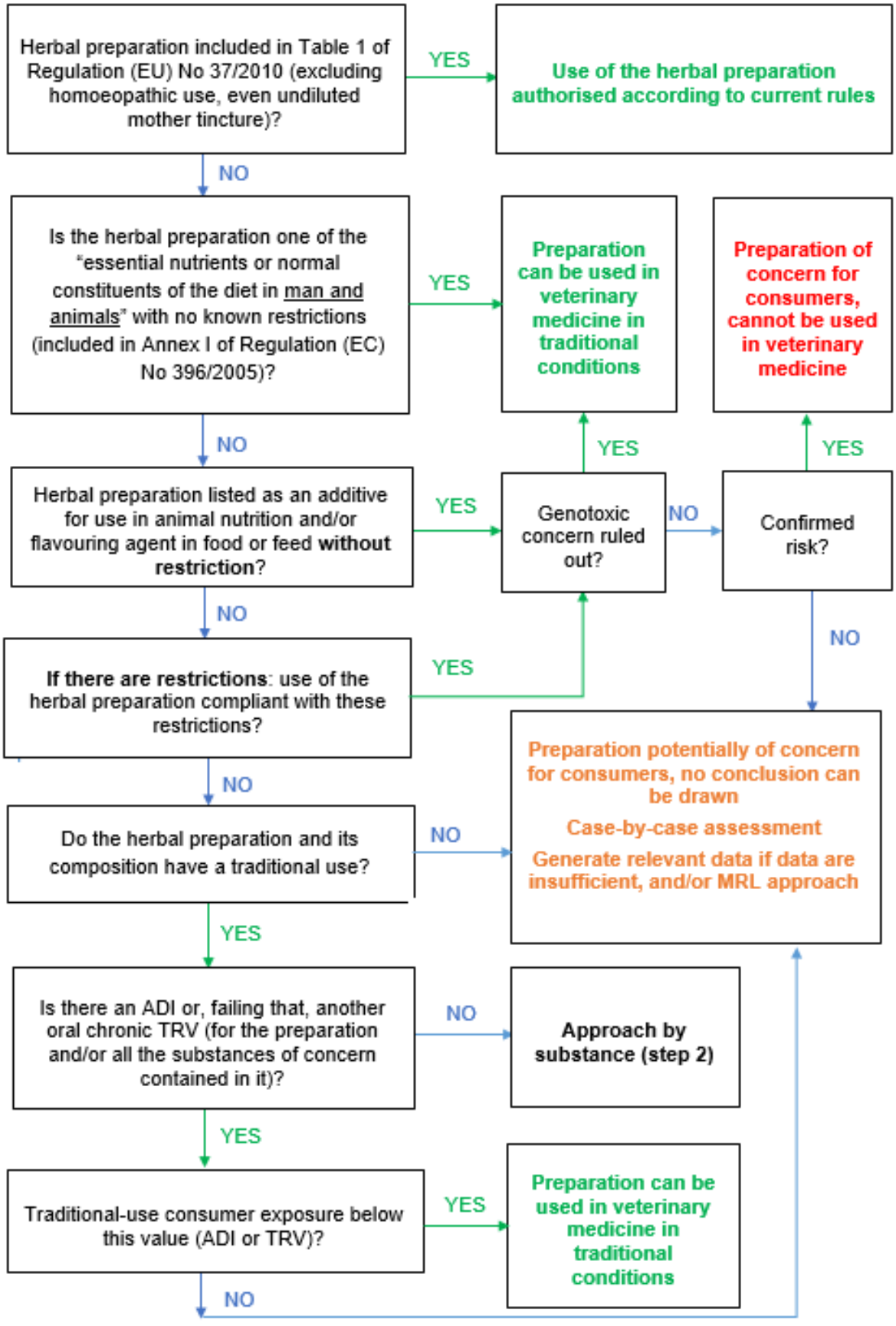

Figure 1 : Decision tree for step 1 : overall approach (herbal preparations))

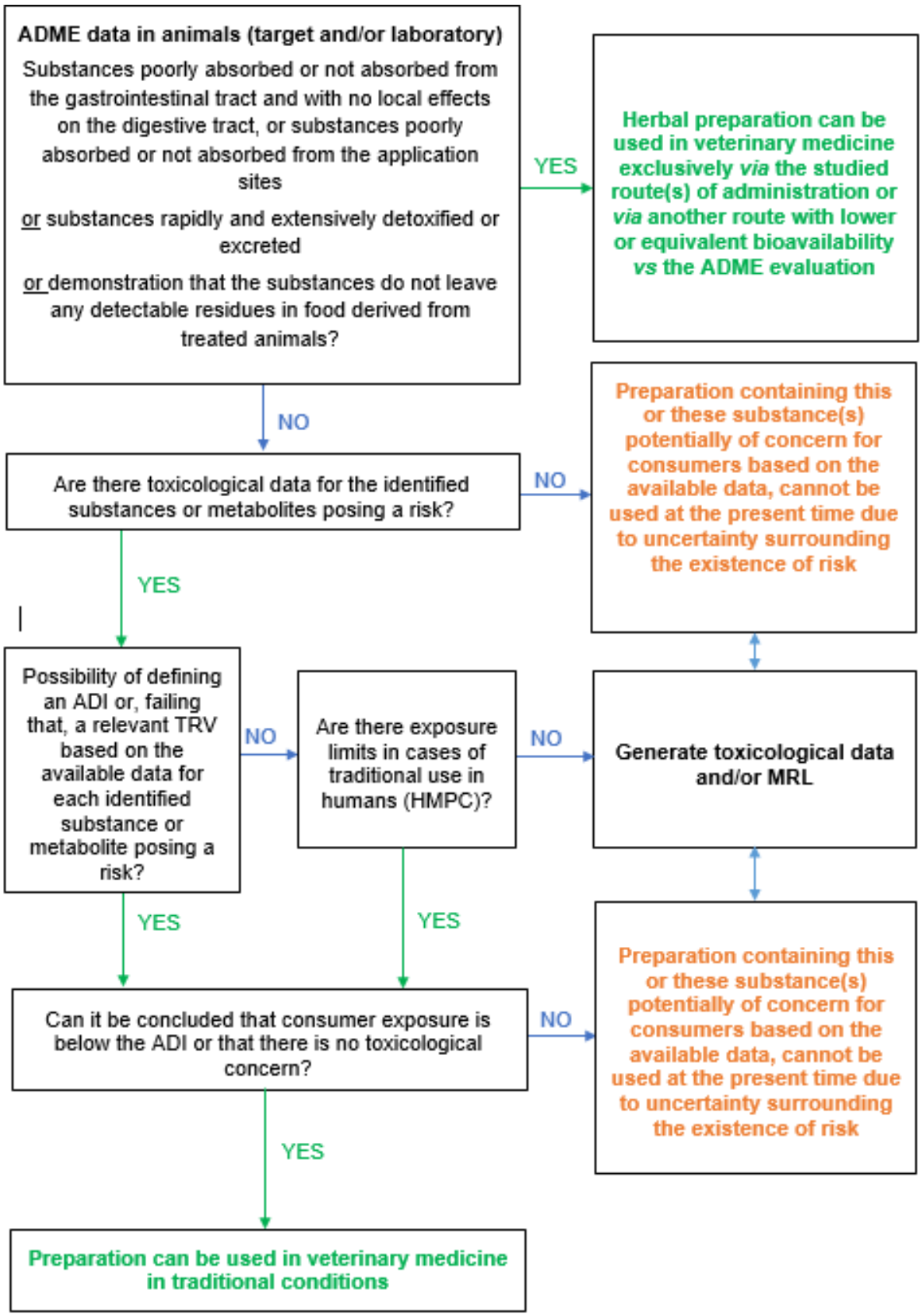

Figure 2: Decision tree for step 2: approach by chemically defined substance when the overall approach is not possible

3.3. Conclusion and answers to the questions in the internal request

Previous works on the possible submission of simplified MA application dossiers for herbal veterinary medicinal products (ANSES 2016) highlighted several potential obstacles for MA applications including the lack of an MRL status for the majority of the plants, herbal preparations and EOs of interest. Without an MRL status, these cannot be used in veterinary medicinal products for food-producing animals. The term “veterinary medicinal products” encompasses medicinal products with MAs as well as extemporaneous preparations. The conclusions of these works recommended determining the MRL status of these herbal substances so they may be used in veterinary medicinal products intended for food-producing animals, and using the available data in regulations other than those on veterinary medicinal products.

Uses of phytotherapy and aromatherapy in animal husbandry are already well established. They are expected to develop further, with the boom of organic agriculture and in the wake of changes in agricultural practices encouraged, among others, by the French State. One of the objectives is to control the development of resistance to antimicrobial and antiparasitic substances contained in the medicinal products currently on the market (Ecoantibio plan, etc.). According to the hearings held to prepare this report, there are several profiles of users of phytotherapy and aromatherapy for food-producing animals:

- Some use phytotherapy and aromatherapy in compliance with fixed withdrawal periods in veterinary medicine but complain that these are restrictive.
- Others have no notion of a potential risk to consumers, especially since they handle products of natural origin that are often used in humans. They therefore do not comply with withdrawal periods. Not all ensure that the plant, herbal preparation or EO is included in Table 1 of Regulation (EU) No 37/2010.

There is also the issue of borderline products: plants, herbal preparations and EOs are widely used in non-medicinal products, primarily having the status of “complementary feed” or feed additive. These products have uses, or are the subject of claims, that are sometimes very similar to those of veterinary medicinal products without fulfilling the same requirements. Circumvention of veterinary medicinal product status is common and has been addressed in recommendations issued by the European Commission[1]. Such products are readily available to farmers and veterinarians, since the regulations applying to them do not impose any withdrawal period. It is also important to note that the labels on these products often lack detail and precision. There are therefore uncertainties as to their composition and quality, with problems concerning the definition of the plants (indication of the species, part, origin, chemotype, etc.) and preparations used, and also concerning the doses or concentrations of the herbal active substances.

Many plants and herbal preparations used in animal husbandry have a long tradition of use and are assumed to be safe. The regulatory framework for veterinary medicinal products appears, also for this reason, to be rigid and unsuitable for plants and EOs. Current uses and

[1] 2011/25/EU: Commission Recommendation of 14 January 2011 establishing guidelines for the distinction between feed materials, feed additives, biocidal products and veterinary medicinal products

practices not supervised by healthcare professionals can go against the protection of consumers – due either to the therapeutic practices themselves or to the poor quality of the available products. It will be necessary to find a solution to enable phytotherapy and aromatherapy to be used in a way that meets the expectations of professionals and consumers, guarantees consumer safety, and ensures compliance with current veterinary medicine legislation.

Based on this work, a consumer risk assessment methodology, specific to plants and herbal preparations, including EOs, is being proposed with a supporting two-step decision tree that can guide assessors throughout their assessment. This specific method classifies preparations into one of the following three categories:

- Preparation that can be used in veterinary medicine for food-producing animals without any risk to consumers. These preparations must be included on a list in order to be authorised in medicinal products intended for food-producing animals. There may be restrictions on use, for example concerning routes of administration;
- Preparation considered as potentially of concern for consumers based on the available data (which means it cannot be used at the present time). A case-by-case assessment is necessary with the possibility of generating additional data or using the MRL approach.
- Preparation that cannot be used in veterinary medicine for food-producing animals due to concern for consumers.

As highlighted in the inventory of uses, and considering the traditional nature of phytotherapy and aromatherapy and the ways in which knowledge relating to them is currently passed on, there is sometimes a lack of precision with regard to the plant species (ambiguous common names, etc.), variety and chemotype used. The favoured preparations and conditions of use vary, according to the hearings. The WG considered the above when evaluating those uses that appeared the most common.

Unfortunately, there is frequently a lack of scientific data relating to plants and herbal preparations including EOs. Their chemical composition is often only partially defined. The lack of robust data (toxicological, pharmacokinetic, residue data, etc.) can impact the possibility of carrying out a consumer risk assessment. In general, substantial research work is needed to assess the efficacy, safety and benefit-risk ratio of phytotherapy and aromatherapy. It seems essential to acquire data on residues in particular when assessing consumer safety.

The information collected with regard to French Overseas *Départements* and Regions (DROMs) is not sufficient to have an overview of practices. The medical traditions and plants in these territories, which are different from those in metropolitan France, are associated with specific phytotherapy and aromatherapy practices in animal husbandry. Numerous overseas plants have been added to the list of medicinal plants in the French Pharmacopoeia. Furthermore, a large body of ethnobotanical and ethnopharmacological data is available for the DROMs. In the field, plants not considered as medicinal, and also toxic plants (whether or not they are included on list B of medicinal plants), may be used.

3.4. Recommendations of the WG and the CES ERCA

The MRL regulations are European. Implementing regulations are issued by the European Commission following opinions by EMA. The issue of the MRL status of plants and herbal preparations is therefore European and can only be managed at that level.

ANSES may present its report and opinion at European level to encourage a harmonised approach to this issue. The methodology set out in this report may be submitted to EMA, with the aim of including plants with no risk to consumers in Table 1 of Regulation (EU) No 37/2010 or on a new specific list that will need to be created. In parallel, a list of plants considered as potentially of concern for consumers will need to be established. The priority list of EMA's Committee on Herbal Medicinal Products (HMPC) may be used for this. This list shows the plants assessed and mentions those species and preparations not meeting the definition of traditional use.

Studying the data available in other regulations will lead to the rapid extension of the list of plants that can be used in veterinary medicine for food-producing animals. The WG and the CES ERCA recommend also referring to toxicological data and considering the potential non-traditional nature of preparations.

The WG and the CES ERCA recommend monitoring practices and communicating about the classification of herbal preparations. It will be necessary to verify the identity and quality of the products used (pharmaceutical raw materials (PRMs)).

Monitoring through Total Diet Studies (TDSs) is recommended and should include, for example, some residue markers for plants.

In order to make up for the lack of data in the field of phytotherapy and aromatherapy in animal husbandry, research and development should be encouraged with support provided for research programmes whose priorities are the publication of:

- Toxicological data;
- Pharmacokinetic data on residues and metabolism;
- Consumption and exposure data;
- Data on the chemical compositions of the preparations used;
- Recommendations concerning new approach methodologies (NAMs), such as computational toxicology, new cell models, etc.[2]

Inclusion on a roadmap of the French National Research Agency (ANR) is desirable with a definition of priority plants and herbal preparations.

The proposal of an appropriate approach for granting an MRL status for plants and herbal preparations, including EOs, and the assessment of their consumer safety, should be accompanied by an assessment of their efficacy and benefits, in particular as part of the Ecoantibio plan. Moreover, the continuation of this process and the promotion of phytotherapy

[2] EFSA, Modern methodologies and tools for human hazard assessment of chemicals. EFSA Journal, 2014, 12(4), 3638, https://doi.org/10.2903/j.efsa.2014.3638

and aromatherapy in animal husbandry cannot be dissociated from work aiming to consider the sustainability of plant resources and take into account production and supply chains, since this agricultural sector is dynamic in France.

Lastly, it is desirable that professional organisations, directorates general (DGAL, DGS and DGCCRF) and various stakeholders in this field (veterinarians and farmers) continue to be jointly involved in work intended to facilitate the use of phytotherapy and aromatherapy medicinal products in animal husbandry.

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

The French Agency for Food, Environmental and Occupational Health & Safety endorses the conclusions and recommendations of its CES ERCA on the consumer risk analysis and management methodology specific to plants and herbal preparations including EOs proposed by the MV PHYTO AROMA WG and recommends:

- In France:
    - An ANSES WG will have as an initial objective to draw up lists of plants/EOs:
        - not of concern for consumers,
        - potentially of concern for consumers,
        - of concern.

      This work should use the methodology proposed in the report. The ultimate goal would be to prepare MRL-setting dossiers for submission to EMA based on this work;
    - The possible use of these herbal substances not of concern for consumers for veterinary therapeutic purposes whenever they are PRMs;
    - The identification, by a suitable WG, of missing data for a given plant of interest, and the dissemination of this information to project leaders to encourage research and development. The priorities are the publication of:
        - Toxicological data,
        - Residue data,
        - Exposure data,
        - Data on pharmaceutical quality,
        - Recommendations concerning new approach methodologies (NAMs);
    - The submission and evaluation, in marketing authorisation dossiers for phytotherapy veterinary medicinal products, of data on product efficacy with acceptable levels of evidence (ANSES 2016);

- The monitoring of EFSA's tender entitled “Case Studies NAMs Essential Oils as Feed Additives” by the WG on Plants in veterinary medicinal products, and also more generally the monitoring of work undertaken at European level;

- Strengthening controls for suppliers' advertisements and documents (claims) of all herbal products, to verify their regulatory status in view of the definition of veterinary medicinal product;

- Further collaborative work with the DGAL, DGCCRF and other administrative authorities in charge of controls;

- Communicating with veterinarians, manufacturers and farmers to raise their awareness concerning the classification of herbal preparations and the consumer risk associated with their use;

- Strengthening regulatory and technical training on the use of these substances for (future) veterinarians and farmers/technicians (national veterinary schools, engineering schools, agricultural secondary schools, etc.) and other stakeholders in production sectors.

- In Europe:

  - Organising a symposium, as part of the French Presidency of the Council of the European Union in 2022, during which this work will be presented. All stakeholders (veterinarians, manufacturers and farmers) and Member States will be invited to share their vision and challenges relating to the use of plants in veterinary medicine. Each speaker will present and share their own knowledge in order to enrich future debates;

  - Promoting this work to encourage discussions on this topic. The proposed methodology will be presented to EMA with the goal of establishing a guideline for the assessment of the consumer risk associated with these products in order to include plants and herbal preparations in Table 1 of Regulation (EU) No 37/2010 or on the list of biological substances considered as not requiring an MRL evaluation as per Regulation (EU) No 2018/782, with regard to residue of veterinary medicinal products in foodstuffs of animal origin;

  - Submitting an MRL application. Some dossiers could be prepared by the WG and submitted by ANSES-ANMV;

  - All of this work at European level will be supported by ANSES-ANMV to provide input for the Commission's analysis of the report and the legislative proposal aiming to introduce a simplified system for registering traditional herbal products used to treat animals as set out in Article 157 of Regulation (EU) 2019/6.

The European Commission is expected to report to the European Parliament and to the Council in 2027, with regard to traditional herbal products used to treat animals in application of Article 157 of Regulation (EU) 2019/6 on veterinary medicinal products.

Dr Roger Genet

State of knowledge on essential oils and plants of interest for phytotherapy and aromatherapy in food-producing animals and proposed human health risk assessment methodology

Request "2020-SA-0083"

Related Requests "2014-SA-0081 - assessment of MA applications for herbal veterinary medicinal products" and "2013-SA-0122 - inventory of alternatives to antibiotics aimed at reducing their use in animal husbandry"

Collective expert appraisal REPORT

"CES ERCA"

"MV PHYTO AROMA WG"

October 2021

Suggested citation

ANSES. (2021). State of knowledge on essential oils and plants of interest for phytotherapy and aromatherapy in food-producing animals aimed at establishing human health risk profiles (Request 2020-SA-0083). Maisons-Alfort: ANSES, 268 p.

Keywords

Aromathérapie, phytothérapie, plante, parties de plante, huile essentielle, plante médicinale, drogue végétale, LMR, évaluation du risque, sécurité du consommateur, médicament vétérinaire, médicament à base de plantes, arbre de décision, toxicologie

Aromatherapy, phytotherapy, plant, plant part, essential oil, medicinal plant, herbal drug, MRL, risk assessment, consumer safety, veterinary medicine, herbal medicine, decision tree, toxicology

Presentation of the participants

PREAMBLE: The expert members of the Expert Committees and Working Groups or designated rapporteurs are all appointed in a personal capacity, *intuitu personae*, and do not represent their parent organisation.

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Mr Sébastien KNOCKAERT – Veterinary practitioner – 4 December 2020

Ms Lucile BROCHOT – Veterinary practitioner – 10 December 2020

Mr Gilles GROSMOND – Veterinary practitioner – 15 December 2020

Mr Michel BOUY – Veterinary practitioner – “Plantes en élevage” Group – 17 December 2020

Mr Michel DERVAL and Mr Léo LISARDE IROLA – Aromatherapists and veterinary practitioners – 22 December 2020

Mr Julien DASPET – Veterinary practitioner – 7 January 2021

Ms Christine FILLIAT – Veterinary practitioner – 15 January 2021

Ms Carine MARIE MAGDELEINE – INRAE Research Engineer – 18 January 2021

Mr Philippe LABRE – Veterinary practitioner – Written reply on 5 March 2021

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Glossary

Food-producing animals: Animals bred, raised, kept, slaughtered or harvested for the purposes of producing food[1].

Aromatherapy: A branch of phytotherapy, corresponding to the use of essential oils for medical purposes.

Chemotype: A distinct variety of a species with a specific chemical composition.

Foodstuffs of animal origin: Meat, offal, fish, milk, eggs and honey[1].

Herbal drug: According to the European Pharmacopoeia, 10th edition (monograph 1433): A whole, fragmented or cut (medicinal) plant or plant part used in an unprocessed state, usually in a dried form but sometimes fresh. The word “plant” is used in its broadest sense and also encompasses algae, fungi and lichen as well as certain exudates that have not been subjected to specific treatments (EDQM 2019).

Gemmotherapy: A branch of phytotherapy, involving the use of buds and emerging shoots in the form of glycerine macerates or mother tinctures.

Essential oil: According to the European Pharmacopoeia, 10th edition (monograph 2098): A fragrant product, generally of complex composition, obtained from a botanically defined plant raw material, either by steam distillation, dry distillation, or by an appropriate mechanical process without heating. The essential oil is most often separated from the aqueous phase by a physical process that does not result in a significant change in its composition (EDQM 2019).

MRL: Maximum residue limit. This is the maximum concentration (expressed in mg/kg or µg/kg) of a residue of a pharmacologically active substance which may be permitted in food of animal origin[1].

Phytotherapy: Use for therapeutic purposes of parts of medicinal plants, plant extracts, and certain purified extracts, with the exception of isolated substances (EMA 2010b).

Residues of pharmacologically active substances: All pharmacologically active substances, whether active substances, excipients or degradation products, and their metabolites which remain in food obtained from animals.

Substance: A pure, chemically defined compound.

[1] Regulation (EC) No 470/2009

Herbal substance: A plant or herbal preparation used as an active ingredient in phytotherapy.

Withdrawal period: The period necessary between the last administration of a veterinary medicinal product to animals, under normal conditions of use, and the production of foodstuffs from such animals, in order to protect public health by ensuring that such foodstuffs do not contain residues in quantities in excess of the MRLs for active substances laid down pursuant to Regulation (EC) No 470/2009.

This definition is changing in the new Regulation (EU) 2019/6, Art (4) 34, becoming: “Minimum period between the last administration of a veterinary medicinal product to an animal and the production of foodstuffs from that animal which under normal conditions of use is necessary to ensure that such foodstuffs do not contain residues in quantities harmful to public health”.

Fixed withdrawal period: The withdrawal period applied in the context of the “therapeutic cascade”.

Traditional use: Medicinal use for at least 30 years in France and at least 15 years in the European Union. Traditional use of a plant included in the French Pharmacopoeia is accepted according to literature studies.

Well-established use: Use of an active substance as a medicinal product with recognised efficacy for at least 10 years (in France and in the European Community). For a plant or herbal medicinal product, “well-established use” also indicates it has an acceptable level of safety.

Acronyms and abbreviations

ADI	:	Acceptable daily intake
ADME	:	Absorption, distribution, metabolism and excretion
AFVAC	:	French Association of Veterinarians for Pets
AFVP	:	French Association of Veterinary Phytotherapists
ALAN	:	Animal Nutrition
ANMV	:	French Agency for Veterinary Medicinal Products
ANR	:	French Research Agency
ANSES	:	French Agency for Food, Environmental and Occupational Health & Safety
ANSM	:	French Health Products Safety Agency
AS	:	Active substance
AVEF	:	French Equine Veterinary Association
BW	:	Body weight
CES	:	Expert Committee
CSP	:	French Public Health Code
CT	:	Chemotype
CTD	:	Common Technical Document
CVMP	:	Committee for Medicinal Products for Veterinary Use
DER	:	Drug-extract ratio
DGAL	:	French Directorate General for Food
DGCCRF	:	French Directorate General for Competition, Consumer Affairs and Fraud Control
DGS		French Directorate General for Health
DNEL	:	Derived no effect level
DROM	:	French Overseas *Départements* and Regions
ECHA	:	European Chemicals Agency
EFSA	:	European Food Safety Authority
EMA	:	European Medicines Agency
EO	:	Essential oil

EPMAR	:	European public MRL assessment report
ESCOP	:	European Scientific Cooperative on Phytotherapy
FAO	:	Food and Agriculture Organization of the United Nations
FDA	:	US Food and Drug Administration
FEEDAP	:	EFSA Panel on Additives and Products or Substances used in Animal Feed
GDS	:	Health protection group
GRAS	:	Generally recognised as safe
HMPC	:	EMA Committee on Herbal Medicinal Products
HPLC		High-performance liquid chromatography
IARC	:	International Agency for Research on Cancer
IDELE	:	French Livestock Institute
IFIP	:	French Pork and Pig Institute
IFRA	:	International Fragrance Association
INRAE	:	French National Research Institute for Agriculture, Food and the Environment
IP	:	Intraperitoneal (route)
ISO	:	International Organization for Standardization
ITAB	:	French research institute for organic farming
ITEIPMAI	:	French research institute for perfume, medicinal and aromatic plants
iTV	:	Indicative toxicity value
IV	:	Intravenous (route)
JECFA	:	Joint FAO/WHO Expert Committee on Food Additives
JMPR	:	Joint FAO/WHO Meeting on Pesticide Residues
LD	:	Lethal dose
LOAEL	:	Lowest observed adverse effect level
LOEL	:	Lowest observed effect level
MIC	:	Minimum inhibitory concentration
MR	:	Marker residue
MRL	:	Maximum residue limit
MSDI	:	Maximised survey-derived daily intake

NAMs	:	New approach methodologies
NDA	:	EFSA Panel on Nutrition, Novel Foods and Food Allergens
NOAEL	:	No observed adverse effect level
NOEL	:	No observed effect level
NPLC	:	Natural preparation of low concern
NSBU	:	Natural substance for biostimulant use
NTP	:	US National Toxicology Program
OECD	:	Organisation for Economic Co-operation and Development
PBPK	:	Physiologically based pharmacokinetic (modelling)
Ph. Eur.	:	European Pharmacopoeia
PK	:	Pharmacokinetics
PO	:	*Per os*
PPP	:	Plant protection product
PRM	:	Pharmaceutical raw material
REACH	:	Registration, Evaluation, Authorisation and Restriction of Chemicals
RéPAAS	:	Veterinary Phyto-Aromatherapy Network
SCF	:	European Commission Scientific Committee on Food
SNGTV	:	French National Society of Veterinary Technical Groups
SPC	:	Summary of Product Characteristics
TAU	:	Temporary authorisation for use
TDS	:	Total Diet Study
TLC	:	Thin layer chromatography
TR	:	Total residue
TRV	:	Toxicity reference value
TTC	:	Threshold of toxicological concern
VICH	:	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
WG	:	Working Group
WHO	:	World Health Organization

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1 Background, purpose and procedure for carrying out the expert appraisal

The initial text of the internal request decision can be found in Annex 1.

1.1 Background

This internal request followed on from the report on the “Inventory of alternatives to antibiotics aimed at reducing their use in animal husbandry” (Anses 2018) and from one of the conclusions of the report on the “Assessment of marketing authorisation applications for herbal veterinary medicinal products” (Anses 2016) concerning the primary challenge for MA applications for these substances: the lack of an appropriate maximum residue limit (MRL) status for the large majority of plants of interest in veterinary medicine.

MRLs are regulatory thresholds for residues of substances contained in veterinary medicinal products that are found in foodstuffs derived from treated animals.

They are defined for a given substance, species and tissue, or foodstuff. They aim to guarantee a safe exposure level for consumers as well as a lack of technological impact.

Concerning the classification of pharmacologically active substances administered to food-producing animals regarding MRLs, Regulation (EU) No 37/2010 includes two tables:

- Table 1 corresponds to allowed substances (with possible use and/or species restrictions);
- Table 2 corresponds to prohibited substances (where no MRL can be set).

Some substances are considered, after assessment by the European Medicines Agency (EMA), as not falling within the scope of Regulation (EC) No 470/2009 with regard to MRLs. These appear on the “out of scope” list of EMA's Committee for Medicinal Products for Veterinary Use (CVMP) (EMA 2020c). They include substances naturally occurring in the body and substances in the human diet that do not pose any risks to consumer health.

If a future herbal veterinary medicinal product is intended for food-producing animals, each plant, herbal preparation or essential oil (EO) it contains must be listed in Table 1 of Regulation (EU) No 37/2010 or be included on the “out of scope” list. Therefore, the issue of the MRL status of EOs and plants is fundamental for the preventive and curative phytotherapy and aromatherapy treatment of food-producing animals, both when assessing MA application dossiers and when prescribing a product for off-label use, for example an extemporaneous herbal preparation (principle of the “therapeutic cascade”, Art. L.5143-4 of the French Public Health Code (CSP)) (see 4.1.4.).

In addition, the use of phyto/aromatherapy is becoming more and more widespread on farms, in response to the development of organic agriculture and the need to reduce the use of antibiotics (One Health, Ecoantibio plan), and also due to the development of xenobiotic resistance in all pathogens.

However, the large majority of the plants, herbal preparations and EOs commonly used in veterinary medicine have not been assessed under Regulation (EC) No 470/2009 and therefore cannot currently be used in veterinary medicinal products intended for food-producing animals or be prescribed by a veterinarian as part of the “therapeutic cascade” (Art. L.5143-4 of the CSP). Even so, products containing medicinal plants are often administered to

animals, as complete or complementary feed. It should also be noted that many forms of veterinary phytotherapy are based on a long tradition of use that was deeply rooted in rural areas in the past.

Currently, only two proprietary herbal veterinary products intended for food-producing animals benefit from an MA in France: COTHIVET® and APILIFE VAR®. Each of the substances contained in these medicinal products has an MRL status.

The development of phyto/aromatherapy in food-producing animals requires a prior MRL assessment of plants and herbal preparations including EOs in order to guarantee a safe consumer exposure level. This assessment is the responsibility of EMA. In a context where efforts are being made to control resistance to antibiotics and other classes of xenobiotics and to find therapeutic alternatives, and in response to the development of organic agriculture, possibilities for assessing hazards and risks to consumers need to be studied, to meet the expectations of farmers, veterinarians and consumers.

It is important to note that in phyto/aromatherapy, the definition and quality of products are essential. Strict botanical identification of the plant used is a prerequisite, as is knowledge of its origin. Differences in varieties, cultivars or chemotypes (CTs), geographic locations and harvest periods are likely to induce widely varying compositions. Plant parts have to be defined. In addition, it is necessary to clearly define preparations. For extracts, the method used to treat the plant raw material, the extraction solvent and process (extraction temperature, duration, etc.), and the drug-extract ratio (DER) need to be defined. These factors influence the qualitative and quantitative chemical composition of preparations as well as their therapeutic potential and even their toxicity. Any purification processes implemented have to be defined. For aromatherapy (use of EOs), the recognised methods of extraction for therapeutic purposes are defined in pharmacopoeias (EDQM 2019). These products generally have complex compositions and can sometimes contain more than 100 compounds. EOs can be rectified (crystallisation, fractional distillation, etc.), which adds another determining factor.

As a result, the MRL approach (according to Regulation (EC) No 470/2009) appears to be unsuitable.

Therefore, an internal request on plants and herbal preparations, including EOs, of interest in veterinary medicine seemed necessary to assess the risks to consumer health. The objective was to propose a consumer risk assessment approach taking into account the specific characteristics of these herbal products.

1.2 Purpose of the request

The work carried out involved a preliminary review of the state of knowledge on plants and EOs of interest for phyto/aromatherapy in food-producing animals, in order to establish human health risk profiles using:

- available data from the development of monographs for herbal medicinal products for human use;
- available data from assessments of plants in other regulations, in particular those on animal feed and plant protection products (PPPs);

- the identification of plants, herbal preparations and EOs similar to those considered by EMA as not posing any risks to consumer health (listed in Table 1 of Regulation (EU) No 37/2010);
- the identification of plants, herbal preparations and EOs whose toxicity is known in humans and that can also potentially pose a risk to consumers if used in veterinary phyto/aromatherapy.

This work aimed to provide, in its conclusion, insights for the adoption of a tailored approach for granting an MRL status for plants and herbal preparations, including EOs.

This work did not examine the efficacy or the benefit/risk ratio of plants used in veterinary medicine. It was a first step before a comprehensive assessment of the consumer health risks associated with the identified plants and herbal preparations, including EOs.

1.3 Procedure: means implemented and organisation

The French Agency for Food, Environmental and Occupational Health & Safety (ANSES) entrusted examination of this request to the Working Group on Phytotherapy and aromatherapy veterinary medicinal products (MV PHYTO AROMA WG), set up by a decision of 31 July 2020 following a call for applications and reporting to the Expert Committee on Assessment of physico-chemical risks in food (CES ERCA).

The methodological and scientific aspects of the WG's expert appraisal work were regularly submitted to the CES. The report produced by the Working Group takes account of the observations and additional information provided by the CES members. The expert appraisal work was adopted by the CES ERCA on 19 October 2021, unanimously by the experts present.

This work was therefore conducted by a group of experts with complementary skills.

The expert appraisal was carried out in accordance with French Standard NF X 50-110 “Quality in Expert Appraisals – General Requirements of Competence for Expert Appraisals (May 2003)”.

1.4 Prevention of risks of conflicts of interest

ANSES analyses interests declared by experts before they are appointed and throughout their work in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals.

The experts’ declarations of interests are made public on the following website: https://dpi.sante.gouv.fr/.

2 Specific characteristics of plants, herbal preparations and essential oils and regulatory clarifications

2.1 Types of preparations concerned and notion of tradition

Veterinary phytotherapy is based on a long-standing tradition, involving the selection and rejection of plants on primarily empirical bases, which was developed in parallel with human phytotherapy. According to the ethnobotanical and veterinary literature, surveys of animal husbandry practices and specific teaching and training, the plants and preparations used in veterinary phytotherapy and aromatherapy, whether for internal or external use, are more or less the same as those used in human medicine.

Plants considered medicinal in Europe and France are listed by EMA and the French Health Products Safety Agency (ANSM).

In France, any plant considered medicinal is included on the list of medicinal plants in the French Pharmacopoeia. This is divided into two parts:

- a "List A of traditionally used medicinal plants"[2], which comprises 459 plants (as of January 2021) and specifies the parts used ("herbal drugs"). These are listed as being used in traditional medicine in Europe and the French overseas territories and/or, if applicable, in Chinese traditional medicine or Ayurvedic Indian traditional medicine. The plants listed are used in phytotherapy, potentially for their EOs in aromatherapy, and sometimes in homeopathy. Their toxicity may be mentioned, and there may be a restriction stating they should only be used on the skin. Their inclusion on List A does not prevent them from appearing on the lists of poisonous substances and narcotics;
- a "List B of medicinal plants traditionally used in unprocessed or prepared form whose potential adverse effects outweigh the expected therapeutic benefit"[3], which comprises 159 plants or genera (as of January 2021) and specifies their herbal drugs. These are also listed as being used in European and French overseas, Chinese or Ayurvedic traditional medicine.

These plants are not reserved for human medicine and may be prescribed in veterinary practice.

EMA keeps a list of the plants used in unprocessed or prepared form, including as EOs, which can potentially be contained in human herbal medicinal products for self-medication. These plants must have been in use for a sufficiently long period, worldwide and in Europe, to be considered as traditional-use plants, prejudging their plausible efficacy and probable safety in defined conditions of use (see Section 4.2). Of the plants that have been examined by EMA, 166 have finalised monographs (of which 57 have been revised) for a traditional and/or well-established use, eight are currently being studied, and 22 have been addressed in a public

[2] https://ansm.sante.fr/uploads/2021/03/25/liste-a-des-plantes-medicinales-utilisees-traditionnellement-4.pdf
[3] https://ansm.sante.fr/uploads/2021/03/25/liste-b-des-plantes-medicinales-utilisees-traditionnellement.pdf

statement (EMA 2021). Some monographs published by EMA concern specific or generic mixtures of preparations of several plants.

The preparations considered by EMA for these plants are those traditionally used (based on their period of use). The following are referred to, depending on the herbal drug in question:

- plant in unprocessed form;
- comminuted plant for infusion, decoction or maceration;
- powder;
- fresh plant juice;
- oil;
- aqueous or hydro-alcoholic (dry, fluid, soft) extracts with a variable ethanol content and a defined DER;
- more rarely, other extracts (methanol, acetone, other organic extracts, macerates in wine), with a defined DER;
- tinctures, with a defined DER;
- essential oils (as defined in the Ph. Eur.);
- possibly hydrosols.

The extracts used may, as appropriate, be titrated or quantified. A number of the herbal drugs and extracts listed by EMA are defined in the Ph. Eur. or national pharmacopoeias.

As part of veterinary and animal husbandry practices, use of the plant in unprocessed or powdered form or as an aqueous extract seems prominent, but other preparations can be used.

The therapeutic nature of plants and herbal preparations does not prevent them from being used for nutritional or other potential purposes. Similarly, herbal compounds contained in medicinal plant preparations are often likely to be found in food or other consumer goods. EMA only takes the risk related to cumulative exposure into account for certain substances.

2.2 MRL approach and herbal preparations

All pharmacologically active substances contained in a veterinary medicinal product intended for food-producing animals must be listed in Table 1 of Regulation (EU) No 37/2010. Substances not appearing in this table are not permitted in livestock animals. Those that are prohibited are listed in Table 2 of Regulation (EU) No 37/2010. One of the major challenges is the very low proportion of plants and EOs that are listed in Table 1 of Regulation (EU) No 37/2010 and are therefore permitted in veterinary medicine for the treatment of food-producing animals. The lack of an MRL is a major obstacle to obtaining an MA for a veterinary medicinal product. Requests to include substances in Table 1 are managed outside of any MA and must be submitted upstream. Without an MA, the only possible way in which an active substance (AS) can be used as part of the “therapeutic cascade” (see Section 4.1.4) is in the form of extemporaneous preparations provided that it has an MRL status. A fixed withdrawal period is applied in the context of the “therapeutic cascade”.

MRLs are defined for a given substance, species and tissue, or foodstuff. Each individual substance is assessed and classified, as herbal substances[4] do not have a specific status. EOs are also examined substance by substance. In view of the complex and variable compositions of plants and EOs, and the difficulty of assessing each of the substances they contain, the current MRL approach is not appropriate.

[4] In the sense of plants and herbal preparations

3 Survey on uses in animal husbandry

There are no official data on sales volumes for plants and EOs used in veterinary medicine or for products containing medicinal plants administered to animals. In order to determine which uses of phytotherapy and aromatherapy in animal husbandry seemed significant, hearings were held. These led to the identification of priority plants and EOs with regard to the extent of their use.

3.1 Methodology used for the hearings

Initially, the main organisations likely to have an overview of uses in veterinary medicine were contacted:

- The French research institute for organic farming (ITAB), which has a "list of 220 plants for therapeutic purposes in animal husbandry which can be used for first-line self-medication by farmers, subject to the skills of users" (Experton et Bouy 2017);
- The Veterinary Phyto-Aromatherapy Network (RéPAAS), encompassing the French Association of Veterinarians for Pets (AFVAC), the French Equine Veterinary Association (AVEF) and the French National Society of Veterinary Technical Groups (SNGTV). This network has a list used by practitioners which includes 106 plant species and 163 EOs identified in the field. This list is not meant to be exhaustive but rather aims to catalogue the plants and EOs commonly used by veterinary practitioners;
- The French Federation of Health Protection Groups (GDS France), which is the national agricultural organisation responsible for issues of animal health and hygiene as well as quality in health terms;
- The French research institute for perfume, medicinal and aromatic plants (ITEIPMAI), which is a technical institute approved by the Ministry of Agriculture that carries out applied research to assist the perfume, medicinal and aromatic plant sector;
- The French Livestock Institute (IDELE), which is a technical institute for ruminant livestock. Among other things, IDELE is in charge of projects dealing with the health and welfare of ruminants.

Most of these organisations affirmed that they did not have sufficient knowledge on uses in animal husbandry.

In 2017, ANSES-ANMV (French Agency for Veterinary Medicinal Products) produced a list of plants of interest for livestock animals, after consulting with stakeholders. The list of these plants is available in Annex 4. Of the 100 identified plants, 40 had an MRL status and 21 an MRL status with use restrictions (homeopathic, topical or oral use). Of the 39 others, 24 were authorised in food supplements[5] (with possible restrictions), 15 had a human EMA monograph, and 18 had a European (Ph. Eur.) or French Pharmacopoeia monograph. EMA was then asked whether it would be possible to simplify the procedure for submitting MRL dossiers for these plants (extracts or essential oils) having human safety data. This request was unsuccessful, due to a lack of information about phytotherapy uses in the various Member States and because EMA had other priorities.

[5] According to Ministerial Order of 24 June 2014 establishing the list of plants other than fungi authorised in food supplements, as well as the conditions for their use

The lists of plants and EOs produced by ITAB, RéPAAS and ANSES were of major interest for the selection of priority plants and EOs, and were consulted in addition to the hearings.

Many training courses on phytotherapy and aromatherapy in animal husbandry, drawing from field experience and practices, are provided to farmers, in particular by chambers of agriculture. Moreover, various universities offer training programmes for veterinarians. In the second phase of the expert appraisal, veterinarians (primarily), technicians and producers (also acting as trainers) were interviewed. They were selected to cover the various livestock species and regions in France. Some named additional individuals who could be interviewed or referred the Agency to colleagues.

In the French overseas *Départements* and Regions (DROMs), no chambers of agriculture offer training on phytotherapy or aromatherapy. Only one hearing was conducted through the French National Research Institute for Agriculture, Food and the Environment (INRAE) in Guadeloupe to find out about uses outside of metropolitan France.

A total of 24 people were contacted; 11 hearings were held as conference calls and one individual submitted their comments in writing. To make the hearings more efficient, a questionnaire was prepared and sent to the people interviewed beforehand (Annex 2).

Lastly, the French National Order of Veterinarians, the French Veterinary Academy, the French National Academy of Pharmacy, the French Agriculture Academy and the French Association of Veterinary Phytotherapists (AFVP) were contacted. They were asked about:

- the information they had regarding uses, the number of practitioners, and economic, scientific and regulatory data on the use of medicinal plants and EOs in animal husbandry,
- their opinion of current veterinary phytotherapy and aromatherapy practices in food-producing animals.

3.2 Inventory from the hearings

A digital inventory of the plants and EOs mentioned during the hearings was prepared based on the transcripts. In this inventory, when an EO or plant was mentioned, it was only taken into account once per hearing. If a plant was mentioned as not being used, it was not included in the inventory. Mentions of herbal preparations and EOs being used to purify buildings did not fall within the scope of the internal request and were therefore excluded.

In total, 80 plants and herbal preparations (excluding EOs) and 60 EOs, were inventoried during the hearings. The list is available in Annex 3.

Practices in animal husbandry mainly involve external or internal uses. The therapeutic indications for each plant and EO are not described in detail here. A wide variety of uses are observed. The preparations used, as well as the directions for use, dosages, durations and

regimens, are diverse. Preventive seasonal treatments are sometimes proposed. The exposure of animals therefore heavily depends on the veterinarian, technician or farmer and is not uniformly standardised. The uses mentioned are generally based on field trials and empirical practices with dosage adjustments according to the results observed. It is important to note that the identified uses provide feedback on animal husbandry practices but have no formal scientific validation. Moreover, not enough people were interviewed to be representative of all uses.

The types of preparations also differ widely. The preparations used fall within the framework defined by EMA for human phytotherapy. Usually, plants in unprocessed or powdered form, used in lick tubs in particular, were mentioned. The various types of herbal preparations – especially aqueous and hydro-alcoholic extracts – did not show specific concentrations of certain classes of herbal compounds and were considered as powders in the initial assessments, without prejudice to the differential solubility of the compounds. The practice of gemmotherapy was anecdotal in the inventory.

Plant species and parts are not always well defined. When parts of plants were not explicitly named or when plants were referred to by their French names, those that are most generally used, corresponding to the traditional uses recognised by the French Pharmacopoeia (Lists A and B of medicinal plants), were selected for the inventory, in accordance with the lists proposed by ITAB and RéPAAS and the specialist literature on veterinary phyto/aromatherapy. Manufactured products were sometimes mentioned: major ambiguities concerning the identities of plants and preparations were noted (incorrect, incomplete or approximate names used for plants and EOs; lack of specification or errors in the names of preparations). It appears important for manufacturers of herbal products (feed additives, complementary feed) to give detailed, accurate information about the preparations sold.

Concerning the DROMs, major differences in the use of plants and EOs in animal husbandry were noted as compared with metropolitan France; the one specific hearing for the overseas territories primarily dealt with plants as dewormers. The plants mentioned were primarily tropical plants and were not necessarily included in the French Pharmacopoeia. Additional hearings would be necessary to better cover these territories. These plants were not taken into account in the inventory, as their uses are specific to local plant species, with a few exceptions for cosmopolitan plants. There were only three species in common with practices in metropolitan France.

The information obtained regarding uses in animal husbandry in metropolitan France mainly involved the treatment of cattle and small ruminants, as well as poultry. As the focus of the internal request was MRLs, the various objectives of different production sectors (meat, milk, eggs) were taken into account. Pig farming was poorly represented in the hearings due to a lack of individuals with knowledge on uses in this farming type, despite several hearings in areas with a high density of pig farms. Palatability issues limiting uses of phyto/aromatherapy in pigs were also reported. The French Pork and Pig Institute (IFIP) was contacted but did not have any information regarding uses. In 2015, the Brittany Chamber of Agriculture conducted a survey of 30 companies proposing alternative products in the pig production sector. The published results of this survey were not detailed enough to be included in the inventory

(Lemoine, Calvar et Dubois 2016). Some uses involving horses were noted. Uses for other food-producing species (bees, fish, snails, etc.) were mentioned but remained anecdotal.

This inventory provided an initial basis for the work in the consumer risk assessment stage, which will be called the identification stage in the rest of the report, in the absence of phyto/aromatherapy sales data in the veterinary sector. The plants and EOs in this inventory are all included on the ITAB and RéPAAS lists.

3.3 Selection criteria

In order to capitalise on the hearings and highlight the most commonly used plants and EOs, weights were assigned (expressed as percentages of mentions). The work in the identification stage was carried out with those most frequently mentioned, with a convergence threshold set at 40%. This threshold enabled a realistic number of cases to be addressed over a limited time period. The goal of this first step was to define a methodology that could later be used to assess a larger number of plants and EOs. Where appropriate, similar plants and EOs were considered jointly. It is important to note that all of these most frequently mentioned plants and EOs were of particular practical importance for the people interviewed (efficacy, safety, frequency of use, multiple mentions during the same hearing).

3.4 Observed biases

Various biases were noted:

- The identification of certain plants, preparations and EOs whose uses are anecdotal or insignificant because they are only exceptional, according to the people interviewed.
- The emergence of minor plants that would not have been mentioned spontaneously but were brought up during certain hearings when the discussions were more extensive.
- Some of the people interviewed talked about companies that offer the same plants and EOs in combination in different products, possibly causing them to be over-represented in the inventory. However, the individual ingredients in these products were mentioned repeatedly by all of the people interviewed, and this bias was considered negligible.
- There were ambiguities regarding the names of the species actually used, for example for “cinnamon”, whose exact species was not always mentioned (e.g. Chinese cinnamon or Ceylon cinnamon), and for EOs that can be derived from different species (e.g. “Melaleuca EO”: in this case, tea tree (*Melaleuca alternifolia*) EO and Melaleuca EO with eucalyptol as its main component could be distinguished from one another without ambiguity). Such cases were interpreted based on the cost of purchase or the availability of the plants and herbal preparations. Sometimes there were similar ambiguities for EO CTs.

3.5 List of the plants, essential oils and substances selected for the identification stage

The list of the plants and EOs considered in the identification stage is shown in Table 1 and Table 2. A literature analysis was carried out for these plants and EOs.

Table 1: List of the plants selected for the identification stage

Common name of the plant	Latin name	Parts concerned	ITAB list	RéPAAS list	ANMV list of 100 plants of interest
Garlic	*Allium sativum* L.	Bulbs	Yes	Yes	Yes
Common mugwort	*Artemisia vulgaris* L.	Leaves, flowering tops	Yes	Yes	Yes
Artichoke	*Cynara scolymus* L.	Leaves	Yes	Yes	Yes
Milk thistle	*Silybum marianum* (L.) Gaertn.	Whole plant	Yes	Yes	Yes
Echinacea	*Echinacea angustifolia* DC.	Underground parts	Yes	Yes	Yes
	Echinacea pallida Nutt.	Underground parts	Yes	Yes	Yes
	Echinacea purpurea Moench	Flowering aerial parts, underground parts	Yes	Yes	Yes
Dandelion	*Taraxacum officinale* Web.	Aerial parts and/or underground parts	Yes	Yes	Yes
Bramble	*Rubus fruticosus* L., *Rubus* sp.	Leaves	Yes	Yes	No
Tansy	*Tanacetum vulgare* L.	Aerial parts	Yes	Yes	Yes

Table 2: List of the EOs selected for the identification stage

Common name of the EO	Latin name	Producing organ	ITAB list	RéPAAS list	ANMV list of 101 plants of interest
Linalool and linalyl acetate EOs:					
- **Lavandin EO**[6] (all clones)	*Lavandula x intermedia* Emeric ex Loise	Flowering tops	Yes ("*Lavandula* sp.")	Yes (Abrial, Super clones)	Yes (Super clone)
- **True lavender EO**	*Lavandula angustifolia* Mill.		Yes ("*Lavandula* sp.")	Yes	Yes
Palmarosa EO	*Cymbopogon martinii* Roxb. var. *martinii*	Aerial parts	Yes	Yes	Yes
Ravintsara EO	*Cinnamomum camphora* L. CT cineole	Leaves and branches	Yes	Yes	Yes
Tea tree EO	*Melaleuca alternifolia*	Leaves and terminal branches	Yes	Yes	Yes

In addition, a literature search was carried out for the substances significantly present in the most frequently mentioned EOs (Table 3). Consumer risk assessments of these substances helped the experts to assess a large number of EOs containing them. It is important to specify that the use of these substances in a veterinary medicinal product requires the establishment of an MRL status according to Regulation (EC) No 470/2009.

[6] True lavender (*Lavandula angustifolia* Mill.) EO was only mentioned once. Because its composition is similar to that of lavandin EO, the data concerning it were taken into consideration.

Table 3: List of the EO substances selected for the identification stage

Substance name
Carvacrol
Cinnamaldehyde
Citral (neral / geranial)
Geraniol
Linalool
Limonene
Pinene
Thujone

The aim of this work was to establish a risk profile for plants and EOs without an MRL status. Therefore, all plants, EOs and substances already listed in Table 1 of Regulation (EU) No 37/2010, or included on the "out of scope" list, were excluded from the identification stage. An exception was made for plants included on these lists solely for their use in homeopathy, even when undiluted homeopathic mother tinctures are concerned. Therefore, the identification stage did not deal with nettle or with cinnamon, eucalyptus, bay laurel or common thyme EO[7]. Eucalyptol, rosemary (EO and leaves) and thymol are listed in Table 1 of Regulation (EU) No 37/2010. Echinacea was included because the uses mentioned during the hearings involved oral administration, whereas only its topical use is permitted in Table 1 of Regulation (EU) No 37/2010.

If the part of the plant was not specified, the work focused on the usual plant part.

In the inventory of uses, the frequency of EOs containing high proportions of linalool and linalyl acetate was noted. These EOs are generally used in the same way and for the same indications, with no target-species specificity. The EOs in question (Table 2), which have very similar compositions, are those derived from several clones of lavandin, English lavender and clary sage[8]. When considered jointly, their use was significant in the hearings. A literature search was carried out for linalool and for lavender and lavandin EOs.

During the hearings, oregano EO was frequently mentioned. It was generally the EO derived from common oregano (*Origanum vulgare* L.)[9], but there could be uncertainty as to the species and CTs used. Moreover, oregano EOs are relatively similar to certain thymol thyme CTs (Tisserand and Young, 2014), as defined in the European Pharmacopoeia (EDQM 2019). Thyme EO is included in Table 1 of Regulation (EU) No 37/2010. Oregano EOs are usually very high in carvacrol and thymol; thymol is also listed in Table 1 of Regulation (EU) No

[7] No distinction between CTs; the EO described in the European Pharmacopoeia corresponds to the thymol CT.
[8] The normal composition of clary sage EO is as follows: linalyl acetate (66.5%), linalool (8.9%), germacrene D (9.4%) and sclareol (2.4%) (Tisserand and Young, 2014).
[9] 54.5% mentions

37/2010. Therefore, the WG carried out a literature search for carvacrol and did not examine the literature relating to oregano EO.

4 Review of the data provided in other regulations

4.1 Veterinary medicinal products

4.1.1 Definition of a veterinary medicinal product

A veterinary medicinal product is defined as:

"Any substance or combination of substances presented for treating or preventing disease in animals, or any substance or combination of substances which may be used in or administered to animals either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis"[10].

Therefore, a product containing herbal substances that is presented for treating or preventing disease in animals is considered a veterinary medicinal product.

Medicinal products contain substances that may be of human (such as blood and blood products), animal (micro-organisms, organ parts, animal secretions, etc.), chemical[11] (natural or synthetic chemical components) or plant origin.

A herbal substance is a plant, plant part or plant secretion, or is obtained via the extraction of herbal products such as EOs as defined for veterinary medicinal products in Article R.5141-1 of the CSP.

The definition of medicinal product specifies that when, based all of its characteristics, a product is likely to meet both the definition of a medicinal product and that of other product categories governed by EU or national law, it shall be, in case of doubt, considered a medicinal product[12]. A product likely to be covered by several regulations is called a "borderline product"[13].

Such cases are relatively frequent in view of the regulations on veterinary medicinal products, animal feed, and biocidal products. Guidelines published by the European Commission set out criteria for classifying products under one of the regulations.

If a product with medicinal product claims does not meet the requirements of the regulations on animal feed or biocides, it is by default governed by the regulations on veterinary medicinal products.

[10] Articles L.5111-1 and L.5141-1 of the CSP

[11] Chemical substances can be biological or synthetic (example of insulin, which can be both). They differ from plant and animal substances in terms of their degree of complexity and purification.

[12] Article L.5111-1 of the CSP

[13] https://www.anses.fr/fr/system/files/ANMVnotedepositionqualificationdesproduitsfronti%C3%A8res.pdf

4.1.2 Marketing Authorisation

The placing on the market of a veterinary medicinal product requires that an MA first be obtained, as defined in Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products and in Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency[14].

When submitting an MA application dossier for a medicinal product for food-producing animals, the applicant must first submit an MRL establishment dossier to EMA for substances not listed in Table 1 of Regulation (EU) No 37/2010 (see Section 4.1.3).

At European level, no specific provisions have been adopted for herbal medicinal products in veterinary medicine. The general provisions of the Community code relating to veterinary medicinal products apply on a *de facto* basis, as do the provisions of Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009 laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin, repealing Council Regulation (EEC) No 2377/90 and amending Directive 2001/82/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council.

Directive 2001/82/EC sets out rules for submitting and assessing MA applications for veterinary medicinal products. Its annexes describe the content of dossiers and the studies to be presented to substantiate applications.

This Directive nonetheless provides for the ability to submit “simplified” MA application dossiers[15] if the active substances have been in well-established use in the European Community for at least 10 years and have recognised efficacy and an acceptable level of safety.

For veterinary medicinal products containing plants or EOs, there is no simplified registration procedure like the one available for medicinal products for human use (see corresponding chapter).

MA application dossiers are divided into four parts:

- Part I: administrative data
- Part II: data on the pharmaceutical quality of the product, including in particular the composition and method of production of the finished product, a description of the active substances and other components of the product, and the controls implemented for the raw materials and the final product.
- Part III: data on the product’s safety and residue studies
- Part IV: data on the product’s efficacy.

[14] This Directive will be replaced as of January 2022 by Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products. However, this will have little or no impact on the requirements relating to MAs and the content of MRL dossiers.
[15] Article 22 of Regulation (EU) 2019/6 on veterinary medicinal products

In this dossier, the company should demonstrate the pharmaceutical quality of the veterinary medicinal product, its efficacy, and its safety for animals, the person administering the medicinal product, and the consumer of food derived from treated animals; it should also assess its possible environmental impacts.

As part of this internal request, the major points to be considered were the toxicological profile of the active substance(s) contained in the veterinary medicinal product on the one hand, and the residue part on the other.

For the safety part, general toxicology data, obtained mainly from studies conducted with laboratory animals (acute toxicity, toxicity after repeated administration, mutagenicity, carcinogenicity, reproductive toxicity and potentially other types of toxicity studies when appropriate) or *in vitro* studies, should be provided.

For a medicinal product for food-producing animals, these studies have been assessed upstream by the CVMP when examining the MRL dossier and are not reviewed (reference is made to the European public MRL assessment report (EPMAR) prepared by the CVMP, with no re-assessment of the data). However, the applicant should undertake an assessment of the risks for users of the veterinary medicinal product, assess the environmental impact of the medicinal product and provide tolerance data for the product in relation to the target species.

For the residue part, withdrawal periods must be determined by studying residue depletion for a veterinary medicinal product when the target species is a food-producing animal. Therefore, a withdrawal period should always be defined by comparing the residual concentrations observed in the depletion study with the MRL values of the various components of the medicinal product.

In the case of several active substances, the longest withdrawal period should be considered for the veterinary medicinal product.

All of these safety and residue studies shall comply with the recommendations of European or even international guidelines (OECD[16], EMA, VICH[17]).

As part of a generic application, if bioequivalence[18] with a reference medicinal product is demonstrated, only an assessment of the environmental impact and withdrawal period is required.

4.1.3 MRL

Any pharmacologically active substance intended to be administered to food-producing animals must have been assessed by EMA in terms of the risk of residues in foodstuffs of animal origin, for the target species of the medicinal product in question.

[16] Organisation for Economic Co-operation and Development
[17] Veterinary International Conference on Harmonization
[18] No significant difference in the absorption of an active substance or its metabolites at the site of action

MRL application dossiers comprise a toxicology part, a residue part, and a risk management part. Data on the toxicity, pharmacology and pharmacokinetics (PK) of the substance are therefore provided.

The toxicology part consists of studies conducted in laboratory animals by oral administration (toxicity after repeated administration; mutagenicity / carcinogenicity; toxicity to reproduction – fertility / foetotoxicity / embryotoxicity / teratogenicity; other toxicities as relevant – immunotoxicity / neurotoxicity, etc.), *in vitro* studies, pharmacology data, and data on the minimum inhibitory concentration (MIC) for substances with an antimicrobial effect. These data should enable a toxicological and/or pharmacological and/or microbiological acceptable daily intake (ADI) to be established for consumers, based on the lowest no-effect level selected from these studies, after applying safety factors to take into account inter-species variability, individual variability and, where appropriate, the severity of the observed effects and the quality and robustness of the studies.

In this first part of the MRL dossier, absorption, distribution, metabolism and excretion (ADME) studies conducted with the substance administered orally to laboratory animals should also be provided to characterise the substance's oral absorption and metabolic profile in these species. Since the fate of a substance varies from one species to the next, the data from these studies can be extrapolated to the situation in humans.

The residue part presents ADME studies for the substance in the target species as well as depletion studies which are often associated with radioactive and physicochemical assays of the substance and its metabolites. These studies characterise absorption, the marker residue (MR), and the distribution of the residues in various foodstuffs.

All of these studies should comply with the recommendations of the dedicated VICH guidelines and meet the requirements of guidelines such as those published and validated by the OECD.

In the last part of the MRL dossier, all of the available information is taken into account to set a quantified MRL value or conclude that no MRL is required or no MRL can be established. The “no MRL required” conclusion is often due to very low or even non-existent consumer exposure (examples: very limited oral absorption, very rapid elimination).

Pharmacologically active substances are listed in alphabetical order in both tables in Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding MRLs in foodstuffs of animal origin:

- Table 1 corresponds to allowed substances;
- Table 2 corresponds to prohibited substances.

These tables contain the following information: name of the pharmacologically active substance, MR, animal species, quantified MRL values or “no MRL required”, target tissues, other provisions, and therapeutic classification.

After an assessment by EMA, some substances are considered as not falling within the scope of Regulation (EC) No 470/2009 with regard to MRLs. These substances appear on the “out of scope” list. They include substances naturally occurring in the body and foodstuffs in the human diet that do not pose any risks to consumer health.

Biological substances not requiring an MRL assessment are put on a “biological substances” list. These include, for example, stem cells, probiotic compounds such as bacteria and yeasts, and recombinant bovine interleukin-8.

Substances contained in a veterinary medicinal product for a food-producing animal must either be listed in Table 1 of Regulation (EU) No 37/2010 or be on the “out of scope” or “biological substances” lists.

Case of herbal substances

Since 1997, following a decision of the CVMP, herbal substances[19] have not had a general status as is assigned to substances contained in homeopathic veterinary medicinal products (EMA 1998, 1999). EOs have also been examined individually.

When submitting an MA application dossier for food-producing animals, the applicant must first submit an MRL establishment dossier to EMA (see Commission Implementing Regulation (EU) 2017/12 of 6 January 2017) for herbal substances not listed in Table 1 of Regulation (EU) No 37/2010.

Only one plant genus is listed in Table 2 of Regulation (EU) No 37/2010. This is *Aristolochia* spp. and all preparations thereof, since no MRL can be set. Therefore, its use for food-producing animals is strictly prohibited.

Certain plants are included in Table 1 of Regulation (EU) No 37/2010 with use and/or species restrictions.

Of the 125 plants listed in Table 1 of Regulation (EU) No 37/2010 (Annex 5), there are:

- 124 substances (including 21 EOs) for which it is stated “no MRL required” for the plant and/or plant extract.
    - 54 substances for which it is stated “no MRL required” with no restrictions on use;
    - 41 substances that are reserved for homeopathic use. Of these plants, 21 can be used as undiluted mother tincture, which is not consistent with the restriction “For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias”. Subject to a legal analysis by the European Commission, the competent authority for MRLs, it should be possible to use these substances as mother tinctures in phytotherapy;

[19] In the sense of plants and herbal preparations

        - 29 substances for which it is stated “no MRL required” but with restrictions other than those related to homeopathic use (route of administration, excipient, etc.).
- One substance (isoeugenol) for which a quantified MRL value is given for fish “muscle and skin”.

There are 19 plants on the “out of scope” list.

For MA dossiers, when an AS has the “no MRL required” status, the residue documentation to be provided is simplified.

In EPMARs, when no MRL is required, one of the recurring arguments is that only a small number of animals is exposed. This can conflict with the broad use of phytotherapy in animal production sectors.

However, the large majority of the pharmacologically active herbal substances frequently used in phytotherapy are not included in Table 1 of Regulation (EU) No 37/2010 or on the “out of scope” list and cannot, at the present time, feature in the composition of veterinary medicinal products for food-producing animals or be prescribed by a veterinarian.

When submitting an MA dossier, the applicant must first submit an MRL establishment dossier to EMA (see Commission Implementing Regulation (EU) 2017/12 of 6 January 2017) for herbal substances not listed in Table 1 of Regulation (EU) No 37/2010.

The current MRL assessment approach (according to the EU regulations on veterinary medicinal products) seems difficult, if not impossible, due to the complex and extremely varied quantitative and qualitative chemical composition of a given EO or plant.

4.1.4 The “therapeutic cascade”

Directive 2001/82/EC amended by Directive 2004/28/EC provides for and regulates the off-label use of veterinary medicinal products. It is transposed in France by Article L.5143-4 of the CSP which states that veterinarians must as a priority prescribe a veterinary medicinal product authorised for the species of animal in question and for the therapeutic indication mentioned in the MA.

Moreover, Article L.5143-4 of the CSP stipulates that when a veterinarian prescribes a medicinal product for food-producing animals, the substances with pharmacological action it contains must be among those listed in Table 1 of the Annex to Regulation (EU) No 37/2010.

Use of the principle of the “therapeutic cascade” (Annex 6) requires prior verification of several points:

1) The veterinarian must check that there is no appropriate and available authorised (MA, temporary authorisation for use (TAU) or import authorisation) medicinal product (withdrawal from the market by the holder or problem of supply by the holder),
2) For use in food-producing animals, the veterinarian must:
    - Make sure the substance is listed in Table 1 of Regulation (EU) No 37/2010 or included on the list of essential substances for equines[20]
    - Set a withdrawal period at least equal to the fixed withdrawal period (Annex 7).

4.1.5 Specific case of herbal veterinary medicinal products

In dossiers for medicinal products with well-established use, applicants are permitted to not provide the results of clinical and non-clinical trials on the medicinal product's efficacy and safety, and replace them with references to the published, recognised literature. The literature information provided must establish the efficacy and safety of the veterinary medicinal product.

The content of these dossiers is detailed in 10° of Article R.5121-20 of the CSP, reproduced in full below.

"10° When the application involves a traditionally used medicinal product whose only active substances are one or more herbal substances, as defined in 1° of Article R.5141-1, or herbal preparations or a combination of several herbal substances or herbal preparations, the dossier provided in support of the application shall include, in addition to pharmaceutical data, the results of appropriate non-clinical and clinical trials when the applicant cannot demonstrate, by a detailed reference to the published literature recognised in the tradition of veterinary herbal medicine practised in France or in the European Union, that the medicinal product has been in well-established use for at least 10 years in a European Union Member State or in another State of the European Economic Area and that it shows all guarantees of safety".

In the collective expert appraisal report corresponding to Internal Request "2014-SA-0081 – MA Veterinary phytotherapy" (Anses 2016) on the assessment of MA applications for herbal medicinal products, the documentation to be provided for each part is specified and simplifications are defined. This information is summarised in Table 4 below.

[20] https://www.anses.fr/fr/system/files/ANMV-AMM-Substances-actives-equides-20310415.pdf

Table 4: Simplifications for a veterinary phytotherapy MA by dossier part

Quality part	Safety part	Efficacy part
• Possible choice of an essential tracer substance to ensure quality and the range of concentrations in the herbal drug and the finished product • Possibility of submitting a pharmacopoeia certificate	• Toxicological profile: possible reference to the literature, with long-standing or traditional use (except for genotoxicity: at least one *in vitro* test) • User safety: minimum requirements with focus on exposure • Tolerance: a study with the finished product and restrictions if necessary	• Possible reference to the literature, for pharmacodynamic and PK effects (unless there are no data, for any species or model) • Clinical trials not required if demonstrated well-established use

Moreover, in its opinion, ANSES identified three main obstacles (Anses 2016):

- Concerning herbal veterinary medicinal products for food-producing animals, the lack of an MRL status for the large majority of the plants used;
- The need for strict identification and full characterisation of plants or parts of plants using literature data;
- The small number of scientific publications with a high level of evidence.

One solution depending on the situation may be to use the principle of the “therapeutic cascade” (see 4.1.4), but this does not eliminate the need for an MRL status.

Based on this review of the available data on veterinary medicinal products, the following resources are of interest:

- **Tables 1 and 2 of the MRL Regulation**
- **French Pharmacopoeia**
- **European Pharmacopoeia**
- **Herbal medicines monographs of EMA's Committee for Medicinal Products for Human Use (CHMP)**
- **Pharmacovigilance data**

4.2 Medicinal products for human use

4.2.1 Definitions

4.2.1.1 General definition of a medicinal product

The CSP (Article L.5111-1) defines a medicinal product as: *"Any substance or combination of substances presented for treating or preventing disease in humans or animals, or any substance or combination of substances which may be used in or administered to humans or animals with a view to establishing a medical diagnosis or restoring, correcting or modifying their physiological functions by exerting a pharmacological, immunological or metabolic action".*

Although herbal medicinal products for human use fall under the general regulations on medicinal products, they nonetheless have some specific characteristics.

4.2.1.2 Herbal medicinal products

A herbal medicinal product is a medicinal product whose AS is exclusively one or more herbal substances or herbal preparations or a combination of several herbal substances or herbal preparations (Article L.5121-1, 16° of the CSP). It may take the form of a proprietary medicinal product, a pharmaceutical preparation (magistral or officinal) or a herbal drug.

Herbal substances encompass all mainly whole, fragmented or cut plants, plant parts, algae, fungi and lichen in an unprocessed, dried or fresh form; certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name (genus, species, variety and author).

Herbal preparations are obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates (Art. R.5121-1).

4.2.1.2.1 Plants in the form of proprietary medicinal products

A proprietary medicinal product is any ready-prepared medicinal product placed on the market under a special name and in a special pack (Article L.5111-2 of the CSP). A proprietary herbal medicinal product is a medicinal product whose AS is of plant origin, i.e. made from one or more plants. The AS may be concentrated in the form of an extract, such as an EO, obtained from a part of the plant (leaves, roots, etc.) or the whole plant. Its placing on the French market depends on the issuing of an MA or registration by the ANSM.

4.2.1.2.2 Plants in magistral or officinal preparations

These preparations are medicinal products prepared in a pharmacy for the specific needs of one or more patients (Article L.5121-1 of the CSP).

There are two types of preparations made from medicinal plants, extracts or essential oils:

- Magistral preparations: prepared in accordance with a medical prescription for an individual patient, due to the lack of an available or suitable proprietary medicinal product. They are

prepared by a dispensing pharmacy or an in-house pharmacy of a healthcare facility (hospital pharmacy, etc.).

- Officinal preparations: included in the national pharmacopoeia or formulary. They are prepared in a dispensing pharmacy and are intended to be supplied directly to the patients served by that pharmacy. Blends for herbal teas fall within this framework: they can be prepared by dispensing pharmacists in accordance with the conditions described in a monograph of the national formulary.

All magistral and officinal preparations must be prepared and supplied under the responsibility of a pharmacist in compliance with good pharmacy practice[21].

4.2.1.2.3 Herbal drugs

Herbal drugs include medicinal and aromatic plants and their derivatives. They are supplied in bulk, either in unprocessed or prepared form (extracts or EOs). They can be used whole or in the form of a plant part and have medicinal properties. The French Pharmacopoeia states that they can also be used for food, culinary or hygiene purposes.

Some medicinal plants with therapeutic use are included on a list of the French Pharmacopoeia. List A is that of traditionally used medicinal plants, some of which have been identified as possibly also having food and/or culinary uses[22]. List B corresponds to medicinal plants traditionally used in unprocessed or prepared form whose potential adverse effects outweigh the expected therapeutic benefit[23].

4.2.2 Regulations

4.2.2.1 European Regulations

The legal framework concerning herbal medicinal products for human use is defined by Directive 2001/83/EC amended by Directive 2004/24/EC and Regulation (EC) No 726/2004. All industrially produced herbal medicinal products must obtain an MA prior to being placed on the market.

The division of competences between centralised MAs and national MAs is established in the Annex to Regulation (EC) No 726/2004 of 31 March 2004. The centralised procedure, which falls within the scope of the European Medicines Agency (EMA), applies to specific medicinal products.

For a herbal medicinal product, obtaining a centralised MA is optional (this occurs when the applicant considers there are advantages to placing it on the market in all Member States). When a company wants to market its medicinal product in more than one Member State, the mutual recognition (for medicinal products that already have an MA) or centralised (for medicinal products that have not yet been authorised) procedure is initiated.

[21] AFSSAPS, 3 December 2007: https://ansm.sante.fr/uploads/2020/10/26/20201026-bonnes-pratiques-de-preparation.pdf. It can be noted that the good pharmacy practice guidelines are being revised. The ANSM's work is expected to be finalised in 2022.
[22] https://ansm.sante.fr/uploads/2021/03/25/liste-a-des-plantes-medicinales-utilisees-traditionnellement-4.pdf
[23] https://ansm.sante.fr/uploads/2021/03/25/liste-b-des-plantes-medicinales-utilisees-traditionnellement.pdf

Otherwise, the medicinal product must obtain an MA according to the national procedure (see Section 4.2.2.3).

Table 5: The various regulatory pathways for bringing a herbal medicinal product to market in the EU

Regulatory pathway	Main safety and efficacy requirements	Where to apply
Traditional-use registration (Article 16a(1) of Directive 2001/83/EC amended by Directive 2004/24/EC)	• No clinical trials or safety and efficacy studies are required as long as sufficient safety data and plausible efficacy are demonstrated. • Involves assessment of mostly bibliographic safety and efficacy data. • The medicinal product must have been in use for at least 30 years, including at least 15 years within the EU. • The medicinal product is intended to be used without medical supervision and is not administered by injection.	• Competent national authority of a Member State for national, mutual recognition and decentralised procedures.
Well-established medicinal use MA (Article 10a of Directive 2001/83/EC Regulation (EC) No 726/2004)	• Scientific literature establishing that the active substances in the medicinal products have been in well-established medicinal use within the EU for at least 10 years, with recognised efficacy and an acceptable level of safety. • Involves assessment of mostly bibliographic safety and efficacy data.	• Competent national authority of a Member State for national, mutual recognition and decentralised procedures. • EMA if centralised procedure.
Stand-alone or mixed application (Article 8(3) of Directive 2001/83/EC Regulation (EC) No 726/2004)	• Safety and efficacy data from the company's own development or a combination of own studies and bibliographic data.	• Competent national authority of a Member State for national, mutual recognition and decentralised procedures. • EMA if centralised procedure.

Focus on documents to be provided when submitting an application: the Common Technical Document (CTD) format

The CTD provides a common international format between Europe, the United States and Japan for the submission of MA application dossiers.

It defines the organisation of quality, safety and efficacy data. This format is mandatory for all types of MA applications, regardless of the registration procedure (i.e. national, mutual

recognition, decentralised or centralised procedure) and the application type (new chemical entity, generic application, etc.). This CTD format is also mandatory irrespective of the type of product (chemical, herbal or homeopathic medicinal product, vaccine, etc.).

The CTD format defines five parts of MA application dossiers, referred to as modules:

- Module 1: administrative information
- Module 2: summary of quality, safety and efficacy data
- Module 3: detailed quality information
- Module 4: detailed safety information (non-clinical)
- Module 5: detailed efficacy information (clinical).

4.2.2.2 The Committee on Herbal Medicinal Products (HMPC)

In view of the specific characteristics of herbal medicinal products, a European Committee on Herbal Medicinal Products (HMPC) was created within EMA. The HMPC facilitates the harmonised registration and authorisation of herbal medicinal products by all EU Member States. Within EMA, it is responsible for establishing EU herbal monographs and drafting an EU list of herbal preparations and substances.

On the basis of the scientific opinion of the HMPC, a list of herbal substances, preparations, and combinations for use in certain traditional herbal medicinal products was established by Commission Decision 2008/911/EC.

- **EU herbal monographs**

EU monographs constitute a common knowledge base that facilitates the preparation of registration dossiers in all Member States[24]. They concern herbal substances meeting certain conditions such as a sufficiently long period of medicinal use in the European Union.

EU monographs provide all information necessary for the use of a medicinal product containing a herbal substance[25]: the therapeutic indication of the herbal product, the dosage, the target population for which the herbal product is intended, and safety information such as on adverse effects and interactions with other medicines.

Monographs form the basis for the required individual medicinal product information such as the summary of product characteristics (SPC) and the package leaflet. They are published together with other documents, including an assessment report containing reviews of all available data relevant for the medicinal use of the herbal substance(s).

An EU monograph can be used in application reference material by an MA applicant (well-established medicinal use part) or by a traditional-use registration applicant (traditional use part).

Final monographs are taken into account by Member States when examining an application. While Member States are not obliged to follow the exact content of a monograph as adopted by the HMPC, any decision not to accept the content should be duly justified.

[24] https://www.ema.europa.eu/en/human-regulatory/herbal-products/european-union-monographs-list-entries

[25] In the sense of plant or herbal preparation

4.2.2.3 National regulations

Proprietary herbal medicinal products cannot be marketed in France without an authorisation issued by the ANSM. This authorisation guarantees their quality, safety and therapeutic efficacy for the claimed indications.

A herbal medicinal product can be authorised in one of three ways. Each corresponds to a specific application dossier. Its content varies depending on the plant's characteristics and how long it has been in use.

- **MA application based on a complete dossier**

The safety and efficacy of the medicinal product must be demonstrated based on non-clinical and clinical trials (Articles R.5121 and R.5121-25 of the CSP).

The application format must comply with the presentation requirements for standard MA applications (CTD format with five complete modules).

The dossier must be “complete”. It must include quality, safety and efficacy data from the company's own development or a combination of own studies and literature data.

- **MA application based on well-established medicinal use: bibliographic dossier**

The level of safety must be considered acceptable and efficacy must be recognised on the basis of use.

The applicant must demonstrate, by referring to appropriate literature documentation, that the application concerns a product whose active substance(s):

- have been in well-established medicinal use for at least 10 years in France, the European Union, or the European Economic Area;
- have recognised efficacy;
- and have an acceptable level of safety.

The simplified submission dossier contains Modules 1 to 5:

- Modules 1 to 3 are the same as those submitted for a “complete” MA application (as described above).
- Modules 4 and 5 contain a detailed scientific bibliography that addresses non-clinical and clinical characteristics based on use for at least 10 years in France or the European Union.

These products authorised based on well-established medicinal use can be included on the list of generic groups of herbal medicinal products in the conditions set out in Decree No 2016-469 of 14 April 2016.

- **Registration application for traditional herbal medicinal products**

Efficacy must be considered plausible based on a long period of use and experience. Safety must be documented in the form of an expert report and safety data. Where appropriate, additional studies may be requested (Articles L.5121-14-1 and R.5121-107-3 *et seq* of the CSP).

This simplified authorisation procedure is to be used for medicinal products characterised as "traditional herbal medicinal products" when they meet the following five cumulative criteria:

- have indications exclusively appropriate to traditional herbal medicinal products intended and designed for use without the supervision of a medical practitioner for diagnostic purposes, for prescription or for the monitoring of treatment;
- be exclusively for administration in accordance with a specified route, dose/concentration and posology;
- be an oral, external and/or inhalation preparation;
- the period of traditional medicinal use has been at least 30 years before the date of the application, including at least 15 years within the EU;
- the data on the traditional use of the medicinal product are sufficient: in particular, the product proves not to be harmful in the specified conditions of use and the pharmacological effects or efficacy of the medicinal product are plausible on the basis of long-standing use and experience.

The submitted dossier contains five modules. The chemical and pharmaceutical information (Module 3) is the same as for medicinal products with MA.

The non-clinical (Module 4) and clinical (Module 5) reports are simplified. The applicant must provide:

- bibliographic and expert evidence that the medicinal product has been in medicinal use for at least 30 years at the time of the application, including at least 15 years in the EU or the European Economic Area;
- a literature review of safety data together with an expert report;
- and any data required to assess the safety of the medicinal product.

■ **Case of MAs issued before Directive 2004/24/EC**

Directive 2004/24/EC of 31 March 2004, amending Directive 2001/83/EC of 6 November 2001 on the Community code relating to medicinal products for human use, provides for a specific authorisation regime as a registration of traditional herbal medicinal products.

For traditional herbal medicinal products that were placed on the market before 27 April 2007, an application had to be submitted to AFSSAPS as part of a validation procedure for the updating of dossiers.

Temporarily, these products could continue to be marketed until possible notification of refusal of registration by the ANSM.

4.2.2.4 Focus on the regulations on plants and EOs

▶ **Plants in medicinal products for human use**

Plants used for therapeutic purposes are included in the French Pharmacopoeia.

Medicinal plants in the French Pharmacopoeia can only be sold by pharmacists (Article L.4211-1, 5° of the CSP), subject to certain exceptions established by decree.

The list set out in the Decree includes 148 medicinal plants or plant parts that, in the form specified in the list in the Decree, can be sold by people other than pharmacists[26].

- **EOs in medicinal products for human use**

In the French regulations, 15 EOs are identified as having a negative benefit/risk ratio (Decree No 2007-1198 of 3 August 2007)[27].

These are only available through pharmacies, due to their abortive, neurotoxic (wormwood, thuja, common sage), irritant (savin, mustard), phototoxic (rue) or carcinogenic (sassafras) properties:

- Grand wormwood (*Artemisia absinthium* L.),
- Roman wormwood (*Artemisia pontica* L.),
- Common mugwort (*Artemisia vulgaris* L.),
- White wormwood (*Artemisia herba alba* Asso),
- Tree wormwood (*Artemisia arborescens* L.),
- Arborvitae or Northern white cedar (*Thuja occidentalis* L.) and Korean arborvitae (*Thuja koraiensis* Nakai), known as "cedar leaf",
- Hyssop (*Hyssopus officinalis* L.),
- Common sage (*Salvia officinalis* L.),
- Tansy (*Tanacetum vulgare* L.),
- Thuja (*Thuja plicata* Donn ex D. Don.),
- Sassafras (*Sassafras albidum* [Nutt.] Nees),
- Savin (*Juniperus sabina* L.),
- Rue (*Ruta graveolens* L.),
- Mexican tea (*Chenopodium ambrosioides* and *Chenopodium anthelminticum* L.),
- Indian mustard (*Brassica juncea* [L.] Czernj. & Cosson).

Point 6 of the Decree states that: "*The retail sale and any dispensing to the public of the essential oils listed in the decree, and their dilutions and preparations, constituting neither cosmetic products nor cleaning products nor foodstuffs nor beverages, are reserved for pharmacists*".

EOs that are not subject to the pharmaceutical monopoly

EOs that are not subject to the pharmaceutical monopoly are sold over the counter and distributed through various channels (pharmacists, specialist stores, etc.). They must not have therapeutic claims when their composition is not guaranteed with regard to their potential therapeutic effects.

Control

The control of product compliance (microbial contamination or detection of pyrrolizidine alkaloids, falsification, compliance with labelling requirements, etc.) is the responsibility of the ANSM, which can take health control measures (withdrawal of products or batches).

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[26] Decree No 2008-841 of 22 August 2008 on the sale to the public of medicinal plants in the French Pharmacopoeia, amending Article D.4211-11 of the CSP https://www.legifrance.gouv.fr/codes/id/LEGIARTI000019377852/2008-08-27

[27] https://www.legifrance.gouv.fr/codes/article_lc/LEGIARTI000006913469/#LEGIARTI000006913469

Surveillance
Surveillance falls under the pharmacovigilance scheme, which requires that health professionals and pharmaceutical companies report any adverse effects suspected of being caused by a medicinal product; patients can also report such effects[28].

Based on this review of the available data on medicinal products for human use, the following resources are of interest:

- **List A and List B of medicinal plants traditionally used in unprocessed or prepared form**
- **EMA HMPC opinions**
- **French Pharmacopoeia**
- **European Pharmacopoeia**
- **Herbal medicinal products authorised for human medicine in France**
- **Pharmacovigilance data**

4.3 Food supplements and other foodstuffs for human use

4.3.1 Definitions

According to Decree No 2006-352 of 20 March 2006 on food supplements, these are defined as being foodstuffs[29] whose purpose is to supplement the normal human diet.

Food supplements are concentrated sources of nutrients or other substances, alone or in combination, that have a nutritional or physiological effect.

They are marketed in dose form, namely presentation forms such as capsules, lozenges, tablets, pills and other similar forms, as well as sachets of powder, ampoules of fluid, bottles with a dropper and other similar forms of liquid or powder preparations designed to be taken in low-quantity measured units.

Food supplements contain nutrients (vitamins or minerals), substances with a nutritional or physiological purpose, or plants and plant preparations.

4.3.2 Regulations

4.3.2.1 European Regulations

In Europe, food supplements are subject to all of the general provisions of food law, as well as to specific rules defined by Directive 2002/46/EC of the European Parliament and of the

[28] https://ansm.sante.fr/documents/reference/declarer-un-effet-indesirable
[29] A “foodstuff” is any substance or product, whether processed, partially processed or unprocessed, intended to be or reasonably expected to be ingested by humans. This term excludes animal feed, live animals (with some exceptions), medicinal products, cosmetics, tobacco, narcotics, psychotropic substances and contaminants.

Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements, transposed into French law by Decree No 2006-352.

The addition of vitamins, minerals and certain other substances to foodstuffs, including food supplements, must comply with the provisions of Regulation (EC) No 1925/2006. Moreover, food supplements can contain other ingredients whose use in human food is traditional or recognised as such under Regulation (EU) 2015/2283 on novel foods, or ingredients that are authorised in accordance with this regulation.

Nutrition and health claims made in commercial communications for food supplements must comply with the provisions of Regulation (EC) No 1924/2006. Furthermore, Regulation (EU) No 432/2012 establishes a list of permitted health claims made on foods. It should be noted that numerous applications for health claims made on plants used in food supplements are pending assessment by the European Commission. These claims can be used, in accordance with the existing regulations, pending assessment or a change in the assessment conditions.

It should also be noted that there is no harmonised list of plants in Europe. However, any plant preparation contained in a food supplement authorised in a country of the European Union is likely to be authorised for the same product in France as part of the mutual recognition principle, in accordance with Article 16 of Decree No 2006-352.

4.3.2.2 National regulations and specific features

In France, based on Decree No 2006-352 of 20 March 2006 on food supplements, the following implementing Ministerial Orders have been issued:

- Ministerial Order of 9 May 2006 on nutrients that may be used in the manufacture of food supplements;
- Ministerial Order of 24 June 2014 establishing the list of plants other than fungi authorised in food supplements, as well as the conditions for their use;
- Ministerial Order of 26 September 2016 establishing the list of substances with a nutritional or physiological purpose authorised in food supplements, as well as the conditions for their use.

4.3.2.3 Focus on the regulations on plants and EOs

- **Plants in food supplements**

In France, the use of plants in food supplements and their conditions of use are regulated by the Ministerial Order of 24 June 2014. The aim of this Order is to ensure the quality of the plant preparations used in food supplements. In addition to the articles specifying its scope, the Order contains three annexes.

Annex I of this Order establishes a national positive list of plants. However, this list is not exhaustive and is limited to the plants authorised in food supplements in France in accordance with the principle of the free movement of goods. Moreover, it should be noted that certain plants in the Order may be included on List A or B of medicinal plants traditionally used in unprocessed or prepared form.

When it was published in 2014, this list comprised 540 plants. In 2019, the Directorate General for Competition Policy, Consumer Affairs and Fraud Control (DGCCRF) published a new list of 1011 plants.

For some plants, conditions of use as well as restrictions (quantitative or qualitative) or warnings concerning high-risk uses may be specified. Moreover, some plants may contain

nutrients or substances with a nutritional or physiological purpose for which maximum levels apply, in accordance with the Ministerial Order of 9 May 2006 and the Ministerial Order of 26 September 2016 respectively, and with the health recommendations relating to nutrients (DGCCRF, 2019).

Annex II of the Order sets out information to be provided by food sector operators concerning the characterisation of plant preparations. This is the information for the quality dossier for plants and plant preparations. This dossier must be made available to the DGCCRF's control services.

Annex III of the Order sets out information to be provided by food sector operators concerning the safety of plant preparations.

The safety of use of a herbal food supplement is mainly the responsibility of its manufacturer, who is required to conduct a case-by-case analysis to identify potential hazards.

■ EOs in food supplements

It should be noted that the Ministerial Order of 24 June 2014 does not expressly authorise any EOs. When this Order entered into force on 1 January 2015, any food supplement containing an EO had to be declared to the DGCCRF pursuant to Article 16 of Decree No 2006-352.

In 2019, the DGCCRF published a list of plants whose EOs are considered as traditional, with 77 EOs that can be used in food supplements[30]. It should be noted that this list does not mention the notions of producing organ and CT.

A supporting document giving health recommendations for the use of EOs in food supplements was published along with this list[31].

■ Marketing declaration to the DGCCRF

As foodstuffs, food supplements are not products subject to authorisation requiring an *a priori* risk assessment, like medicinal products for human use, veterinary medicinal products, biocidal products and PPPs. It should therefore be remembered that the DGCCRF is the competent decision-making and management authority for food supplements.

The only way to apply for authorisation to market a food supplement is to submit a declaration to the DGCCRF. Lack of response within two months of receipt of the complete declaration dossier constitutes MA.

Authorisation to market a food supplement may be refused on the following grounds:

- if there are no documents or information certifying that the plant or plant preparation, or the product, is lawfully manufactured or marketed in another EU Member State or another party to the Agreement on the European Economic Area;
- if scientific evidence, provided by ANSES in particular, demonstrates that the product poses a health risk.

[30] https://www.economie.gouv.fr/files/files/directions_services/dgccrf/securite/produits_alimentaires/Complement_alimentaire/CA_Liste_HE_janvier2019.pdf
[31] https://www.economie.gouv.fr/files/files/directions_services/dgccrf/securite/produits_alimentaires/Complement_alimentaire/CA_RS_HE_janvier2019.pdf

Since 26 April 2016, declarations have been sent to the DGCCRF via a dedicated teleservice called Téléicare. The list of food supplements declared via this service since 26 April 2016 is available on the electronic submission site of the DGCCRF.

As part of these declarations, the DGCCRF can ask ANSES to assess the risks associated with the use of a plant or plant preparation in food supplements and recommend quantitative or qualitative restrictions guaranteeing its safety of use. ANSES can also issue internal requests concerning authorised plants and plant preparations involved in alerts issued by the nutrivigilance scheme or other national or international surveillance schemes.

4.3.3 ANSES's nutrivigilance scheme

4.3.3.1 Description of the scheme

The French Act on Regional Health Governance (2009-879) of 21 July 2009 tasked ANSES with “implementing the vigilance scheme for novel foods, food supplements, foods to which substances have been added for nutritional or physiological purposes and products intended for particular nutritional uses”.

The purpose of this health surveillance scheme, which is part of the French health and safety system, is to improve consumer health by rapidly identifying any acute adverse effects linked to the consumption of these foods, in order to recommend the implementation of corrective or preventive measures by decision-makers.

The national nutrivigilance scheme relies on health professionals (mainly physicians and pharmacists), manufacturers, distributors and individuals, who contact ANSES[32] to report any adverse effects[33] potentially caused by the consumption of food supplements or, more broadly, any other food covered by the law.

In the same way as for other French vigilance schemes, and given the gravity of the consequences in terms of health and the resulting manufacturing decisions, an appropriate and objective method of analysis is required to determine the relationship of causality between a product concerned by the national nutrivigilance scheme and the adverse effect reported. Referred to as the “method of determining causality in nutrivigilance”, this method assesses the degree of causality of one or more products in the occurrence of the adverse effect reported, as part of a standardised approach designed to resolve any differences in opinion that may exist between observers.

[32] Directly on the ANSES website (www.anses.fr) or via the Adverse Health Event Reporting Portal put in place by the Ministry of Health (https://signalement.social-sante.gouv.fr)

[33] In accordance with Article R.1323-3 of the CSP, “the term adverse effect refers to any harmful reaction occurring in humans under normal conditions of use of a food, or resulting from use that does not comply with its purpose, with normal use or with the instructions for use or special precautions for use specified on the labelling”.

4.3.3.2 Method

The method of determining causality in nutrivigilance is designed to provide the basis for an objective and reproducible assessment of the relationship of causality between a product concerned by the national nutrivigilance scheme and the adverse effect reported to ANSES.

It will be applied by the ANSES Nutrivigilance Unit as well as by the experts mandated by the Agency to analyse reports of adverse effects in nutrivigilance.

The method of determining causality in nutrivigilance enables an intrinsic causality score and an extrinsic causality score to be established; these are independent of one another.

The intrinsic causality score is based on the combination of two scores, one chronological, the other aetiological.

The extrinsic causality score is based on the knowledge available in the scientific literature relating to the adverse effects of each ingredient in the products analysed.

This method of determining causality is systematically applied when analysing sufficiently well documented reports of adverse effects received by ANSES as part of the nutrivigilance scheme. For each report, a collective expert appraisal is conducted and validated by the Nutrivigilance WG. This method was updated as part of Internal Request No 2018-SA-0026; the corresponding opinion is available on ANSES's website.

The numerous opinions published since the creation of the nutrivigilance scheme include the following:

- Request No 2017-SA-0215: Opinion on three cases of allergy to food supplements containing pollen or hive products;
- Request No 2014-SA-0096: Risks associated with the consumption of food supplements containing spirulina;
- Request No 2012-SA-0200: Risks associated with the presence in food supplements of p-synephrine or ingredients obtained from *Citrus* spp. fruits containing this substance;
- Request No 2010-SA-0294: Relevance of the work conducted by a supplier of food supplement ingredients to ensure the safety of the yam (*Dioscorea*) alcohol extracts produced.

4.3.4 The assessments of ANSES's WG on Plants

4.3.4.1 Background

The WG on Plants was created in 2016 following the entry into force of the Ministerial Order of 24 June 2014. It reports to the CES on Human nutrition, which validates the opinions relating to its expert appraisal work.

The primary mission of the WG on Plants is to identify and assess plants and parts of plants that are authorised in food supplements and can pose risks to human health when consumed in food.

In this context, it can receive formal requests from the DGCCRF or issue internal requests following health alerts, in particular from the nutrivigilance scheme.

To date, based on the work of the WG on Plants, ANSES has published three opinions, for the following plants:

- macroalgae, microalgae and halophytes (Request No 2017-SA-0086);
- plants containing berberine (Request No 2018-SA-0095);
- Melaleuca EO (Request No 2018-SA-0096).

ANSES has also assessed plants containing coumarin (Request No 2018-SA-0180).

Therefore, the conditions of use in food supplements of almost 85 plants have been assessed in order to guarantee their safe use in food supplements and other foodstuffs.

4.3.4.2 Assessment of plants and plant extracts

As part of their work, the experts and rapporteurs from the WG on Plants use all of the data available in the literature, produced by national and international health agencies and vigilance schemes. The scientific reports most frequently used in the WG's work include the scientific opinions of the European Food Safety Authority (EFSA) and the monographs of EMA and the World Health Organization (WHO).

The WG's expert appraisal work presents the complete chemical characterisation of a substance or botanical characterisation of a plant. Indeed, there are many misunderstandings and uncertainties concerning the plants and parts of plants used in food supplements.

The PK, pharmacological and metabolism data used come from the scientific literature, as do the toxicological data when there are no toxicity reference values (TRVs) for the substance being assessed. These data are taken into account to determine at-risk populations and sometimes a recommended maximum intake.

If toxicological studies are available, the CES on Health reference values can be called on to propose, depending on the quality of the studies used, a TRV or an indicative toxicity value (iTV).

Vigilance data on the adverse effects associated with the consumption of food supplements containing the plant or plant preparation being assessed are identified in collaboration with the nutrivigilance scheme; they are obtained from poison control centres (PCCs), the pharmacovigilance scheme, all EU MS and EFSA programmes, and the websites of the US Food and Drug Administration (FDA) and Health Canada. Data concerning drug interactions can also be obtained from these vigilance schemes, and be supplemented by a literature review. These data can be used to support the qualitative or quantitative restrictions proposed or add warnings related to the use of food supplements containing the plant or plant preparation.

As part of the expert appraisal work, all known uses of the plant are described (food, food supplements, medicinal products, cosmetics and other). However, only oral exposure is taken into account when assessing the health risks associated with the consumption of food supplements. When consumption data are available (INCA 3 study, for example), exposure is estimated in comparison with the TRV. This assessment can then lead to a quantitative estimate of the risk.

It should be remembered that the conclusions and recommendations of the WG on Plants set out in ANSES's opinions only concern the safety of use of plants or parts of plants that can be used in food supplements. These supplements can contain many other ingredients.

In addition, ANSES's conclusions constitute scientific evidence that can be taken into account by the DGCCRF, the competent authority responsible for withdrawing food supplements from the market or modifying their conditions of use.

Based on this review of the available data on food supplements and other foodstuffs for human use, the following resources are of interest:

- **Ministerial Order of 24 June 2014 establishing the list of plants other than fungi authorised in food supplements, as well as the conditions for their use**
- **DGCCRF lists of plants including EOs that are considered as traditional, published in 2019**
- **Opinions of ANSES's WG on Plants**
- **Nutrivigilance data**

4.4 Plant protection products, fertilisers and biocides

Concerning these different types of products, there are several regulations on a variety of scales between national and European level.

4.4.1 Plant protection products

4.4.1.1 Regulations on plant protection products

4.4.1.1.1 European level

The placing of plant protection products on the market in Europe is broken down into several steps. Initially, the active substance (AS) contained in one or more products must be approved in Europe according to Regulation (EC) No 1107/2009. Next, MRLs of this AS must be set for each foodstuff according to Regulation (EC) No 396/2005. Once the AS has been approved and the MRLs adopted, MAs can be granted for the PPPs containing the substance. A list of the products of plant origin included in the normal human diet is available in Annex I of Regulation (EC) No 396/2005.

Regulation (EC) No 1107/2009 distinguishes between three categories of substances that will be authorised for different periods: active substances, low-risk active substances, and basic substances. Plants and plant extracts are found in each of these categories.

- Low-risk active substances

An AS shall not be considered a low-risk AS where it is or has to be classified as at least one of the following: carcinogenic, mutagenic, toxic to reproduction, sensitising chemical, very toxic or toxic, explosive, or corrosive. Article 22 of Regulation (EC) No 1107/2009 specifies that a substance also shall not be considered a low-risk AS if:

- it is persistent (half-life in soil of more than 60 days),
- the bioconcentration factor is higher than 100,

- it is deemed to be an endocrine disruptor, or it has neurotoxic or immunotoxic effects.

In 2021, 23 substances meet these criteria. These include some plants (tea, garlic extracts, etc.), several micro-organisms and a series of substances that are awaiting approval (these substances are assumed to fit in this category). These substances are approved for a period of no longer than 15 years.

■ Basic substances

These are defined as being “substances which are not predominantly used as plant protection products [but which] may be of value for plant protection, but the economic interest of applying for approval may be limited”. They are approved for an unlimited period of time. They include, for example, sugar, whey, vinegar, beer and plants such as horsetail, mustard, sunflower oil, nettle and onion.

4.4.1.1.2 National level: biocontrol substances and natural preparations of low concern for plant protection purposes

The concept of biocontrol is national; it was introduced in October 2014 by the Act on the future of agriculture, amending the Rural and Maritime Fishing Code (Article L.253-6 as amended) (extract): “The plan (national action plan setting objectives to reduce the risks and effects of PPP use, or Ecophyto) includes measures aimed at developing biocontrol products, which are agents and products using natural mechanisms for the integrated control of crop pests. In particular, they include:

- 1° Macro-organisms;
- 2° PPPs containing micro-organisms, chemical mediators such as pheromones and kairomones, and natural substances of plant, animal or mineral origin”.

Article L.253-1 of the Rural Code introduces the concept of “natural preparations of low concern”, made exclusively of either basic substances as defined in Article 23 of Regulation (EC) No 1107/2009 (no MA) or natural substances for biostimulant use (fertiliser).

Decree No 2009-792 introduces the concept of natural preparations of low concern for plant protection purposes and establishes provisions for their placing on the market. This text defines a “natural preparation of low concern” as any preparation that meets the following two conditions: be made exclusively from one or more non-GM natural components and be obtained via a process accessible to any end user.

There is a whole series of measures in France aimed at facilitating the placing of these products on the market, such as submissions without notification, exchanges via pre-submission forms, priority processing in relation to all other types of dossiers in the assessment, notification and decision-publishing processes, and dedicated teams in both the coordination and assessment units.

4.4.1.2 Assessment documents

4.4.1.2.1 Regulation (EU) No 283/2013 and Regulation (EU) No 284/2013

Regulation (EU) No 283/2013 sets out the data requirements for active substances, in accordance with Regulation (EC) No 1107/2009, and its Annex IV indicates the official methods that should be implemented to fulfil these requirements. Regulation (EU) No 284/2013 sets out the data requirements for preparations containing these substances, in accordance with Regulation (EC) No 1107/2009. The requirements may differ depending on the type of substance (micro-organism, pheromone, etc.).

4.4.1.2.2 Guidance document for plant extracts

In Europe, the guidance document for plant extracts (SANCO/10472/2003) states that for these extracts, hazards and exposure should be identified conventionally but arguments and a review of the literature or other legislation can be submitted instead of studies.

This guidance document defines three groups of plants:

- Group 1: substances that are known to have no notable health effects (these are food-grade plants) and for which a very simplified assessment will be sufficient.
- Group 2: substances that may contain a known component (e.g. orange oil containing D-limonene) whose toxicological properties have already been identified.
- Group 3: substances that do not fit in either of the above two categories and for which an identification and complete risk characterisation should be required. Unknown components present in significant quantities (more than 10% of the extract) will have to be identified, and a complete risk assessment will then need to be conducted.
- A distinction is therefore made between identified components known for not being toxicologically relevant, known components with identified toxicological properties, and other components of the extract that will need to be identified and quantified. Once each component has been identified, hazard characterisation studies will need to be submitted in order for TRVs to be established. In some cases, extrapolations (read-across) and *in silico* (QSAR, for example) models or Threshold of Toxicological Concern (TTC) approaches can be implemented.

Concerning the assessment of exposure, data will need to be provided. In some cases, exposure can be compared with usage and consumption histories, for example by comparing treatment-related exposure with natural exposure, thereby eliminating the need for detailed toxicological data.

4.4.1.2.3 Guidance document on criteria for the inclusion of active substances into Annex IV of Regulation (EC) No 396/2005

This document enabling a substance to be exempted from MRLs does not apply to plant extracts in general. In fact, it determines which substances can be included in Annex IV of Regulation (EC) No 396/2005, i.e. substances for which an MRL does not need to be set (Annex 8).

These are:

- basic substances,
- foods,

- substances for which there is no toxicological concern (no concern, no classification),
- substances for which exposure to the treatment will be lower than natural exposure if natural exposure is usual and chronic,
- substances for which the absolute absence of exposure has been demonstrated irrespective of the use.

In all other cases, an MRL shall be set for a given AS in all foodstuffs according to Regulation (EC) No 396/2005, with a default limit of quantification set at 0.01 mg/kg.

4.4.2 Fertilisers

In France, fertilisers and biostimulants cannot be placed on the market or used without obtaining an MA, issued under the conditions set out in Article L.255-7 of the Rural and Maritime Fishing Code, i.e. following an assessment that, in the specified conditions of use, shows the lack of harmful effects on human health, animal health and the environment and demonstrates its efficacy with regard to plants and plant products or soils.

In Europe, Regulation (EU) 2019/1009 published in the Official Journal of the European Union on 26 June 2019 provides a framework for biostimulants by defining them based on their function(s) and including them in the class of fertilisers: "'plant biostimulant' means a product stimulating plant nutrition processes independently of the product's nutrient content with the sole aim of improving one or more of the following characteristics of the plant or the plant rhizosphere".

This new Regulation (EU) 2019/1009 will enter into force on 16 July 2022.

Moreover, natural preparations of low concern (NPLCs) are defined in Article L.253-1 of the Rural and Maritime Fishing Code. An NPLC is made entirely of either basic substances, as defined in Article 23 of Regulation (EC) No 1107/2009, or natural substances for biostimulant use (NSBUs). NPLCs are obtained via a process accessible to any end user.

NSBUs are defined in the applicable national regulations. In accordance with Point 4° of Article L.255-5 of the Rural and Maritime Fishing Code, NSBUs are exempt from MA. However, they are subject to an authorisation and assessment procedure, whose terms are set by the regulations and codified in Article D.255-30-1 of the Rural and Maritime Fishing Code.

Implementing Decree No 2019-329 of 16 April 2019 lays down the authorisation procedure and conditions for NSBUs and for NPLCs containing them. Therefore, an NSBU is authorised, where applicable with specific requirements for use, via its inclusion on a list published by an Order of the Minister of Agriculture, when:

- it is of plant, animal (excluding micro-organisms) or mineral origin and is not genetically modified;
- it is obtained via a process accessible to any end user, which means it is unprocessed or processed only by manual, mechanical or gravitational means, by dissolution in water or alcohol, by flotation, by extraction with water or alcohol, by steam distillation or by heating solely to remove water;
- except in cases where the substance is mentioned in Article D.4211-11 of the CSP, it has undergone an assessment conducted by ANSES demonstrating the lack of harmful effects on human health, animal health and the environment.

The Ministerial Order of 27 April 2016 establishing the list of NSBUs authorises, as natural substances for biostimulant use, the plants and parts of plants mentioned in Article D.4211-11 of the CSP, in the form in which they are listed or when they result from a process accessible to any end user as defined in Article D.255-30-1 of the Rural and Maritime Fishing Code, as described above.

The Decree of 16 April 2019 states that an Order of the Minister of Agriculture can set out criteria for this assessment and introduces the exemption from assessment by ANSES of NSBUs derived from edible parts of plants used in food or feed when they are contained in an NPLC compliant with approved specifications in accordance with Point 3 of Article L.255-5 of the Rural and Maritime Fishing Code.

Lastly, the Ministerial Order of 14 June 2021 defines the specifications to be followed for the manufacture, marketing and use of NPLCs.

Article R.255-29 of the Rural and Maritime Fishing Code states that the specifications mentioned in Point 3 of Article L.255-5 shall be approved by an Order of the Minister of Agriculture, after an opinion by ANSES.

4.4.3 Biocidal products

The placing of biocidal substances and products on the market in Europe is governed by Regulation (EU) No 528/2012. To encourage the use of alternative products that have more favourable characteristics for the environment or human or animal health than synthetic substances, this Regulation provides for a simplified authorisation procedure for such biocidal products. To be eligible for the simplified procedure, the biocidal product must contain one or more substances listed in Annex I of the Regulation, not contain any substances of concern or nanomaterials, be sufficiently effective, and not require personal protective equipment for its handling and use. The list of active substances in Annex I includes substances identified as posing a low risk in accordance with Annex IV of Regulation (EC) No 1907/2006 or Annex I or IA of Directive 98/8/EC, substances authorised as food additives in accordance with Regulation (EC) No 1333/2008, pheromones, and other substances considered as having low toxicity, such as weak acids, alcohols, and vegetable oils used in cosmetics and food. There is no specific category for plant extracts, which may or may not be among the active substances in Annex I (Annex 9).

Based on this review of the available data on fertilisers, biocides and PPPs, the following resources are of interest:

- **List of the products of plant (or animal) origin included in the normal human diet: Annex I of Regulation (EC) No 396/2005**
- **EFSA assessments of active substances**

4.5 Feed additives

4.5.1 Definitions

According to Regulation (EC) No 1831/2003, 'feed additives' means substances, micro-organisms or preparations, other than feed material and premixtures, which are intentionally added to feed or water in order to perform, in particular, one or more of the following functions:

- Favourably affect the characteristics of feed;
- Favourably affect the characteristics of animal products;
- Favourably affect the colour of ornamental fish and birds;
- Satisfy the nutritional needs of animals;
- Favourably affect the environmental consequences of animal production;
- Favourably affect animal production, performance or welfare, particularly by affecting the gastro-intestinal flora or digestibility of feedingstuffs;
- Have a coccidiostatic or histomonostatic effect.

There are five categories of feed additives depending on their functions and properties:

- Technological additives: any substance added to feed for a technological purpose;
- Sensory additives: any substance, the addition of which to feed improves or changes the organoleptic properties of the feed, or the visual characteristics of the food derived from animals;
- Nutritional additives;
- Zootechnical additives: any additive used to favourably affect the performance of animals in good health or used to favourably affect the environment;
- Coccidiostats and histomonostats.

4.5.2 European Regulations

Regulation (EC) No 1831/2003 governs the conditions for the authorisation and use of additives in animal nutrition throughout the European Union. Any additive must be authorised by the European Commission before it can be marketed. Authorisation is subject to a prior assessment by EFSA.

The authorisation application dossier must contain, among other things:

- Identification of the additive;
- Efficacy in the claimed function(s);
- Risks to the animal consuming it, the consumer of foods produced by the animal, the user handling it, and the environment.

The list of authorised additives is available in the European Union Register of Feed Additives: EU Register | Food Safety (europa.eu). Annex I contains the list of current authorisations and Annex II the list of authorisations that will be withdrawn in the short term.

This Regulation covers all additives, including plant extracts.

This Regulation provided for the submission of authorisation dossiers for all the additives present on the market. This process started in 2010 and should be finalised in 2026. Currently, 160 plant extract dossiers and more than 600 “chemically defined” additive dossiers are awaiting re-authorisation.

4.5.3 Assessment

The scientific assessment undertaken by EFSA must demonstrate that at the doses used, the additive has no negative effects on animal or human health or on the environment. The EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) is responsible for issuing scientific opinions relating to the safety and/or efficacy of products and substances used in animal feed.

4.5.3.1 Regulatory references

Regulation (EC) No 1831/2003 states that EFSA should establish guidelines for the authorisation of feed additives. The following guides have been published by EFSA and are available on its website:

- Guidance on the identity, characterisation and conditions of use of feed additives, EFSA 2017[34]
- Guidance on the characterisation of microorganisms used as feed additives or as production organisms, EFSA 2018[35]
- Guidance on the assessment of the safety of feed additives for the target species, EFSA 2017[36]
- Guidance on the assessment of the safety of feed additives for the consumer, EFSA 2017[37]
- Guidance on the assessment of the efficacy of feed additives, EFSA 2018[38]
- Guidance on studies concerning the safety of use of the additive for users/workers, EFSA 2012[39]
- Guidance on the assessment of the safety of feed additives for the environment, EFSA 2019[40]

These guides are updated on a regular basis.

[34] https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2017.5023
[35] https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5206
[36] https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2017.5021
[37] https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2017.5022
[38] https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5274
[39] https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2012.2539
[40] https://efsa.onlinelibrary.wiley.com/doi/abs/10.2903/sp.efsa.2019.EN-1595

4.5.3.2 Guides for the assessment of plants and plant extracts

EFSA has written specific guides for the assessment of plants and plant preparations:

- Guidance on Safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements, EFSA 2009[41]
- Compendium of botanicals reported to contain naturally occurring substances of possible concern for human health when used in food and food supplements, EFSA 2012[42]

4.5.3.3 Assessment of the quality dossier

The analytical dossier for a plant extract that must be provided in the authorisation application has the same level of requirements as for a veterinary medicinal product. The composition and characterisation of the extract and active substances must be as detailed as possible, since the aim is to assess the risk associated with the presence of any toxic compounds.

4.5.3.4 Assessment of safety for consumers

The process of assessing the safety of additives for consumers is the same as for veterinary medicinal products, except that there are no depletion studies for additives. For additives, there is a study that enables residues to be characterised, but only at the end of administration. This assessment should evaluate the toxic potential of the substances and determine an acceptable level of human exposure. According to EFSA, the following studies should be able to determine a no-effect level:

- Genotoxicity (Efsa 2011a): *in vitro* studies, which can be supplemented by *in vivo* studies in case of positive results:
    - Ames test (OECD 471)
    - Micronucleus test (OECD 487);
- Subchronic toxicity (Efsa 2009a): 90-day oral studies in a rodent (OECD 408) or non-rodent (OECD 409) species;
- If necessary, chronic toxicity studies and/or studies on toxicity for reproduction and fertility and/or carcinogenicity studies.

Based on the lowest observed no-effect level (generally in the subchronic toxicity study), an ADI is calculated.

The second step is the ADME study (when required) and the assessment of potential exposure to residues. This assessment is based on measured residues from studies or the data available in the literature:

- ADME studies: *in vivo* radiolabelled studies in target species and laboratory animals, or *in vitro* studies;
- Residue studies: radiolabelled study with total residue (TR) and MR characterisation in samples collected at the end of the administration period.

[41] https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2009.1249
[42] https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2012.2663

These studies should enable a conclusion to be drawn with regard to metabolism (rate and comparison between the various species) and the metabolites formed (MR/TR ratio). It is difficult to implement this approach for natural-origin products.

Consumer exposure is assessed based on the EFSA Comprehensive European food consumption database (data collected at individual level) and estimated residue levels in foods of animal origin.

The calculated ADI is then compared with consumer exposure to residues. If this consumption is lower than the ADI with a sufficient safety margin, the additive will be considered as safe to use by consumers. If the safety margin is insufficient or if consumption is higher than the ADI, there are two possible options. The first, which is the determination of MRLs and a withdrawal period, is never used for additives. The second option is to lower the maximum levels in the food.

4.5.3.5 Exemptions and possible simplifications for consumer safety

The basis for exemptions is the food compatibility of a plant or substance through the human diet or its consumption via additives already on the market or through the diet of animals.

Exemptions from providing studies apply if:

- the additive is authorised in human food and no ADI has been determined;
- or the additive is part of the human diet with no restrictions.

To use these exemptions, it is necessary to ensure that the metabolism of the substances in the target species is similar to that in laboratory animals and humans. To do so, literature data can be used, or an *in vitro* study can be provided comparing metabolism in cultures or liver cell fractions from rats or the target species.

- or the additive is not absorbed orally.

To use this exemption, non-significant absorption must be proven by providing literature data.

- or the substances naturally occur in food or feed at significant concentrations.

In the case of additives authorised in human food, for which an ADI has been determined or for which there is a risk of increased consumption of this substance through residues in foodstuffs of animal origin, residue studies are necessary. Based on the measured concentrations, consumer exposure is then estimated and compared with the ADI.

4.5.3.6 Tolerance for the target species

The no-effect level for the animal can be determined based on:

- toxicity studies conducted for the animal, or based on literature data. A maximum intake for the target animal can be extrapolated by applying a safety factor to the no-effect levels from the selected studies. Maximum concentrations in feed can then be determined by comparing this intake with the weight of the animal and its feed consumption;

- or tolerance studies with multiple doses generally over a period of 42 days depending on the species. The monitored parameters depend on the dose;
- or the component-based approach.

Based on this review of the available data on feed additives, the following resources are of interest:

- **European Union Register of Feed Additives**
- **Opinions of EFSA's FEEDAP**

4.6 Other regulations and guidelines

Flavouring substances

The risks associated with flavouring substances are assessed by EFSA's Panel on Food Additives and Flavourings (FAF). All of the substances already on the market have been assessed by chemical group. The list of authorised flavouring substances was established in 2012 by the European Commission based on these EFSA assessments. The list of flavouring substances authorised in food is available in Implementing Regulation (EU) No 872/2012.

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)

REACH Regulation (EC) No 1907/2006 requires that manufacturers and importers in Europe register chemical substances (above a certain tonnage threshold) with the European Chemicals Agency (ECHA). The REACH Regulation is supplemented by Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances (CLP Regulation).

On the ECHA website[43], the status of each substance is available (pre-registered, registered or exempt from registration), as is its classification according to the CLP Regulation. For registered substances, registration data are available, including toxicological data and assessment reports.

Monographs of the World Health Organization (WHO)

From 1999 to 2009, the WHO published monographs on the most commonly used medicinal plants. These monographs are intended to provide scientific information on safety, efficacy and quality control. They are not pharmacopoeial monographs but constitute complete scientific references for medicines regulatory agencies and for healthcare professionals.

European Scientific Cooperative on Phytotherapy (ESCOP)

ESCOP, an organisation representing national phytotherapy societies, has published monographs on plants. It has a Scientific Committee made up of European experts that conducts reviews of the available scientific data on the safety and pharmacology of plants.

EFSA reports on novel foods and food allergens

[43] https://www.echa.europa.eu/web/guest/home

Novel foods are foods that were not consumed to a significant degree in Europe before May 1997; they are defined in Regulation (EU) 2015/2283. EFSA is responsible for assessing the safety of novel foods as requested by the European Commission. A catalogue can be consulted on the website of the European Commission to find out the status of different foods[44]. Assessments of these novel foods are available on the EFSA website.

The EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) deals with questions related to human nutrition, novel foods, nutrient sources, foods for special groups such as infant formulae, health claims on food products, dietary reference values, and food allergies. This panel's scientific opinions are available on the EFSA website.

- **Data of the Joint FAO/WHO Expert Committee on Food Additives (JECFA)**

JECFA is an international scientific expert committee administered jointly by the Food and Agriculture Organization of the United Nations (FAO) and the WHO. Initially created to evaluate the safety of food additives, JECFA also evaluates contaminants, natural toxins and residues of veterinary medicinal products in animal products. JECFA's scientific opinions are available on its website.

[44] https://ec.europa.eu/food/safety/novel_food/catalogue/search/public/index.cfm#

To summarise, here is the list of all of the resources of interest used to document the preliminary assessment that was undertaken for plants and/or preparations used in phytotherapy and aromatherapy for food-producing animals:

- **Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding MRLs in foodstuffs of animal origin**
- **List A of traditionally used medicinal plants, French Pharmacopoeia**
- **List B of medicinal plants traditionally used in unprocessed or prepared form whose potential adverse effects outweigh the expected therapeutic benefit, French Pharmacopoeia**
- **EMA HMPC opinions**
- **French Pharmacopoeia**
- **European Pharmacopoeia**
- **MAs in France**
- **Pharmacovigilance data**
- **Ministerial Order of 24 June 2014 establishing the list of plants other than fungi authorised in food supplements, as well as the conditions for their use**
- **Lists of plants including essential oils that are considered as traditional, DGCCRF 2019**
- **ANSES reports and opinions**
- **Nutrivigilance data**
- **List of the products of plant (or animal) origin included in the normal human diet: Annex I of Regulation (EC) No 396/2005**
- **EFSA assessments of active substances**
- **European Union Register of Feed Additives**
- **EFSA FEEDAP opinions**
- **Regulation (EU) No 872/2012 on the list of flavouring substances authorised in food**
- **ECHA website**
- **WHO monographs on medicinal plants**
- **ESCOP monographs**
- **EFSA novel food catalogue**
- **EFSA NDA opinions**
- **JECFA opinions.**

5 Proposed consumer risk assessment methodology for herbal veterinary medicinal products

This objective of this report is to propose an approach tailored to the specific characteristics of plants, herbal preparations and/or EOs and their traditional uses, which is different from the current MRL approach.

The proposed approach uses the notions enabling the “no MRL is required” conclusion to be drawn for substances with the MRL approach (see Regulation (EU) 2018/782). This approach was developed following the work on the plants and preparations identified in the preliminary consumer risk assessment (see Section 6).

The aim is to classify each plant, herbal preparation and/or EO into one of the following three categories:

- Preparation that can be used in veterinary medicine without any risk to consumers;
- Preparation potentially of concern for consumers based on the available data, which means it cannot be used at the present time;
- Preparation that cannot be used in veterinary medicine due to a risk to consumers.

To that end, a decision tree is proposed. It was developed and should be used based on the methodology explained below.

5.1 Methodology

The approach is an overall approach, i.e. it takes into account all of the available data on plants, herbal preparations and/or EOs as used in animals. Therefore, it is necessary to know, at the very least, what is used (plant part, preparation) and how it is administered (mode/route of administration, dosage). That is why this methodology only applies to traditionally used plants, herbal preparations and/or EOs for which this information is known.

The term “herbal preparation”, usually used for plants processed using methods such as extraction, distillation, expression, fractioning, purification, concentration or fermentation, will be used in the text and the decision tree for easier reading, instead of “plants, herbal preparations and/or EOs”.

In light of the specific nature of their components, EOs have to undergo assessments separate from those of the plants used to obtain them.

5.1.1 Data search

The data used come from various national (ANSM, including the French Pharmacopoeia, ANSES, etc.), European (EMA, EFSA, REACH, Pharmacopoeia, etc.) and international (JECFA, JMPR[45], WHO, etc.) organisations. To supplement and/or update these data, it may be necessary to carry out a literature search. The various regulations, organisations and sources recommended, as well as the search data, are listed below.

- Regulations:
  - Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin (Annex I);
  - Commission Regulation (EU) 2018/62 of 17 January 2018 replacing Annex I to Regulation (EC) No 396/2005 of the European Parliament and of the Council (Annex I);
  - Commission Implementing Regulation (EU) No 872/2012 of 1 October 2012 adopting the list of flavouring substances provided for by Regulation (EC) No 2232/96 of the European Parliament and of the Council, introducing it in Annex I to Regulation (EC) No 1334/2008 of the European Parliament and of the Council and repealing Commission Regulation (EC) No 1565/2000 and Commission Decision 1999/217/EC;
  - List of the products of plant (or animal) origin included in the normal human diet: Annex I of Regulation (EC) No 396/2005;
  - Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition (Annex I);
  - Ministerial Order of 24 June 2014 establishing the list of plants other than fungi authorised in food supplements, as well as the conditions for their use.

- Agency opinions:
  - Opinions of EMA's HMPC
  - Opinions of EFSA's FEEDAP
  - Opinions of EFSA's NDA
  - ANSES reports and opinions
  - JECFA opinions
  - EFSA assessments of pesticide active substances
  - Opinions of the European Commission's Scientific Committee on Food (SCF)

- Other resources:
  - List A of traditionally used medicinal plants, French Pharmacopoeia
  - List B of medicinal plants traditionally used in unprocessed or prepared form whose potential adverse effects outweigh the expected therapeutic benefit, French Pharmacopoeia
  - Monographs of the European and French Pharmacopoeias
  - MAs in France

[45] Joint FAO-WHO Meeting on Pesticide Residues

- Standards of the International Organization for Standardization (ISO)
- WHO monographs on medicinal plants
- List of plants whose essential oils are considered as traditional, DGCCRF 2019
- Data by substance on the ECHA website
- Joint FAO/WHO Meeting on Pesticide Residues (JMPR)
- EFSA
- European Union Register of Feed Additives
- ESCOP monographs
- Novel food catalogue of the European Commission
- Pharmacovigilance and nutrivigilance data

- Books and thesis:
  - "Essential Oil Safety. A Guide for Health Care Professionals" book by R. Tisserand and R. Young
  - "Pharmacognosy. Phytochemistry. Medicinal Plants" book by J. Bruneton
  - "*Aromathérapie vétérinaire : établissement du profil toxicologique en vue d'une évaluation du danger pour le consommateur de denrées alimentaires d'origine animale*" thesis by Céline Guilbaut (ENVN)

The following data should be systematically sought since they are necessary for the assessment:

- The composition of the plant, herbal preparation or EO with a determined CT
- Use in animals and/or humans
- ADI or other TRVs related to the issue of residues in foodstuffs
- Toxicological data
- Nutrivigilance data
- ADME data in laboratory animals, food-producing animals or humans
- Consumer exposure data
- Other official lists may be consulted on a case-by-case basis.

5.1.2 General data, uses and composition

To start, it is important to define the herbal preparation that will be assessed. All the data and conclusions will focus on this herbal preparation and therefore may not be systematically extrapolated to another preparation obtained from the same plant.

It is necessary to ensure that the herbal preparation considered is indeed a traditional-use preparation (see 2.1), as defined by Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use (Article 16c 1(c)).

A number of European regulations should be consulted. If the herbal preparation is listed in Table 1 of Regulation (EU) No 37/2010, its use is authorised in food-producing animals

according to the provisions of this text. The information given in the “Other Provisions (according to Article 14(7) of Regulation (EC) No 470/2009)” column should be examined. This information must limit use of the preparation in veterinary medicine (route of administration, homeopathic use restrictions, etc.). If these provisions are restrictive, further assessment is necessary. For example, when Table 1 of Regulation (EU) No 37/2010 states “For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding to the mother tincture and dilutions thereof only”, the herbal preparation cannot be used in veterinary medicine as part of phytotherapy.

It can be noted that inclusion in Table 2 of Regulation (EU) No 37/2010, which strictly prohibits any use of a substance in food-producing animals, according to Regulation (EC) No 470/2009, currently only concerns, when it comes to plants, the genus *Aristolochia* and all preparations thereof.

Secondly, it is necessary to check whether the herbal preparation is one of the “essential nutrients or normal constituents of the diet in man and animals” with no known restrictions (see Regulation (EU) 2018/782). For that purpose, an exhaustive list of the plants included in the normal human diet is available (Annex I of Regulation (EC) No 396/2005). This list is used for the assessment of plant protection products. There is no official list that can be referred to in order to find out whether a herbal preparation is part of the normal diet of animals. The presence of a plant during grazing, or obvious dietary uses of preparations for animals not grazing, and the list of feed additives, are sources of information that can be used. If a herbal preparation is authorised in food or feed without restrictions, its veterinary use appears possible. EOs are not directly considered as being part of the normal human diet.

Similarly, authorisation of a herbal preparation as an additive for use in animal nutrition (Regulation (EC) No 1831/2003) or as a flavouring agent (Regulation (EU) No 872/2012) in food or feed without restriction enables it to be used in veterinary medicine, provided that there is no genotoxic concern for flavouring agents in particular, as food and feed additives have no genotoxic potential. If the risk is confirmed by *in vivo* genotoxicity data, the preparation is of concern for consumers and cannot be used in veterinary medicine. If any doubt remains as to the genotoxic potential, the preparation should be considered as potentially of concern for consumers and in this case, no conclusion can be drawn. A case-by-case assessment is necessary with the possibility of generating additional data in order to deal with the issue of the possible use of the MRL approach.

All restrictions and provisions shall have the meanings assigned to them in the regulations, according to recommendations of use by route of administration, sub-population, ADI, content in food/feed, etc. It is necessary to ensure that they are compatible with the use of the herbal preparation in veterinary medicine. Otherwise, the assessment should continue.

The assessment can continue when the herbal preparation has a traditional use. Otherwise, the preparation should be considered as potentially of concern for consumers and no conclusion can be drawn. A case-by-case assessment is necessary with the possibility of generating additional data in order to deal with the issue of the possible use of the MRL approach.

Use in human food supplements is not taken into account in the first steps of the assessment, as these are only authorised following a limited assessment of consumer risk. Similarly, authorisation in human medicine is not taken into account in the first steps of the assessment, since this authorisation is based on a positive benefit/risk ratio. Moreover, drug exposure tends to be occasional and does not fit with the consumer risk approach, which is based on “lifelong” exposure.

5.1.3 ADIs, TRVs and consumer exposure

There are very few relevant TRVs for plants, herbal preparations and EOs as a whole. That is why it may be necessary at this point to be aware of substances of concern that are contained in herbal preparations and thus define substances that should be monitored as markers. These components should be identified and quantified. This approach is used for plant protection products (OCDE 2017).

Substances of concern are substances that are of major toxicological concern, that are potentially genotoxic (e.g. methyl eugenol) or that have a structural alert known to have genotoxic properties. This notion of substances of concern is based on current knowledge. The notion of structure-activity relationship can be used for substances for which few toxicological data are available.

To identify these components, the pharmacopoeial standards are used as a priority, followed by AFNOR standards, when available. Otherwise, the compositions described in the literature (for example, in books such as “Essential Oil Safety” by Tisserand and Young and “Pharmacognosy – Phytochemistry, Medicinal Plants (5th edition)” by Jean Bruneton) are considered.

Dosages of human medicinal products can serve as TRVs as a last resort. Vigilance data (pharmacovigilance, nutrivigilance, etc.) should also be taken into account when available.

Exposure should be estimated according to a worst-case scenario. The ingested quantity of substances can be estimated in relation to the dosage of the preparation in animals. Bioavailability in animals is assumed to be 100%. Taking the standard food basket of 500 g meat, 1.5 L milk and 100 g eggs for a 60 kg bw human (Regulation (EU) 2018/782), it is then possible to estimate a theoretical maximum level of consumer exposure and compare it with the ADI (e.g. methyl eugenol for tea tree EO).

If consumer exposure is below the TRV, the preparation can be used in traditional conditions. Otherwise, the preparation should be considered as potentially of concern for consumers and no conclusion can be drawn. A case-by-case assessment is necessary with the possibility of generating additional data in order to solve the issue or the possibility of using the MRL approach.

If components are identified as posing a risk (genotoxic, for example), it will not be possible to use the herbal preparation in a veterinary medicinal product without a more comprehensive assessment or even an MRL approach.

5.1.4 Approach by substance

If TRVs are not available for the herbal preparation and/or for any of the substances of concern contained in the plant, a substance-by-substance approach should be used.

5.1.4.1 ADME and residue data

ADME data for the target animals, or for laboratory animals, are needed. If data are available for humans, they should be used as well.

Absorption data should be taken into account initially:

- For the target animals, if absorption according to the route of administration of the herbal preparation is negligible, consumer exposure will also be negligible. In this case, the herbal preparation may be used in animals by this route of administration. Use of the herbal preparation will have to be limited to this sole route of administration.
- If oral absorption of the substance is negligible in consumers and is not known as having local effects on the digestive tract, the herbal preparation may be used in a veterinary medicinal product for food-producing animals.

The metabolic profile of the substance and its elimination should be taken into account.

As with an assessment using the MRL approach, *in vitro* to *in vivo* extrapolation (laboratory animals/food-producing animals) is possible, with the application of uncertainty factors (see Regulation (EU) 2018/782). In addition, PK approaches such as physiologically based pharmacokinetic modelling (PBPK) can be used when these are available and have been validated for food-producing animals.

Extensive and rapid metabolism into metabolites with no identified risks to humans or animals also enables a herbal preparation to be used. Data on metabolism in hepatocytes or microsomes can also be used.

Unfortunately, few ADME data are available for herbal preparations. Predictive models for pesticide metabolism are currently being developed by the OECD. These tools should be able to predict the fate of substances and provide information about their toxicokinetics. They could be used for veterinary medicinal products if the database was supplemented for this use. EMA has published opinions on the transformation products of certain EO components. Tools for predicting toxicity have also been developed at European level and include Toxtree[46] and QSAR Toolbox[47].

[46] https://ec.europa.eu/jrc/en/eurl/ecvam
[47] https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm

5.1.4.2 Toxicological data

At this point of the approach, it is necessary to determine the toxicological profile of the substance or of its metabolites that are potentially of concern.

If metabolites are identified as being of concern (of genotoxic concern, for example), it will not be possible to use the herbal preparation in veterinary medicine without a more comprehensive assessment or even an MRL approach.

If the available toxicological data are not sufficient for one of the substances of concern, use of the preparation cannot be authorised, due to uncertainty surrounding the existence of risk.

5.1.4.3 Determining an ADI

If there are sufficient toxicological data for the studied substance or the metabolite that poses a risk, a TRV should be defined by a competent authority; this should be the ADI as a priority or, failing that, another relevant TRV. Such information is seldom available for components or metabolites in plants, parts of plants or EOs.

If there are no toxicological data, the TTC approach can be used for each substance of concern. EFSA uses this method for plants. This approach may only be used on a case-by-case basis for minority substances in the preparation (e.g. low-exposure metabolites).

5.1.4.4 Exposure limits in cases of traditional use in humans

If an ADI cannot be defined, all the available data concerning observed effects in humans should be taken into account (use in human medicine, nutrivigilance, epidemiology, etc.). Exposure benchmarks can be used, for example dosages in human medicine.

If there are no exposure limits in cases of traditional use in humans, studies will need to be undertaken. The MRL approach is required.

5.1.4.5 Consumer exposure

If an ADI is available, the last step involves checking that consumer exposure does not exceed it, or ensuring that there is no toxicological concern.

If residue data are available, i.e. concentrations of substances or metabolites potentially of concern in food (muscle, liver, kidneys, fat, milk, eggs) derived from animals having received the herbal preparation or substance, then these can be used to assess consumer exposure.

If consumer exposure is above the ADI, the preparation or substance cannot be used in veterinary medicinal products for food-producing animals. The MRL approach should be implemented to refine the consumer risk.

If consumer exposure is below the ADI, the herbal preparation containing this substance can be used in traditional conditions. The analysis will need to be repeated for the other substances of concern in the herbal preparation.

Veterinary use of the herbal preparation will be authorised in food-producing animals when this analysis is favourable for all of the substances identified as being of concern.

5.2 Decision tree

The approach presented in the previous section has been organised in the form of a two-step decision tree.

The first step in the tree applies to plants and herbal preparations. This step can lead to a preparation being considered as potentially of concern for consumers. In this case, additional data will be needed to conclude as to the consumer risk, or else the MRL approach should be used.

If it cannot be concluded in the first step that there is no risk or concern for consumers, a substance-by-substance assessment should be carried out (step 2).

When there is doubt regarding a response, the assessment should follow the decision tree to the most unfavourable situation, in order to protect consumers.

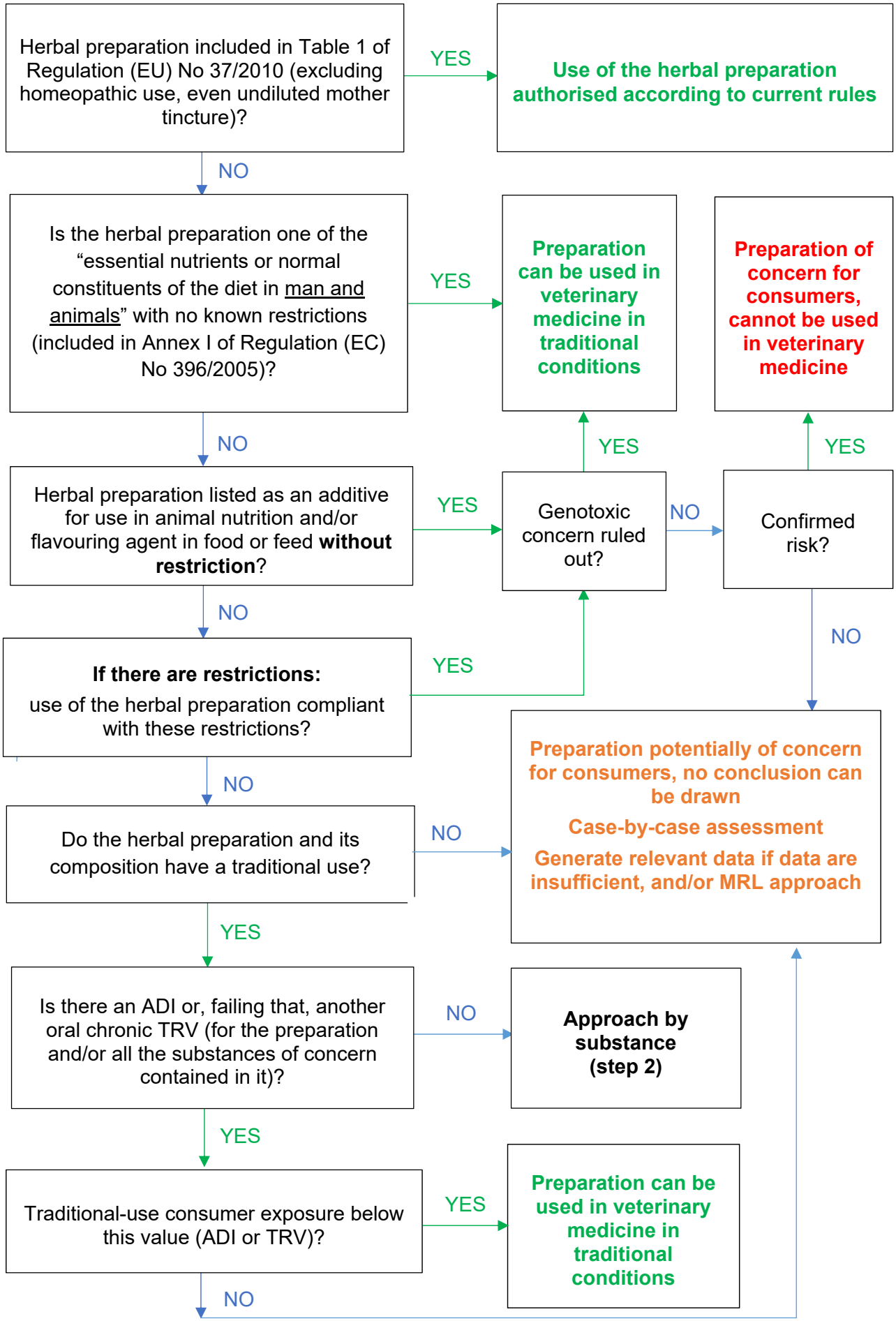


Figure 1: Decision tree for step 1: overall approach (herbal preparations)

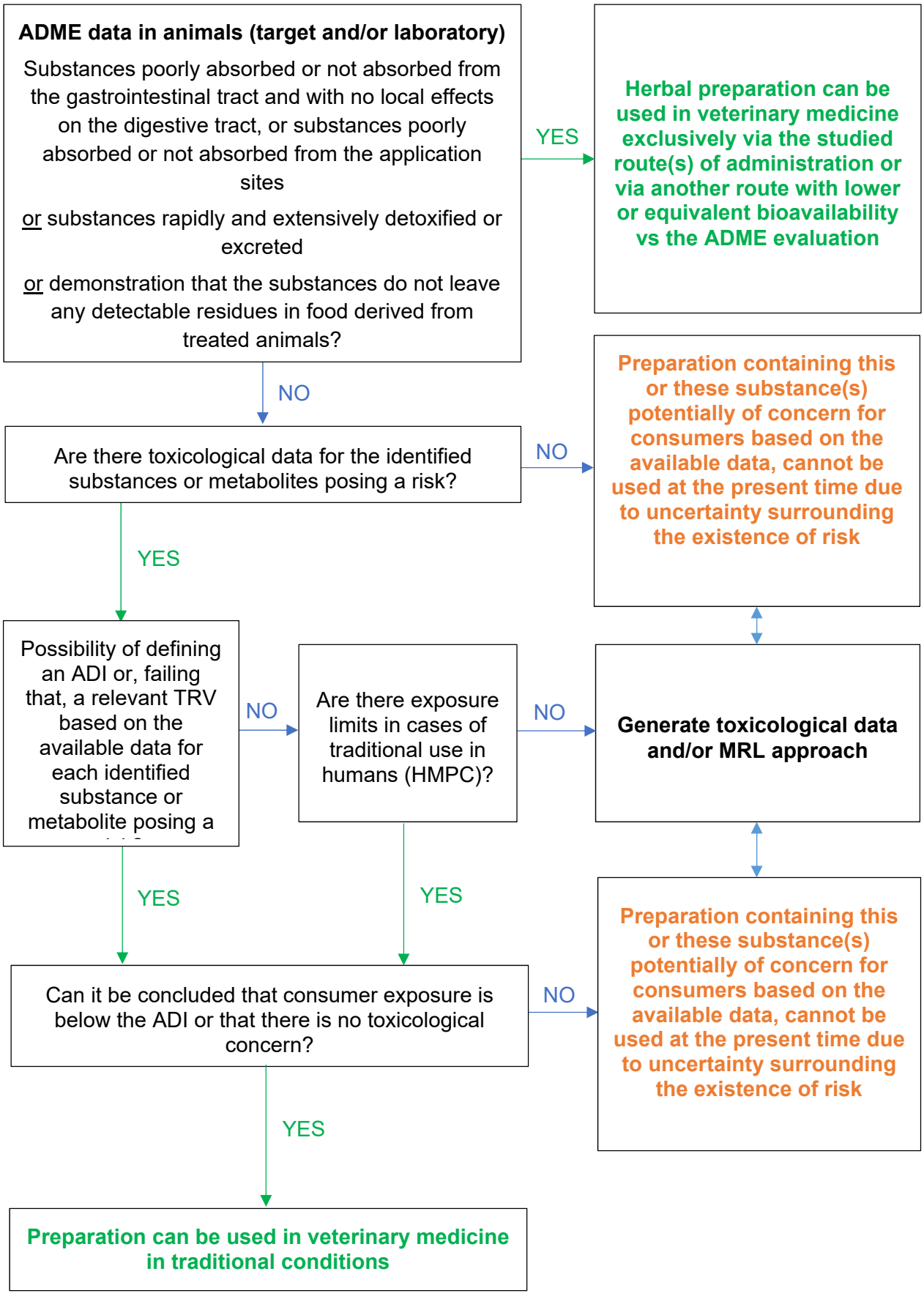


Figure 2: Decision tree for step 2: approach by chemically defined substance when the overall approach is not possible

6 Preliminary consumer risk assessment for the identified plants and herbal preparations

For each of the plants, substances and EOs selected following the inventory of uses in animal husbandry, a preliminary assessment of risks to consumers of foods was conducted. This preliminary work led to the establishment of the decision tree proposed in Section 5.

The following data were extracted from the various sources mentioned above:

- General data;
- Status in the regulations and guidelines;
- Opinions of European agencies;
- Composition;
- Presence in the normal diet of animals and humans;
- Human exposure;
- Toxicological data;
- PK and residue data;
- Reported adverse effects.

Concerning health vigilance data, nutrivigilance data were extracted but the ANSM's pharmacovigilance data could not be recovered. A search was also performed in the databases of the US FDA and Health Canada.

6.1 Summary of the assessments

The conclusions are summarised in the following table:

Table 6: Summary of the assessments for the substances analysed

	No concern for consumers	Additional data needed to draw a conclusion
Plants	Garlic Milk thistle Echinacea Dandelion Bramble	Common mugwort Artichoke Tansy
EOs	True lavender and lavandin EOs Ravintsara EO Tea tree EO	Palmarosa EO
Substances	Carvacrol Cinnamaldehyde Citral Geraniol Linalool Limonene Pinene	Thujone

All the assessments enabled the identified plants, EOs and substances of interest to be classified into one of three categories. None of the assessments concluded there was any concern for consumers of foods. Conversely, 16 of the 21 assessments determined there was no concern. The five remaining assessments could not rule out or confirm any concern for consumers. Additional data are therefore needed to draw conclusions for common mugwort, artichoke, tansy, palmarosa EO and thujone.

Several elements were decisive when drawing conclusions for each plant, EO and substance:

- Presence in the normal diet of humans and/or animals;
- Existence of regulatory data or limits;
- Toxicological data, especially data on genotoxicity, mutagenicity and reprotoxicity;
- PK and residue data.

The intermediate “additional data” category includes assessments for which several or all of these were not available.

Each assessment is summarised below, with a conclusion regarding concerns associated with the consumption of foodstuffs.

6.2 Plants

6.2.1 Garlic

6.2.1.1 General data

Table 7: General data on garlic

Common name	Garlic
Latin name	*Allium sativum* L., Liliaceae
Parts of the plant concerned	Bulbs

6.2.1.2 Status in the regulations and guidelines

Table 8: Status of garlic in the regulations and guidelines

MRLs	**Regulation (EU) No 37/2010**	Not listed
Medicinal products for human use	**List of medicinal plants**	List A
	Pharmacopoeias	“Garlic powder” and “garlic bulb for homeopathic preparations” monographs (Ph. Eur.)
	WHO	Monograph (fresh or dried bulb) (WHO 1999)
	MAs in France	Traditional-use

Food supplements	**Ministerial Order of 24 June 2014** **DGCCRF 2019**	Listed without restrictions
Novel foods	**EFSA catalogue**	Not listed
Feed additives	**Regulation (EC) No 1831/2003**	Category 2b, in the form of garlic oleoresin (CAS 8000-78-0), oil (CAS 8000-78-0), garlic extract, and garlic tincture
Flavouring substances	**Regulation (EU) No 872/2012**	Not listed

6.2.1.3 Opinions of European agencies

Table 9: Opinions of European agencies on garlic

EMA HMPC	Assessment report Herbal monograph (EMA 2017a, 2017c)
EFSA – Assessments of pesticide active substances	A monograph on “garlic extract” (Efsa 2020a)

Only data concerning garlic bulb and garlic bulb powder are given below.

6.2.1.4 Composition

The composition of garlic is described in various official sources (pharmacopoeias, WHO, EMA HMPC). It is complex and can vary depending on the method used to process the herbal drug.

In addition to carbohydrates, garlic contains enzymes (alliinase, peroxidase, myronidase), saponins, and volatile sulphur compounds (0.1 to 0.36%). The main component of fresh garlic is alliin (S-allyl-L-(+)-cysteine sulfoxide). Following tissue disruption, this compound is degraded by alliinase to produce 2-propenesulfenic acid, converted into allicin (diallyl disulfide; 0.3% m/m fresh weight). It is considered that 1 mg alliin is equivalent to 0.45 mg allicin (ESCOP 2019; Barnes, Anderson et Phillipson 2002; Paris et Moyse 1981). According to the European Pharmacopoeia, garlic powder must contain at least 0.45% allicin. Degradation and condensation products are then spontaneously formed: other thiosulfinates (including *E*-ajoene, *Z*-ajoene), sulfides, and vinyldithiins (2-vinyl-(4H)-1,3-dithiin, 3-vinyl-(4H)-1,2-dithiin). According to EFSA, four markers have been identified: diallyl sulfide, disulfide, trisulfide and tetrasulfide.

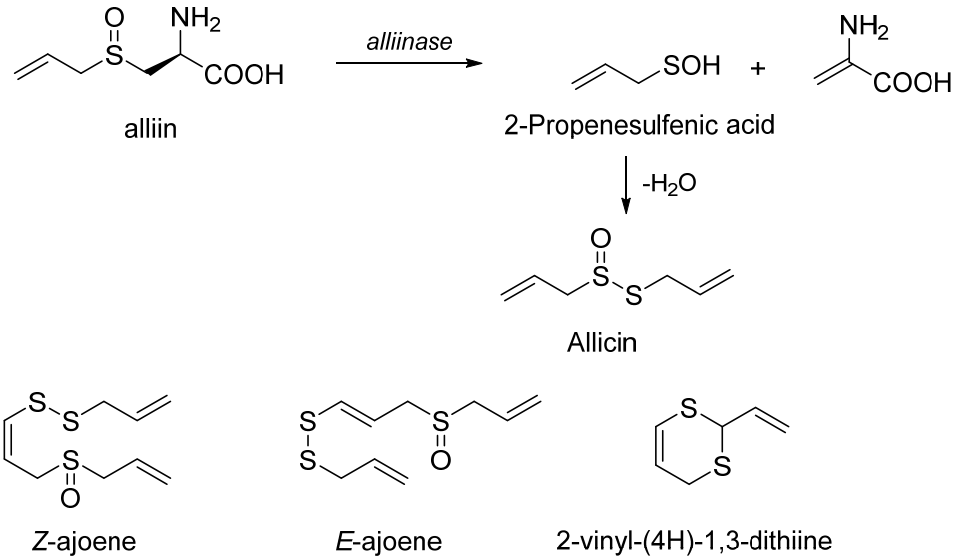


Figure 3: Components of garlic

6.2.1.5 Presence in the normal human diet

Garlic is present in the normal human diet.

6.2.1.6 Presence in the normal diet of animals

In light of its use in human nutrition, this point is not documented.

6.2.1.7 Human exposure

In humans (WHO and EMA HMPC), maximum daily doses are defined:

- 5 g raw garlic/day according to the WHO.
- 1.2 or 1.38 g garlic powder/day according to the WHO and EMA HMPC respectively.

According to the EMA monograph[48] (2017a, 2017c), due to a lack of data, pharmaceutical garlic preparations are not recommended for individuals under the age of 18 or 12 years (depending on the type of indication), or during pregnancy and lactation.

Given that garlic is part of the human diet, EFSA did not consider it necessary to characterise its toxicity or define an ADI.

As a precautionary measure, due to the risk of bleeding, garlic consumption should be avoided seven days before surgery (EMA 2017a, 2017c).

Consumption data in humans

In Europe, chronic exposure to garlic ranges from 0.002 to 0.065 g/kg bw/day, which corresponds to daily consumption of 0.013 to 3.9 g depending on the region (Efsa 2020a).

The 36 diets listed in EFSA's PRIMo 3.1 model calculated exposure to garlic extracts expressed as garlic as between 0.03 and 0.46 g/kg bw/day. The highest chronic consumption

[48] EMA monograph: powder, oil extract (DER 2-3:1), hydro-alcoholic extract (34% ethanol) (EMA 2017a)

of garlic was 0.0833 g/kg bw/day, equal to 4.9 g/day. The 97.5th percentile was 0.64 g/kg bw/day, corresponding to an intake of 42.7 g/day (this was for the UK vegetarian diet).

6.2.1.8 Animal exposure

This information is not necessary, because humans are directly exposed to garlic (bulbs) via their diet.

6.2.1.9 Toxicological data

Table 10: Toxicological data on garlic

	Observations	Conclusions	References
Toxicity after a single administration			
Little information is available. Garlic is considered as having low toxicity and is Generally Recognised as Safe (GRAS) by the FDA.			
Toxicity after repeated administration			
Garlic powder	Rats, *PO*	LOEL[49] = 300 mg/kg bw/day. Equivalent human dose = 50 mg garlic powder/kg bw/day, i.e. 2.5 g/day for a 50 kg adult. An impact on human fertility could not be ruled out.	Dixit et Joshi (1982)
Garlic	Healthy volunteers, *PO*, 10 g garlic/day, two months	No adverse effects	(ESCOP 2019)
Genotoxicity/Mutagenicity			
No regulatory studies Preparations containing garlic or its components cause chromosome aberrations *in vitro* and *in vivo* Negative Ames tests: non-mutagenic			(EMA 2017a, 2017c)
Carcinogenicity: no studies			
Reprotoxicity and developmental toxicity			
No regulatory studies Effect on spermatogenesis (rats) at doses at least twice as high as the maximum daily dose in humans			(EMA 2017a, 2017c)
Other			
Allergic reactions Risk of postoperative bleeding Interactions with warfarin			(WHO 1999; EMA 2017a, 2017c)

[49] Lowest observed effect level

6.2.1.10 PK and residue data

- In light of its dietary use in humans, EFSA did not deem it necessary to have kinetic data for humans or animals.
- Excretion into breast milk has been observed.
- There are no PK data for garlic but PK data are available for allicin and S-allylcysteine (EMA 2017a, 2017c).
- A PK interaction with propranolol was observed in rats (its absorption was increased and its clearance reduced).
- In rats, alliin is absorbed and eliminated more rapidly than the other two components, allicin and vinyldithiins. After oral administration of a dose of 8 mg/kg bw, T_{max} values were 10, 30-60 and 120 mins respectively for alliin, allicin and vinyldithiins. Excretion is primarily renal (ESCOP).

6.2.1.11 Reported adverse effects

- **Cases from nutrivigilance**

Four cases have been reported. They involved food supplements containing garlic: dermatological (severity 1), rheumatological and hepatic (severity 3) and gastrointestinal (severity 1) effects.

- **Cases recorded in Canada and the United States**

There has been one reported case in Canada and two serious cases in the United States: neurological and/or gastrointestinal effects.

The products involved were not monovalent.

6.2.1.12 Summary of the assessment

For use of liquid garlic extract as a pesticide (EFSA), garlic is classified in Annex IV, i.e. as a substance that does not need an MRL. The main argument is that human exposure to garlic via the ingestion of plants treated with these garlic extracts would be much lower than with dietary use. The same reasoning could be used for garlic (bulb or bulb powder) as a veterinary medicinal product.

Considering that garlic (bulb and bulb powder):

- **is not listed in Table 1 of Regulation (EU) No 37/2010;**
- **is widely present in the normal human diet;**
- **has a chronic exposure level of 0.002 to 0.065 g/kg bw/day in humans in Europe;**
- **has very low toxicity and is not mutagenic;**

the WG concludes, based on the available data, that this plant is not of concern for consumers of foods derived from animals that have received it in the context of veterinary medicine.

6.2.2 Common mugwort

6.2.2.1 General data

Table 11: General data on common mugwort

Common name	Common mugwort
Latin name	*Artemisia vulgaris* L., Asteraceae
Synonyms	58 synonyms on the website of The Plant List: all varieties or forms of *A. vulgaris*
Parts of the plant concerned	Aerial parts, leaves, flowering tops

6.2.2.2 Status in the regulations and guidelines

Table 12: Status of common mugwort in the regulations and guidelines

MRLs	**Regulation (EU) No 37/2010**	Not listed (the species *A. abrotanum* was covered by an EMA/CVMP opinion (EMEA 1999a), for its homeopathic mother tincture (no MRL dossier for this tincture and its dilutions; uses: oral route, parenteral route)). The opinion mentions that the substances of concern in *A. abrotanum* are components of the EO (primarily eucalyptol; thujone) and refers to *A. absinthium*.
Medicinal products for human use	**List of medicinal plants**	List A, non-monopoly NB: EO subject to the pharmaceutical monopoly
	Pharmacopoeias	No monograph in the European or French Pharmacopoeia
	WHO	No herbal monograph
	MAs in France	Phytotherapy: no medicinal products; listed in *Cahier de l'agence n°3* (herbal medicinal products, 1986): the two herbal drugs have traditionally been used as aperitifs and for painful menstruation.
Food supplements	**Ministerial Order of 24 June 2014; DGCCRF 2019**	Listed Parts used: leaves, flowers, stems Substances to be monitored: thujone, eucalyptol, camphor The EO is prohibited in food supplements in France
Novel foods	**EFSA catalogue**	Not listed
Feed additives	**Regulation (EU) No 1831/2003**	Tincture authorised as a flavouring substance (all animal species)

		NB: EO in Annex II (2020 register) [*Artemisia vulgaris* L.: Mugwort oil CAS 8008-93-3 CoE 72 EINECS 284-503-2]
Flavouring substances	**Regulation (EU) No 872/2012**	Not listed

6.2.2.3 Opinions of European agencies

Table 13: Opinions of European agencies on common mugwort

EFSA FEEDAP	Opinion on the use of the tincture as a sensory additive, all animal species

6.2.2.4 Composition

Common mugwort contains volatile monoterpenes and produces a small amount of EO (1-2 ml/kg), with a highly variable composition. The standard compounds found include camphor, borneol, vulgarol, terpene carbons (constant) and thujone (inconstant, often absent) (Bruneton 2016). A recent review (Ekiert *et al.* 2020) reported low levels of thujone (α- and β-: 0 to 4.5%; low to moderate levels for *cis*-thujone: 0-**12.9%**) and the presence of the following majority compounds: **eucalyptol** (1,8-cineole) (2.6-17.6%), chrysanthenyl acetate (0-23.6%), **camphor** (0-**47.7**%), β-caryophyllene (0-38%), and germacrene D (5-15%). Its variability, related to geographic origin in particular, is described in several reviews. Different CTs have been reported for the same producing country (Judzentiene et Budiene 2018; Abiri *et al.* 2018).

The plant also contains flavonoids (quercetin, kaempferol glycosides and analogues; other standard flavonoids; vitexin has been described (4 mg/kg)), polyynes, sesquiterpene lactones (vulgarin, psilostachin, yomogin) at varying levels (Bruneton 2016), coumarins (aesculin, umbelliferone, scopoletin), phenolic acids (derived from caffeoylquinic acid), carotenoids, and cyanogenic glycosides (prunasin, level not reported).

Some authors have reported the presence of artemisinin (0-2.3% m/m). Atypical tricyclic sesquiterpenes have also been described (there are no published quantitative data).

6.2.2.5 Presence in the normal human diet

Common mugwort is not included in the normal human diet, except when used anecdotally as a flavouring agent. The plant is on the list of recognised herbal flavouring substances in Europe[50] ("Council of Europe 1981 Blue Book"). The food compatibility of the plant is therefore recognised in this framework[51].

There are restrictions relating to thujone in food in Europe[52]:

Table 14: Restrictions relating to thujone in food in Europe (in mg/kg)

Thujone (α and β)	Alcoholic beverages, except those produced from *Artemisia* species	10 mg/kg

[50] Eight *Artemisia* species are listed: *A. absinthium* L., *A. abrotanum* L., *A. caerulescens* L., *A. vulgaris* L., *A. campestris* L., *A. glacialis* L., *A. maritima* L., *A. umbelliformis* Lam., *A. pontica* L.
[51] See DGCCRF document: https://www.economie.gouv.fr/files/directions_services/dgccrf/manifestations/colloques/aromes_alimentaires/04_mainguet.pdf
[52] Regulation (EC) No 1334/2008

	Alcoholic beverages produced from *Artemisia* species	35 mg/kg
	Non-alcoholic beverages produced from *Artemisia* species	0.5 mg/kg

6.2.2.6 Presence in the normal diet of animals

Common mugwort may be present in the diet of animals, since the plant is abundant in the wild.

6.2.2.7 Human exposure

JECFA has not published any data on *A. vulgaris*. However, JEFCA published reports on thujone[53] (no ADI due to a lack of data), camphor[54] and 1,8-cineole[55] (no safety concern at current levels of intake when used as a flavouring agent).

The National Toxicology Program (NTP) proposed an ADI of 0.11 mg/kg bw/day (i.e. around 6.5 mg/day for a 60 kg adult), based on the risk of seizure in rats, with chronic exposure (Lachenmeier et Uebelacker 2010). EMA considered a maximum thujone intake of 6 mg/day for a maximum duration of use of two weeks for phytotherapy medicinal products containing common sage, in adults (EMA 2016).

6.2.2.8 Animal exposure

EFSA's FEEDAP issued an opinion (two texts) (Efsa 2019a, 2020c) on a tincture derived from *A. vulgaris* when used as a sensory additive in feed for all animal species, at the dose of 2 to 400 mg/kg feed. Chemical characterisation showed that it contained 0.1% total polyphenols, less than 0.005% thujone, and 0.001% eucalyptol.

6.2.2.9 Toxicological data

There is a lack of toxicological data for the plant. The assessment of a tincture by EFSA's FEEDAP was based on the compounds it contained, not the preparation or other extracts: references were made to exposure to phenolic acid derivatives[56] and EO components[57] in the EFSA FEEDAP opinions (Efsa 2019a, 2020c).

[53] http://www.inchem.org/documents/jecfa/jecmono/v16je25.htm
[54] http://www.inchem.org/documents/jecfa/jeceval/jec_344.htm
[55] http://www.inchem.org/documents/jecfa/jeceval/jec_840.htm
[56] "none of the individual compounds would exceed the threshold value for Cramer Class I (ranging from 0.3 mg/kg feed for poultry to 1.5 mg/kg feed for salmonids and dogs) no concern for the target species arises from the phenolic fraction".
[57] "At the maximum proposed use level, the concentration of 1,8-cineole in feed would be 4.4 µg/kg feed, that of a- and b-thujone (belonging to Cramer Class II) would be below 20 µg/kg feed. Since none of these components would exceed the threshold value for Cramer Class II (ranging from 0.1 mg/kg feed for poultry to 0.5 mg/kg feed for salmonids and dogs), the presence of these impurities is not considered of concern for the target species".

Table 15: Toxicological data on common mugwort

	Observations	Conclusions	References
Toxicity after a single administration			
No data			
Toxicity after repeated administration			
Extract not characterised	Mice, oral route: 1 g/kg/day, 14 days	No changes in hepatic, renal or haematological parameters	(Kodippili *et al.* 2011; Batiha *et al.* 2020; Soon *et al.* 2019)
Genotoxicity			
Methanol extract, characterised for its polyphenols (including a quercetin glycoside)	Micronucleus test (lymphocyte cytokinesis-block micronucleus assay)	**Significant increase in micronuclei** at 50-250 µg/ml but not 10 µg/ml	(Jakovljević *et al.* 2020)
Carcinogenicity			
No data			

It is important to note that the *in vitro* genotoxicity data were obtained at high concentrations, with an extract rich in compounds having no known *in vivo* genotoxicity (Harwood et al. 2007*).*

6.2.2.10 PK and residue data

There are no specific data for the plant. Data are available for components of its EO.

6.2.2.11 Summary of the assessment

Considering that, for common mugwort and preparations thereof (excluding EOs):

- **this plant is not listed in Table 1 of Regulation (EU) No 37/2010;**
- **this plant may be present in the human diet as a flavouring agent and may be present in the diet of animals;**
- **the presence of small quantities of thujone has been described;**
- **an *in vitro* genotoxicity alert was identified;**
- **very few toxicological data are available;**
- **no PK data or data on potential residues are available;**

the WG considers that in the absence of additional and sufficient data, despite the probable lack of risk suggested by its presence in the diet of animals, it cannot conclude that there is no concern for consumers of foods derived from animals that have received it in the context of veterinary medicine.

6.2.3 Artichoke

6.2.3.1 General data

Table 16: General data on artichoke

Common name	Artichoke
Latin name	*Cynara scolymus* L., Asteraceae[58]
Synonyms	*Cynara cardunculus* L., *Cynara cardunculus var. scolymus* (L.) Benth., among others
Parts of the plant concerned	Leaves

6.2.3.2 Status in the regulations and guidelines

Table 17: Status of artichoke in the regulations and guidelines

MRLs	**Regulation (EU) No 37/2010**	Not listed
Medicinal products for human use	**List of medicinal plants**	List A
	Pharmacopoeias	Ph. Eur.: artichoke (leaf) (04/2018: 1866, corrected 10.0), dry leaf extract (01/2010: 2389)
	WHO	Assessment report Monograph (*Cynara cardunculus* L. leaf) (WHO 2009)
	MAs in France	CHOPHYTOL® HEPANEPHROL®
Food supplements	**Ministerial Order of 24 June 2014** **DGCCRF 2019**	Listed without restrictions Parts used: leaves and flower heads
Novel foods	**EFSA catalogue**	Not listed
Feed additives	**Regulation (EU) No 1831/2003**	Listed
Flavouring substances	**Regulation (EU) No 872/2012**	Not listed

6.2.3.3 Opinions of European agencies

Table 18: Opinions of European agencies on artichoke

[58] sources: The Plant List, World Flora Online

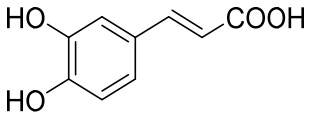
EMA HMPC	Assessment report on *Cynara cardunculus* L. (EMA 2018a) Herbal monograph (EMA 2018c)
EFSA NDA Panel	Scientific Opinion on the substantiation of a health claim related to the combination of artichoke leaf dry extract standardised in caffeoylquinic acids, monacolin K in red yeast rice, sugar-cane derived policosanols, OPC from French maritime pine bark, garlic dry extract standardised in allicin, d-α-tocopheryl hydrogen succinate, riboflavin and inositol hexanicotinate in Limicol® and reduction of blood LDL-cholesterol concentrations pursuant to Article 14 of Regulation (EC) No 1924/2006 (Efsa 2013c)

6.2.3.4 Composition

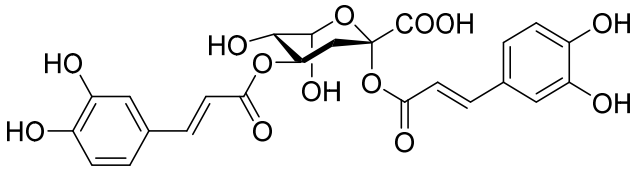
According to the EMA HMPC report (2018a), the various components of artichoke are as follows:

- phenolic acids (up to 2%): caffeic acid, chlorogenic acid, and mono- and dicaffeoylquinic acids (cynarin). According to the Ph. Eur., the whole or cut dried leaves contain at least 0.7% chlorogenic acid. Cynarin, found in the green parts of the plant, is considered one of artichoke's main biologically active secondary metabolites.
- flavonoids: scolymoside, cynaroside, rutoside, isoquercetin;
- lactone sesquiterpenes, including cynaropicrin.

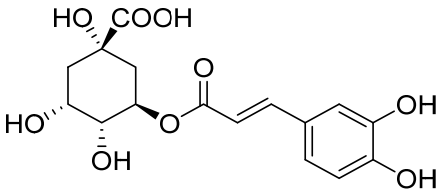
Caffeic acid



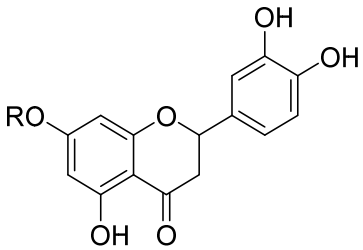
Cynarin
(Dicaffeoylquinic acid)



Chlorogenic acid



Cynaroside (R = β-D-glucose)
Scolymoside (R = β-D-rhamnosyl-(1→4)-β-D-glucose)



Cynaropicrin

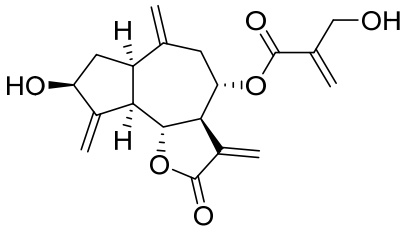


Figure 4: Main components of artichoke

- **Preparations (EMA 2018a)**
- Comminuted dried leaves for herbal tea;
- Powdered dried leaves;
- Dry aqueous extract of dried leaves, extraction solvent water;
- Dry aqueous extract of fresh leaves, extraction solvent water;
- Soft aqueous extract of dried leaves, extraction solvent water;
- Soft hydro-alcoholic extract (20% ethanol) of dried leaves.

6.2.3.5 Presence in the normal human diet

The leaves are not part of the human diet; only the base of the flower head and bracts is consumed.

6.2.3.6 Presence in the normal diet of animals

Artichoke is not considered as being part of the normal diet of animals. It can, however, be consumed.

6.2.3.7 Human exposure

Humans are not exposed as such to artichoke extracts through their diet, but there are food supplements containing artichoke that can be used to set no observed adverse effect levels.

The food supplement LIMICOL® contains, among other things, 200 mg of artichoke leaf dry extract per tablet with a minimum of 5% cynarin. Consuming three tablets per day for 16 weeks (i.e. 600 mg/day and 30 to 36 mg cynarin) has a significant effect on lowering cholesterol. EFSA indicates a single restriction with regard to the use of this food supplement, in relation to the presence of red rice which may be contaminated by citrinin, a mycotoxin. There is no ADI, but the data on the use of LIMICOL® can be used to define a TRV. The daily no adverse effect level is 600 mg/person/day, i.e. for a 60 kg individual, a no observed adverse effect level (NOAEL) of 10 mg/kg bw/day of artichoke leaf extract, which corresponds to 30 mg/person/day of cynarin, i.e. 0.5 mg/kg bw/day (for a 60 kg adult). EMA has a specific monograph on the plant[59].

EMA's HMPC underlines the fact that there are no genotoxicity or reprotoxicity data.

In human phytotherapy, artichoke extracts are authorised in France, at doses of up to 600 mg per day for two weeks with 5% cynarin.

[59] EMA monograph: plant for herbal tea, dry and soft aqueous extracts (DER up to 20 15-35:1), soft hydro-alcoholic extract 20% (DER 2.5-3.5:1).

6.2.3.8 Animal exposure

Not applicable.

6.2.3.9 Toxicological data

Table 19: Toxicological data on artichoke

	Observations	Conclusions	References
Toxicity after a single administration			
Artichoke leaf hydro-alcoholic extract (19% caffeoylquinic acid)	Rats (males), *PO*	LD_{30} (lethal dose) 2000 mg/kg bw	(EMA 2018a)
	Rats (males), Intraperitoneal (IP)	LD_{10} > 1000 mg/kg bw	
Purified extract (46% caffeoylquinic acid)	Rats, *PO*	LD_{40} = 2000 mg/kg bw	
	Rats, IP	LD_{50} = 265 mg/kg	
Leaf hydro-alcoholic extract	Rats, *PO*	LD_{50} = 2000 mg/kg bw	
	Rats, IP	LD_{50} = 1000 mg/kg bw	
Cynarin	Mice, *PO*	LD_{50} = 1900 mg/kg bw	
	Rats, IP	LD_{50} = 800 mg/kg bw	
	Rabbits Intravenous (IV)	LD_{50} = 1000 mg/kg bw	
Toxicity after repeated administration			
Cynarin	Rats, IP 50 to 400 mg/kg bw/day, 15 days	No macroscopic or histological abnormalities or changes in blood parameters	(EMA 2018a)
	Rats, application of 1 to 3 g/kg of leaf extract to the skin	No effect on blood parameters	
		Not irritating to the skin or eyes	
Leaf dry extract	1 g/kg bw/day, male Wistar rats, 60 days	No effect on testicles, sperm motility or testicular antioxidant capacities. The extracts reduce the adverse effects of nandrolone on testicular function	(Mohammed *et al.* 2020)

In vitro genotoxicity		
Micronuclei in CHO-K1 Chinese hamster ovary cells Leaf aqueous extracts (m/v 1:10, 80°C, 30 minutes, followed by lyophilisation; main active substances: flavonoids, phenolic acids and saponins).	After 1 and 24 h of incubation, the extracts induced a statistically significant increase in micronuclei frequencies.	(Jacociunas *et al.* 2013)
Comet assay in HepG2 cells Leaf extract Cells with or without H_20_2 pretreatment, exposed for 1 to 24 h to 0.62-2.5 mg/L of extracts	Induction of DNA damage and at the same time, protective effect against H_2O_2 damage in pretreatment alone.	(da Silva *et al.* 2017)
Cynarin Chromosome aberration, sister chromatid exchange (SCE), micronucleus and comet assays in human lymphocytes	No DNA damage in the micronucleus, comet and chromosome aberration assays. Increased SCE frequency only at the high concentration. In addition, cynarin inhibited the clastogenic properties of mitomycin C (MMC) and H_20_2.	(Erikel, Yuzbasioglu et Unal 2019)
Chlorogenic acid and caffeic acid Comet and micronucleus assays in HL60 and Jurkat cells	Negative	(Hernandes *et al.* 2020)
***In vivo* genotoxicity**		
SMART assay in *Drosophila* Leaf and flower head extracts	No effect with the extracts alone	(Jacociunas *et al.* 2013)
Comet assay (circulating blood and bone marrow) and bone marrow micronucleus (MN) assay Leaf extracts given by gavage (500, 1000 and 2000 mg/kg/day) for three consecutive days	Levels of the main components: • Chlorogenic acid 778 µg/g • Caffeic acid 43.8 µg/g • Rutoside 309 µg/g • Isoquercetin 1388 µg/g Statistically significant increase in DNA fragmentation only in the bone marrow cells at the high dose. No MN induction	(Zan *et al.* 2013)

Carcinogenicity
Caffeic acid is classified in Group 2B (possibly carcinogenic to humans) by the IARC, based on positive results in animals, in the nonglandular stomach of rats and in the kidneys in carcinogenicity studies. It should be noted that chlorogenic acid is metabolised into caffeic acid in humans.

6.2.3.10 PK and residue data

In metabolism studies in healthy volunteers using two artichoke leaf extracts (28.9% dicaffeoylquinic acid and 8.8% flavonoids for extract A, and 6.2% dicaffeoylquinic acid and 0.94% flavonoids for extract B), only certain metabolites were found, whereas no parent compounds were detected in plasma (Wittemer *et al.* 2005; Wittemer et Veit 2003).

6.2.3.11 Summary of the assessment

Considering that, for artichoke (leaf):

- **this plant is not listed in Table 1 of Regulation (EU) No 37/2010;**
- **this plant is not present in the human diet, but it may be present in the diet of animals;**
- **this plant is not listed as a feed or food additive or flavouring agent;**
- **there is uncertainty concerning its genotoxicity;**

the WG considers that in the absence of additional and sufficient data, it cannot conclude that there is no concern for consumers of foods derived from animals that have received it in the context of veterinary medicine.

6.2.4 Milk thistle

6.2.4.1 General data

Table 20: General data on milk thistle

Common name	Milk thistle
Latin name	*Silybum marianum* (L.) Gaertn., Asteraceae
Parts of the plant concerned	Fruit

6.2.4.2 Status in the regulations and guidelines

Table 21: Status of milk thistle in the regulations and guidelines

MRLs	**Regulation (EU) No 37/2010**	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding to the mother tincture and dilutions thereof only.
Medicinal products for human use	**List of medicinal plants**	List A
	Pharmacopoeias	Ph. Eur. 01/2014:1860 Milk thistle and Ph. Eur. 01/2014:2071 Milk thistle (dry extract, refined and standardised)
	WHO	Monograph (fruit) (WHO 2009)
	MAs in France	LEGALON® 70 mg, coated tablets, two tablets, two or three times a day, one coated tablet contains: 86.5-94.5 mg milk thistle dry extract (*Silybum marianum* L. Gaertn) corresponding to 70 mg silymarin expressed as silibinin. ARKOGELULES® CHARDON MARIE, capsules (daily dose: 170 mg milk thistle fruit powder, i.e. 27 mg silymarin).
Food supplements	**Ministerial Order of 24 June 2014** **DGCCRF 2019**	Listed without restrictions Parts used: aerial parts and fruit
Novel foods	**EFSA catalogue**	Aerial parts not included in the Novel Food catalogue (used in food supplements before 1997)
Feed additives	**Regulation (EU) No 1831/2003**	Listed
Flavouring substances	**Regulation (EU) No 872/2012**	Not listed

REACH	Silymarin is a pre-registered substance. According to the classification provided by the notifiers to ECHA, this substance is suspected of having harmful effects on fertility and offspring and can cause damage to organs after prolonged and repeated exposure.

6.2.4.3 Opinions of European agencies

Table 22: Opinions of European agencies on milk thistle

EMA HMPC	Assessment report (EMA 2018b) Monograph (fruit) (EMA 2018e)[60]
EFSA NDA Panel	Scientific Opinion on the substantiation of a health claim related to silymarin BIO-C® and increase in production of breast milk after delivery. The expert panel concluded that there was no relationship between the consumption of silymarin BIO-C® and increased production of breast milk. In this study, 50 volunteers received either a placebo or 420 mg/day of milk thistle extract containing 40 to 80% silymarin, for 63 days (Efsa 2010).

6.2.4.4 Composition

- **According to EMA, milk thistle fruit contains (EMA 2018b):**

- Flavonolignans (1.3-3%):
  - silibinin, isosilibinin (A and B), silicristin and silidianin. All of these compounds, identified as active ingredients, are known as silymarin (silibinin (or silybin) A and B (50-60%), isosilibinin (or isosilybin) A and B (5%), silichristin A and B (20%) and silidianin (10%)). The fruit contains at least 1.5% and the refined and standardised dry extract 35 to 60% according to the Ph. Eur.
- Flavonoids:
  - Flavones: apigenin, chrysoeriol, eriodictyol;
  - Flavonols: taxifolin, quercetin, dihydrokaempferol, kaempferol.
- Lipids (20-30%):
  - Linoleic (35-55%), oleic (24-30%), palmitic (8-12%), linolenic (3-7%), behenic (3-9%) acids, etc.
- Phytosterols (0.2-0.6%):
  - β-sitosterol.
- Other compounds: dehydrodiconiferyl alcohol, 5,7-dihydroxychromone; EO (mostly monoterpenes).

[60] a) Comminuted herbal substance for herbal tea; b) Powdered herbal substance; c) Dry extract (DER 20-70:1), extraction solvent acetone; d) Dry extract (DER 30-40:1), extraction solvent ethanol 96% (V/V); e) Dry extract (DER 20-35:1), extraction solvent ethyl acetate; f) Dry extract (DER 26-45:1), extraction solvent ethyl acetate; g) Dry extract (DER 36-44:1), extraction solvent ethyl acetate; h) Dry extract (DER 20-34:1), extraction solvent methanol 90% (V/V); i) Soft extract (DER 10-17:1), extraction solvent ethanol 60% (V/V).

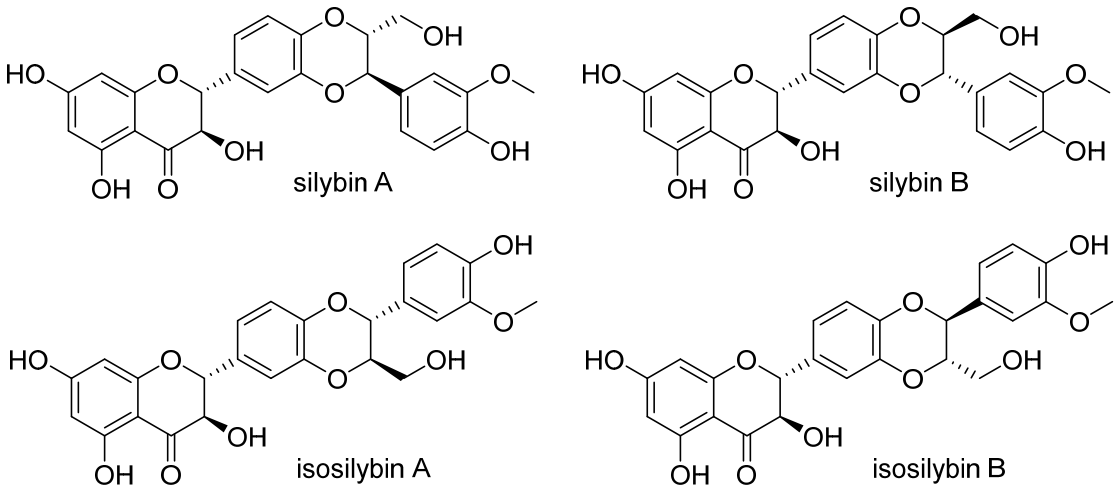


Figure 5: Flavanolignans in milk thistle

6.2.4.5 Presence in the normal human diet

Milk thistle is not present in the normal human diet.

6.2.4.6 Presence in the normal diet of animals

Milk thistle may be present in the diet of animals, since the plant exists in the wild.

6.2.4.7 Human exposure

- No known food additive or flavouring restrictions;
- Not recommended for pregnant and lactating women in the EMA opinions;
- Human exposure:
- based on the available data for human phytotherapy and food supplements, a NOAEL can be derived;
- the medicinal product LEGALON® 70 mg, coated tablets, contains 86.5-94.5 mg refined and standardised milk thistle dry extract (*Silybum marianum* (L.) Gaertn) corresponding to 70 mg silymarin expressed as silibinin. The dosage is two tablets, two or three times a day. The maximum dosage of six tablets/day, i.e. 570 mg/person/day, corresponds to exposure to 10 mg extract/kg bw/day. This equals 420 mg/person/day of silymarin, i.e. 7 mg silymarin/kg bw/day.

6.2.4.8 Animal exposure

Milk thistle is listed in Table 1 of Regulation (EU) No 37/2010 with the following restriction: for use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding to the mother tincture and dilutions thereof only.

A standardised glycerine-based liquid milk thistle extract is marketed by Wamine laboratory, PHYTOSTANDARD®:

- Target species: pets, exotic pets, farm animals;
- 1 ml/5 kg, 200 mg/kg for five days, three times a day, or once daily for 20 days.

6.2.4.9 Toxicological data

Table 23: Toxicological data on milk thistle

	Observations	Conclusions	References
Toxicity after a single oral administration			
Silybum marianum fruit extracts	Mice 500 to 2000 mg/kg bw	No mortality at 48h	(EMA 2018b)
Extract	Mice 20 g/kg bw	No mortality	
	Dogs 1 g/kg bw		
Silymarin	Rats, mice 2500 to 5000 mg/kg bw	No mortality	
Toxicity after repeated oral administration			
Silymarin	Rats 1 g/kg bw/day, 15 days 100 mg/kg, 16 or 22 weeks	No observed adverse effects	(EMA 2018b)
Extract in feed	F344/N rats 260 to 4500 mg/kg bw/day, three months	Decreased sperm motility at the three highest concentrations. NOAEL[61] = 525 mg/kg	(NTP 2011)
	Mice, 3125, 6250, 12,500, 25,000 or 50,000 ppm (640, 1340, 2500, 5280 or 11,620 mg/kg for males and 580, 1180, 2335, 4800 or 9680 mg/kg for females)	Males: at the two highest doses, significant decrease in absolute and relative thymus weights NOAEL = 2500 mg/kg	
	Male and female rats: administration via feed; 0, 12,500, 25,000 or 50,000 ppm milk thistle extract (equivalent to average daily doses of approximately 570, 1180 or 2520 mg/kg for males and 630, 1300 or 2750 mg/kg for females) for 105 to 106 weeks	Females: at the two highest doses: significantly increased incidences of clear cell and mixed cell focus of the liver NOAEL = 630 mg/kg bw/day	
Carcinogenicity			
According to the National Toxicology Program (NTP), there was no evidence of carcinogenic potential in male and female F344/N rats or male and female B6C3F1 mice exposed for two years to 12,500, 25,000 or 50,000 ppm milk thistle extract in feed.			

[61] No observed adverse effect level

In vitro genotoxicity		
Ames test TA98, TA100, TA102, TA104, TA1535 and *E.coli* WP2 uvrA/pKM101 with and without the S9 fraction Five extracts Two ethanol/water extracts (one used for the three-month study and the other for the two-year study) One methanol extract Two water extracts	One negative ethanol/water extract One positive ethanol/water extract in TA98 with rat S9 One positive methanol extract in TA98 with rat and hamster S9 Two negative water extracts	(NTP 2011)
Silymarin	Positive in TA98 and TA100 with rat S9	(NTP 2011)
Silybin	Negative	(NTP 2011)
***In vivo* genotoxicity**		
Micronucleus test in circulating erythrocytes	Mice, 3125, 6250, 12,500, 25,000 or 50,000 ppm (640, 1340, 2500, 5280 or 11,620 mg/kg/day for males and 580, 1180, 2335, 4800 or 9680 mg/kg/day for females), three months. Negative	(NTP 2011)
BM chromosome aberration test in mice	Ethanol extract containing 80% silymarin Mice, oral administration, 2, 4, 8 and 20 mg/kg bw/day, 21 days Negative	(Anwar *et al.* 2018)
Gene mutations in the colon of F344 gpt delta transgenic rats	F344 gpt delta rats, 500 ppm silymarin, four weeks Negative	(Toyoda-Hokaiwado *et al.* 2011)

None of the available data show any genotoxic concern associated with milk thistle or silymarin extracts.

6.2.4.10 PK and residue data

No data

6.2.4.11 Summary of the assessment

The NOAEL of milk thistle extract in the two-year study in rats was 630 mg/kg bw/day based on a slight hepatic effect at 1300 mg/kg bw/day. Based on this NOAEL, a benchmark dose of 6.3 mg/kg bw/day was derived. This value is close to the values from clinical studies in humans, where 7 mg/kg bw/day of extract for 63 days had no effect (silymarin BIO-C®).

Considering that, for milk thistle:

- **this plant is not listed in Table 1 of Regulation (EU) No 37/2010;**
- **this plant is not present in the human diet, but it may be present in the diet of animals;**
- **this plant and refined extracts are used in medicinal products for human use and in homeopathic veterinary medicinal products;**
- **this plant is widely used as a food and feed supplement and additive;**
- **this plant has low toxicity and is not genotoxic or carcinogenic;**
- **the exposure values for animals are similar to those with traditional human exposure;**

the WG concludes, based on the available data, that this plant is not of concern for consumers of foods derived from animals that have received it in the context of veterinary medicine.

6.2.5 Echinacea

6.2.5.1 General data

Table 24: General data on Echinacea

Common names	Purple coneflower, narrow-leaved coneflower, pale coneflower
Latin name	*Echinacea angustifolia* DC., *Echinacea pallida* Nutt., *Echinacea purpurea* Moench
Parts of the plant concerned	Purple coneflower: aerial parts, roots Pale coneflower, narrow-leaved coneflower: roots

6.2.5.2 Status in the regulations and guidelines

Table 25: Status of Echinacea in the regulations and guidelines

MRLs	**Regulation (EU) No 37/2010**	• Echinacea: - For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding to the mother tincture and dilutions thereof only. For topical use only. - For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding in the products not exceeding one part per ten only. • *Echinacea purpurea*: for topical use only
Medicinal products for human use	**List of medicinal plants**	List A (all species and parts concerned)
	Pharmacopoeias	Ph. Eur.: 1823: *Echinacea purpurea* (flowering aerial parts); 1824: *Echinacea purpurea* (roots); 1527: *Echinacea angustifolia* (roots); 1529: *Echinacea pallida* (roots)
	WHO	*Echinacea radix*; *Herba Echinacea purpurea* (volume 1)
	MAs in France	There is a medicinal product with well-established use containing aerial parts of purple coneflower (ECHINACEE POUPRE HUMEXPHYTO) on the French market.
Food supplements	**Ministerial Order of 24 June 2014; DGCCRF 2019**	Listed without restrictions Parts used: subterranean organs

		Substances to be monitored: echinacoside, cynarin, chicoric acid
Novel foods	**EFSA catalogue**	Not included in the Novel Food catalogue for plants and herbal preparations (consumed before 1997). Extracts from *in vitro* callus cultures: novel food authorised in food supplements.
Feed additives	**Regulation (EU) No 1831/2003**	*Echinacea purpurea* and *Echinacea angustifolia* extracts are listed in Annex I of the European register.
Flavouring substances	**Regulation (EU) No 872/2012**	Not listed

6.2.5.3 Opinions of European agencies

Table 26: Opinions of European agencies on Echinacea

EMA HMPC	Each plant part concerned has its own herbal monograph (EMA 2012c, 2015b, 2017d, 2018d)
EFSA NDA Panel	Two scientific opinions on the substantiation of health claims have been published. Safety was not assessed.

6.2.5.4 Composition

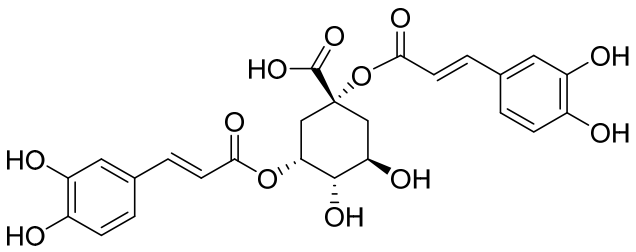
- **Composition**

The three Echinacea species have similar compositions: the phenolic acids they contain are used as markers for their control. The Ph. Eur. recommends:

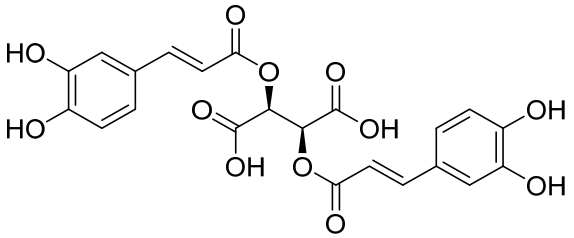
- *Echinacea purpurea* (flowering aerial parts): > 0.1% chicoric acid (dicaffeoylquinic acid) and caftaric acid,
- *Echinacea purpurea* (roots): > 0.5% chicoric acid and caftaric acid,
- *Echinacea angustifolia* (roots) (1527): > 0.5% echinacoside; with thin layer chromatography (TLC) and high-performance liquid chromatography (HPLC), cynarin (= dicaffeoylquinic acid) was detected; it was abundant but not quantified. Small amounts of other phenolic acids (including chicoric acid) were identified.
- *Echinacea pallida* (roots) (1529): > 0.2% echinacoside; the phenolic acid profile with HPLC was similar to that of *E. angustifolia.*

Alkylamides (dodecatetraenoic acid isobutylamides) may be responsible for the immunostimulating and anti-inflammatory activity of these plants. They are usually found in the roots at a concentration of over 0.01%. They are also contained in the aerial parts. The identity of these compounds varies depending on the species. Polyacetylene derivatives have been described. Potentially active polysaccharides are also present. Small quantities of pyrrolizidine alkaloids have been identified. They are not likely to be hepatotoxic (saturated derivatives, not reactive once metabolised).

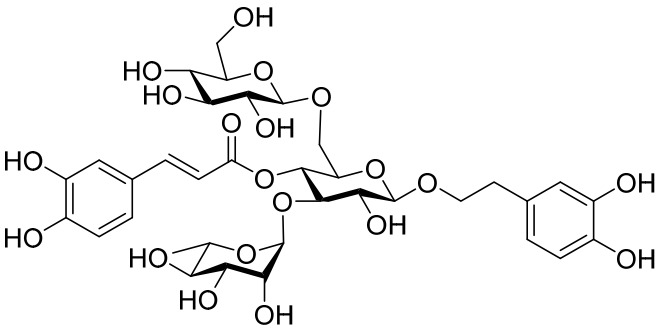
Cynarin



Chicoric acid



Echinacoside



Alkylamide: example: dodeca-2E,4E,8Z,10Z-tetraenoic acid isobutylamide

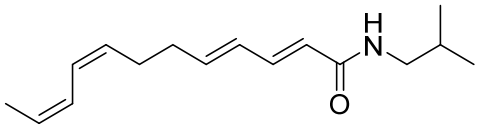


Figure 6: Chemical structure of the components of Echinacea

- **Preparations:**

Plants in unprocessed form, powders, juices, high-dose aqueous and hydro-alcoholic extracts.

6.2.5.5 Presence in the normal human diet

Echinacea is not part of the human diet.

6.2.5.6 Presence in the normal diet of animals

The aerial parts may be present in the diet of animals in areas where the plant is found.

6.2.5.7 Human exposure

- No food additive or flavouring restrictions
- According to the EMA opinions, due to the lack of data, pharmaceutical Echinacea preparations are not recommended for pregnant or lactating women or for children under 12 years of age.
- Human exposure:

- There is no maximum level in food supplements.
- The EMA (HMPC) recommendations, for 10 days of use, give the following exposure levels:
    - Purple coneflower (aerial parts): 9 to 22.5 g/day fresh plant equivalent;
    - Purple coneflower (roots): 220 mg to 2.7 g/day dried plant equivalent; children: aqueous extract only: 200 to 400 mg/day dried plant equivalent;
    - Narrow-leaved coneflower (roots): 0.5 to 1.5 g/day dried plant equivalent;
    - Pale coneflower (roots): 96 mg to 480 mg/day dried plant equivalent.

6.2.5.8 Animal exposure

Purple and narrow-leaved coneflower (unspecified organs) are authorised as feed additives for dogs and cats; their tinctures are authorised for all animal species. There are no restrictions.

6.2.5.9 Toxicological data

Table 27: Toxicological data on Echinacea

	Observations	Conclusions	References
Toxicity after a single administration			
Aerial parts of purple coneflower	Rats, oral route: 30 g/kg juice	No observed toxicity	(EMA 2014a)
Roots of purple coneflower	Mice, oral route: 3 g/kg (extract)	No observed toxicity	
Other species	No data, but the preclinical pharmacological studies show no toxicity		
Toxicity after repeated administration			
Aerial parts of purple coneflower	Rats, oral route: 2.4-8 g juice/kg bw/day, four weeks	Fall in alkaline phosphatase (ALP) (males), rise in prothrombin time (females), with no correlation with the dose; no signs of toxicity	(EMA 2014a, 2018b)
***In vitro* genotoxicity**			
Aerial parts of purple coneflower: lyophilised juice, ethanol extract; miscellaneous components	*Salmonella* Typhimurium (TA98, TA100, TA1535, TA1537, TA1538), with and without metabolic activation (S9); mouse lymphoma TK assay (MLA), *in vitro* micronucleus assay in human lymphocytes, and *in vivo* micronucleus	Non-genotoxic	(EMA 2014a, 2018b)

	assay in bone marrow of mice (25 g/kg)		
Carcinogenicity			
Aerial parts of purple coneflower: juice	No morphological transformation of embryonic hamster cells	Non-carcinogenic *in vitro*	(EMA 2014a)
Other species; roots		No data	
Reprotoxicity and developmental toxicity			
Pale coneflower: powder	Rabbits; 3 g/kg feed, 90 and 125 days	No change in haematological parameters (except for a decrease in basophils in adults), no reprotoxicity	(EMA 2017b)

Despite the lack of available toxicological data for Echinacea roots, the data on the aerial parts of purple coneflower suggest good tolerance. There is also extensive clinical hindsight.

6.2.5.10 Reported adverse effects

For Echinacea, the clinical assessments undertaken have shown good tolerance (David et Cunningham 2019). However, EMA reports some pharmacovigilance data and published cases of allergies, some of which were severe. Some cases of thrombocytopenic purpura and reduced white blood cell counts have been observed. However, EMA considers Echinacea to be safe.

It should not be used by people with immune disorders (EMA, WHO).

6.2.5.11 PK and residue data

Echinacea alkylamides were investigated in a PK study in rats. Their bioavailability was around 30 to 50% (Jedlinszki *et al.* 2014).

There are no residue data.

6.2.5.12 Summary of the assessment

Considering that narrow-leaved, pale and purple coneflower (all parts):

- **are not listed in Table 1 of Regulation (EU) No 37/2010;**
- **are not present in the human diet but may be present in the diet of animals;**
- **are used in medicinal products for human use;**
- **are used as food and feed supplements and additives;**
- **have low toxicity and are not genotoxic or carcinogenic;**
- **have exposure values for animals similar to those with traditional human exposure;**

the WG concludes, based on the available data, that these plants are not of concern for consumers of foods derived from animals that have received them in the context of veterinary medicine.

6.2.6 Dandelion

6.2.6.1 General data

Table 28: General data on dandelion

Common name	Dandelion
Latin name	*Taraxacum officinale* Weber ex Wigg. (Asteraceae)
Synonyms	*Taraxacum campylodes* G.E. Haglund, *Leontodon officinale* With.
Parts of the plant concerned	Aerial parts and roots

6.2.6.2 Status in the regulations and guidelines

Table 29: Status of dandelion in the regulations and guidelines

MRLs	**Regulation (EU) No 37/2010**	Not listed
Medicinal products for human use	**List of medicinal plants**	List A (roots, leaves (not subject to the pharmaceutical monopoly, unprocessed), aerial parts (not subject to the pharmaceutical monopoly, unprocessed))
	Pharmacopoeias	Ph. Eur. 07/2012:1851 on Dandelion (aerial parts and roots)
	WHO	*Radix cum Herba Taraxaci* monograph (WHO 2007)
	MAs in France	No: Three herbal medicinal products containing dandelion were withdrawn from the market in 2020
Food supplements	**Ministerial Order of 24 June 2014; DGCCRF 2019**	Listed without restrictions
Novel foods	**EFSA catalogue**	Not included in the Novel Food catalogue for plants and herbal preparations (consumed before 1997).
Feed additives	**Regulation (EU) No 1831/2003**	Yes
Flavouring substances	**Regulation (EU) No 872/2012**	Not listed

6.2.6.3 Opinions of European agencies

Table 30: Opinions of European agencies on dandelion

EMA HMPC	There is an assessment report on the whole plant (EMA 2009) There are several monographs: for the leaves alone (EMA 2008), the aerial parts and roots (EMA 2019), and the roots alone (EMA 2020b)

6.2.6.4 Composition

The composition of dandelion powders and extracts is complex (EMA 2008, 2019, 2020b; Bruneton 2016). To summarise, four main groups of compounds are mentioned for the aerial and underground parts, with quantitative and qualitative variations:

- Sesquiterpene lactones: eudesmanolides (tetrahydroridentine B, taraxacoside β-D-glucopyranoside), germacranolides (taraxinic acid and 11, 13-dihydrotaraxic acid in the form of β-D-glucopyranose esters, ainslioside).
- Pentacyclic triterpenes and sterols: taraxasterol, ψ-taraxasterol, taraxerol and their hydroxy and acetyl derivatives; arnidol and faradiol, α- and β-amyrins, β-sitosterol and stigmasterol, lupeol.
- Phenolic acids: in the roots: chicoric acid and its isomers, caffeic acid, chlorogenic acid, p-coumaric acid, ferulic acid, hydroxyphenylacetic acid; in the leaves: in addition to the metabolites listed for the roots, presence of other hydroxycinnamic acid derivatives.
- Flavonoids: glycosylated derivatives of luteolin, quercetin and isorhamnetin, in the aerial parts.

The roots contain inulin (level subject to seasonal variations, from 2 to 40%).

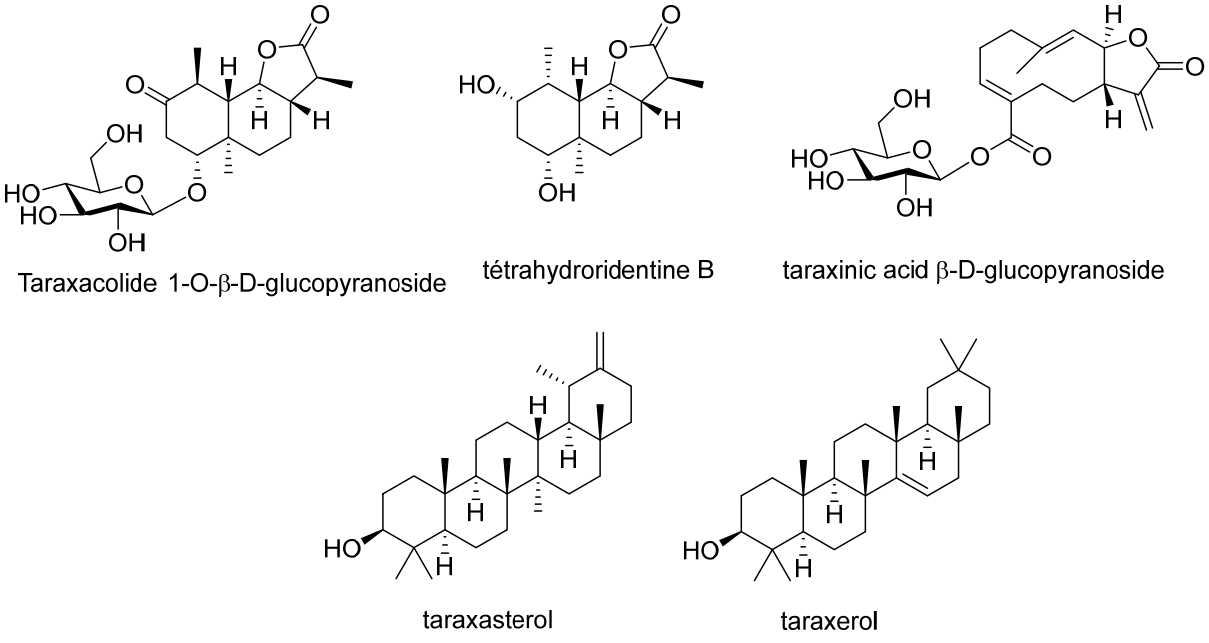


Figure 7: Structure of the terpene components in dandelion

6.2.6.5 Presence in the normal human diet

Dandelion is present in the normal human diet.

Leaves: used more occasionally than regularly; however, for some people, may be consumed fairly regularly when in season.

Roots: as for chicory, teas and coffee substitutes containing roasted roots are available on the market[62].

6.2.6.6 Presence in the normal diet of animals

The aerial parts of dandelion are present in the normal diet of herbivores.

6.2.6.7 Human exposure

In human phytotherapy, EMA mentions the following traditional preparations:

- For the whole plant: fresh juice, powder, dry and liquid hydro-alcoholic extracts (30-60%); daily exposure corresponds to 3 to 5 g dried plant;
- For the leaves: fresh juice, drug for herbal tea, liquid hydro-alcoholic extract (25%); daily exposure corresponds to 30 g dried plant per day, as herbal tea;
- For the roots: fresh juice, drug for herbal tea, liquid hydro-alcoholic extract (30%), tincture; daily exposure corresponds to 15 g dried plant per day.

6.2.6.8 Animal exposure

Dandelion (aerial parts) is present in the normal diet of herbivores. It is not identified by EFSA's FEEDAP or NDA Panel as a feed additive or complementary feed.

6.2.6.9 Toxicological data

Table 31: Toxicological data on dandelion (whole plant, roots or aerial parts)

	Observations	Conclusions	References
Toxicity after a single administration			
Dried leaves or roots and ethanol extracts	Mice IP	LD_{50} leaves = 28.8 g/kg bw LD_{50} roots = 36.6 g/kg bw	(ESCOP 2003)
Ethanol extracts	Mice and rats, *PO*	No toxicity at 10 g/kg bw	(ESCOP 2003; Tita *et al.* 1993)
	Mice and rats, IP	No toxicity at 4 g/kg bw	
"No visible signs of acute toxicity were observed after oral administration of dried whole dandelion plants at 3-6 g/kg body weight in rats". Other data summarised in the above table also suggest low toxicity.			(EMA 2009)

[62] https://ec.europa.eu/food/system/files/2017-09/fs_food-improvement-agents_guidance_1333-2008_annex-2.pdf

Toxicity after repeated administration			
Dandelion	Rabbits, *PO* 3 to 6 g/kg bw	No signs of toxicity	(Leslie et Salmon 1979)
***In vitro* mutagenicity/genotoxicity**			
Numerous *in vitro* and *in vivo* studies do not suggest any genotoxic, mutagenic or carcinogenic effects for dandelion root, leaf or whole plant extracts			(Chatterjee *et al.* 2011; Nguyen *et al.* 2019; Ovadje *et al.* 2016; Ovadje *et al.* 2011; Rehman *et al.* 2017) (Karakuş, Değer et Yıldırım 2017; Leslie et Salmon 1979).
Due to the small number of data obtained directly for *T. officinale*, certain data concern congeneric species whose species names are given.[63]			(Schütz, Carle et Schieber 2006{Martinez, 2015 #335)
Aqueous extracts of *T. formosanum*	Ames test *Salmonella*	No mutagenesis	(Tsai, Chang et Tseng 2020)
Extracts of *T. mirabile* and *T. farinosum* but not *T. officinale*	Ames test *Salmonella*	No mutagenicity	(Uysal *et al.* 2016)
Reprotoxicity and developmental toxicity			
Ethanol extracts	Rabbits and rats 1.6 ml/kg	No effects on fertility or prenatal development (teratogenicity)	(Leslie et Salmon 1979; WHO 2007)

EMA's general conclusion is as follows (EMA 2009): “Reliable data on acute toxicity are only available for whole crude drug and some extracts. Oral administration of preparations from *Taraxaci radix cum herba* can be regarded as safe at traditionally used doses with the exception of patients with renal failure and/or diabetes, and/or heart failure. In those conditions, the use should be avoided because of possible complications due to hyperkalemia.

Although toxicological data on dandelion are very limited, neither the European traditional use nor known constituents suggest that there is any risk associated with the use of dandelion root and herb”.

[63] The genus is chemically homogeneous

6.2.6.10 PK and residue data

In the EMA opinion (2009): “Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof: No data available for Taraxaci radix cum herba”.

6.2.6.11 Reported adverse effects

Since 2011, 17 reports involving food supplements have been identified in the nutrivigilance database.

Allergic reactions associated with sesquiterpene lactones have been reported (EMA 2008, 2009; WHO 2007). Moreover, the EMA report (2009) stresses the high potassium content of dandelion extracts which, depending on the dosages proposed in phytotherapy, may require monitoring in children.

6.2.6.12 Summary of the assessment

Considering that, for dandelion (aerial parts, underground parts and whole plant):

- **this plant is not listed in Table 1 of Regulation (EU) No 37/2010;**
- **this plant is present in the human diet (leaves, underground parts) and in the diet of herbivores (aerial parts);**
- **this plant is used in food and feed supplements and as a food and feed additive;**
- **there have been no alerts concerning potential genotoxicity or mutagenicity, as the assessments conducted for congeneric species have shown negative results;**
- **despite the lack of PK and potential residue data;**

the WG concludes, based on the available data, that this plant is not of concern for consumers of foods derived from animals that have received it in the context of veterinary medicine.

6.2.7 Bramble

6.2.7.1 General data

Table 32: General data on bramble

Common name	Bramble
Latin name	*Rubus fruticosus* auct. [L.]; *Rubus vulgaris* Weihe & Nees *(Rubus sect Rubus* for the fruit*)*
Synonyms	The taxonomy is complex. There are many synonyms. The genus "*Rubus* sp." is listed in the French Pharmacopoeia (List A) Blackberry for the **fruit**
Parts of the plant concerned	Leaves

6.2.7.2 Status in the regulations and guidelines

Table 33: Status of bramble in the regulations and guidelines

MRLs	**Regulation (EU) No 37/2010**	No
Medicinal products for human use	**List of medicinal plants**	List A (*Rubus* sp.), leaves, not subject to the monopoly, unprocessed
	Pharmacopoeias	No monograph in the European or French Pharmacopoeia
	WHO	No herbal monograph
	MAs in France	No medicinal products registered in France
Food supplements	**Ministerial Order of 24 June 2014; DGCCRF 2019**	Listed without restrictions Parts used: leaves, fruit, young shoots
Novel foods	**EFSA catalogue**	Not listed
Feed additives	**Regulation (EU) No 1831/2003**	As *Rubus* spp. (e.g. *Rubus fruticosus* L.): Blackberry tincture CoE 408
Flavouring substances	**Regulation (EU) No 872/2012**	Not listed

6.2.7.3 Opinions of European agencies

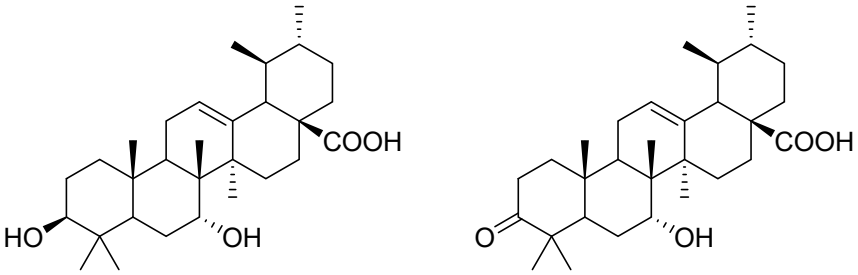
Table 34: Opinions of European agencies on bramble

EMA HMPC	There are no opinions for *Rubus fruticosus* but there is an EMA/HMPC/44211/2012 monograph for raspberry leaf: *Rubus idaeus* L., folium

6.2.7.4 Composition

- **Bramble leaves (*Rubus* sp.)** (Bruneton 2009; Ziemlewska, Zagórska-Dziok et Nizioł-Łukaszewska 2021; Wichtl et Anton 2003)

Bramble leaves contain flavonoids, hydrolysable tannins (8 to 14%, at least 5% according to pharmacopoeias; mainly ellagitannin dimers), citric and isocitric acids, and triterpenes (rubutic and rubinic acids, β-amyrin).



rubitic acid rubinic acid

Figure 8: Structure of the triterpenes in bramble leaves

6.2.7.5 Presence in the normal human diet

The fruit of various *Rubus* sp. species including the fruit of *Rubus fruticosus (Rubus sect Rubus)* and *Rubus idaeus* are listed in the *Codex Alimentarius.*

6.2.7.6 Presence in the normal diet of animals

Bramble is present in the pastures of ruminants in some livestock management systems.

6.2.7.7 Human exposure

There are known uses in human phytotherapy.

The HMPC monograph (EMA 2014c) on raspberry leaf lists traditional uses as herbal tea (up to 8 g/day) and in the form of dry aqueous extract (around 1 g/day). There are no mentioned cases of overdose. Use is not recommended for children under the age of 12 or for lactating and breastfeeding women (due to a lack of data).

6.2.7.8 Animal exposure

Bramble is present in the normal diet of herbivore animals (Popay et Field 1996). In animals, *Rubus sp.* is authorised as a feed supplement and additive.

6.2.7.9 Toxicological data

Table 35: Toxicological data on bramble

	Observations	Conclusion	References
Toxicity after a single administration			
Aqueous extract of *R. fruticosus* leaves	Mice, *PO*	LD_{50} = 8.1 g/kg bw	(Zia-Ul-Haq *et al.* 2014)
Korean bramble (*Rubus coreanus*, not *R. fruticosus*)	Rats, *PO,* gavage Acute toxicity study = 14 days of observation	No toxicity NOAEL = 2500 mg/kg bw/day	(Om *et al.* 2016)
Toxicity after repeated administration			
Korean bramble (*Rubus coreanus*, not *R. fruticosus*)	Rats, *PO,* gavage Chronic toxicity by daily administration (13 weeks)	No toxicity NOAEL = 2500 mg/kg bw/day	(Om *et al.* 2016)
Mixture of aqueous extracts of five plants including *R. fruticosus* (10% of the mixture)	Rat model of type 1 diabetes, *PO*, 10 and 20 g/kg bw 28 days	No toxicity reported	(Madić *et al.* 2021)
***In vitro* mutagenicity/genotoxicity**			
Leaf aqueous extract	*Allium cepa* genotoxicity study 1200 µg/ml at 48 h	Negative result	(Madić *et al.* 2019)

6.2.7.10 PK and residue data

No data.

6.2.7.11 Summary of the assessment

Considering that, for bramble (leaves):

- **this plant is not listed in Table 1 of Regulation (EU) No 37/2010;**
- **this part of the plant is not part of the human diet;**
- **this plant is part of the diet of herbivores, especially small ruminants;**
- **there is no EMA (HMPC) opinion on the use of this part of the plant in human phytotherapy; however, an EMA opinion is available on the use of *Rubus idaeus* leaves, with information on the recommended maximum intakes;**
- **the few studies that are available show a lack of acute and chronic toxicity;**
- **there have been no alerts concerning potential genotoxicity or mutagenicity;**

the WG concludes, based on the available data, that this plant is not of concern for consumers of foods derived from animals that have received it in the context of veterinary medicine.

6.2.8 Tansy

6.2.8.1 General data

Table 36: General data on tansy

Common name	Tansy
Latin name	*Tanacetum vulgare* L.
Synonyms	Common tansy
Parts of the plant concerned	Leaves and flowering tops

6.2.8.2 Status in the regulations and guidelines

Table 37: Status of tansy in the regulations and guidelines

MRLs	**Regulation (EU) No 37/2010**	Not listed
Medicinal products for human use	**List of medicinal plants in the French Pharmacopoeia**	List B (flowering tops) NB: EO subject to the pharmaceutical monopoly
	Pharmacopoeias	No monograph in the European or French Pharmacopoeia
	WHO	No herbal monograph; the WHO mentions the aerial parts of feverfew (*Tanacetum parthenium* (L.) Schultz Bip.), whose composition is different
	MAs in France	A homeopathic medicinal product subject to registration
Food supplements	**Ministerial Order of 24 June 2014; DGCCRF 2019**	Listed with restrictions
Novel foods	**EFSA catalogue**	Aerial parts not included in the Novel Food catalogue (used in food supplements before 1997)
Feed additives	**Regulation (EU) No 1831/2003**	Listed in tincture form (*Tanacetum vulgare* L.: Tansy tincture)
Flavouring substances	**Regulation (EU) No 872/2012**	Not listed

6.2.8.3 Opinions of European agencies

Table 38: Opinions of European agencies on tansy

EMA HMPC	Not listed Assessment report and monograph concerning another species of the genus (*T. parthenium*)
EFSA – Assessments of pesticide active substances	Assessment report on *Tanacetum vulgare* following an authorisation application for use in plant protection as repellent on orchards, vineyards, vegetables and ornamentals

6.2.8.4 Composition

Tansy contains:

- flavonoids including casticin (Ivanescu *et al.* 2018)
- volatile monoterpenes (Cote *et al.* 2017) including thujone, (-)-camphor and 1,8-cineole (Burkhard *et al.* 1999). There are several CTs. The main components of the EO are, depending on the origin, β-thujone, artemisia ketone, borneol and bornyl acetate, (E)-pineocarvol, α-pinene, terpinene-4-ol, camphor, 1,8-cineole and α-thujone (Cote *et al.* 2017; Tisserand et Young 2014). Sesquiterpenes have also been identified in the EO.
- sesquiterpene lactones (Rosselli *et al.* 2012).

According to EFSA (2014b), “From the information provided it seems that the chemical nature of the plant is very complex and there are large variations in composition from region to region and from country to country. There is no proposed specification and no supporting data for a specification”.

6.2.8.5 Presence in the normal human diet

Tansy is not present in the normal human diet, except when used as a flavouring agent (Conseildel'Europe 1981).

6.2.8.6 Presence in the normal diet of animals

Tansy is present in the normal diet of animals.

6.2.8.7 Human exposure

- **JEFCA ADI:**

According to EFSA (2014b), “Since the toxicological profile of *Tanacetum vulgare* could not be fully quantified, a reliable consumer risk assessment could not be performed”.

- **Maximum human exposure to the plant (oral route):**

Tansy contains several epileptogenic compounds (thujone, camphor and 1,8-cineole) that can cause seizures in humans (Burkhard *et al.* 1999). The neurotoxicity of thujone-containing EOs (thuja, wormwood, tansy, common sage) is known: these EOs produce epileptiform and tetaniform convulsions and mental and sensory disorders requiring hospitalisation. The accidents they have caused led to the introduction, in France, of restrictive legislation: Act No 84-534 of 30 June 1984 supplemented Article L-512 of the CSP by indicating: “the retail sale and any dispensing to the public of the essential oils listed in the decree, and their dilutions and preparations, constituting neither cosmetic or personal hygiene products nor cleaning products nor foodstuffs or beverages, are reserved for pharmacists”. Decree No 86-778 of 23

June 1986 added essences from wormwood, Roman wormwood, mugwort, cedar, hyssop, sage, tansy and thuja to the list set out in the above text (Bruneton 2016).

There can also be exposure, albeit only secondarily, via alcohols, as is the case with mugwort.

6.2.8.8 Animal exposure

Tansy is present in the standard diet of animals (including in pastures).

6.2.8.9 Toxicological data

Table 39: Toxicological data on tansy

	Observations	Conclusions	References
Toxicity after a single oral administration			
Aqueous extract of *T. vulgare* leaves	Mice, 0 to 13 g/kg bw	LD_{50} = 9.9 g/kg	(Lahlou, Israili et Lyoussi 2008; Pooja *et al.* 2016)
Toxicity after repeated oral administration			
Aqueous extract of *T. vulgare* leaves	Rats, 100, 300 and 600 mg/kg bw/day, 90 days	No mortality, no clinical signs and no change in blood haematological or biochemical parameters were observed, except for hypoglycaemia NOEL[64] = 0.6 g/kg/day	

Tansy has been investigated in acute, subacute and subchronic oral toxicity studies in rats and mice.

Tansy has very **low acute, subacute and subchronic oral toxicity** in rats and mice and therefore, by extrapolation, in livestock production animals.

6.2.8.10 PK and residue data

No data.

[64] No observed effect level

6.2.8.11 Reported adverse effects

- **Cases from nutrivigilance**

No cases have been reported.

- **Cases recorded in Canada and the United States**

From 1 January 1965 to 31 January 2021, 33 nutrivigilance cases were recorded in Canada, usually with digestive (reduced appetite, vomiting, change of stool colour, melaena, diarrhoea), muscular (myalgia), joint (arthralgia) and neurological (sensations of dizziness) adverse effects. These cases involved *Tanacetum parthenium*.

Between 2004 and 2021, five nutrivigilance cases were recorded in the United States, with a wide variety of adverse effects. These cases involved *Tanacetum parthenium*.

6.2.8.12 Summary of the assessment

Considering that, for tansy and preparations thereof (excluding EOs):

- **this plant is not listed in Table 1 of Regulation (EU) No 37/2010;**
- **this plant is present in the human diet as a flavouring agent and is present in the diet of animals;**
- **the presence of thujone has been described;**
- **very few PK and toxicological data are available (especially in terms of genotoxicity, mutagenicity and reprotoxicity); a TRV cannot be defined in the current state of knowledge;**

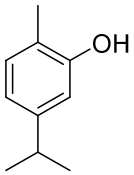
the WG considers that in the absence of sufficient data, it cannot conclude that there is no concern for consumers of foods derived from animals that have received it in the context of veterinary medicine.

6.3 Substances in essential oils

6.3.1 Carvacrol

6.3.1.1 General data

Table 40: General data on carvacrol

Common name	Carvacrol
IUPAC name	2-Methyl-5-propan-2-ylphenol
Synonyms	*p*-Cymene-2-ol, 2-hydroxy-*p*-cymene, isopropyl-*o*-cresol, isothymol
CAS No.	499-75-2
EINECS No.	207-889-6
FLAVIS No.	[04.031]
CoE No.	2055
JECFA No.	710
FEMA No.	2245
Physico-chemical properties	Chemical formula: $C_{10}H_{14}O$ Molecular weight: 150.22 g/mol Description: colourless or pale yellow liquid with a pungent odour Solubility in water at 20°C: 0.33 g/L LogP: 3.33
Chemical structure	

6.3.1.2 Status in the regulations and guidelines

Table 41: Status of carvacrol in the regulations and guidelines

MRLs	**Regulation (EU) No 37/2010**	Not listed
Medicinal products for human use	**WHO**	No herbal monograph
	MAs in France	No medicinal products registered in France
Food supplements	**Ministerial Order of 24 June 2014; DGCCRF 2019**	Not listed
Novel foods	**EFSA catalogue**	Not listed

Feed additives	**Regulation (EU) No 1831/2003**	Authorised as a sensory feed additive
Flavouring substances	**Regulation (EU) No 872/2012**	Listed
Human medicine in France		No MAs
REACH		Registered

6.3.1.3 Opinions of European agencies

Table 42: Opinions of European agencies on carvacrol

EMA HMPC	An assessment report on thyme preparations (*Thymus vulgaris* L., *Thymus zygis* L., aetheroleum) (EMA 2020a)
EFSA FEEDAP	Opinions on the safety and efficacy of carvacrol as a flavouring additive in the feed of all animal species (2012e), on an EO from *Origanum vulgare* containing around 78% carvacrol (2019a), and on four zootechnical additives containing carvacrol EO
EFSA AFC[65]	The use of carvacrol as a flavouring substance in food was also assessed by the AFC panel in 2008 (Efsa 2008c).
ANSES	In 2014, the CES on Animal feed (CES ALAN) issued an opinion on the creation of a new functional group of decontaminating feed additives in which the anti-*Salmonella* efficacy of carvacrol was studied in animal feed. As part of this opinion, the CES ALAN assessed the impact of carvacrol EO on animal health, human health and the environment, as well as the possible consequences of its use in terms of the development of resistance in harmful micro-organisms, in particular *Salmonella*.
JECFA	Carvacrol was assessed as food flavouring by JECFA (WHO 2000) and was authorised as a flavouring substance that can be used in food. ADI: No safety problems at the current levels of ingestion when it is used as a flavouring agent (WHO 2001)

6.3.1.4 Presence in EOs

According to Tisserand and Young (2014), the EOs that contain the most carvacrol are listed in the following table.

[65] Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food

Table 43: List of the EOs that contain the most carvacrol

Ajowan	1.0-16.4%
Black cumin, *Nigella sativa* L. (seeds)	0.5-4.2%
Marjoram, *Origanum majorana* L. (CT carvacrol) (leaves)	76.4-81.0%
Marjoram, *Origanum majorana* L. (CT linalool) (leaves)	23.3%
Oregano, *Origanum vulgare* L. (aerial parts)	61.6-83.4%
Savory, *Satureja hortensis* L., *Satureja montana* L. (aerial parts)	43.6-75.0%
Thyme, *Thymus vulgaris* L. (CT carvacrol) (aerial parts)	41.8%
Thyme, *Thymus vulgaris* L. (CT thymol) (aerial parts)	5.5-16.3%
Thyme, *Thymus vulgaris* L. (CT limonene) (aerial parts)	20.5%
Thyme, *Thymus vulgaris* L. (CT linalool) (aerial parts)	1.0-1.1%
Thyme, *Thymus zygis* L. (CT carvacrol) (aerial parts)	43.9%
Thyme, *Thymus zygis* L. (CT thymol/carvacrol) (aerial parts)	22.8%
Thyme, *Thymus zygis* L. (CT thymol) (aerial parts)	Traces - 5.9%
Thyme, *Thymus vulgaris* L.*, Thymus zygis* L. (aerial parts) (Ph. Eur., 10th edition)	0.5-5.5%
Wild thyme, *Thymus serpyllum* L. (CT thymol/carvacrol) (aerial parts)	15.6-27.8%

6.3.1.5 Presence in the normal human diet

Carvacrol is a flavouring substance authorised in food. Its main characteristics, summarised below, concerning absorption, distribution, metabolism and excretion, have been described by the WHO (2000) and in various EFSA opinions (Efsa 2006, 2008b, 2012e).

6.3.1.6 Presence in the normal diet of animals

Two zootechnical additives, containing carvacrol among other substances, are authorised in the European Union (EU), under Implementing Regulation (EU) 2015/1490 and Implementing Regulation (EU) 2020/160.

6.3.1.7 Human exposure

The FEEDAP Panel of EFSA's Scientific Committee (Efsa 2020b, 2019b) considered it was appropriate to use the TTC approach: carvacrol is a Cramer Class I compound and the corresponding safe level of daily exposure was 30 µg/kg bw/day.

Regardless of the age group (infants, young children, other children, adolescents, adults, elderly and very elderly people), the highest estimate of chronic dietary exposure to carvacrol ranged from 1.0 (very elderly people) to 2.6 (other children) µg/kg bw/day. Considering adults – probably the most exposed class of consumers – the estimated level of chronic exposure

was 1.5 µg/kg bw/day, corresponding to 5% of the safe intake derived from the TTC. Moreover, according to the FLAVIS database, exposure to the substance as a food flavouring in the European Union is only 14 µg/person/day (based on the maximum daily intake derived from surveys), which corresponds to 1% of the TTC (1800 µg/person/day). Therefore, no toxicological concern for consumer safety has been identified.

6.3.1.8 Toxicological data

Table 44: Toxicological data on carvacrol

	Observations	Conclusions	References
Toxicity after a single oral administration			
Carvacrol	Rabbits	LD_{50} = 100 mg/kg bw	(Caujolle et Franck 1944; Jenner *et al.* 1964; D.L.J. Opdyke 1979a; Tisserand et Young 2014)
	Rats	LD_{50} = 810 mg/kg bw	
Toxicity after repeated administration			
Carvacrol	Piglets, residue studies, 400 to 480 mg carvacrol/kg feed/day, 45 days	Residue concentrations < detection and quantification limits for carvacrol	(Efsa 2020b)
Genotoxicity/Mutagenicity			
Carvacrol	Ames test *Salmonella* Typhimurium 30 to 300 µg/plate (without metabolic activation) and 300 to 500 µg/plate (with metabolic activation)	No mutagenic effect	(Efsa 2020b; Ipek *et al.* 2005; Kono, Yoshida et Itaya 1995; Tisserand et Young 2014)
	Comet assay (V79 cells) 150, 750 or 3750 mg/L	Non-genotoxic	(Undeger *et al.* 2009)
	Rats, IV 10, 30, 50 or 70 mg/kg bw	No dose-dependent genotoxic effect in bone marrow cells	(Azirak et Rencuzogullari 2008)
	In vitro in human cells, in the presence of hydrogen peroxide	Prevention of DNA breaks	(Slamenová *et al.* 2007)

Reprotoxicity and developmental toxicity			
Satureja khuzestanica (a plant whose EO contains 93.9% carvacrol)	Rats (pregnant females), 100, 500 or 1000 ppm *Satureja khuzistanica* Jamzad EO (containing 93.9% carvacrol) via drinking water, during days 0 to 15 of gestation	No signs of maternal toxicity or teratogenicity Significant increase in the number of implantations and live foetuses at the two highest doses	(Abdollahi 2004; Abdollahi *et al.* 2003)
Hepatotoxicity			
At 73 mg/kg with IP administration, carvacrol was not hepatotoxic in rats and protected against hepatotoxicity induced by ischaemia-reperfusion (Canbek *et al.* 2008). There was also not any toxicity at 125 mg/kg with IP administration (Jiménez *et al.* 1993).			

6.3.1.9 PK and residue data

ADME characteristics

Carvacrol is rapidly absorbed by the gastrointestinal tract. The detoxification of carvacrol requires its sulfate conjugation via sulfotransferases (SULT) that catalyse the transfer of a sulfonate group from an active sulfate, 3'-phosphoadenosine 5'-phosphosulfate (PAPS), and/or glucuronic acid, to produce inactive metabolites enabling it to be excreted primarily in urine (Scheline 1991; WHO 2000). In fact, Austgulen *et al*. (1987) showed that carvacrol was eliminated in the urine of rats in conjugated form, 24 hours after administration by intragastric intubation. Similarly, Schröder and Vollmer (1932) showed that carvacrol was excreted in the urine of rabbits.

In 2001, the Joint FAO/WHO Expert Committee on Food Additives considered that the chemical structure of carvacrol enabled effective metabolic detoxification, leading this substance to be classified as having low toxic potential via the oral route. This committee deemed that the levels of exposure to carvacrol were not likely to saturate the metabolic pathways involved in its metabolism and elimination.

Residue studies

Residue studies conducted in piglets exposed for 45 days to a dose of 400 to 480 mg carvacrol/kg feed showed that the residue concentrations in the adipose tissue, muscle, liver and kidney samples were below the limits of detection and quantification for carvacrol (LOQs: 0.1 mg/kg adipose tissue, 0.3 mg/kg muscle, 0.25 mg/kg liver and 0.25 mg/kg kidney).

6.3.1.10 Summary of the assessment

Considering that carvacrol:

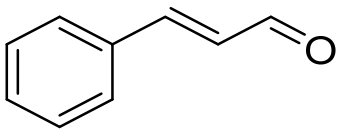
- **is not listed in Table 1 of Regulation (EU) No 37/2010;**
- **is included on the list of flavouring substances, without restrictions (Regulation (EU) No 872/2012);**
- **is authorised as a component of several feed additives;**
- **is not genotoxic or reprotoxic;**
- **is rapidly metabolised and excreted;**
- **was investigated in residue studies in piglets showing that it was not detected in their fat, muscle, liver or kidneys;**

the WG concludes, based on the available data, that the presence of carvacrol is not of concern for consumers of foods derived from animals that have received plants and/or EOs containing this substance in the context of veterinary medicine.

6.3.2 Cinnamaldehyde

6.3.2.1 General data

Table 45: General data on cinnamaldehyde

Common name	Cinnamaldehyde
IUPAC name	(2*E*)-3-Phenylprop-2-enal
Synonyms	(*E*)-Cinnamaldehyde, benzylidene acetaldehyde, cassia aldehyde, β-phenylacrolein
CAS No.	104-55-2
EINECS No.	203-213-9
FLAVIS No.	[05.014]
CoE No.	102
JECFA No.	656
FEMA No.	2286
Physico-chemical properties	Chemical formula: C_9H_8O Molecular weight: 132.16 g/mol Description: yellow oil with a cinnamon odour and a sweet taste Functional class: flavouring agent Solubility in water: 1.42 g/L LogP: 1.9
Chemical structure	

6.3.2.2 Status in the regulations and guidelines

Table 46: Status of cinnamaldehyde in the regulations and guidelines

MRLs	**Regulation (EU) No 37/2010**	Not listed
Medicinal products for human use	**WHO**	No herbal monograph
	MAs in France	No medicinal products registered in France
Food supplements	**Ministerial Order of 24**	Not listed

	June 2014; DGCCRF 2019	
Novel foods	**EFSA catalogue**	Not listed
Feed additives	**Regulation (EU) No 1831/2003**	Authorised as a sensory feed additive with a specific entry in the European Union Register of Feed Additives in accordance with Regulation (EC) No 1831/2003 (2; b; Natural or corresponding synthetic chemically defined flavourings). A registered zootechnical additive containing cinnamaldehyde is authorised in the European Union (EU) under Implementing Regulation (EU) 2015/1490.
Flavouring substances	**Regulation (EU) No 872/2012**	Listed
REACH		According to the classification provided by companies to ECHA in REACH registrations, cinnamaldehyde causes serious eye irritation, is harmful to aquatic life with long-lasting effects, is harmful in contact with the skin, causes skin irritation and can cause an allergic skin reaction. The substance is therefore registered as follows: - Substance subject to restrictions in Annex III of the Cosmetics Regulation - Prohibited/restricted allergenic fragrance in toys (Annex II, Sec III) - Active biocidal substance (abandoned claim) **<u>Hazard identification</u>** Cinnamaldehyde is classified as follows in terms of hazards: Health hazard/Hazardous to the ozone layer (GHS07). May cause an allergic skin reaction or severe eye irritation; be harmful if swallowed or inhaled; harm the environment. This is associated with the following hazards: H315 causes skin irritation; H317 may cause an allergic skin reaction; H319 causes serious eye irritation; H412 harmful to aquatic life with long-lasting effects.

	Moreover, cinnamaldehyde is not considered to be a persistent, bioaccumulative and toxic (PBT/vPvB) substance.

6.3.2.3 Opinions of European agencies

Table 47: Opinions of European agencies on cinnamaldehyde

EMA HMPC	An assessment report concerning Ceylon cinnamon bark whose EO consists primarily of cinnamaldehyde (EMA 2010a)
EFSA FEEDAP	A scientific opinion on the safety and efficacy of XTRACT® Evolution B (carvacrol, cinnamaldehyde and capsicum oleoresin) as a feed additive for chickens for fattening (Efsa 2015b). A scientific opinion on the safety and efficacy of aryl-substituted primary alcohol, aldehyde, acid, ester and acetal derivatives belonging to chemical group 22 when used as flavourings for all animal species (Efsa 2017).
EFSA CEF Panel	The use of cinnamaldehyde as food flavouring was assessed by the EFSA CEF Panel in 2008; three scientific opinions are available (Efsa 2008b, 2008a, 2009b).
ANSES	In 2014, the CES ALAN issued an opinion (Anses 2014) on the creation of a new functional group of decontaminating feed additives in which the anti-*Salmonella* efficacy of cinnamaldehyde was studied in animal feed. In February 2018, the CES ALAN and the WG on Alternatives to antibiotics issued a collective expert appraisal report (Anses 2018) on the inventory of alternatives to antibiotics aimed at reducing their use in animal husbandry, in particular in fish and broiler chickens. Cinnamaldehyde has been registered in the catalogue of PPPs and their uses, fertilisers and growing media authorised in France (ANSES E-Phy[66]) since 19 July 2018, indicating that it has not been approved by the European Union but is preregistered with ECHA under the REACH Regulation for 1000 to 10,000 tonnes per year.
JECFA	Cinnamaldehyde was assessed by the Joint FAO/WHO Expert Committee on Food Additives at its 55th meeting (WHO 2000): no safety problems were identified at the current levels of ingestion when it is used as a flavouring agent.

[66] https://ephy.anses.fr/

6.3.2.4 Presence in EOs:

The EOs that contain the most cinnamaldehyde are listed in the following table (Tisserand et Young 2014).

Table 48: List of the EOs that contain the most cinnamaldehyde

Chinese cinnamon (“cassia”) EO, *Cinnamomum cassia* Blume (syn. *Cinnamomum aromaticum* Nees).	
Bark:	(*E*)-Cinnamaldehyde: 73.2-89.4% (*Z*)-Cinnamaldehyde: 0.8-12.3%
Leaves:	(*E*)-Cinnamaldehyde: 54.6-90.1% (*Z*)-Cinnamaldehyde: 0.4-10.5%
Ceylon cinnamon EO, *Cinnamomum verum* J. Presl. (syn. *Cinnamomum zeylanicum* Blume)	
Bark:	(*E*)-Cinnamaldehyde: 63.1-75.7%
Leaves:	(*E*)-Cinnamaldehyde: 0.6-1.1%

6.3.2.5 Presence in the normal human diet

Cinnamaldehyde is authorised as a sensory feed additive with a specific entry in the European Union Register of Feed Additives in accordance with Regulation (EC) No 1831/2003 (2; b; Natural or corresponding synthetic chemically defined flavourings).

6.3.2.6 Presence in the normal diet of animals

A zootechnical additive containing cinnamaldehyde is authorised in the European Union (EU) under Implementing Regulation (EU) 2015/1490.

6.3.2.7 Human exposure

Concentrations of cinnamaldehyde detected in oils from natural sources, such as the inner bark and leaves of *Cinnamomum* trees used to produce cinnamon, can reach 750 g/kg. The total annual production volume of “cinnamyl” compounds intended to be used as flavouring agents is around 60 tonnes in Europe and 480 tonnes in the United States. Cinnamaldehyde accounts for around 30% of the total annual production volume in Europe and over 93% of that in the United States. In Europe, the per capita daily intake of cinnamaldehyde is estimated at 2.5 mg. The estimated per capita daily intakes of all other flavouring agents in this group of compounds range from 0.003 to 690 µg, with most values being at the lower end of this range.

Of all of the 55 “cinnamyl” substances assessed by the WHO, 90% have been classified, with regard to their chemical structure, as having low toxic potential and being metabolised into harmless products. Moreover, the estimated daily intakes of 51 of these substances (47 Class I and four Class II substances) remain below the thresholds of concern for their structural classes (1800 µg/day and 540 µg/day respectively).

For cinnamaldehyde, the per capita daily intake is 2.5 mg in Europe (42 µg/kg bw) and 59 mg in the United States (990 µg/kg bw). This largely exceeds the threshold of concern for the

structural class. The WHO's assessment therefore took into account the NOAEL of 620 mg/kg bw/day based on a 90-day subchronic toxicity study in rats.

The WHO committee therefore concluded that cinnamaldehyde should not pose any safety problems.

6.3.2.8 Animal exposure

For cinnamaldehyde, a normal level of use as a feed additive is reported as 25 mg/kg feed and a high level is considered as being around 125 mg/kg feed. The safety assessments were carried out based on the highest level of cinnamaldehyde use. The FEEDAP Panel concluded that the use of cinnamaldehyde did not pose any safety problems, at the highest use level (125 mg/kg) in complete feed for salmonids, veal calves and dogs, and at the normal use level (25 mg/kg) for other species. Moreover, no food safety concern would arise for the consumer from the use of cinnamaldehyde up to the highest proposed safe use levels in feed (Efsa 2017).

6.3.2.9 Toxicological data

Table 49: Toxicological data on cinnamaldehyde

	Observations	Conclusions	References
Toxicity after a single administration			
Cinnamaldehyde	Rats, *PO*	LD_{50} = 2220 to 3400 mg/kg bw	(Adams, Cohen et Doull 2004; Jenner *et al.* 1964; D. Opdyke 1979b; Sporn, Dinu et Stanciu 1965; Tisserand et Young 2014)
	Guinea pigs, *PO*	LD_{50} = 1160 mg/kg bw	
	Mice, IP	LD_{50} = 200 and 2320 mg/kg bw	
Toxicity after repeated administration			
Cinnamaldehyde	Rats, *PO* via feed: 0.1%, 0.25% and 1.0% (around 50, 125 and 500 mg/kg/day),16 weeks	No observed effects at 0.1% or 0.25%; at 1.0%, slight swelling of liver cells was observed, in addition to slight hyperkeratosis of the squamous part of the stomach	(Hagan, Hansen et Fitzhugh 1967; Feron, Til et De Vrijer 1991)
Microencapsulated cinnamaldehyde	Rats and mice, *PO:* 275 to 4000 mg/kg bw/day, 15 weeks	Mice, NOAEL = 625 mg/kg bw (olfactory epithelial degeneration) Rats, NOAEL = 275 mg/kg bw (diffuse multifocal	(Hooth, Sills et Burka 2004; NTP 2004) (Efsa 2017) (WHO 2000) ECHA

	Mice, *PO:* 625 to 5475 mg/kg bw/day, 15 weeks	white nodules of the forestomach mucosa) The FEEDAP Panel selected a NOAEL = 275 mg/kg bw/day in rats as a group NOAEL for cinnamaldehyde and related cinnamyl derivatives. Mice LOAEL[67] = 1310 mg/kg bw/day NOAEL = 656 mg/kg bw/day Rats, 125 mg/kg bw/day < NOAEL < 1000 mg/kg bw/day	
Genotoxicity/Mutagenicity			
Cinnamaldehyde	Ames test (with or without S9) in *Salmonella* Typhimurium strains: TA98, TA100, TA102, TA104, TA1535 and TA1537	NTP: cinnamaldehyde was non-mutagenic in the Ames test (with or without S9), in strains TA98, TA102, TA104, TA1535 and TA1537. Only the strain TA100 with S9 showed an effect in certain studies.	(Tisserand et Young 2014; NTP 2000; Dillon, Combes et Zeiger 1998; Ishidate, Sofuni et Yoshikawa 1984; Lutz, Eder et Neudecker 1982; Eder, Deininger et Muth 1991; Sasaki et Endo 1978; Marnett, Hurd et Hollstein 1985; Mortelmans, Haworth et Lawlor 1986; Azizan et Blevins 1995; Shaughnessy, Setzer et DeMarini 2001)

[67] Lowest observed adverse effect level

	DNA repair test in *Bacillus subtilis*	Detection of a mutagenic effect	(Sekizawa et Shibamoto 1982)
	In vitro in human colon cancer cells and *E. coli*	No mutagenic effects	(Shaughnessy, Schaaper et Umbach 2006; King, Shaughnessy et Mure 2007)
	Liver micronucleus assays in mice and rats	Marginal increase in the frequency of micronucleated hepatocytes	(Hayashi, Kishi et Sofuni 1998; Mereto, Brambilla-Campart et Ghia 1994)
	In vitro in mouse bone marrow cells exposed to X-rays	Decrease in chromosome aberrations	(Sasaki, Ohta et Imanishi 1990)
Carcinogenicity			
Cinnamaldehyde	Mice, *PO:* 125, 270 or 550 mg/kg/day, two years	No increase in the incidence of neoplastic and non-neoplastic lesions	(Hooth, Sills et Burka 2004; NTP 2004)
	F344/N rats, *PO* a) 0, 235, 470, 940, 1880 mg/kg bw/day, five days per week (12 doses in total) b) 0, 235, 470, 940, 1880 or 3750 mg/kg bw/day in a volume of 5 ml/kg bw, 16 days (12 doses in total)	Lowest dose: no effect ≥ 470 mg/kg: minor or moderate hyperplasia of the forestomach in males 1800 and 3750 mg/kg: distension of the gastrointestinal tract 940 mg/kg (females): reduced body weight (bw)	ECHA[68]
Reprotoxicity and developmental toxicity			
Cinnamaldehyde	*In vitro* study in chicken embryos, 72 hours of incubation	Teratogenic value of 43.05% compared to a control value of 7.9%	(Forschmidt 1979)
	Mice (pregnant females), *PO:*	No significant effect on weight gain in the mothers or birth weight in the	(Hardin, Schuler et Burg 1987)

[68] https://echa.europa.eu/fr/registration-dossier/-/registered-dossier/14462/7/8

	1200 mg/kg bw/day from gestation day 6 to 13	offspring compared to the controls	
	Rats (pregnant females), subcutaneous (SC) route: 50, 75 or 100 mg/kg cinnamaldehyde in DMSO administered to pregnant rats, only one injection 3h before to 24h after injection of 5-AC	Inhibition of foetal alterations induced by 5-azacytidine No increase in foetal mortality	(Kurishita et Ihara 1990)
	Rats, *PO,* 2 mg cinnamaldehyde administered to two generations of animals for 223 or 210 days	No change in the body weight of the adults or offspring, the number of pregnant females, or the development and viability of the newborns The level of hepatic lipids increased by 20% regardless of the generation	(Sporn, Dinu et Stanciu 1965) ECHA[69]
Nephrotoxicity and hepatotoxicity			
Cinnamaldehyde	Rats, gavage: 2.14, 6.96, 22.62 or 73.5 mg/kg cinnamaldehyde for 10, 30 or 90 days Rats, 4100, 8200, 16,500 or 33,000 ppm microencapsulated cinnamaldehyde via feed, i.e. around 275, 625, 1300 or 4000 mg trans-cinnamaldehyde/kg bw (males) and 300, 570, 1090 or 3100 mg/kg bw (females)	73.5 mg/kg bw/day for 90 days: histological changes in the kidneys associated with proteinuria, creatinuria, and an increase in the activity of kidney, blood and urine enzymes. This increased enzymatic activity was consistent with doses that saturate detoxification mechanisms. > 1300 mg/kg bw/day: modified levels of urinary creatinine and total protein	(Gowder et Devaraj 2008) (NTP 2004)

[69] https://echa.europa.eu/fr/registration-dossier/-/registered-dossier/14462/7/5/2

		Nephrotoxicity also found at doses above 1300 mg/kg bw/day	
Cinnamaldehyde	Rats, IP Rats, IV, 25 or 50 mg/kg/day, seven days	Hepatic glutathione reduced by 47% after 30 minutes and 65% after two hours (Boyland et Chasseaud 1970) The activity of S-transferase glutathione was reduced by 43%, but glutathione levels were not reduced In rat hepatocytes, one hour of exposure to cinnamaldehyde caused glutathione levels to decrease rapidly, and in a dose-dependent manner, by up by 80% Rapid hepatocyte glutathione depletion by cinnamaldehyde induced ROS formation and lipid peroxidation	(Boyland and Chasseaud 1970) (Choi, Lee et Ka 2001) (Swales et Caldwell 1992)

6.3.2.10 PK and residue data

- **ADME characteristics**

Cinnamaldehyde is rapidly absorbed by the intestines. In male F344 rats administered 330 mg/kg bw radiolabelled cinnamaldehyde by gavage, 77 to 83% of the dose was excreted in the urine within 24h and 0.9% to 16% in the faeces. After 72h, 90% was found in the urine. IP administration of an equivalent dose of cinnamaldehyde to groups of CD-1 mice showed a similar pattern of excretion in the urine and faeces at 24h (75-93%) and 72h (> 93%) ((Nutley 1990) cited by (WHO 2000)).

The tissue distribution and excretion of cinnamaldehyde were studied in male F344 rats pretreated with oral doses of 5, 50 or 500 mg/kg bw cinnamaldehyde by gavage once a day for seven days and then given the same single oral dose of [^{14}C]-cinnamaldehyde 24h later. As stated above, after 24h, more than 80% of the dose was recovered in the urine and less than 7% in the faeces. The level of radioactivity in the blood remained below 0.15% of the dose after 24h for all the doses tested. The radiolabel was distributed primarily in the gastrointestinal tract, kidneys and liver. A small fraction of the dose was found in the fat (0.2 to 0.9%) and less than 0.3% in the brain, heart, lungs, spleen and testicles. After 72h, recovery in the urine and faeces reached 95%. The elimination half-life of cinnamaldehyde was therefore estimated at 5 to 9h for whole blood and the liver, 5 to 8h for the muscle, and 17.3 (at 5 mg/kg) to 73h (at 500 mg/kg) for the adipose tissue. The radiolabel could still be detected in the fat of the animals

sacrificed three days after receiving 50 or 500 mg cinnamaldehyde/kg bw (Sapienza *et al.* 1993).

In general, the enzymatic pathways involved in the metabolism of cinnamaldehyde are: (i) oxidation of the alcohol function into acid to form cinnamic acid; (ii) β-oxidation of the side chain, leading to the formation of benzoic acid; (iii) conjugation with amino acids such as glycine to form hippuric acid, promoting its elimination in urine; or (iii') conjugation with glucuronic acid or glutathione, which remains a minor pathway (Efsa 2008a; WHO 2000).

The main metabolic pathway, in rats, for single or multiple doses of 5 or 50 mg/kg, is degradation into benzoic acid via β-oxidation and excretion in urine primarily in the form of hippuric acid (81.6-84.8%), with much smaller quantities of benzoic acid (3.4-5.1%) and cinnamic acid (1.0-1.6%). Multiple oral doses of 500 mg/kg cinnamaldehyde in rats were metabolised via a very different pathway than with single doses of 500 mg/kg or with lower multiple doses: urinary levels of 7.6% hippuric acid, 2.1% cinnamic acid and 73.3% benzoic acid were observed (Sapienza *et al.* 1993)

In another study, Peters and Caldwell (1994) showed that the main urinary metabolite was hippuric acid (71-75% in mice and 73-87% in rats). Small quantities of 3-hydroxy-3-phenylpropionic acid (0.4-4%), benzoic acid (0.4-3%) and benzoyl glucuronide (0.8-7.0%) were also detected. In mice only, cinnamic acid was excreted in the form of hippuric acid (glycine conjugate: 4-13%). In both species, around 6 to 9% of the dose was excreted within 24 hours in the form of cinnamaldehyde conjugated with glutathione.

After the hydrolysis of cinnamaldehyde, the CoA ligases that convert cinnamic acid and its analogue 3-phenylpropionic acid to the respective CoA esters (the first step to proceed to β-oxidation and amino acid conjugation) were shown to be expressed in the liver and kidneys of ruminants (Vessey et Hu 1995), the gut of pigs (Vessey 2001) and the liver and kidneys of fish (Schlenk *et al.* 2008). In ruminants, the metabolism of these compounds largely starts in the rumen. When cinnamic acid was infused in the rumen or abomasum of ruminants, 70% was recovered in the urine as benzoic acid conjugates (Martin 1982a). In the rumen, 3-phenylpropionic acid originated by microbial metabolism of hydroxycinnamic acids was absorbed and oxidised in the body and eliminated as benzoic acid in urine (Martin 1982b). In sheep, Pagella *et al.* (1997) also showed that 3-phenylpropionic acid infused in the rumen was excreted in the urine mainly as hippuric acid.

Conjugation of carboxylic acids with amino acids exhibits some species specificity. After oral administration of 50 mg/kg radiolabelled benzoate to several animal species (rabbits, pigs, cats and dogs), all eliminated almost all of the initial dose in the urine after 24h as hippuric acid. In dogs, approximately 20% was excreted as benzoyl glucuronide (Bridges *et al.* 1970). Many other target species can also form glucuronides, although this is generally a minor route of excretion. Several types of birds, including chickens, excrete benzoic acid as ornithuric acid (Baldwin, Robinson et Williams 1960; Letizia *et al.* 2005). In fish, benzoic acid is conjugated mainly with taurine (Schlenk *et al.* 2008). Although at a minor rate, glycuronoconjugates can be formed and conjugation with glucuronic acid can also be carried out by all target species (Gusson *et al.* 2006; James 1987; Watkins et Klaassen 1986). Therefore, mammals, fish and birds have the ability to metabolise and excrete flavouring substances, and there is no evidence that they or their metabolites accumulate in tissues. Furthermore, the FEEDAP Panel notes that for feline species, the capacity for conjugation is limited (Court 2013; Shrestha *et al.* 2011).

In human skin, cinnamaldehyde is metabolised into cinnamyl alcohol and cinnamic acid (Weibel et Hansen 1989). Applying cinnamaldehyde to female human skin showed that 9.4% was absorbed within 24 hours. This was detected as 2.6% cinnamaldehyde, 2.4% cinnamyl alcohol and 4.4% cinnamic acid (Smith, Moore et Elahi 2000).

6.3.2.11 Summary of the assessment

Considering that cinnamaldehyde:

- **is not listed in Table 1 of Regulation (EU) No 37/2010;**
- **is included on the list of flavouring substances, without restrictions (Regulation (EU) No 872/2012);**
- **is authorised as a feed additive;**
- **is not genotoxic or reprotoxic;**
- **has an ADI of 1.25 mg/kg bw/day;**

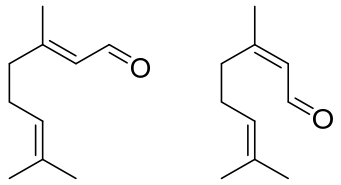
the WG concludes, based on the available data, that the presence of cinnamaldehyde is not of concern for consumers of foods derived from animals that have received plants and/or EOs containing this substance in the context of veterinary medicine.

6.3.3 Citral

6.3.3.1 General data

Citral is a mixture of two substances in equilibrium, geraniol 60-65% and neral 35-40%, both of which are found in plants.

Table 50: General data on citral

Common name	Citral (geranial 60-65% + neral 35-40%)
Synonyms	Citral Geranial: Citral A, *trans*-citral, α-citral, a-citral Neral: Citral B, *cis*-citral
IUPAC name	3,7-Dimethyl-2,6-octadienal
CAS No.	5392-40-5: stereoisomer mixture 141-27-5: geranial (2*E*) 106-26-3: neral (2*Z*)
EC No.	226-394-6
Physico-chemical properties	Chemical formula: $C_{10}H_{16}O$ Molecular weight: 153.23 g/mol Description: light yellow liquid with a lemon-like odour Solubility in water: 0.59 g/L (25°C)[70] LogP: 2.76[71]
Chemical structure	 geranial neral

6.3.3.2 Status in the regulations and guidelines

Table 51: Status of citral in the regulations and guidelines

MRLs	**Regulation (EU) No 37/2010**	Not listed
MAs in France		BRONCHORECTINE® suppositories with citral

[70] https://pubchem.ncbi.nlm.nih.gov/compound/Citral#section=Solubility
[71] ILO International Chemical Safety Cards (ICSCs) and ECHA

Food supplements	**Ministerial Order of 24 June 2014**; **DGCCRF 2019**	Not listed
Novel foods	**EFSA catalogue**	Not listed
Feed additives	**Regulation (EU) No 1831/2003**	Yes
Flavouring substances	**Regulation (EU) No 872/2012**	Yes, under the name citral
REACH		Registered

6.3.3.3 Opinions of European agencies

Table 52: Opinions of European agencies on citral

EMA HMPC	An assessment report on *Citrus bergamia* Risso et Poiteau, aetheroleum (EMA 2012a)
EFSA FEEDAP	A scientific opinion on the safety and efficacy of FRESTA® F for weaned piglets (Efsa 2011b) and an opinion on the safety and efficacy of α,β-unsaturated straight-chain and branched-chain aliphatic primary alcohols, aldehydes, acids and esters belonging to chemical group 3 when used as flavourings for all animal species (Efsa 2016b)
EFSA CEF Panel	A scientific opinion on Flavouring Group Evaluation 06, Revision 4 (FGE.06Rev4): Straight- and branched-chain aliphatic unsaturated primary alcohols, aldehydes, carboxylic acids and esters from chemical groups 1, 3 and 4 (Efsa 2013b)

6.3.3.4 Presence in EOs

According to “Essential Oil Safety” (Tisserand et Young), citral is found in the following plants:

Table 53: List of the EOs that contain the most citral

Lemongrass, *Cymbopogon flexuosus* Nees ex Steud. (syn. *Cymbopogon citratus* DC) (leaves)	Geranial: 45.1-54.5% / 36.7-55.9% Neral: 30.1-36.1% / 25.0-35.2% [72]
Aromatic litsea, *Litsea cubeba* (Lour.) Pers. (fruit)	Geranial: 37.9-40.6% Neral: 25.5-33.8%[72]
Lemon verbena, *Aloysia triphylla* L’Herit. (leaves)	Geranial: 29.5-38.3% Neral: 22.9-29.6%
Lemon balm, *Melissa officinalis* L. (aerial parts)	Geranial: 12.5-38.3% Neral: 9.7-26.1%

[72] Values of the International Fragrance Association (IFRA)

Lemon thyme, *Thymus x citriodorus* (Pers.) Schreb. (aerial parts)	Geranial: 9.2% Neral: 7.1%
Lemon, *Citrus* x *limon* L. (leaves)	Geranial: 10.9-39% Neral: 6.5-25.3%
Lemon, *Citrus* x *limon* L. (zest, expression)	Geranial: 0.5-4.3%; 0.5-2.3% (Ph. Eur.) Neral: 0.4-2%; 0.3-1.5% (Ph. Eur.)
Sweet orange, *Citrus x sinensis* (L.) Osbeck. (zest, expression)	Geranial: 0.03-0.2% (Ph. Eur.) Neral: 0.02-0.1% (Ph. Eur.)
Palmarosa, *Cymbopogon martinii* Roxb. var. *martinii* (leaves)	Geranial: 0.5-1.9%

6.3.3.5 Presence in the normal human diet

Geranial is not listed in Annex I of Regulation (EC) No 396/2005.

Geranial is on the list of flavouring substances under the name “citral” (containing 60-65% geranial and 35-40% neral), with no use restrictions.

6.3.3.6 Presence in the normal diet of animals

Citral is

- listed in the European Union Register of Feed Additives in accordance with Regulation (EC) No 1831/2003;
- classified under “2; b; Natural or corresponding synthetic chemically defined flavourings”[73].

It has been authorised without a time limit, in accordance with Directive 70/524/EEC, as a feed additive for all animal species. Citral is mentioned in Commission Implementing Regulation (EU) 2020/1396 of 5 October 2020 concerning the authorisation of geraniol, citral, 3,7,11-trimethyldodeca-2,6,10-trien-1-ol, (Z)-nerol, geranyl acetate, geranyl butyrate, geranyl formate, geranyl propionate, neryl propionate, neryl formate, neryl acetate, neryl isobutyrate, geranyl isobutyrate and prenyl acetate as feed additives for all animal species except for marine animals.

The recommended maximum level for citral is 25 mg/kg complete feedingstuff with a moisture content of 12%.

6.3.3.7 Human exposure

Citral is present in the normal human diet and is used as a food additive, with an ADI of 0.5 mg/kg bw (WHO 2003) (based on its metabolism, rapid excretion, and low toxicity in short-term studies).

[73] https://ec.europa.eu/food/sites/food/files/safety/docs/animal-feed_additives_eu-register_1831-03.pdf

Several exposure data were found in the various study reports cited in Section 6.3.3.3. The estimated per capita daily intake was 6849 µg in Europe and 6990 µg in the United States (EMA 2012a). Citral is not endogenous in humans.

In a 2013 report (Efsa 2013b), EFSA's CEF Panel concluded that when citral is used as a flavouring, it is efficiently metabolised and does not saturate the metabolic pathways. For these reasons, and in light of the toxicological data on citral, it also considered that the total combined intake (0.3 mg/kg bw/day) would not pose any safety problems.

Two other exposure approaches (estimated per capita daily exposure (maximised survey-derived daily intake (MSDI)) and daily human exposure for a 60 kg individual in 2016) have been reported. They led to the conclusion that citral does not pose any safety problems.

6.3.3.8 Animal exposure

Normal diet

Citral is safe for all target species at the proposed maximum use level of 25 mg/kg feed (with no withdrawal period). The normal level of use is 5 mg/kg feed (Efsa 2016b).

Feed additive

Geranial is listed in the European Union Register of Feed Additives in accordance with Regulation (EC) No 1831/2003 (2; b; Natural or corresponding synthetic chemically defined flavourings).

6.3.3.9 Toxicological data

Table 54: Toxicological data on citral

	Observations	Conclusions	References
Toxicity after a single oral administration			
Citral	Rats	LD_{50}= 4.96 g/kg	(Efsa 2013b; Tisserand et Young 2014) FAO, WHO, 1967[74] ECHA
	Mice	Maximum non-lethal dose = 900 mg/kg	(Tisserand et Young 2014)
	Mice	LD_{50} oral = 3297 mg/kg bw	(Efsa 2013b)

[74] https://apps.who.int/food-additives-contaminants-jecfa-database/chemical.aspx?chemID=3486

		LD_{50} oral = 2007 mg/kg bw and 2464 mg/kg bw	
	Rats (females), gavage, observation for two days	LD_{50} = 4895 mg/kg	ECHA
Citral	Rats: 2150, 3160, 4640, 6810 and 10,000 mg/kg bw, observation for 14 days	LD_{50} = 6800 mg/kg bw	(Efsa 2013b) ECHA
Toxicity after repeated administration			
Citral	Rats: 0, 50, 125 and 500 mg/kg/day, 13 weeks	NOAEL = 500 mg/kg bw/day	(Efsa 2016b)
Microencapsulated citral	Mice and rats, 3900, 7800, 15,600 or 31,300 ppm, 14 weeks	NOAEL rats = 10,000 ppm (500 mg/kg) NOAEL mice = 7800 ppm (905 mg/kg)	(Tisserand et Young 2014)
Citral	Mice (28 days), 0, 534, 1068, 2137, 4275 or 8550 mg/kg bw, 12 days	NOEL < 534 mg/kg bw/day (increased liver weights) Probably adaptive effects on the liver (enzymatic activation)	(WHO 2003)
Microencapsulated citral	Mice, 14 days	NOAEL = 4275 mg/kg bw/day (weight reduction)	
Citral via feed	Mice: 0, 745, 1840, 3915 and 8810 mg/kg bw/day (males) and 0, 790, 1820, 3870 and 7550 mg/kg bw/day (females) Rats: 0, 345, 820 and 1785 mg/kg bw/day (males) and 0, 335, 675 and 1330 mg/kg bw/day (females) 14 weeks	Mice: NOAEL (M) < 745 mg/kg bw NOAEL (F) < 790 mg/kg bw Rats: NOAEL (F) = 675 mg/kg bw/day NOAEL (M) = 345 mg/kg bw/day The FEEDAP Panel selected a NOAEL = 345 mg/kg bw/day (90-day study in rats)	(Efsa 2016b)

Citral via feed	Rats and mice, 0, 50, 100 and 210 mg citral/kg bw/day for rats and 0, 60, 120 and 260 mg/kg bw/day for mice Duration: two years (as a carcinogenicity study)	<u>Rats</u> NOAEL = 100 mg/kg bw/day LOAEL = 210 mg/kg bw/day <u>Mice</u> LOAEL = 60 mg/kg bw/day (F) & 120 mg/kg bw/day (M)	ECHA
Citral, feeding or gavage	Several mouse and rat studies, 12-14 days or 12-14 weeks	<u>Mice</u> NOAEL < 534 mg/kg bw/day (M, F, gavage) NOAEL = 4275 mg/kg bw/day (M, F, feed, 14 days) NOAEL = 60 mg/kg bw/day (F) and 120 mg/kg bw/day (M) <u>Rats</u> NOAEL = 1140 mg/kg bw (M) & 2280 mg/kg bw (F) (gavage, 12 days) NOAEL = 570 mg/kg NOAEL = 100 mg/kg bw/day (weight reduction, especially for F)	(Efsa 2013b)
Genotoxicity/Mutagenicity			
Citral	Various tests carried out: Ames, with and without S9, chromosome aberration test, *in vitro* study in CHO cells, hamster cell test, mouse micronucleus test	Negative results Non-mutagenic Non-genotoxic Non-clastogenic	(Tisserand et Young 2014; Efsa 2013b; EMA 2015a; WHO 2003) ECHA
Carcinogenicity			
Microencapsulated citral, via feed	Mice: 0, 60, 120 and 260 mg/kg bw/day, 104-105 weeks	NOAEL mice = 120 mg/kg bw/day (M) & 60 mg/kg bw/day (F) (moderate weight reduction)	(Efsa 2013b) ECHA

	Rats: up to 100 mg/kg bw/day, 104-105 weeks	NOAEL rats = 100 mg/kg bw/day Citral is not carcinogenic in mice or rats	
	1000, 2000 or 4000 mg/kg/day, two years (repeated dose toxicity) Rats: 0 (untreated or placebo), 50, 100 and 210 mg citral/kg bw/day Mice: 0 (untreated or placebo), 60, 120 and 260 mg citral/kg bw/day	Rats: NOAEL = 100 mg/kg bw/day LOAEL = 210 mg/kg bw/day Mice: NOAEL > 210 mg/kg bw/day LOAEL (F) = 60 mg/kg bw/day & 120 mg/kg bw/day (M) Non-carcinogenic	(Efsa 2016b; Tisserand et Young 2014; WHO 2003) ECHA
Reprotoxicity and developmental toxicity			
Citral	Rats, gavage: 0, 60, 125, 250, 500 and 1000 mg/kg bw/day, from day 6 to 15 of gestation	Maximum oral dose = 0.6 mg/kg/day, based on the NOAEL = 60 mg/kg/day, after applying an uncertainty factor of 100 $LOAEL_{development}$ = 60 mg/kg bw/day; $LOAEL_{maternal}$ = 60 mg/kg bw/day Non-teratogenic	(Tisserand et Young 2014; Efsa 2013b; WHO 2003) ECHA
	Citral and geranial: injection in embryonated chicken eggs	Malformations in the chick embryos	(Tisserand et Young 2014)
	Rats, oral route: 0, 50, 160 and 500 mg/kg bw/day, from two weeks before mating to gestation day 20	$NOAEL_{maternal}$ = 50 mg/kg bw/day $NOAEL_{development}$ = 160 mg/kg bw/day	(WHO 2003)
Citral	Rats, gavage, 14 days Rabbits, gavage, 29 days	Rats $NOAEL_{reprotox}$ = 1000 mg/kg bw/day	ECHA

		$NOAEL_{maternal}$ = $NOAEL_{development}$ = 200 mg/kg bw/day Rabbits $NOAEL_{maternal}$ = $NOAEL_{development}$ = 60 mg/kg bw/day	

Citral is non-mutagenic, non-genotoxic, non-carcinogenic and non-teratogenic in laboratory animals (rats, mice and/or rabbits) according to the data from the literature.

6.3.3.10 PK and residue data

- **Data in animals**

Table 55: Animal PK and residue data on citral

Parameter	Observations	References
Absorption Oral bioavailability	Rats and mice (males) Single dose of radiolabelled citral, gavage Rats: 5, 770 or 960 mg/kg bw/day Mice: 100 mg/kg bw/day Rapid and near-complete absorption in the gastrointestinal tract (90-95%) and no bioaccumulation **Absorption and distribution** The lipophilic nature of citral (log Pow: 2.76) promotes oral absorption and diffusion through the cell membranes => wide dispersion through tissue with no evidence of major accumulation Quantity in tissue 72h after administration below 2% of the applied dose	ECHA
Metabolism	Rats: ω-oxidation and β-oxidation of geraniol and citral = mixture of diacids and hydroxyacids Metabolic pathways of geraniol-related terpenoid alcohols (citronellol and nerol) and aldehydes (geranial, citronellal and neral): similar in all animal species Major metabolite: glucuronide of geranic acid found in bile Several carboxylic acids found in urine: metabolites resulting from oxidation of the aldehyde function (geranic acid) or from ω-oxidation and reduction and hydration of the double bond at C2 (2,6-dimethyl-2,6-octadienedioic acid and 2,6-dimethyl-2-enedioic acid) (WHO 2003)	Figure III.4 of the EFSA CEF report (2013b)

	Citral is a potent inhibitor of ALDH-mediated oxidation of acetaldehyde, with reduction to the corresponding alcohols by rat hepatic alcohol dehydrogenase (ADH). These alcohols may then undergo cytochrome P450-mediated ω-hydroxylation. Treating rats with citral has also induced hepatic cytochrome P450 and glucuronyltransferase.	
	Rapid first-pass liver metabolism (a few minutes) with no saturation up to the highest investigated doses of 500 mg/kg bw More hydrophilic metabolites with additional polar -COOH and -OH groups have been identified in urine, and glucuronic acid conjugates have been found in bile. Seven metabolites of citral were characterised in urine and bile after oral exposure (E-3,7-dimethyl-2,6-octadienoic acid; 3,8-dihydroxy-3,7-dimethyl-6-octenoic acid; 3,9-dihydroxy-3,7-dimethyl-6-octenoic acid; E-3,7-dimethyl-2,6-octadienedioic acid; Z-3,7-dimethyl-2,6-octadienedioic acid; 3 -hydroxy-3,7,dimethyl-6-octenedioic acid; 3,7-dimethyl-6-octenedioic acid). The parent compound, i.e. citral, was not detected.	ECHA
Distribution	The relative amount in tissue is independent of the dose or route of administration. The highest tissue concentrations have been observed in liver (1.5-2%), muscle, blood, and adipose tissue. Citral is distributed in body tissues with no major accumulation (< 2% of 14C in tissue 72h post-administration).	ECHA
Excretion	Rats: after oral administration, 60% of citral is excreted in urine, 17% in faeces, and 20% in exhaled air. Citral is significantly (27%) eliminated in bile, although most of its metabolites end up in urine. Rabbits: citral is oxidised and a carboxylated (E)-methyl group is formed. Geranic acid and 8-carboxygeranic acid (Hildebrandt acid) are excreted in urine.	(Tisserand et Young 2014)
	Excretion is complete after 96h in rats and after 120h in mice The excretion profile does not change depending on the dose	(Efsa 2013b; WHO 2003)
	Excretion kinetics (% of 14C-dose): within 24h, 45% in urine, 6% in faeces, 16% in air and < 1% as 14C-citral; within 72h, 80% is excreted and 3% is in tissue.	ECHA

Residues	Citral is rapidly distributed in the body, metabolised, and excreted as polar metabolites in urine, faeces and exhaled air. No accumulation in the body is expected.	(WHO 2003)

Citral is rapidly absorbed, metabolised and excreted, primarily in urine, and then in faeces and exhaled air (the majority within 24h). There is rapid distribution in the body regardless of the administered dose and evidence of enterohepatic circulation of citral metabolites. There is no evidence of bioaccumulation.

6.3.3.11 Reported adverse effects

- **Cases from nutrivigilance**

No cases have been reported.

- **Cases from pharmacovigilance**

EMA issued an opinion concerning suppositories containing terpene derivatives. The pharmacovigilance data showed that neurological adverse effects (e.g. convulsions) had occurred in infants treated with suppositories containing citral. As a result, suppositories containing citral are contraindicated for children aged under 30 months and children with a history of epilepsy or febrile convulsions.

- **Cases recorded in Canada and the United States**

No cases have been reported.

6.3.3.12 Summary of the assessment

Considering that citral:

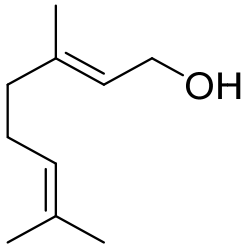
- **is not listed in Table 1 of Regulation (EU) No 37/2010;**
- **is included on the list of flavouring substances, without restrictions (Regulation (EU) No 872/2012);**
- **is used as a feed additive and is considered safe for animals at a concentration of 25 mg/kg complete feed;**
- **has a maximum exposure level reported in the literature of 0.3 mg/kg bw/day (combined intakes);**
- **is rapidly metabolised and excreted;**
- **does not generate any high-risk metabolites;**
- **is not mutagenic or carcinogenic;**
- **has an ADI = 0.5 mg/kg bw/day;**

the WG concludes, based on the available data, that the presence of citral is not of concern for consumers of foods derived from animals that have received plants and/or EOs containing this substance in the context of veterinary medicine.

6.3.4 Geraniol

6.3.4.1 General data

Table 56: General data on geraniol

Common name	Geraniol
Synonyms	(*E*)-Geraniol, *trans*-geraniol, Geranyl alcohol, Lemonol, *E*-nerol
IUCPA name	3,7-dimethylocta-2,6-dien-1-ol
CAS No.	106-24-1
EC No.	203-377-1
Physico-chemical properties	Chemical formula: $C_{10}H_{18}O$ Molecular weight: 154.25 g/mol Description: colourless to pale yellow liquid with a sweet rose odour Solubility in water: 0.1 g/L (25°C) LogP: 3.56
Chemical structure	

6.3.4.2 Status in the regulations and guidelines

Table 57: Status of geraniol in the regulations and guidelines

MRLs	**Regulation (EU) No 37/2010**	Not listed
MAs in France		No medicinal products registered in France
Food supplements	**Ministerial Order of 24 June 2014; DGCCRF 2019**	Not listed
Novel foods	**EFSA catalogue**	Not listed
Feed additives	**Regulation (EU) No 1831/2003**	Listed without restrictions for all animal species
Flavouring substances	**Regulation (EU) No 872/2012**	Listed, flavouring substance with no restrictions

REACH	Registered

6.3.4.3 Opinions of European agencies

Table 58: Opinions of European agencies on geraniol

EFSA FEEDAP	A scientific opinion on the safety and efficacy of α,β-unsaturated straight-chain and branched-chain aliphatic primary alcohols, aldehydes, acids and esters belonging to chemical group 3 when used as flavourings for all animal species (Efsa 2016b)
EFSA – Assessments of pesticide active substances	Assessment reports on geraniol as an AS
JECFA	Assessment as part of the 61st JECFA meeting (WHO 2003)

6.3.4.4 Presence in EOs

According to Tisserand and Young (2014), a non-exhaustive list of the EOs that contain geraniol is given below:

Table 59: List of EOs containing geraniol

Ceylon citronella, *Cymbopogon nardus* L. (leaves)	16.8-29.1%
Java citronella, *Cymbopogon winterianus* Jowitt (leaves)	22.1-25.4% (20-25%, Ph. Eur.)
Lemon, *Citrus* x *limon* L. (leaves)	0.5-15.0%
Coriander, *Coriandrum sativum* L. (fruit)	0.3-5.3%
Narrow-leaved peppermint, *Eucalyptus radiata* Sieber ex DC (leaves)	0.2-2.8%
Bourbon geranium, *Pelargonium* x *asperum* Ehrh. ex Willd (leaves)	8.7-8.9% / 15.7-18.0% / 15.1-20.6% / 7.3-30.3% depending on the CT
Lavandin, *Lavandula* x *intermedia* Emeric ex Loisel. (flowering aerial parts)	1.5% (not queried in the French Pharmacopoeia (Grosso clone))
Lemongrass, *Cymbopogon flexuosus* Nees ex Steud. (syn. *Cymbopogon citratus* DC) (leaves)	0-6.7% / 0.2-3.8%, depending on the CT
Aromatic litsea, *Litsea cubeba* (Lour.) Pers. (fruit)	0.5-1.6%
Lemon balm, *Melissa officinalis* L. (aerial parts)	1.0-8.1%
Orange (neroli), *Citrus* x *aurantium* L. (flowers)	2.8-3.6% / 0.8-2.3%, depending on the CT
Orange (petitgrain), *Citrus* x *aurantium* L. (leaves)	1.4-2.3% / 2.1-3.0%, depending on the CT
Palmarosa, *Cymbopogon martinii* Roxb. Var. *martinii* (leaves)	74.5-81.0%
Clary sage, *Salvia sclarea* L. (flowering aerial parts)	0% / 0.6-1.2%, depending on the CT
Thyme CT geraniol, *Thymus vulgaris* L. (aerial parts)	24.9%

6.3.4.5 Presence in the normal human diet

Geraniol is not present in the normal human diet but is included on the list of flavouring substances with no use restrictions.

6.3.4.6 Presence in the normal diet of animals

Numerous plants containing geraniol are found in pastures (Efsa 2016b).

6.3.4.7 Human exposure

EFSA:

ADI = 0.5 mg/kg bw/day (group ADI, expressed as citral: similar molecular weight to geraniol) (Efsa 2016b).

The monograph for geraniol (EFSA website[75]) proposes that the ADI derived by JECFA of 0.5 mg/kg bw/day should be used for geraniol.

The average daily intake that results from the use of geraniol as a food additive has been estimated at 5.2 and 11 µg/kg bw/day respectively in the United States and Europe (see JECFA data below). If consumption of geraniol from natural sources in Europe is nine times the quantity of the substance consumed as a food additive, then the average consumption of naturally occurring geraniol is around 0.1 mg/kg bw/day; this value is far higher than the ADI..

Table 60: Routes of human exposure to geraniol (UK 2016)

	Route of exposure	**Estimated exposure level (mg AS/kg bw/day)**
Wine consumption	Oral	0.000005 – 0.005
Food additives	Oral	0.0052 – 0.011
Natural sources	Oral	0.1
Cosmetic products	Dermal	0.1289
Massage oils	Dermal	1.5
Deodorants	Inhalation	0.001

Due to the omnipresence of geraniol in vegetation and its low toxicity, geraniol has obtained the GRAS status for use as a food additive in the United States[76].

EFSA FEEDAP (Efsa 2016b):

Geraniol is included in the EU database on flavouring substances and is authorised in the EU as a food flavouring without any limitations. Its use is therefore authorised in food in the EU.

[75] https://www.efsa.europa.eu/en/consultations/call/public-consultation-active-substance-geraniol
[76] US Food and Drug Administration, 21 CFR, Part 182, Section 182.60, eCFR :: 21 CFR Part 182 -- Substances Generally Recognized as Safe

Human exposure (with a maximum concentration of 25 mg/kg in food) has been estimated at 25.5 µg/kg $bw^{0.75}$ per day[77].

6.3.4.8 Animal exposure

- **Normal diet (EFSA FEEDAP)**

Table 61: Maximum safe concentration of geraniol in feed for different target animals (Efsa 2016b)

Table 4: Maximum safe concentration in feed for different target animals for (**A**) citral, geraniol, (*Z*)-nerol and related esters (NOAEL (345 mg/kg bw per day); (**B**) farnesol (NOAEL 1,000 mg/kg bw with an UF of 200)

Target animal	Default values		Maximum safe intake/feed concentration			
	Body weight (kg)	Feed intake (g/day)[(a)]	Intake (mg/day)		Concentration (mg/kg feed)[(b)]	
			A	B	A	B
Salmonids	2	40	7	10	173	251
Veal calves (milk replacer)	100	2,000	345	500	173	250
Cattle for fattening	400	8,000	1,380	2,000	152	220
Dairy Cows	650	20,000	2,243	3,250	99	143
Piglets	20	1,000	69	100	69	100
Pigs for fattening	100	3,000	345	500	115	167
Sows	200	6,000	690	1,000	115	167
Chickens for fattening	2	120	7	10	57	83

Exposure data for target species (Z-geraniol):

- Use level considered as safe in feed for all animal species: a normal use level of 5 mg/kg feed and a high use level of 25 mg/kg complete feed.
- Exposure of target animals (with a maximum concentration of 25 mg/kg in feed): 588 µg/kg $bw^{0.75}$ per day for salmon, 2.632 for piglets and 3,885 for dairy cows.

- **Feed additive**

Geraniol is listed in the European Union Register of Feed Additives in accordance with Regulation (EC) No 1831/2003 (2; b; Natural or corresponding synthetic chemically defined flavourings).

6.3.4.9 Toxicological data

Table 62: Toxicological data on geraniol

	Observations	Conclusions	References
Toxicity after a single administration			
Geraniol	Rats, oral route	LD_{50} = 3.6 g/kg LD_{50} = 4.9 g/kg	(Tisserand et Young 2014; WHO 2004)

[77] Metabolic body weight (kg $bw^{0.75}$) for a 60 kg individual = 21.6.

Toxicity after repeated administration			
Geraniol	Rats, gavage: 200 mg/kg/day, 10 days	No signs of hepatotoxicity	(Guilbault 2020)
Geraniol	Rats, in feed: 1000 ppm (50 mg/kg), 28 weeks, or 10,000 ppm (500 mg/kg), 16 weeks	No adverse effects	(Tisserand et Young 2014; WHO 2004)
Geranyl acetate 71% / citronellyl acetate 29%	Rats, gavage: 0, 62, 125, 250, 500 or 1000 mg/kg bw/day, 14 days	Geraniol NOAEL extrapolated with molecular weights = 588 mg/kg bw/day	(NTP 1987)
	Mice, gavage: 0, 125, 250, 500, 1000 or 2000 mg/kg bw/day, 14 days	Geraniol NOAEL extrapolated with molecular weights = 279 mg/kg bw/day	
Geraniol	Rats: 1000 mg/kg in feed: for 16 weeks or for 27-28 weeks	NOAEL = 500 mg/kg bw/day NOAEL = 50 mg/kg bw/day	(Tisserand et Young 2014; WHO 2004)
	90-day study in rats	NOAEL = 345 mg/kg bw/day (group NOAEL for citral, geraniol, (Z)-nerol (the *cis* isomer of geraniol) and related esters)	(Efsa 2016b)
Genotoxicity/Mutagenicity			
Geraniol	*In vitro,* from 100 to 2000 µg/ml: - Comet assay - Ames test - Micronucleus test	Non-genotoxic and non-mutagenic	(Tisserand et Young 2014; WHO 2004) (Guilbault 2020)
Carcinogenicity			
Citral and geranyl acetate	No studies with geraniol See citral	Given the structural similarities with citral and geranyl acetate, which are not carcinogenic,	ECHA

		geraniol is considered non-carcinogenic	
Reprotoxicity and developmental toxicity			
Geraniol	Toxicity for fertility: - Rats, reaction mass of geraniol and nerol (60:40) dissolved in corn oil; actual dose ingested: 1000 mg/kg bw/day - Rats, nerol, via feed (*trans*-isomer of geraniol, so same expected behaviour) in 2% corn oil	NOAEL: 600 mg/kg bw/day NOAEL: > 12,000 ppm (corresponding to 720 mg/kg bw/day)	ECHA
Geraniol	Oral developmental toxicity/teratogenicity	NOAEL: 300 mg/kg bw/day	ECHA

Geraniol is non-mutagenic, non-genotoxic, and non-carcinogenic in laboratory animals (rats, mice) according to the data from the literature.

6.3.4.10 PK and residue data

- **Data in animals**

Table 63: Animal PK and residue data on geraniol

Parameter	Observations	References
Absorption Oral bioavailability	Geraniol belongs to a class of structurally related chemicals that are readily absorbed by the gastrointestinal tract, rapidly distributed throughout the body and metabolised into polar metabolites that are readily excreted in urine with no signs of accumulation. For geraniol, two main metabolic pathways have been identified, involving successive oxidation reactions at the side chains to produce polar acidic metabolites excreted in urine.	(Efsa 2012b)
Metabolism	Significantly increased CYP450 concentrations in rat liver after three days of administration of geraniol.	(WHO 2004)
	After administering repeated doses of 800 mg [1-3H]-geraniol/kg bw by gavage daily for 20 days to male rats, two primary pathways leading to five urinary metabolites were identified:	(Efsa 2016b)

	Pathway 1: the alcohol is first oxidised to geranic acid (3,7-dimethyl-2,6-octadieneoic acid), which is subsequently hydrated to yield 3,7-dimethyl-3-hydroxy-6-octenoic acid. Pathway 2: the alcohol undergoes ω-oxidation mediated by liver cytochrome P450 to yield 8-hydroxygeraniol. Selective oxidation at C8 yields 8-carboxygeraniol, which is further oxidised to the main urinary metabolite, 2,6-dimethyl-2,6-octadienedioic acid (Chadha and Madyastha, 1984).	
Distribution	See comments below	
Excretion		
Residues		

No distribution, elimination or residue studies are available for geraniol.

Geraniol and food additives with similar structures such as citral are readily absorbed by the gastrointestinal tract, should be rapidly distributed in the body, and are metabolised and excreted as polar metabolites, without any accumulation in the body (JECFA, 2013).

It should be noted that the above conclusions are primarily the results of studies conducted with citral but are considered applicable to the entire group (including geraniol) (CE 2011).

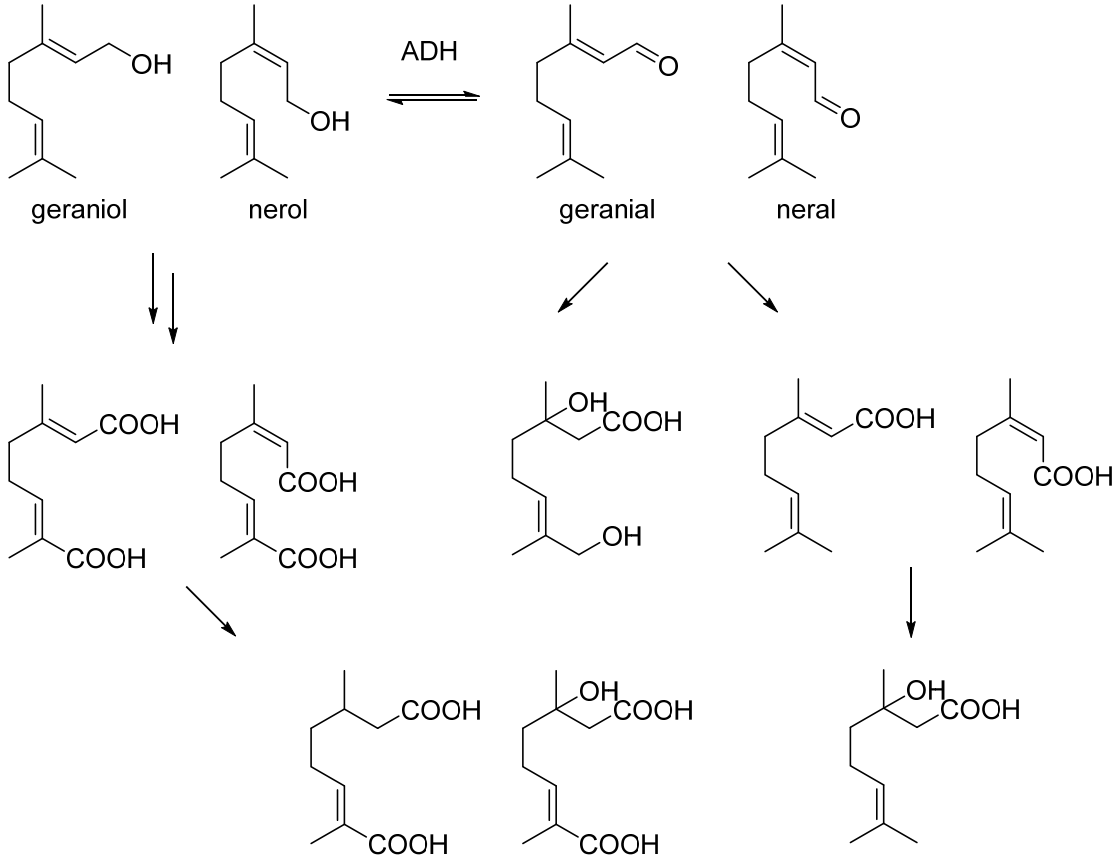


Figure 9: Metabolism of geraniol, neral and citral (WHO 2004)

INRS: 170h after oral administration, geraniol was essentially found in the kidneys, liver and adrenal glands, but at low levels. It underwent alcoholic oxidation, oxygenation, hydration, reduction and conjugation steps to form polar metabolites. Alternatively, the carboxylic acid formed by oxidation of the acetate function was assumed to be rapidly metabolised to geraniol through the action of hydrolases. It was primarily and rapidly eliminated in urine (54%). Approximately 11% of the administered dose was found in exhaled air and 24% in faeces.

- **Human data:**

None.

6.3.4.11 Summary of the assessment

Considering that, for geraniol:

- **this substance is not listed in Table 1 of Regulation (EU) No 37/2010;**
- **this substance is used as a feed additive;**
- **this substance is included on the list of flavouring substances, without restrictions (Regulation (EU) No 872/2012);**
- **this substance is naturally found in pastures;**
- **a human exposure level of 25.5 µg/kg bw/day is authorised for its use as a food additive (with a maximum concentration of 25 mg/kg in food);**
- **the average intake of this substance is around 0.1 mg/kg bw/day;**
- **this substance is not genotoxic, reprotoxic or carcinogenic;**
- **this substance is rapidly metabolised and excreted;**
- **an ADI of 0.5 mg/kg bw/day has been defined;**

the WG concludes, based on the available data, that the presence of geraniol is not of concern for consumers of foods derived from animals that have received plants and/or EOs containing this substance in the context of veterinary medicine.

6.3.5 Limonene

6.3.5.1 General data

Table 64: General data on limonene

Common name	Limonene (D-limonene = (*R*)-(+)-limonene; L-limonene = (*S*)-(-)-limonene)
IUCPA name	(*RS*)-1-Methyl-4-prop-1-en-2-yl-cyclohexene
CAS No.	(*RS*): 138-86-3 (*R*)-(+): 5989-27-5 (*S*)-(-): 5989-54-8
EC No.	(*RS*): 205-341-0 (*R*)-(+): 227-813-5 (*R*) (*S*)-(-): 227-815-6
Physico-chemical properties	Chemical formula: $C_{10}H_{16}$ Molecular weight: 136.23 g/mol Description: colourless liquid, with an odour of lemon Solubility in water: 7.57 mg/L (25°C) LogP: 4.57
Chemical structure	 (*R*)-(+)-limonene D-limonene (*S*)-(-)-limonene L-limonene

6.3.5.2 Status in the regulations and guidelines

Table 65: Status of limonene in the regulations and guidelines

MRLs	**Regulation (EU) No 37/2010**	Not listed
MAs in France		No medicinal products registered in France
Food supplements	**Ministerial Order of 24 June 2014; DGCCRF 2019**	Not listed
Novel foods	**EFSA catalogue**	Not listed
Feed additives	**Regulation (EU) No 1831/2003**	Listed

Flavouring substances	**Regulation (EU) No 872/2012**	Listed, flavouring substance with no restrictions

6.3.5.3 Opinions of European agencies

Table 66: Opinions of European agencies on limonene

EFSA – Assessments of pesticide active substances	Assessment reports on orange oil as an AS (Efsa 2013a)
AFSSA	Opinion on an MA application for the PREV-AM preparation containing sweet orange EO by the company VIVAGRO (AFSSA 2009)
JECFA	Evaluation for the 63rd JECFA meeting (WHO 2005)

6.3.5.4 Presence in EOs

According to “Essential Oil Safety” (Tisserand et Young), limonene is found in the following standard essential oils:

Table 67: List of EOs containing limonene

Angelica, *Angelica archangelica* L. (roots)	6.0-13.2%
Angelica, *Angelica archangelica* L. (fruit)	2.3-38.7%
Bergamot, *Citrus bergamia* Risso & Poit. (zest, expression)	27.4-52.0% / 33.0-42.0% (French Pharmacopoeia)
Caraway, *Carum carvi* L. (fruit)	36.9-48.8%
Celery, *Apium graveolens* L. (leaves)	26.3%
Celery, *Apium graveolens* L. (fruit)	68.0-75.0%
Ceylon citronella, *Cymbopogon nardus* L. (leaves)	2.6-11.3%
Java citronella, *Cymbopogon winterianus* Jowitt (leaves)	1.0-5.0% (Ph. Eur.)
Clementine, *Citrus clementina* Hort, ex Tanaka (zest)	94.8-95.0%
Coriander, *Coriandrum sativum* L. (fruit)	1.5-5.0% (Ph. Eur.)
Blue gum, *Eucalyptus globulus* Labill. (leaves)	1.8-9.0% (0.05-15%, Ph. Eur.)
Juniper, *Juniperus communis* L. (cones)	0-10.9% (2-12%, Ph. Eur.)
Silver fir, *Abies alba* Mill. (cones)	28.5-34.1%
Silver fir, *Abies alba* Mill. (leaves)	54.7%
Grapefruit, *Citrus* x *paradisi* Macfady (zest, expression)	84.8-95.4%

Lemon, *Citrus* x *limon* L. (zest, expression)	56.6-76.0% (56-78%, Ph. Eur.)
Mandarin, *Citrus reticulata* Blanco (zest)	65.3-74.2% (65-75%, Ph. Eur.)
Niaouli, *Melaleuca quinquenervia* Cav. (leaves)	6-12% (5-10%, Ph. Eur.)
Sweet orange, *Citrus* × *sinensis* (L.) Osbeck. (zest, expression)	93.2-94.9% (92-97%, Ph. Eur.)

6.3.5.5 Presence in the normal human diet

Limonene is present in the normal human diet.

6.3.5.6 Presence in the normal diet of animals

Limonene is a normal component of animal feed and fodder.

6.3.5.7 Human exposure

- via food: normal diet (citrus fruit), food additive
- estimated intake in Europe = 660 mg/kg bw/day (WHO 2005)
- via PPPs (AFSSA 2009)

6.3.5.8 Animal exposure

D-limonene: 0.21 g/day in poultry, 0.41 g/day in dogs, 6.4-17.2 g/day in pigs and 78-146 g/day in cattle.

6.3.5.9 Toxicological data

Table 68: Toxicological data on limonene

	Observations	Conclusions	References
Toxicity after a single oral administration			
Limonene	Rats Mice (males) Mice (females)	LD_{50} > 5 g/kg LD_{50} = 6.3 ml/kg LD_{50} = 8.1 ml/kg	(Tisserand et Young 2014) (Efsa 2012a)
	Rats	LD_{50} > 2,000 mg/kg	(AFSSA 2009)
Toxicity after repeated oral administration			
Limonene	Rats: up to 75 mg/kg/day, 90 days Rats and mice: D-limonene up to 6600 mg/kg bw/day, 16 days Rats: - up to 300 mg/kg/day	75 mg: development of nephropathy in male rats only Nephrotoxicity not relevant for humans (depends on the species and sex)	(Tisserand et Young 2014) (Efsa 2012a) (Efsa 2015a) (INRS 2010) (NTP 1990)

	- up to 2770 mg/kg/day to 13 weeks of administration	Hypertrophy of the liver = adaptive effect Overall NOEL = 75 mg/kg	(Kanerva et Alden 1987) (Webb *et al.* 1990) JECFA/WHO (2004)[78]
Genotoxicity/Mutagenicity			
Limonene	12 reports Comet assay	Non-mutagenic / non-genotoxic Non-genotoxic in the tissues studied (brain, bone marrow, colon, kidneys, lungs, liver, stomach)	(Efsa 2012a; INRS 2010; Tisserand et Young 2014; Guilbault 2020)
Carcinogenicity			
Renal carcinogenicity only in male rats (F344/N) Non-mutagenic in the kidneys and liver of male Big Blue® rats, suggesting that renal carcinogenicity is related to a non-genotoxic mechanism (species-/sex-/strain-dependent). The mechanism underlying its carcinogenic activity cannot be extrapolated to humans. No carcinogenic potential identified in humans. No promoter activity when administered in food. In oxidised form: non-carcinogenic. Inhibits the activation of tobacco-specific natural killer cells in the lungs and hepatic microsomes of mice.			(Efsa 2012a; INRS 2010; Tisserand et Young 2014)
Reprotoxicity and developmental toxicity			
Limonene	Rabbits (pregnant females): up to 1000 mg/kg/day from day 6 to 18 of gestation Mice (pregnant females): up to 2363 mg/kg/day from day 7 to 12 of gestation Rats (pregnant females): 2869 mg/kg bw/day from day 9 to 15 of gestation	NOEL = 500 mg/kg NOEL = 591 mg/kg Non-teratogenic	(INRS 2010; Tisserand et Young 2014)

[78] https://apps.who.int/food-additives-contaminants-jecfa-database/chemical.aspx?chemID=1179

	Crosses the placenta		

In humans, after a single intake of 20 g limonene, signs of digestive irritation (diarrhoea) and reversible proteinuria were observed with no renal impairment. No significant chronic toxicity was noted. Limonene is not carcinogenic or teratogenic in laboratory animals (rats, mice, rabbits) according to the data from the literature (INRS 2010).

6.3.5.10 PK and residue data

- **Animal data (INRS 2010):**

Table 69: Animal PK and residue data on limonene

Parameter	Observations
Absorption/oral bioavailability	In the gastrointestinal tract 50-96% in rats, guinea pigs, hamsters, dogs Low absorption from the biliary system
Metabolism	25-30% of the administered dose = D-limonene and its glucuronide 7-11% = perillic acid
Distribution	In animals: C_{max} at 2h, high concentration for 10h then negligible at 48h Rapid, essentially hepatic and renal distribution No accumulation
Excretion	In urine: 25-30% of the administered dose as D-limonene and its glucuronide and 7-11% as perillic acid Excretion within two to three days 75 to 95% in urine

- **Human data (INRS 2010):**

Table 70: Human PK and residue data on limonene

Parameter	Observations
Absorption/oral bioavailability	In the gastrointestinal tract 50-80% Low absorption from the biliary system
Excretion	Excretion within two to three days 75 to 95% in urine

6.3.5.11 Summary of the assessment

Considering that, for limonene:

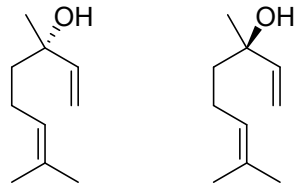
- **this substance is not listed in Table 1 of Regulation (EU) No 37/2010;**
- **this substance is a natural component of food and feed;**
- **this substance is included on the list of flavouring substances, without restrictions (Regulation (EU) No 872/2012);**
- **this substance is not genotoxic, reprotoxic or carcinogenic;**
- **this substance is rapidly metabolised and excreted;**
- **EFSA established an ADI of 0.75 mg/kg bw/day but FAO and JECFA concluded there was no need to establish an ADI;**

the WG concludes, based on the available data, that the presence of limonene is not of concern for consumers of foods derived from animals that have received plants and/or EOs containing this substance in the context of veterinary medicine.

6.3.6 Linalool

6.3.6.1 General data

Table 71: General data on linalool

Common name	Linalool
IUPAC name	(3*RS*)-3,7-Dimethylocta-1,6-dien-3-ol
Synonyms	DL-linalool (*S*)-(+)-Linalool: D-linalool: coriandrol (*R*)-(-)-Linalool: L-linalool: licareol
CAS No.	78-70-6 (*S*)-(+)-Linalool: 126-90-9 (*R*)-(-)-Linalool: 126-91-0
EC No.	201-134-4 (*S*)-(+)-Linalool: 204-810-7 (*R*)-(-)-Linalool: 204-811-2
Physico-chemical properties	Chemical formula: $C_{10}H_{18}O$ Molecular weight: 154.25 g/mol Description: colourless liquid with a floral odour (*S* enantiomer: petitgrain odour; *R* enantiomer: lavender odour) Solubility in water: 1.56 g/L (25°C) LogP: 3.28
Chemical structure	 (*S*)-(+)-linalool D-linalool (*R*)-(-)-linalool L-linalool

6.3.6.2 Status in the regulations and guidelines

Table 72: Status of linalool in the regulations and guidelines

MRLs	**Regulation (EU) No 37/2010**	Not listed
MAs in France		Present as flavouring in some medicinal products

Food supplements	**Ministerial Order of 24 June 2014; DGCCRF 2019**	Not listed
Novel foods	**EFSA catalogue**	Not listed
Feed additives	**Regulation (EU) No 1831/2003**	Listed
Flavouring substances	**Regulation (EU) No 872/2012**	Listed
REACH		Registered

6.3.6.3 Opinions of European agencies

Table 73: Opinions of European agencies on linalool

EMA HMPC	An assessment report on true lavender (EMA 2012b) A monograph on true lavender essential oil (EMA 2012d)
EFSA FEEDAP	Scientific opinion on the safety and efficacy of aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols and esters with esters containing tertiary alcohols ethers (chemical group 6) when used as flavourings for all animal species (Efsa 2012d)

6.3.6.4 Presence in EOs

According to “Essential Oil Safety” (Tisserand et Young), linalool is found in the following EOs. (*R*)-(-)-linalool is the majority substance, unless stated otherwise:

Table 74: List of EOs containing linalool

Basil, *Ocimum basilicum* L. (leaves, CT estragole)	Traces-8.6%
Basil, *Ocimum basilicum* L. (leaves, CT linalool)	34.4%
Bergamot, *Citrus bergamia* Risso & Poit, (zest, expression)	1.7-20.6%; 7.0-15.0% (French Pharmacopoeia) (linalyl acetate: 22.0-33.0%, French Pharmacopoeia)
Ceylon cinnamon, *Cinnamomum verum* J. Presl., syn. = *Cinnamomum zeylanicum* Blume (bark)	0.2-7.0%
Ceylon cinnamon, *Cinnamomum verum* J. Presl., syn. = *Cinnamomum zeylanicum* Blume (leaves)	0.2-7.0%
Clary sage, *Salvia* sclarea L. (flowering aerial parts)	9.0-16.0% / 10.4-19.3% (linalyl acetate: 49.0-73.6% / 45.3-61.8%; depending on the CT)

Coriander, *Coriandrum sativum* L. (fruit)	59.0-87.5% (ratio: (*S*)-(+)-linalool: 83.9%; (*R*)-(-)-linalool: 16.1%) (Ozek *et al.* 2010)
Ho wood, *Cinnamomum camphora* L. (leaves, CT linalool)	66.7-90.6%
Immortelle, *Helichrysum italicum* (Roth) G. Don (flowering aerial parts)	Absent / 1.5-2.8% / 17.3%, depending on the CT
Lavandin, *Lavandula* x *intermedia* Emeric ex Loisel (flowering aerial parts), Abrial clone	30-38% (linalyl acetate: 20-30%)
Lavandin, *Lavandula* x *intermedia* Emeric ex Loisel (flowering aerial parts), Grosso clone	26.2-37.5%; 24-37% (French Pharmacopoeia) (linalyl acetate: 22.5-28.0%; 25-38%, French Pharmacopoeia)
Lavandin, *Lavandula* x *intermedia* Emeric ex Loisel (flowering aerial parts), Super clone	29.4-32.7% (linalyl acetate: 38.6-44.3%)
Narrow-leaved lavender (true lavender, English lavender), *Lavandula angustifolia* Mill. (flowering aerial parts)	30-45% (20-45%, Ph. Eur.) (linalyl acetate: 33-46%; 25-47%, Ph. Eur.) (varies depending on the CT)
Spike lavender, *Lavandula latifolia* Medik. (syn. *Lavandula spica* L.) (flowering aerial parts)	27.2-43.1%
Orange (neroli), *Citrus* x *aurantium* L. (flowers)	43.7-54.3% / 31.4-47.1%, depending on the CT
Orange (petitgrain bigarade), *Citrus* x *aurantium* L. (leaves)	12.3-24.2% (linalyl acetate: 51-71%)
Rosewood, *Aniba rosaeodora* Ducke (wood)	82.3-90.3%
Thyme CT geraniol, *Thymus vulgaris* L. (aerial parts)	2.6%
Thyme CT linalool, *Thymus vulgaris* L. (aerial parts)	73.6-79%
Thyme CT thymol, *Thymus vulgaris* L. (aerial parts)	1.3-3.1%
Ylang-ylang, *Cananga odorata* J. D. Hook. & T. Thompson f. *odorata*	7-30%, depending on the CT

6.3.6.5 Presence in the normal human diet

Linalool is not listed in Annex I of Regulation (EC) No 396/2005 but is included on the list of flavouring substances with no use restrictions.

It is naturally found in food.

6.3.6.6 Presence in the normal diet of animals

Linalool is listed in the European Union Register of Feed Additives in accordance with Regulation (EC) No 1831/2003 and is classified in “2; b; Natural or corresponding synthetic chemically defined flavourings” (see Annex I, list of additives).

6.3.6.7 Human exposure

Linalool is present in the normal human diet and is used as a food additive. A group ADI of 0-0.5 mg/kg bw was established, expressed as citral, for citral, citronellol, geranyl acetate, linalool and linalyl acetate (WHO 1998)[79].

A combined intake for citronellol, citral, geranyl acetate, linalool and linalyl acetate was estimated at around 0.20 mg/kg bw/day in Europe and 0.15 mg/kg bw/day in the United States (WHO 1998) and therefore does not exceed the selected ADI for this compound. JECFA concluded that there was no safety concern for this compound at the current estimated intake levels.

A daily human exposure level of 102 µg/kg bw was reported for a 60 kg individual (Efsa 2012d). This level is also below the ADI for this compound.

6.3.6.8 Animal exposure

- **Normal diet:**

The high use level of 25 mg/kg feed (with no withdrawal period) proposed for linalool is safe for salmon, calves, cattle for fattening, and pets (excluding cats) without a margin of safety (MoS) except for dogs (MoS = 1.4). The safe use level for pigs and dairy cows is 20, for piglets 12 and for poultry 10 mg/kg complete feed. The normal use level is 5 mg/kg complete feed (EFSA 2012d).

This same report concluded that the absence of a margin of safety would not allow the simultaneous administration of linalool in feed and drinking water.

The EFSA FEEDAP report from 2012 reported the following exposure levels for the target animals:

- 588 µg/kg “metabolic” bw ($kg^{0.75}$)/day for salmon;
- 2632 µg/kg “metabolic” bw ($kg^{0.75}$)/day for pigs;
- 3885 µg/kg “metabolic” bw ($kg^{0.75}$)/day for dairy cows.

These data indicate that intake by the target animals exceeds that of humans, resulting from the use of linalool in feed. Safety for the target species at the feed concentration applied cannot be derived from the risk assessment for food use.

As an alternative, the maximum feed concentration which can be considered as safe for the target animal can be derived from the NOAEL when suitable data are available.

[79] https://apps.who.int/food-additives-contaminants-jecfa-database/chemical.aspx?chemID=2904

A 28-day study in rats treated orally with coriander EO containing 72.9% linalool (0, 160, 400 and 1000 mg/kg bw/day) was used to derive a NOAEL of 117 mg linalool/kg bw/day (corresponding to 160 mg coriander oil/kg bw/day) based on effects on the liver and kidneys observed at the two highest tested doses. After applying a safety factor of 100 to this NOAEL (inter-species and inter-individual variability) and an additional factor of 2 (short study duration), a maximum safe intake of 0.6 mg/kg bw was approximated for linalool.

Table 75: Derived maximum safe concentration in feed for different target animals for linalool and its derivatives (Efsa 2012d)

Table 5: Derived maximum safe concentration in feed for different target animals (calculated using the NOAEL of 117 (mg/kg bw per day) for linalool and its derivatives and of 250 (mg/kg bw per day) for terpineol and its derivatives)

Target animal	Default settings		Maximum safe intake/feed concentration			
	Body weight (kg)	Feed intake (g/d)	Intake (mg/d)		Concentration (mg/kg feed)	
			A	B	A	B
Salmonids	2	40	1	3	29	63
Veal calves (milk replacer)	100	2000	59	125	29	63
Cattle for fattening	400	8000	234	500	29	63
Pigs for fattening	100	3000	59	125	20	42
Sows	200	6000	117	250	20	42
Dairy Cows	650	20000	380	813	19	41
Turkeys for fattening	12	400	7	15	18	38
Piglets	20	1000	12	25	12	25
Chickens for fattening	2	120	1	3	10	21
Laying hens	2	120	1	3	10	21
Dogs	15	250	9	19	35	75
Cats	3	60	0.4	0.8	6	12*

A: Linalool, linalyl acetate, linalyl butyrate, linalyl formate, linalyl propionate and linalyl isobutyrate
B: Terpineol, α-terpineol, terpineol acetate and 4-terpinenol.
*: The safety factor for cats is increased by an additional factor of five because of the reduced capacity of glucuronidation in this species.

- **Feed additive**

Linalool is listed in the European Union Register of Feed Additives in accordance with Regulation (EC) No 1831/2003 (2; b; Natural or corresponding synthetic chemically defined flavourings).

6.3.6.9 Toxicological data

Table 76: Toxicological data on linalool

	Observations	Conclusions	References
Toxicity after a single oral administration			
Linalool	Rats	LD_{50} = 2.79 g/kg	(Tisserand et Young 2014) FAO, 1967[80]

[80] http://www.inchem.org/documents/jecfa/jecmono/v44aje23.htm

			ECHA
	Mice	LD_{50} = 2.2, 3.5 and 3.92 g/kg Maximum tolerated dose = 125 mg/kg	(Tisserand et Young 2014) FAO, 1967[81] ECHA
	Mice	Derived no effect level (DNEL) = 2.49 mg/kg bw/day LD_{50} = around 2.2 g/kg bw	ECHA
Toxicity after repeated administration			
Linalool/citronellol (50:50), feed	Rats, via feed, 12 weeks: 50 mg/kg bw/day for each substance	50 mg/kg: slight grown retardation in males with no effect on feed assimilation	FAO, 1967[82]
Linalool	Mice (females), stomach intubation: 94, 188 or 375 mg/kg/day, five days	No effect	(EMA 2012b)
Coriander EO containing 72.9% linalool	Linalool, rats, oral route: 0, 160, 400 and 1000 mg/kg bw/day, 28 days	NOAEL = 117 mg/kg bw/day	ECHA (Efsa 2012d)
Linalool	Rats, 84 days	NOEL > 50 mg/kg bw/day	(WHO 2003)
Genotoxicity/Mutagenicity			
Linalool	In a battery of *in vitro* and *in vivo* tests (Ames, mammalian cell test, chromosome aberration test, micronucleus test (mice), etc.)	No mutagenic or genotoxic effects reported *in vitro* Non-clastogenic and non-mutagenic	(Guilbault 2020; Tisserand et Young 2014; EMA 2012b) ECHA
	Cytogenicity test (mammalian erythrocyte micronucleus test)	No genotoxic effects *in vivo*	ECHA
	Linalool and its urinary metabolites in rats are not mutagenic.		(Tisserand et Young 2014; EMA

[81] http://www.inchem.org/documents/jecfa/jecmono/v44aje23.htm
[82] http://www.inchem.org/documents/jecfa/jecmono/v44aje23.htm

			2012b; WHO 2003)
Carcinogenicity			
Linalool	Mice Rats, oral route, 20 weeks	No tumourigenic potential No increase in the number of tumours	ECHA
Reprotoxicity and developmental toxicity, oral route			
Linalool	Rats, administration from day 7 to 17 of gestation	$NOAEL_{maternal}$ = 500 mg/kg/day	(Tisserand et Young 2014)
Coriander EO 72.9% (-)-linalool	Rats	$NOAEL_{maternal\ and\ development}$ = 365 mg/kg bw/day	ECHA (ICCA 2002) (Letizia *et al.* 2003) (RIFM 1989)
Linalool in corn oil	Rats, 11 days	$NOAEL_{maternal}$ = 500 mg/kg bw/day $NOAEL_{development}$ = 1000 mg/kg bw/day	ECHA (Politano *et al.* 2008)

Linalool is non-mutagenic, non-genotoxic and non-carcinogenic according to the data from the literature.

6.3.6.10 PK and residue data

- **Data in animals**

Table 77: Animal PK and residue data on linalool

Parameter	Observations	References
Metabolism	Oxidation by CYP before glucuronide conjugation	(Tisserand et Young 2014)
	Linalool, high doses, rats: C_{max} after 40 minutes Distribution in blood, plasma, liver, kidney, brain and fat after single exposure in rats (increasing concentrations in plasma, brain, liver, kidney and fat). Measurable linalool concentrations were also detected in these tissues after administration of linalyl acetate and silexan (mixture of linalool and linalyl acetate), indicating that linalyl acetate is metabolised to linalool.	ECHA

Distribution	Linalool, 500 mg/kg, one dose, rats: 0.5% in the liver, 0.6% in the intestines, 0.8% in the skin and 1.2% in the skeletal muscle	(Tisserand et Young 2014)
Excretion	Linalool 14C, 500 mg/kg bw, one intragastric dose, rats, 12 weeks: 96% excreted within 72h: 58-60% in urine, 25-27% in exhaled air (primarily CO_2) and 12-15% in faeces	(Tisserand et Young 2014; Efsa 2012d)
	In vivo, linalool is rapidly eliminated from plasma (half-life = around 45 mins)	ECHA
Residues	Linalool 14C, 500 mg/kg bw, one intragastric dose, rats, 12 weeks: 3-4% detected in tissues Main metabolites in urine and faeces: dihydrolinalool and tetrahydrolinalool, primarily conjugated with sulphate or glucuronic acid	(Efsa 2012d; EMA 2012b)
	Linalool, 800 mg/kg bw, rats (males), 20 days: urinary metabolites formed by CYP450-mediated allylic oxidation of linalool included 8-hydroxylinalool and 8-carboxylinalool. No oxidation of the terminal double bond was observed, indicating no formation of epoxide intermediates.	(Efsa 2012d)

Linalool is rapidly absorbed by the gastrointestinal tract (oral administration), distributed in various tissues, metabolised primarily by the liver (cytochrome P450) and rapidly excreted in urine, faeces and air.

No bioaccumulation is observed and linalool is extensively metabolised to harmless metabolites (ECHA).

Aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols are rapidly absorbed, distributed, metabolised and excreted. Mammals, birds and fish share a similar metabolic capacity to handle these compounds. Due to the digestion metabolism and excretion of these compounds by the target species, it is expected that food residues of the chemical group 6 compounds will give consumer exposure levels that are considerably lower than the levels given to the target species. As the exposure of target species is considered to be safe, the much lower exposure of consumers is also considered to be safe. No safety concern is expected from the use of these compounds up to the highest safe level in feed.

The FEEDAP Panel notes that use of feed flavourings has the potential to alter the organoleptic quality of animal products (e.g. milk, eggs).

- **Human data**

No information was found in the European public reports.

6.3.6.11 Reported adverse effects

- **Cases from nutrivigilance**

No cases have been reported.

- **Cases recorded in Canada and the United States**

No cases have been reported.

6.3.6.12 Summary of the assessment

Considering that, for linalool:

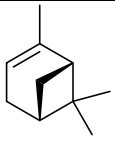
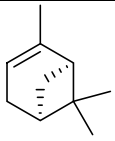
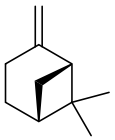
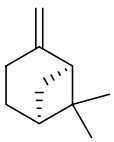
- **this substance is not listed in Table 1 of Regulation (EU) No 37/2010;**
- **this substance is included on the list of flavouring substances, without restrictions (Regulation (EU) No 872/2012);**
- **this substance is authorised as a feed additive for salmon and cattle (including calves) at a concentration of 25 mg/kg complete feed, and is authorised at the concentrations of 20, 12 and 10 mg/kg complete feed respectively for pigs and dairy cows, piglets and poultry;**
- **this substance is rapidly metabolised and excreted (3% found in tissues);**
- **this substance is considered as having low toxicity and as being non-genotoxic and non-carcinogenic;**
- **the level of human exposure is estimated at 0.102 to 0.200 mg/kg bw/day;**
- **an ADI of 0.5 mg/kg bw/day has been defined;**
- **exposure via residues is below the ADI;**

the WG concludes, based on the available data, that the presence of linalool is not of concern for consumers of foods derived from animals that have received plants and/or EOs containing this substance in the context of veterinary medicine.

6.3.7 Pinene

6.3.7.1 General data

Table 78: General data on pinene

Common name	α-pinene	β-pinene
IUPAC name	2,6,6-Trimethylbicyclo[3.1.1]hept-2-ene	6,6-Dimethyl-2-methylidenebicyclo[3.1.1]heptane
Synonyms	Pin-2(3)-ene	Pin-2(10)-ene
CAS No.	80-56-8 (+/-)	127-91-3
EC No.	201-291-9	204-872-5
Physico-chemical properties	Chemical formula: $C_{10}H_{16}$ Molecular weight: 136.23 g/mol Description: colourless liquid with a turpentine odour Solubility: 2.5 mg/L (25°C) / 4.89 mg/mL (25°C) (α-pinene / β-pinene) LogP: 4.83 / 4.16 (α-pinene / β-pinene)	
Chemical structure	 (*R*)-(+)-α-pinene  (*S*)-(-)-α-pinene  (*R*)-(+)-β-pinene  (*S*)-(-)-β-pinene	

6.3.7.2 Status in the regulations and guidelines

Table 79: Status of pinene in the regulations and guidelines

MRLs	**Regulation (EU) No 37/2010**	Pinene not listed Pinene, *Pinus*: not in Table 1 of Regulation (EU) No 37/2010 - but: - *Terebinthinae aetheroleum rectificatum*[83]: residue: All food-producing species, no MRL required, for topical use only

[83] Turpentine EO in the Ph. Eur.: EO obtained by steam distillation, followed by rectification at a temperature below 180°C, of the oleoresin obtained by tapping from *Pinus pinaster* Aiton and/or *Pinus massoniana* D.Don. An appropriate antioxidant can be added. GC analysis: – α-pinene: 70.0 to 85.0% – β-pinene: 5.0 to 20.0%

		- *Terebinthinae laricina:* All food-producing species, no MRL required, for topical use only
MAs in France		Present in medicinal products containing EOs
Food supplements	**Ministerial Order of 24 June 2014; DGCCRF 2019**	Pinene is not an authorised substance, but numerous plants and EOs containing it are authorised in food supplements; for example: EOs of *Pinus mugo* Turra, *Pinus pinaster* Aiton, *Pinus sylvestris* L., *Picea abies* (L.) H. Karst.
Novel foods	**EFSA catalogue**	Not listed
Feed additives	**Regulation (EU) No 1831/2003**	Pinene is included in Annex II. Annex I of the Regulation lists several sources of pinene (group 2b): "*Pinus* spp., e.g*. P. sylvestris* L.: Pine oil white CAS 8002-09-3 CoE 340" and "*Pinus* spp., e.g. *P. sylvestris* L.: Pine tincture CoE 340" (flavourings).
Flavouring substances	**Regulation (EU) No 872/2012**	Listed, without restrictions

6.3.7.3 Opinions of European agencies

Table 80: Opinions of European agencies on pinene

EMA HMPC	Pinene is contained in several EOs with EMA HMPC monographs; for example: EO of *Eucalyptus globulus* leaves: α-pinene: 6.7-9.1%; β-pinene: 0.05-1.5%
EFSA FEEDAP	Safety and efficacy of eight compounds belonging to chemical group 31 (aliphatic and aromatic hydrocarbons) when used as flavourings for all animal species and categories (Efsa 2016a)

6.3.7.4 Presence in EOs

α- and β-pinene are found, often concomitantly, in numerous aromatic plants and EOs; for example, they are abundant in the majority of conifer EOs, including *Abies* and *Pinus* spp. EOs.

Table 81: List of EOs containing pinene

EO	α-pinene	β-pinene
Angelica, *Angelica archangelica* L. (fruit)	8.8-9.2%	-
Angelica, *Angelica archangelica* L. (roots)	4.4-24.0%	0.2-1.2%
Cajeput, *Melaleuca cajuputi* Powell (leaves and branches)	2.1-3.2%	0.8-1.5%

Common gum cistus, *Cistus ladanifer* L. (aerial parts)	3.5-56.0%	-
Ceylon citronella, *Cymbopogon nardus* L. (leaves)	1.9-4.8%	-
Lemon, *Citrus* x *limon* L. (leaves)	0.1-2.2%	3.5-13.6%
Lemon, *Citrus* x *limon* L. (zest, expression)	1.3-4.4% (not queried in the Ph. Eur.)	6.0-17.0%; 7-17% (Ph. Eur.)
Coriander, *Coriandrum sativum* L. (fruit)	0.1-10.5%; 3.0-7.0% (Ph. Eur.)	0.1-8.6% (not queried in the Ph. Eur.)
Cypress, *Cupressus sempervirens* L. (branches)	20.4-52.7%	0.8-2.9%
Spruce, *Picea abies* L. (leaves)	14.2-21.5%	4.8-31.9%
Blue gum, *Eucalyptus globulus* (leaves)	1.3-14.7%; 0.05-10.0% (Ph. Eur.)	0.05-1.5% (Ph. Eur.)
Common fennel, *Foeniculum vulgare* Mil. (fruit)	1.0-10.0% (Ph. Eur.)	(not queried in the Ph. Eur.)
Common fennel, *Foeniculum vulgare* Mil. (aerial parts)	2.0-8.0% / 2.0-11.0% (Spanish / Tasmanian, Ph. Eur.)	1.0-4.0% / not queried (Spanish / Tasmanian, Ph. Eur.)
Juniper, *Juniperus communis* L. (cones)	24.1-55.4%; 20.0-50.0% (Ph. Eur.)	2.1-6.0%; 1.0-12.0% (Ph. Eur.)
Immortelle, *Helichrysum italicum* (Roth) G. Don (flowering aerial parts)	1.5–21.7% depending on the CT	-
Bay laurel, *Laurus nobilis* L. (leaves)	7.1-15.9%	4.9-6.5%
Mandarin, *Citrus reticulata* Blanco (zest)	1.6-3.0% (Ph. Eur.)	1.2-2.0% (Ph. Eur.)
Melaleuca, *Melaleuca alternifolia* (Maiden & Betch) Cheel and other species of *Melaleuca* (branches)	1.0-6.0% (Ph. Eur.)	(not queried in the Ph. Eur.)
Myrtle, *Myrtus communis* L. (leaves)	18.5-56.7%	-
Niaouli, *Melaleuca quinquenervia* Cav. (leaves, CT linalool)	7.0-12.0%; 5.0-15.0% (Ph. Eur.)	1.5-4.5%; 1.0-4.0% (Ph. Eur.)

Orange (neroli), *Citrus* x *aurantium* L. (flowers)	0% / 0.8-1.1% (not queried in the Ph. Eur.)	3.5-5.3% / 10.5-13.0% depending on the CT; 7.0-17.0% (Ph. Eur.)
Douglas fir, *Pseudotsuga menziesii* (Mirbel) Franco (wood)	13.0%	11.6%
Mountain pine, *Pinus mugo* Turra (branches)	10.0-30.0% (Ph. Eur.)	1.3-20.7%; 3.0-14.0% (Ph. Eur.)
Scots pine, *Pinus sylvestris* L. (leaves)	20.3-45.8%; 32.0-60.0% (Ph. Eur.)	1.9-33.3%; 5.0-22.0% (Ph. Eur.)
Rosemary, *Rosmarinus officinalis* L. (aerial parts)	8.3% / 24.0-28.5% / 9.6-12.7% depending on the CT; 18.0-26.0% / 9.0-14.0% (Spanish / Moroccan, Ph. Eur.)	2.2-2.9% / 0.3-5.0% / 5.5-7.8% depending on the CT; 2.0-6.0% / 4.0-9.0% (Spanish / Moroccan, Ph. Eur.)
Silver fir, *Abies alba* Mill. (cones)	18.0-31.7%	3.0-22.5%
Silver fir, *Abies alba* Mill. (leaves)	7.4%	-
Siberian fir, *Abies sibirica* Ledeb. (branches)	10.0-22.0% (French Pharmacopoeia)	1.0-3.0% (French Pharmacopoeia)
Turpentine, *Pinus pinaster* Aiton and/or *Pinus massoniana* D.Don. (oleoresin)	70.0-85.0% (Ph. Eur.)	5.0-20.0% (Ph. Eur.)
Saro, *Cinnamosma fragrans* Baill. (leaves)	4.0-7.0%	5.0-8.0%

6.3.7.5 Presence in the normal human diet

Pinene is on the list of flavouring substances with no use restrictions.

Pinene plants appear in the Council of Europe's Blue Book (1981) listing flavouring substances (for example: *Picea abies* L.; *Pinus sylvestris* L.).

6.3.7.6 Presence in the normal diet of animals

Pinene is no longer listed in the European Union Register of Feed Additives in accordance with Regulation (EC) No 1831/2003 (Annex II) but is contained in numerous herbal preparations mentioned in this Regulation (see Annex I, list of additives, for example: "*Pinus* spp., e.g. *P. sylvestris* L.: Pine oil white CAS 8002-09-3 CoE 340" and "*Pinus* spp., e.g. *P. sylvestris* L.: Pine tincture CoE 340" (flavourings)).[84] α-pinene and β-pinene are considered safe for animal and human health at the concentration of 5 mg/kg feed.

[84] https://ec.europa.eu/food/sites/food/files/safety/docs/animal-feed_additives_eu-register_1831-03.pdf

Moreover, pinene is present in the normal diet of animals.

6.3.7.7 Human exposure

Humans are exposed via the normal diet and through the use of pinene and pinene sources as food additives.

Daily per capita intakes range from 92 to 8300 µg in Europe and from 70 to 2400 µg in the United States. The average level of exposure to α-pinene is 36 µg/kg bw in Europe.

Exposure through food amounts to 83 and 60 µg/kg bw/day for α-pinene and β-pinene, respectively, for use as a feed additive at a rate of 5 mg/kg feed.

In the absence of any health concern, JECFA does not propose an ADI for α-pinene or β-pinene, at their levels of use as flavouring substances.

6.3.7.8 Animal exposure

EFSA's FEEDAP Panel estimated levels of exposure of 118, 526 and 777 µg/kg bw for the sum of α-pinene and β-pinene used as flavouring substances, at maximum feed concentrations, respectively in salmonids, piglets and cows.

6.3.7.9 Toxicological data

Table 82: Toxicological data on pinene

	Observations	Conclusions	References
Toxicity after a single administration			
Pinene	Rats, mice, oral route	LD_{50} > 1800 to 6800 mg/kg bw	(EMEA 2005)
Toxicity after repeated oral administration			
	No data recorded by agencies for α-pinene or β-pinene, but EFSA considers that the data on β-caryophyllene can be extrapolated to these substances Sprague Dawley rats, 90 days	NOAEL = 222 mg/kg/day (changes in blood counts, increased liver size, hepatocellular hypertrophy)	(Efsa 2016a)
Genotoxicity/Mutagenicity			
Pinene	Battery of *in vitro* (Ames test with *Salmonella* Typhimurium strains TA100, TA98, TA97a and TA1535, with and without metabolic activation; *Bacillus subtilis*; chromatid	No mutagenic effects reported *in vitro* Micronucleus test: no mutagenic effects at the dose of 1750 mg/kg *Melaleuca alternifolia* EO	(EMA 2014b)

	exchange test in CHO cells) and *in vivo* (OECD micronucleus test no. 474) tests		
Reprotoxicity and developmental toxicity			
Pinene	Rats and mice, oral route, during gestation	Maternal NOAEL: > 260 mg/kg/day (α-pinene, rats) > 43 and > 93 mg/kg/day (β-pinene, rats and mice, respectively)	(Tisserand et Young 2014)

6.3.7.10 PK and residue data

- **Data in animals**

Table 83: Animal PK and residue data on pinene

Parameter	Observations	References
Metabolism	Pinene is oxidised to alcohol derivatives (terpineol, etc.) and then glucuronoconjugated. Rapid degradation is observed in the rumen of goats (80% within 24h).	(Efsa 2016a)
Residues	α-pinene administered in a mixture with other terpenes (1 g/day, i.e. 700 mg/kg feed) in ewes for 18 days led to a level of 4 µg/ml in milk at the end of the protocol; two days later, the substances had almost disappeared. In goats, this same protocol led to a level of 1 µg/ml in milk (0.4 µg/ml two days later). There was no accumulation in the meat or adipose tissue of calves treated via milk (10 to 40 µl/day of an EO mixture).	(Efsa 2016a)

- **Human data**

No information was found in the European public reports.

6.3.7.11 Reported adverse effects

- **Cases from nutrivigilance**

No cases have been reported.

- **Cases recorded in Canada and the United States**

No cases have been reported.

6.3.7.12 Summary of the assessment

Considering that pinene:

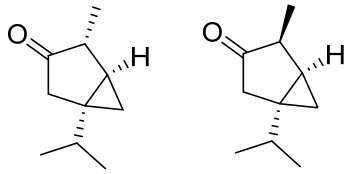
- **is not listed in Table 1 of Regulation (EU) No 37/2010;**
- **is included on the list of flavouring substances, without restrictions (Regulation (EU) No 872/2012);**
- **is deemed safe and is authorised in food-producing animals at a level of 5 mg/kg complete feed;**
- **is considered as having low toxicity and is not mutagenic;**
- **is rapidly metabolised and excreted;**

the WG concludes, based on the available data, that the presence of pinene in plants and/or EOs is not of concern for consumers of foods derived from animals that have received plants and/or EOs containing this substance in the context of veterinary medicine.

6.3.8 Thujone

6.3.8.1 General data

Table 84: General data on thujone

Common name	Thujone
Synonyms	Thujan-3-one, absinthone, 3-sabinone
IUPAC name	α-thujone: (1*S*,4*R*,5*R*)-4-methyl-1-(propan-2-yl)bicyclo[3.1.0]hexan-3-one β-thujone: (1S,4S,5R)-4-methyl-1-propan-2-ylbicyclo[3.1.0]hexan-3-one
CAS No.	α-thujone: 546-80-5 β-thujone: 471-15-8
EC No.	214-405-7
Physico-chemical properties	Chemical formula: $C_{10}H_{16}O$ Molecular weight: 152.23 g/mol Description: colourless to pale yellow liquid with a characteristic odour Solubility in water: 1.56 g/L (25°C) (α-thujone) LogP: 407.7 mg/L (α-thujone)
Other data	 α-(+)-thujone β-(+)-thujone

6.3.8.2 Status in the regulations and guidelines

Table 85: Status of thujone in the regulations and guidelines

MRLs	**Regulation (EU) No 37/2010**	*Thuja occidentalis*, only in homeopathic veterinary medicinal products
MAs in France		No medicinal products registered in France
Food supplements	**Ministerial Order of 24 June 2014; DGCCRF 2019**	Not listed
Novel foods	**EFSA catalogue**	Not listed

Feed additives	**Regulation (EU) No 1831/2003**	Not listed
Flavouring substances	**Regulation (EU) No 872/2012**	Not listed

6.3.8.3 Opinions of European agencies

Table 86: Opinions of European agencies on thujone

EMA HMPC	An assessment report on *Salvia officinalis* L., folium and *Salvia officinalis* L., aetheroleum (EMA 2016)

6.3.8.4 Presence in EOs

The following EOs contain significant amounts of thujone, according to the book by Tisserand and Young (2014):

Table 87: List of EOs containing thujone

EO	α-thujone	β-thujone
Black wormwood, *Artemisia genipi* Weber (aerial parts)	79.8%	10.4%
Hyssop, *Hyssopus officinalis* L. (leaves, flowering tops, CT pinocamphone)	0-0.1% (not queried in the French Pharmacopoeia)	0-0.3% (not queried in the French Pharmacopoeia)
Common mugwort, *Artemisia vulgaris* L. (flowering aerial parts)	11.4%	-
Common sage, *Salvia officinalis* L. (leaves)	13.1-48.5%	3.9-19.1%
Tansy, *Tanacetum vulgare* L. (aerial parts)	1.1%	45.2%
Thuja, *Thuja occidentalis* L. (branches)	48.7-51.5%	7.9-9.9%
Thuja, *Thuja plicata* Donn ex D. Don (leaves)	63.5-84.0%	4.9-15.2%
Common wormwood, *Artemisia absinthium* L. (flowering aerial parts)	2.3-3.4% / 0.1%	33.1-59.9% / 0.6% depending on the CT

6.3.8.5 Presence in the normal human diet

Thujone is found only in certain alcoholic beverages such as absinthe and genépi at set maximum levels (SCF 2002).

6.3.8.6 Presence in the normal diet of animals

Thujone is not present in the normal diet of animals.

6.3.8.7 Human exposure

- Thujone is prohibited as a food additive in the United States.
- Its use as a flavouring agent is not authorised in Europe (Regulation (EC) No 1334/2008).
- Levels of thujone in foods and beverages are regulated in several countries. In Europe, maximum levels of α- and/or β-thujone range from 5 to 35 mg/kg depending on the beverage.
- According to Directive 88/388/EEC of 1988 as amended by Regulation (EC) No 1334/2008, the maximum level of thujone in alcoholic beverages is 10 mg/kg, except in beverages produced from *Artemisia* species: 35 mg/kg for alcoholic beverages and 0.5 mg/kg for non-alcoholic beverages.
- Human exposure of around 1.2 to 2.4 mg thujone/person was calculated based on consumption of 40-80 ml absinthe.
- According to the Scientific Committee on Food – European Commission (SCF 2002), in France and the United Kingdom, the mean intake of thujone is estimated at 0.27 to 1.09 mg/person/day (for a 70 kg adult). This is a worst-case scenario based on maximum quantities.
- The main source of dietary exposure in humans is sage leaves, which are not widely consumed. The pharmacopoeias give the following for sage: 12 ml EO per kg sage leaves, i.e. 10 mg/kg for this EO.

6.3.8.8 Animal exposure

No data

6.3.8.9 Toxicological data

Thujone is a neurotoxic monoterpene ketone (AFSSA 2003).

α-thujone is more toxic than β-thujone.

According to ECHA, α-thujone is classified as a toxic substance via the oral route and β-thujone as a harmful substance via the oral route.

Thujone is listed in the Toxic Substances Control Act (TSCA) inventory.

The book by Tisserand & Young (2014) summarises toxicity studies following oral administration of α-thujone, β-thujone or a mixture of the two. These studies were primarily extracted from the NTP 2011 report and gave rise to the recommended ADI.

In humans, an oral no-effect level (single dose) of 1.25 mg/kg bw, i.e. 75 mg/person, was reported based on the EPMAR for *Thuja occidentalis* (EMEA 1999b).

■ **ADI (oral route)**

In 1999, the Council of Europe set an ADI of 10 µg/kg bw/day for thujone, based on a NOEL of 5 mg/kg bw/day in female rats (convulsions) to which an uncertainty factor of 500 was applied (SCF 2002).

In its 2003 report, the SCF concluded that the data were inadequate to define an ADI (SCF 2002).

EMA proposed a limit of 3 mg/adult; after revision, a limit of 10 µg/kg bw/day was selected (EMA 2012e, 2016).

Lachenmeieir and Uebelacker (2010) proposed a maximum value of 0.11 mg/kg bw/day using a benchmark dose approach based on NTP data (2011) obtained in rats.

Tisserand & Young therefore proposed selecting the value of 0.10 mg/kg bw, i.e. 7 mg for a 70 kg adult.

6.3.8.10 PK and residue data

- Lipophilic nature suggesting good dermal/cutaneous absorption;
- Crossing of the blood-brain barrier;
- Excretion via CYP450-dependent oxidative metabolism;
- α-thujone inhibits CYP2A6, which can prolong and increase its concentration;
- Primarily excreted via the kidneys and lungs.

6.3.8.11 Reported adverse effects

■ **Cases from nutrivigilance**

No cases have been reported.

■ **Cases recorded in Canada and the United States**

No cases have been reported. No medicinal products contain this substance.

6.3.8.12 Summary of the assessment

Considering that thujone:

- **is not listed in Table 1 of Regulation (EU) No 37/2010;**
- **is prohibited as a flavouring agent in Europe;**
- **is prohibited as a food additive in the United States;**
- **has maximum levels in foodstuffs;**
- **has an ADI of 10 µg/kg bw/day;**
- **has neurotoxic potential;**
- **has not been investigated in residue studies;**

the WG considers that in the absence of sufficient data, it cannot conclude that there is no concern relating to thujone for consumers of foods derived from animals that have received plants and/or EOs containing this substance in the context of veterinary medicine.

6.4 EOs

6.4.1 Tea tree EO

6.4.1.1 General data

Table 88: General data on tea tree

Common name	Tea tree
Latin name	*Melaleuca alternifolia* (Maiden & Betche) Cheel
Synonyms	*Melaleuca linariifolia* var. *alternifolia* Maiden & Betche
Parts of the plant concerned	Leaves and terminal branches

6.4.1.2 Status in the regulations and guidelines

Table 89: Status of tea tree in the regulations and guidelines

MRLs	**Regulation (EU) No 37/2010**	Not listed
Medicinal products for human use	**List of medicinal plants in the French Pharmacopoeia**	Not listed
	Pharmacopoeias	Ph. Eur. 01/2008: 1837 Melaleuca (EO of)
	WHO	Volume 2, EOs (WHO 2002)
	MAs in France	No medicinal products registered in France
Food supplements	**DGCCRF 2019**	Listed without restrictions Registered in food supplements
Novel foods	**EFSA catalogue**	Not listed
Feed additives	**Regulation (EU) No 1831/2003**	As *Melaleuca alternifolia* Cheel.: Tea tree oil CAS 68647-73-4 FEMA 3902 CoE 275 EINECS 285-377-1
ISO standards		ISO 4730:2017

6.4.1.3 Opinions of European agencies

Table 90: Opinions of European agencies on tea tree EO

EMA HMPC	An assessment report is available (EMA 2014b) A herbal monograph is available, proposing dermal or oro-mucosal use
EFSA – Assessments of pesticide active substances	A monograph is available (Efsa 2018)
ANSES	An opinion on the use of Melaleuca EOs in food supplements (Anses 2020b)
JECFA (1999)	An assessment on alicyclic terpenoid tertiary alcohols

6.4.1.4 Composition

The composition of tea tree EO (CT I) according to the Ph. Eur. and the ISO 4730:2017 standard is shown in the following table (Anses 2020b).

Table 91: Composition of tea tree EO

	Ph. Eur. 01/2008:1837 corrected 7.0		ISO 4730:2017	
Component	Minimum (%)	Maximum (%)	Minimum (%)	Maximum (%)
α-pinene (pin-2(3)-ene) [a, b]	1.0	6.0	1.0	4.0
Sabinene (4(10)-thujene) [a]		3.5	Traces[85]	3.5
α-terpinene [a, b]	5.0	13.0	6.0	12.0
Limonene [a, b]	0.5	4.0	0.5	1.5
1,8-cineole [a, b, c]		15.0	Traces[85]	10.0
γ-terpinene [a, b]	10.0	28.0	14.0	28.0
p-cymene	0.5	12.0	0.5	8.0
Terpinolene [a, b]	1.5	5.0	1.5	5.0
Terpinen-4-ol (4-terpineol) [a, b]	30.0		35.0[86]	48.0[85]
Aromadendrene		7.0	0.2	3.0
α-terpineol [a, b]	1.5	8.0	2.0	5.0
δ-cadinene			0.2	3.0
Globulol			Traces[85]	1.0

[85] Traces: < 0.01%
[86] 67.71% (S)(+)-terpinen-4-ol and 29.33% (R)(+)-terpinen-4-ol

Viridiflorol			Traces[85]	1.0
Ledene (viridiflorene)			0.1	3.0

[a] Flavouring substance for use in and on foods, with no use restrictions (Regulation (EU) No 872/2012).

[b] Register of feed additives, Annex I, 2020; no restrictions (Regulation (EC) No 1831/2003).

[c] Table 1 of Regulation (EU) No 37/2010; no restrictions.

6.4.1.5 Presence in the normal human diet

Tea tree EO is not present in the normal human diet.

6.4.1.6 Presence in the normal diet of animals

Tea tree EO is not present in the normal diet of animals.

6.4.1.7 Human exposure

- **Food additives, flavourings.**

Tea tree EOs are found in food supplements, used for aromatherapy and used as flavourings in food (Anses 2020b).

- **ADI**

The ADI of EO extracted from tea tree is 0.03 mg/kg/day (Efsa 2018).

The maximum safe intake of terpinen-4-ol is 1.2 mg/kg/day (Anses 2020b) although this is an identified substance of concern contained in *Melaleuca* EOs.

- **EMA**

No proprietary medicinal products were identified in France and there is nothing in particular on this topic in EMA's reports.

- **Maximum oral exposure in humans (Anses 2020b)**
  - Human cases have been reported in the literature with signs of allergy (oral route), neurotoxicity (oral route) and gynecomastia (external route).
  - Concerning toxicovigilance, there were 619 reports (abdominal pain, vomiting, nausea > oropharyngeal pain/irritation > headaches, dizziness, asthenia) potentially related to the consumption of food supplements containing *Melaleuca* EOs in France over the 2006-2019 period. Cases have also been reported in Canada and the United States.

- **Human exposure to methyl eugenol**

Methyl eugenol is an identified substance of concern contained in *Melaleuca* EOs. Maximum levels of methyl eugenol have been set (Regulation (EC) No 1234/2008) in dairy products (20 mg/kg) and meat preparations and products, including poultry and game (15 mg/kg) (Anses 2020b).

- **Human exposure to 1,8-cineole**

1,8-cineole is an identified substance of concern contained in *Melaleuca* EOs. Cases of disorders of the central nervous system (convulsions in particular) following exposure to 1,8-

cineole have been described in children and infants; nevertheless, the levels of 1,8-cineole are lower than in blue gum EO and in practice, tea tree EO is used over short periods.

6.4.1.8 Animal exposure

Not present in the normal diet of animals in Europe or used as a feed additive.

6.4.1.9 Toxicological data

Table 92: Toxicological data on tea tree EO (ANSES 2020a)

EO or substance	Type of study or calculated dose	Conclusion
Toxicity after a single oral administration		
Tea tree EO	LD_{50} (rats)	1400-2700 mg/kg
Terpinen-4-ol	LD_{50} (rats)	1300 mg/kg
Methyl eugenol	LD_{50} (rats)	2500 mg/kg
Ascaridole	LD_{50} (rats) LD_{50} (mice)	200 mg/kg 400 mg/kg
Toxicity after repeated administration		
Terpinen-4-ol	NOAEL (rats, 28 days)	No renal toxicity 400 mg/kg/day
Methyl eugenol	NOAEL (rats and mice, 90 days)	10 mg/kg/day
Mutagenicity/Genotoxicity		
Tea tree EO	Ames test, micronucleus test and chromosome aberration test in human lymphocytes	Negative results (*for the Ames test, the results should be taken with caution given the high antimicrobial activity of tea tree EO*)
Terpinen-4-ol	Predictive toxicology (QSAR)	No mutagenic or genotoxic alerts
Methyl eugenol	Numerous primary DNA damage and gene and chromosome mutation tests	Induction of primary DNA lesions by methyl eugenol and its metabolites *in vitro*; positive or negative *in vivo* results depending on the study
Ascaridole	Predictive toxicology (QSAR)	No mutagenicity or genotoxicity alerts; a potential hepatotoxicity alert

Carcinogenicity		
Methyl eugenol	*In vivo* carcinogenicity studies (rats and mice)	Multispecific and multisite human carcinogen
Ascaridole	Little information	
Reprotoxicity and developmental toxicity		
Terpinen-4-ol	NOAEL (maternal toxicity study, rats)	250 mg/kg/day
Methyl eugenol	LOAEL (maternal toxicity study, rats) LOAEL (developmental study, rats)	80 mg/kg/day 200 mg/kg/day
Other		
Tea tree EO	IC_{50} (several *in vitro* cell lines including human monocytes and granulocytes)	20 – 2700 µg/ml
	Oestrogenic activity shown *in vitro* but never *in vivo*	
Terpinen-4-ol	*In vitro* study in swine spermatozoa	Decrease in motility between 0.08 and 0.83 mg/ml
Ascaridole	Dermal toxicity: immuno-sensitising	

Substances of concern in tea tree EO

- **Terpinen-4-ol**
- **Methyl eugenol**
  - It is contained in tea tree EO in low proportions ranging from 0.01 to 0.4% (Anses 2020b) and is completely metabolised in rodents.
  - It is classified as a CMR substance after a single administration (REACH) and as a possible human carcinogen (IARC).
  - Adjusted $BMDL_{10}$ values = 7.9 – 34 mg/kg/day have been established (these vary depending on the author).
- **Ascaridole (newly-formed compound)**

Ascaridole is a newly-formed compound (endoperoxide) formed by the peroxidation of α-terpinene. This peroxidation can be observed in an EO exposed to air, light, or high temperatures.

6.4.1.10 PK and residue data

There are no available data on the oral administration of tea tree EO. However, data are available for terpinen-4-ol and ascaridole.

- **Terpinen-4-ol**

It has an oral, dermal and respiratory absorption rate of 100%. Its distribution is rapid and extensive in animals (salmon, calves, poultry, cows, pigs, dogs, cats, etc.). Very little is known

about its metabolism *in vivo*, but the metabolites are less toxic than the parent compound (Anses 2020b).

- **Ascaridole (newly-formed compound)**

It is rapidly absorbed and rapidly excreted after oral administration in rats with a T_{max} of 15 mins and a $T_{1/2}$ of 30 mins (Anses 2020b).

- **Toxic metabolites for humans**

1,8-cineole has CYP450-inducing effects that can interfere with the metabolism of xenobiotics at high exposure levels. It is therefore considered, *a priori*, as a metabolite of low concern for humans (Anses 2020b).

6.4.1.11 Reported adverse effects

- **Cases from nutrivigilance**

Concerning nutrivigilance in France, there were 10 reports of adverse effects (mainly headaches, dizziness, nausea, vomiting and diarrhoea) potentially related to the consumption of food supplements containing *Melaleuca* EOs between 2011 and 2020.

- **Cases recorded in Canada and the United States**

From 1 January 1965 to 31 January 2021, 53 nutrivigilance cases were recorded in Canada, usually with digestive (nausea, vomiting, diarrhoea), muscular (myalgia), irritative (throat, eyes, skin, etc.) and neurological (sensations of dizziness) effects.

Between 2004 and 2021, four nutrivigilance cases were recorded in the United States. One involved *Melaleuca viridiflora* Gaertn. and induced autoimmune haemolytic anaemia. The three other cases involved *Melaleuca cajuputi* Powell and induced sometimes painful local reactions of the skin and mucosa.

6.4.1.12 Summary of the assessment

- **Maximum tolerable dose in food**

Maximum levels of methyl eugenol in dairy products (20 mg/kg) and meat preparations and products, including poultry and game (15 mg/kg) (Regulation (EC) No 1234/2008).

- **Assumptions**

  - Concentration of methyl eugenol in tea tree EO: 0.01 – 0.4% (ANSES, 2020)
  - Normal administered oral dose: 1 ml/bovine animal and 0.2 ml/sheep or goat (veterinarians interviewed)
  - Normal administered dermal dose: 10 drops, twice daily for cattle and five drops, twice daily for sheep (veterinarians interviewed)
  - 100% of the quantity administered to the animal ends up in the liver, in both kidneys, or in milk
  - Average liver weight: 5 kg (adult cattle), 0.15-0.45 kg (goats or sheep)
  - Average kidney weight: 0.5-1 kg (adult cattle), 0.6-0.9 kg (goats or sheep)

- Daily milk production: 28 L/bovine animal and 1 to 2 L/sheep, bearing in mind that 1 L milk = 1.03 kg milk

■ **Can this dose be reached via residue in foods? No**

For cattle and sheep/goat liver and cattle and sheep/goat kidneys, the maximum level is below the maximum level set for meat and meat preparations, including poultry and game (15 mg/kg):

- Cattle liver: maximum methyl eugenol level of 0.8 mg/kg given the worst-case assumptions.
- Sheep/goat liver: maximum methyl eugenol level of 5.3 mg/kg given the worst-case assumptions.
- Cattle kidneys: maximum methyl eugenol level of 4 mg/kg given the worst-case assumptions.
- Sheep/goat kidneys: maximum methyl eugenol level of 0.67 mg/kg given the worst-case assumptions.

For cattle and sheep milk, the maximum level is below the maximum level in dairy products (20 mg/kg):

- Cattle milk: maximum methyl eugenol level of 0.14 mg/kg given the worst-case assumptions.
- Sheep milk: maximum methyl eugenol level of 3.9 mg/kg given the worst-case assumptions.

Considering that, for tea tree EO:

- **this EO is not listed in Table 1 of Regulation (EU) No 37/2010;**
- **this EO is used as a food additive and flavouring;**
- **its main components are used as food flavourings, with no restrictions (Regulation (EU) No 872/2012);**
- **many robust toxicological data are available for its components;**
- **one of its components, terpinen-4-ol, is extensively metabolised and excreted;**
- **another of its potential components, ascaridole (a newly-formed compound), is rapidly eliminated;**
- **the methyl eugenol levels in foodstuffs of animal origin calculated after treating ruminants with tea tree EO are below the maximum methyl eugenol levels in dairy products and meat preparations and products (Regulation (EC) No 1234/2008);**
- **an ADI of 0.03 mg/kg bw/day has been defined;**

the WG concludes, based on the available data, that tea tree EO is not of concern for consumers of foods derived from animals that have received it in the context of veterinary medicine.

6.4.2 Lavender and lavandin EOs

6.4.2.1 General data

Table 93: General data on lavender and lavandin

Common name	Lavender	Lavandin
Latin name	*Lavandula angustifolia* Mill.	*Lavandula x intermedia* Emeric ex Loise Hybrid between true lavender and spike lavender (*Lavandula latifolia* Medik.) Several clones have been described (Abrial, Grosso, Super)
Synonyms	*Lavandula vera* DC. English lavender, true lavender, narrow-leaved lavender	*Lavandula hybrida* Reverchon, *Lavandula hortensis* Hy, *Lavandula* × *burnatii* Briq. or *Lavandula x burnati clone super*, natural hybrid
Parts of the plant concerned	Flowers, flowering tops	Flowers, flowering tops

6.4.2.2 Status in the regulations and guidelines

Table 94: Status of lavender and lavandin in the regulations and guidelines

		Lavender	Lavandin
MRLs	**Regulation (EU) No 37/2010**	In Table 1, *Lavandulae aetheroleum* for all species, for topical use only	Not listed
Medicinal products for human use	**List of medicinal plants**	List A (not subject to the monopoly in unprocessed form)	List A (not subject to the monopoly in unprocessed form)
	Pharmacopoeias	Monograph for the EO, Ph. Eur.	Monograph for lavandin “grosso” EO, French Pharmacopoeia
	WHO	Monograph for *Aetheroleum Lavandulae*	Monograph for *Aetheroleum Lavandulae* (WHO 2007)

	MAs in France	AROMASOL® drops with essences, SCHWABE® LAVENDER EO PERUBORE® INHALATION	No medicinal products registered in France
Food supplements	**DGCCRF 2019**	Listed	Listed
Novel foods	**EFSA catalogue**	Not listed	Not listed
Feed additives	**Regulation (EU) No 1831/2003**	Listed	Not listed

6.4.2.3 Opinions of European agencies

Table 95: Opinions of European agencies on lavender and lavandin

EMA HMPC	An assessment report on true lavender (plant, EO) and a herbal monograph on true lavender (EO) (EMA 2012b, 2012d)
ANSES	In EO Opinion 2018-SA-0145 on essential-oil based sprays and diffusers for domestic use (Anses 2020a)

6.4.2.4 Composition

The composition of EOs from the various lavandin clones is as follows:

Table 96: Composition of lavandin EOs

Composition of the EO	Lavandin “super” from France (Baudoux 2001)	Lavandin “super” (Tisserand et Young 2014)	Lavandin “grosso” (française 2012)	Lavandin “grosso” (Tisserand et Young 2014)
1,8-cineole [a, b, c]	3.87%	3 to 3.6%	4 to 8%	5.2 to 10.2%
Camphor [d, e]	5.61%	4.5 to 5.3%	6 to 8.5%	6.6 to 12.2%
Linalool [a, b]	28.98%	29.4 to 32.7%	25 to 37%	22.5 to 28.0%
Linalyl acetate [a, b]	33.47%	38.6 to 44.3%	25 to 38%	26.2 to 37.5%
Lavandulyl acetate [a]	3.17%	1.5 to 1.7%		2.3 to 2.4%
Terpinen-4-ol [a, b]				0 to 3.3%
Borneol [a, b]	3.38%	1.7 to 2.9%		2.4 to 2.9%
Limonene [a, b]			0.5 to 1.5%	
α-terpineol [a, b]			0.3 to 1.3%	0 to 1.2%

[a] Flavouring substance for use in and on foods, with no use restrictions (Regulation (EU) No 872/2012).

[b] Register of feed additives, Annex I, 2020; no restrictions (Regulation (EC) No 1831/2003).

[c] Table 1 of Regulation (EU) No 37/2010; no restrictions.

[d] Flavouring substance for use in and on foods, with use restrictions (Regulation (EU) No 872/2012): “In category 1 – not more than 16 mg/kg; In categories 2 and 8 – not more than 50 mg/kg; In category 3 – not more than 20 mg/kg; In categories 5, 6, 7, 12 and 15 – not more than 100 mg/kg; In category 14.1 – not more than 50 mg/l; In category 14.2 – not more than 50 mg/l (except not more than 850 mg/l in *Schweden-bitter*)”.

[e] Table 1 of Regulation (EU) No 37/2010 (restriction: external use only).

Variation in the composition of English lavender (*Lavandula angustifolia*) EO:

Table 97: Composition of true lavender EO (Tisserand et Young 2014)

Composition of the EO	Tisserand and Young (2014)	Ph. Eur. 10th ed.
1,8-cineole (eucalyptol) [a, b, c]		< 2.5%
3-octanone		0.1-5.0%
Camphor [d, e]		< 1.2%
Lavandulol [a]		> 0.1%
Limonene [a, b]		< 1.0%
Linalool [a, b]	44% (30-45%)	20.0-45.0%
Linalyl acetate [a, b]	41.6% (33-46%)	25.0-47.0%
Lavandulyl acetate [a]	3.7%	> 0.2%
Terpinen-4-ol [a, b]	1.5%	0.1-8.0%
Borneol [a, b]	1%	
α-terpineol [a, b]	0.7%	< 2.0%

[a] Flavouring substance for use in and on foods, with no use restrictions (Regulation (EU) No 872/2012).

[b] Register of feed additives, Annex I, 2020; no restrictions (Regulation (EC) No 1831/2003)

[c] Table 1 of Regulation (EU) No 37/2010; no restrictions.

[d] Flavouring substance for use in and on foods, with use restrictions (Regulation (EU) No 872/2012): “In category 1 – not more than 16 mg/kg; In categories 2 and 8 – not more than 50 mg/kg; In category 3 – not more than 20 mg/kg; In categories 5, 6, 7, 12 and 15 – not more than 100 mg/kg; In category 14.1 – not more than 50 mg/l; In category 14.2 – not more than 50 mg/l (except not more than 850 mg/l in *Schweden-bitter*)”.

[e] Table 1 of Regulation (EU) No 37/2010 (restriction: external use only).

6.4.2.5 Presence in the normal human diet

Lavandin and English lavender are not part of the normal human diet except in confectionery and beverages.

6.4.2.6 Presence in the normal diet of animals

Lavandin and English lavender are part of the normal diet of animals.

6.4.2.7 Human exposure

- English lavender and lavandin are included in EFSA's Compendium of Botanicals, which is a database of botanicals that are reported to contain substances of possible concern for human health when present in food (presence of the substances of concern camphor and 1,8-cineole).
- According to EMA, there is a lack of toxicological data on English lavender, in particular genotoxicity, carcinogenicity and reprotoxicity data. EMA therefore advises against its use by pregnant and breastfeeding women.
- Based on the human phytotherapy uses authorised by the ANSM in France and considering the EMA/HMPC monograph on English lavender EO, human exposure levels can be determined. EMA mentions oral use by adults and adolescents, at the dose of 20-80 mg/day.

  The following medicinal products are registered in France:
  - SCHWABE LAVENDER EO, soft capsules: 80 mg EO/capsule, one capsule/day for no more than two weeks
  - DROPS WITH ESSENCES, oral solution, peppermint EO, clove EO, lavender EO, thyme EO (0.5 g lavender EO per 100 g): the dosage of 25 drops, three or four times a day (100 drops/day (4 ml)) corresponds to 200 mg lavender EO/day

6.4.2.8 Animal exposure

Lavender and lavandin EOs are used in sprays to purify livestock buildings. The presence of lavender in animal feed cannot be ruled out.

6.4.2.9 Toxicological data

- **Toxicological data on lavandin**

No data

- **Toxicological data on lavender**

Table 98: Toxicological data on lavender EO

	Observations	Conclusions	References
Toxicity after a single administration			
Lavender EO	Rats, *PO*	LD_{50} = 5 g/kg bw	(EMA 2012b)
		Between 3 and 6 ml/kg bw	(EMA 2012b)
Toxicity after repeated administration			
Linalool	Rats, dermal application: 250 to 4000 mg/kg bw/day, 90 days	4000 mg/kg: 11 out of 20 animals died 1000 mg/kg: weight loss and reduced motor activity 250 mg/kg: reduced motor activity and transient erythema	(EMA 2012b)
1/1 mixture of linalool/citronellol	Rats, via feed: 50 mg/kg bw/day, 90 days	Reduced weight gain in males but no change in blood or urinary parameters after six and 12 weeks; no	(EMA 2012b)

		histopathological effects detected	
Conclusion: English lavender and its main components have low toxicity but can be irritating to the skin			
***In vitro* genotoxicity**			
Linalool and linalyl acetate	Ames test	Negative in TA92, TA1535, TA100, TA1537, TA94 and TA98	(EMA 2012b)
Lavandula angustifolia Mill. EO Linalyl acetate 43% and linalool 32.7%		Negative in *Salmonella* Typhimurium strains TA100 and TA98 and *Escherichia coli* WP2*uvrA* with and without S9	(Evandri *et al.* 2005)
Linalool	MLA/TK	Negative without S9 and weakly positive with S9 from 200 µg/ml	(EMA 2012b)
Linalool	Chromosome aberrations	Negative in CHO cells and hamster fibroblasts	(EMA 2012b)
Linalool and linalyl acetate	Unscheduled DNA synthesis (UDS) test *in vitro* in rat primary hepatocytes	Negative	(EMA 2012b)
Lavender EO	*In vitro* comet assay in HEL 12469 human embryo lung cells	No DNA breaks after 24h of exposure up to the maximum tested dose of 0.3 µl/ml	(Puskarova *et al.* 2017)
Lavender EO, linalool and linalyl acetate	*In vitro* micronucleus test in human lymphocytes	Lavender oil induced MN only at the maximum tested concentration of 100 µg/ml Negative result with linalool up to the maximum tested concentration of 100 µg/ml Significant results with linalyl acetate from 10 µg/ml	(Di Sotto *et al.* 2011)

The Ames test performed with a lavender EO extract was negative. The other *in vitro* data suggest micronucleus-inducing potential in human lymphocytes at high concentrations, which may be due to linalyl acetate. However, given that linalyl acetate is metabolised to linalool and that linalool is not genotoxic, we can conclude that there is no genotoxic concern for English lavender EO.

6.4.2.10 PK and residue data

After a 10-minute abdominal massage with oil containing 2% lavender EO (25% linalool and 35% linalyl acetate), in a healthy volunteer, trace amounts of these two substances were found in the blood within five minutes of finishing the massage, and peak plasma concentrations of

121 ng/ml for linalool and 100 ng/ml for linalyl acetate were reached after 19 minutes. These compounds could not be detected after 90 minutes (EMA 2012b)

6.4.2.11 Reported adverse effects

- **Cases from nutrivigilance**

Adverse effects have been reported to ANSES twice since 2012 following the consumption of food supplements containing lavandin EO. Nausea, vomiting, asthenia, very brief loss of consciousness and dizziness have been reported following the consumption of lavandin, Ho wood, narrow-leaved peppermint, niaouli, rosemary, blue gum, peppermint, ravintsara, clove and tea tree EOs. A case of fulminant hepatitis requiring a transplant was reported following the consumption of capsules containing lavender, mandarin, verbena and marjoram.

- **Cases recorded in Canada and the United States**

No data.

6.4.2.12 Summary of the assessment

English lavender EO and lavandin EOs have similar compositions.

Considering that, for English lavender and lavandin EOs:

- **English lavender is listed in Table 1 of Regulation (EU) No 37/2010 only for a topical use and lavandin EO is not listed;**
- **their main components are used as food flavourings, with no restrictions (Regulation (EU) No 872/2012);**
- **English lavender EO is used in human phytotherapy at doses of up to 20 mg EO/kg bw/day;**
- **these EOs have low toxicity and are not genotoxic;**
- **these EOs contain substances that are rapidly metabolised and excreted;**
- **these EOs do not have TRVs, but safe exposure data are known;**

the WG concludes, based on the available data, that English lavender and lavandin EOs are not of concern for consumers of foods derived from animals that have received them in the context of veterinary medicine.

6.4.3 Palmarosa EO

6.4.3.1 General data

Table 99: General data on palmarosa

Common name	Palmarosa
Latin name	*Cymbopogon martinii* Roxb. var. *martinii*
Synonyms	Motia, rosha grass, *Andropogon martinii* Roxb. var. *martinii*, *Cymbopogon martinii* Roxb. var. *motia*
Parts of the plant concerned	Aerial parts

6.4.3.2 Status in the regulations and guidelines

Table 100: Status of palmarosa in the regulations and guidelines

MRLs	**Regulation (EU) No 37/2010**	Not listed
Medicinal products for human use	**List of medicinal plants**	List A for lemongrass (*Cymbopogon* sp.) (leaves; not subject to the pharmaceutical monopoly, in unprocessed and powdered form)
	Pharmacopoeias	No monograph in the European or French Pharmacopoeia
	WHO	No herbal monograph
	MAs in France	No medicinal products registered in France
ISO standards		ISO 4727:1988(en), EO of palmarosa (*Cymbopogon martinii* (Roxburgh) W. Watson var. motia)
Food supplements	**DGCCRF 2019**	The plant is authorised without restrictions. The EO is registered in food supplements.
Novel foods	**EFSA catalogue**	Not listed
Feed additives	**Regulation (EU) No 1831/2003**	Not listed
Flavouring substances	**Regulation (EU) No 872/2012**	Not listed

6.4.3.3 Opinions of European agencies

Table 101: Opinions of European agencies on palmarosa

ANSES	Summary of knowledge on Shiga Toxin-producing *Escherichia coli* (04/2003). Palmarosa EO mentioned as having “high bactericidal

	activity against *E. coli* O157:H7, due to its composition containing geraniol".

6.4.3.4 Composition

Table 102: Composition of palmarosa EO (Tisserand et Young 2014)

Geraniol [a, b]	74.5-81.0%
Geranyl acetate [a, b]	0.5-10.7%
(*E*,*Z*)-farnesol	0.5-6.1%
Linalool [a, b]	2.6-4.5%
(*E*)-β-ocimene [a, b]	1.3-3.1%
β-caryophyllene [a, b]	0.9-2.6%
Geranial	0.5-1.9%
Caryophyllene oxide (β-caryophyllene epoxide) [a]	0.1-1.8%
Myrcene [a, b]	0.6-1.3%
Elemol [a]	0.2-1.0%
(*Z*,*Z*)-farnesol	0.1-1.0%

[a] Flavouring substance for use in and on foods, with no use restrictions (Regulation (EU) No 872/2012).

[b] Register of feed additives, Annex I, 2020; no restrictions (Regulation (EC) No 1831/2003).

[c] Table 1 of Regulation (EU) No 37/2010; no restrictions.

6.4.3.5 Presence in the normal human diet

Palmarosa EO is not present in the normal human diet.

6.4.3.6 Presence in the normal diet of animals

Palmarosa EO is not present in the normal diet of animals.

6.4.3.7 Human exposure

Palmarosa EO is authorised as a food additive.

The plant *Cymbopogon martini* (Roxb.) Will. Watson is included on the DGCCRF's "List of plants that can be used in food supplements" with no health restrictions.

Palmarosa EO is included on the DGCCRF's "List of plants whose essential oils are considered traditional" (January 2019) and in the related document "Essential oils - Health recommendations for the use of essential oils in food supplements" (January 2019). This list mentions estragole as a high-risk substance for "*Cymbopogon martinii* (Roxb.) J.F. Watson – Palmarosa". However, this substance was not identified as a component of this EO in several publications dealing with its composition.

6.4.3.8 Animal exposure

Most of the components of palmarosa EO are naturally found in pastures (geraniol, (E)-β-ocimene, β-caryophyllene, myrcene (Cornu *et al.* 2005) and geranyl acetate (Carpino *et al.* 2004)). Some (geraniol, linalool and geranial) are authorised as feed additives.

6.4.3.9 Toxicological data

- **Data on the EO**

Table 103: Toxicological data on palmarosa EO

	Observations	Conclusions	References
Toxicity after a single administration			
Palmarosa EO	Rats, oral route	LD_{50} > 5 g/kg	(Guilbault 2020)
Toxicity after repeated administration			
Palmarosa EO Geraniol (majority component)	No data on oral exposure Rats, exposure by inhalation: EO 13.73 mg/L air, geraniol 8.36 mg/L air, duration: 10 minutes every 48h, 30 days	Group exposed to the EO: no signs of toxicity (physical signs, hepatic and renal parameters) Group exposed to geraniol: hepatotoxicity (increased ALT activity)	(Guilbault 2020)
Genotoxicity/Mutagenicity			
Palmarosa EO	*In vitro* comet assay in human lymphocytes	DNA fragmentation from 1000 to 2000 µg/ml	(Guilbault 2020; Sinha *et al.* 2014)
No carcinogenicity, reprotoxicity or developmental toxicity data			

There are no chronic oral exposure data for the EO, but data on geraniol (majority component, over 70%) are available in the dedicated summary. Geraniol is non-mutagenic, non-genotoxic and non-carcinogenic according to the studies available in the literature.

Linalool and geranial are also non-mutagenic, non-genotoxic and non-carcinogenic according to the studies available in the literature (see above).

- **Data on the various components of palmarosa EO**

Table 104: Toxicological data on the substances in palmarosa EO

Component	Toxicological data/Conclusion	References
Geraniol (74.5 - 81.0%)	Non-genotoxic, non-mutagenic, non-carcinogenic, low toxicity	*see 5.2.4.*
Geranyl acetate (0.5 - 10.7%)	Rats: LD_{50} oral = 6.33 g/kg Non-toxic and non-carcinogenic ADI = 0.5 mg/kg bw/day as citral and linalool Non-genotoxic and non-mutagenic Oral NOAEL, rats (103 weeks), for geranyl acetate (71%) / citronellyl acetate (29%) mixture = 1000 mg/kg bw/day Oral LOAEL, rats (103 weeks), for geranyl acetate (71%) / citronellyl acetate (29%) mixture = 2000 mg/kg bw/day	(Tisserand et Young 2014) JECFA (1999)[87]
(E,Z)-farnesol (0.5 - 6.1%) **(Z,Z)-farnesol (0.1 - 1.0%)**	Rats, LD_{50} oral > 5 g/kg Mice, LD_{50} oral = 8.76 g/kg Low oral toxicity, non-mutagenic	(Tisserand et Young 2014)
Linalool (2.6 - 4.5%)	Non-genotoxic, non-mutagenic, non-carcinogenic No risk to consumers	*see 5.2.6.*
(E)-β-ocimene (1.3 - 3.1%)	Rats, LD_{50} oral for these isomers > 5 g/kg Non-toxic Slight inhibitory effect on B16 mouse melanoma cell proliferation (IC_{50} = 250 nM)	(Tisserand et Young 2014)
β-caryophyllene (0.9 - 2.6%)	Rats, LD_{50} oral > 5 g/kg Non-toxic, non-mutagenic	(Tisserand et Young 2014)
Geranial (0.5 - 1.9%)	Non-genotoxic, non-mutagenic, non-carcinogenic No identified risk to consumers	*see 5.2.3.*

[87] http://www.inchem.org/documents/jecfa/jeceval/jec_1271.htm

Caryophyllene oxide (0.1 - 1.8%)	Rats, LD_{50} oral > 5 g/kg Non-toxic, non-mutagenic	(Tisserand et Young 2014)
Myrcene (0.6 - 1.3%)	Rats, $NOAEL_{reprotoxic}$ = 250 mg/kg Chronic toxicity: Renal lesions in male rats: nephrotoxicity Hepatic cancers observed in male mice, not reflected by any toxicity in rats Non-toxic, non-mutagenic	(Tisserand et Young 2014) (Data should be considered with caution: massive doses applied with doubts about purity)

- **Data on elemol (0.2 - 1.0%)**

	Observations	**Conclusions**	**References**
Toxicity after a single administration			
Elemol	Rats, oral route Read-across from elemi oil	LD_{50} = 3370 ± 405 mg/kg bw	ECHA
Toxicity after repeated administration: no data			
Genotoxicity/Mutagenicity			
Elemol (present in an elemol-rich fraction of *Canarium commune* EO obtained from exudate by fractional distillation)	Ames test	Result > 0 with TA98 with metabolic activation Classified in Category 2 (H341) for mutagenicity according to Regulation (EC) No 1272/2008 (CLP Regulation)	ECHA
Elemol	Ames test (*Salmonella* Typhimurium, *Escherichia coli*), elemol in DMSO, up to 5000 µg/plate with and without metabolic activation	No significant increase in the number of revertant colonies Elemol considered as non-mutagenic in a bacterial test system	(Api *et al.* 2017)
Elemol	(*In vitro*) micronucleus test, human peripheral blood lymphocytes, elemol in DMSO, up to 220 µg/ml, with and	No significant increase in the percentage of micronucleated binucleated cells compared with the	(Api *et al.* 2017)

	without metabolic activation	control up to the highest tested dose	
No carcinogenicity, reprotoxicity or developmental toxicity data			

Very small quantities of elemol are found in palmarosa EO.

A positive Ames test is mentioned on the ECHA website. However, this test was carried out with a mixture containing a majority of elemol ("Elemol-rich fraction of essential oil of *Canarium commune* (Burseraceae) obtained from exudate by fractional distillation"). It is stated that the tested elemol-rich fraction also contained methyl eugenol, which may explain the positive result obtained in the Ames test.

Another study conducted with elemol alone showed a negative result for the Ames test (see table above). In the data assessed by the Research Institute for Fragrance Materials (RIFM), total systemic exposure (1.4 µg/kg/day) was compared with the TTC of 30 µg/kg bw/day applicable to Cramer Class I compounds. The systemic exposure dose (dermal exposure and exposure by inhalation) was therefore compared with the oral TTC, which was an unfavourable scenario and led to the conclusion that there was no genotoxic potential.

In the mammalian cell micronucleus test, elemol did not show any genotoxicity.

6.4.3.10 PK and residue data

- **Data in animals**

No animal data are available for palmarosa EO. Only data for certain compounds such as geraniol, geranial and linalool (see summaries by substance) were found.

Since geranyl acetate is an analogue of geraniol, it was considered that it is excreted in the same way.

- Metabolism of farnesol (Tisserand et Young 2014): when rats ingested a mixture of farnesol isomers containing 39% (2E,6E)-farnesol, 24% (2E,6Z)-farnesol, 25% (2Z,6E)-farnesol and 11% (2Z,6Z)-farnesol, 80% of the farnesol found in the plasma was (2E,6E)-farnesol. Oral administration of farnesol isomers to rats for 28 days led to a significant increase in the activity of the following hepatic enzymes: CYP1A, CYP2A1-3, CYP2B1/2, CYP2C11/12, CYP2E1, CYP3A1/2, CYP4A1-3, glutathione reductase, NADPH/quinone oxidoreductase and UGT. The activity of glutathione S-transferase increased in the kidneys (Horn *et al.* 2005).
- **Metabolism of elemol**: 2000 mg/kg bw elemol were administered to rabbits. Urine was collected for 72h. Eighty percent of the administered dose was rapidly eliminated via urine (Asakawa *et al.* 1986).

- **Human data**

No data.

6.4.3.11 Summary of the assessment

Considering that, for palmarosa EO:

- **this EO is not listed in Table 1 of Regulation (EU) No 37/2010;**
- **its main components are used as food flavourings, with no restrictions (Regulation (EU) No 872/2012);**
- **no TRV has been defined;**
- **few toxicological data are available (in particular concerning its carcinogenicity and reprotoxicity);**
- **no ADME data are available;**
- **toxicological data are missing for a number of its components;**

the WG considers that, in the absence of sufficient data, despite normal human exposure to its components, it cannot conclude that palmarosa EO is not of concern for consumers of foods derived from animals that have received it in the context of veterinary medicine.

6.4.4 Ravintsara EO

6.4.4.1 General data

Table 105: General data on ravintsara EO

Common name	Ravintsara
Latin name	*Cinnamomum camphora* (L.) J. Presl
Synonyms	Camphor
Parts of the plant concerned	Leaves
Forms studied	Several CTs (camphor, 1,8-cineole, linalool); that which is normally used in aromatherapy is the 1,8-cineole CT, derived from camphor trees from Madagascar, specifically called “ravintsara”

6.4.4.2 Status in the regulations and guidelines

Table 106: Status of ravintsara EO in the regulations and guidelines

MRLs	**Regulation (EU) No 37/2010**	Not listed but eucalyptol (or 1,8-cineole) is included in Table 1
Medicinal products for human use	**List of medicinal plants**	Not listed
	Pharmacopoeias	No monograph in the European or French Pharmacopoeia
	WHO	No herbal monograph
	Known use in human medicine in France	Not listed
Food supplements	**DGCCRF 2019**	The EO is registered in food supplements.
Novel foods	**EFSA catalogue**	Not listed
Feed additives	**Regulation (EU) No 1831/2003**	Not listed
Flavouring substances	**Regulation (EU) No 872/2012**	Not listed

6.4.4.3 Opinions of European agencies

No opinions are available.

6.4.4.4 Composition

Study of the substances in the EO:

The plant usually used to obtain ravintsara EO is the camphor tree (*Cinnamomum camphora* (L.) J.Presl). Camphor EOs can be produced from the leaves, bark or roots of the plant. Depending on the origin (Australia, Asia or Madagascar), the composition varies widely. The leaves of trees from China, Japan and Taiwan are rich in camphor (up to 50% in the EO produced), whereas the leaves from Madagascar trees do not contain camphor, and their majority compound is 1,8-cineole (or eucalyptol). Three CTs have been described: the camphor CT (Asia and Australia), the 1,8-cineole CT (Australia and Madagascar), and the linalool CT (Asia). Ravintsara EO is the steam-distilled product from the leaves of the Madagascar camphor tree and corresponds to the 1,8-cineole CT.

Composition:

Table 107: Main components of ravintsara EO

1,8-cineole (eucalyptol) [a, b, c]	54%-60%
Sabinene (4(10)-thujene) [a]	10-16%
α-terpineol [a, b]	6-11%
α-pinene [a, b]	3.7-5.1%
Terpinen-4-ol [a, b]	1.9 and 3.1%
β-pinene (pin-2(10)-ene) [a, b]	3.2-3.59%
Myrcene [a, b]	1.3-1.8%
γ-terpinene [a, b]	0.8-1.2%
α-humulene	0.4-1.2%
(*E*)-β-caryophyllene [a, b]	0.4-1.2%

[a] Flavouring substance for use in and on foods, with no use restrictions (Regulation (EU) No 872/2012).

[b] Register of feed additives, Annex I, 2020; no restrictions (Regulation (EC) No 1831/2003)

[c] Table 1 of Regulation (EU) No 37/2010; no restrictions.

Moreover, very small quantities (sometimes trace amounts) of around 35 additional compounds have been identified.

6.4.4.5 Presence in the normal human diet

Ravintsara EO is not present in the normal human diet.

6.4.4.6 Presence in the normal diet of animals

Ravintsara EO is not present in the normal diet of animals.

6.4.4.7 Human exposure

Ravintsara EO is not an additive and does not have a monograph in the Ph. Eur. However, it is readily available commercially, including outside of pharmacies. It is normally used by diffusion and topically, for its anti-infective, expectorant and circulatory properties. It is difficult to assess human exposure.

6.4.4.8 Animal exposure

Ravintsara EO is not an additive or feedingstuff. Animal exposure via feed has not been assessed. However, certain compounds are found in numerous plants consumed by animals.

6.4.4.9 Toxicological data

The toxicological profile of ravintsara EO has not been studied. However, some substances have been assessed by EFSA.

The compounds can be biotransformation enzyme inducers. In addition, hepatomegaly has been observed in toxicological studies, but it was reversible.

Table 108: Toxicological data on ravintsara EO

Component	Observations	Conclusions	References
Toxicity after repeated oral administration			
1,8-cineole	Mice, via feed, 0, 562.5, 1125, 2250 and 4500 mg/kg/day, 28 days	NOAEL = 562.5 mg/kg bw/day At the three highest doses: centrilobular hepatic hypertrophy (males and females)	(Efsa 2012c)
Myrcene	Rats, via feed: 8, 40 and 44 mg/kg/day (males) and 6, 9, 48 and 53 mg/kg/day (females), 90 days	NOAEL = 44 mg/kg/day	(Efsa 2016a)
β-caryophyllene	Rats, via feed: 0, 222, 456 and 1365 mg/kg/day (males) and 0, 263, 1033 and 4278 mg/kg/day (females), 90 days	NOAEL = 222 mg/kg/day Effects observed at the two highest tested doses for both sexes	(Efsa 2016a)
Sabinene α-pinene β-pinene	Reference compound: β-caryophyllene	NOAEL = 222 mg/kg/day, derived from the reference compound (read-across)	(Efsa 2016a)

α-terpineol Terpinen-4-ol	Reference compound: terpineol	NOAEL = 250 mg/kg/day, derived from the reference compound (read-across)	(Efsa 2016a)
α-humulene	Mice *Teucrium alopecurus* EO (12.3% α-humulene): 0, 10, 20 and 30 μg EO/kg bw; intragastric administration for seven days	No mortality or behavioural changes	(Guesmi *et al.* 2018)
***In vitro* genotoxicity**			
1,8-cineole	Comet assay in HCT116 human colorectal cancer cells	Pretreatment with formamidopyrimidine-DNA glycosylase: detection of probable oxidative lesions Pretreatment with N-acetylcysteine prevented this oxidation No reduced viability or cell cycle disruption	(Dorsam *et al.* 2015)
Reprotoxicity			
1,8-cineole	Rats, 1000 mg/kg/day for seven days during the pre-implantation period, i.e. during organogenesis	Reproductive toxicity. This did not call into question the NOAEL	(Caldas *et al.* 2016)

Other compounds do not have a NOAEL but have been assessed using the TTC approach. This method is used for low exposure when there are no toxicological data (it should not be used for regulated substances and products). This method classifies non-genotoxic substances into three categories according to their level of toxicity. The categories were defined by Cramer in an article from 1978 (Cramer, Ford et Hall 1976). The calculations were performed for a 60 kg individual.

- Class I: substances with simple structures and for which modes of metabolism exist: low toxicity, limit of 1800 μg/person/day
- Class II: substances with structures that are less innocuous than class I substances, but do not suggest toxicity like those substances in class III: intermediate toxicity, limit of 540 μg/person/day
- Class III: substances with chemical structures that suggest significant toxicity (reactive functional groups): high toxicity, limit of 90 μg/person/day

For each category, human safety limits are defined, and based on these limits and possible exposure levels, the risk to humans can be assessed.

6.4.4.10 PK and residue data

Overall, data concerning the various substances in the EOs are scarce. There are very few ADME studies. As proven by the metabolites found in urine (myrcene, α-pinene and β-pinene in rabbits for example (Efsa 2016a)), terpenes are absorbed following oral administration. Peak concentrations were observed after 4h in goats for α-pinene and after 8h, plasma concentrations reached zero (Poulopoulou *et al.* 2012). However, in the same study, the absorption of β-caryophyllene was low (plasma concentrations remained low). Absorption therefore varies depending on the terpene. Absorbed terpenes can undergo biotransformations: epoxidation of myrcene (with diol formation through the action of an epoxide hydrolase) and oxidation (usually with appearance of the hydroxyl function, as the reaction is catalysed by CYP450) of α-pinene, β-pinene and β-caryophyllene. For the latter substances, glucuronidation and conjugation with glutathione are observed (Efsa 2016a). The biotransformation enzymes involved are present in the various food-producing animal species (ruminants, pigs, poultry, rabbits).

Terpenes are distributed in the entire body, including fat and muscle. A study published by E. Serrano *et al.* (2011) did not show any accumulation in muscle or fat. The study by Poulopoulo (2012) confirmed the rapid elimination of α-pinene. Terpenes pass into milk. Indeed, studies have shown that terpenes from food plants are found in the milk of cows (e.g. α-thyjene, α-pinene, β-pinene, β-caryophyllene, ɣ-terpinene, myrcene) (Tornambé *et al.* 2006), sheep (e.g. α-pinene, α-thujene, ɣ-terpinene, β-caryophyllene, α-humulene) (Valdivielso *et al.* 2017) and goats (e.g. α-pinene and β-caryophyllene) (Poulopoulou *et al.* 2012). These studies show that terpenes are naturally present in the milk of ruminants, depending on their diet. Of course, terpenes are found when feed rations are supplemented with EOs, for example α-thujene, α-pinene, sabinene, myrcene, ɣ-terpinene, α-terpinene, β-caryophyllene, 1-8 cineole and α-humulene (Tornambé *et al.* 2006).

6.4.4.11 Reported adverse effects

- **Cases from nutrivigilance**

No cases have been reported.

- **Cases recorded in Canada and the United States**

There was one case involving a child under the age of two years exposed to cinnamomum EO and also to other substances such as paracetamol and aspirin. The child died with respiratory and hepatic signs (FDA).

6.4.4.12 Summary of the assessment

Considering that, for ravintsara EO:

- **this EO is not listed in Table 1 of Regulation (EU) No 37/2010;**
- **its main components are used as food flavourings, with no restrictions (Regulation (EU) No 872/2012);**
- **this EO is commonly used, and the products that contain it can be administered orally, among other routes;**
- **its main component (more than 50%), 1,8-cineole (eucalyptol), is listed in Table 1 of Regulation (EU) No 37/2010, with no restrictions;**
- **NOAELs have been defined for its other main components;**
- **its main components are naturally found in plants consumed by herbivores and in the milk and muscle of the animals that have consumed them;**
- **the elimination of its components that have been investigated in PK studies is rapid;**

the WG concludes, based on the available data, that ravintsara EO is not of concern for consumers of foods derived from animals that have received it in the context of veterinary medicine.

7 Conclusions of the Working Group

7.1 Background and limitations of the WG's work

Previous work on the possible submission of simplified MA application dossiers for herbal veterinary medicinal products (Anses 2016) highlighted several potential obstacles for MA[88] applications including the lack of an MRL[89] status for the majority of the plants, herbal preparations and EOs[90] of interest. Without an MRL status, these cannot be used in veterinary medicinal products for food-producing animals. The term “veterinary medicinal products” encompasses medicinal products with MAs as well as extemporaneous preparations. The conclusions of this work recommended determining the MRL status of these herbal substances so they may be used in veterinary medicinal products intended for food-producing animals, and using the available data in regulations other than those on veterinary medicinal products.

Uses of phytotherapy and aromatherapy in animal husbandry are already well established. They are expected to develop further, with the boom in organic agriculture and in the wake of changes in agricultural practices encouraged, among others, by the French State. One of the objectives is to control the development of resistance to antimicrobial and antiparasitic substances contained in the medicinal products currently on the market (Ecoantibio plan, etc.). According to the hearings held to prepare this report, there are several profiles of users of phytotherapy and aromatherapy for food-producing animals:

- Some use phytotherapy and aromatherapy in compliance with fixed withdrawal periods in veterinary medicine but complain that these are restrictive.
- Others have no notion of a potential risk to consumers, especially since they handle products of natural origin that are often used in humans. They therefore do not comply with withdrawal periods. Not all verify whether the plant, herbal preparation or EO is included in Table 1 of Regulation (EU) No 37/2010.

There is also the issue of borderline products: plants, herbal preparations and EOs are widely used in non-medicinal products, primarily having the status of “complementary feed” or feed additive. These products have uses, or are the subject of claims, that are sometimes very similar to those of veterinary medicinal products without fulfilling the same requirements. Circumvention of veterinary medicinal product status is common and has been addressed in recommendations issued by the European Commission[91]. Such products are readily available to farmers and veterinarians, since the regulations applying to them do not impose any withdrawal period. It is also important to note that the labels on these products often lack detail and precision. There are therefore uncertainties as to their composition and quality, with problems concerning the definition of the plants (indication of the species, part, origin, chemotype, etc.) and preparations used, and also concerning the doses or concentrations of the herbal active substances.

[88] Marketing authorisation
[89] Maximum residue limit
[90] Essential oils
[91] 2011/25/EU: Commission Recommendation of 14 January 2011 establishing guidelines for the distinction between feed materials, feed additives, biocidal products and veterinary medicinal products

Many plants and herbal preparations used in animal husbandry have a long tradition of use and are assumed to be safe. The regulatory framework for veterinary medicinal products appears, also for this reason, to be rigid and unsuitable for plants and EOs. Current uses and practices not supervised by healthcare professionals can go against the protection of consumers – due either to the therapeutic practices themselves or to the poor quality of the available products. It will be necessary to find a solution to enable phytotherapy and aromatherapy to be used in a way that meets the expectations of professionals and consumers, guarantees consumer safety, and ensures compliance with current veterinary medicine legislation.

A three-stage approach was used by the WG. The first stage inventoried uses of phytotherapy and aromatherapy in animal husbandry, based on data provided by users, prescribers and trainers. Based on the hearings conducted, a list of the main plants, herbal preparations and EOs used in animal husbandry was drawn up. The number of hearings was limited. This list is therefore not exhaustive. The plants, herbal preparations and EOs mentioned during these hearings are also included on the lists of professional organisations such as ITAB[92] and RéPAAS[93]. As a reminder, these lists propose plants that could be used in animal husbandry for therapeutic purposes without any restrictions. The aim of this first stage was not to produce an exhaustive list of uses in animal husbandry but rather to select significant and relevant cases for the identification stage (third stage).

The second stage consisted in surveying risk assessment methodologies focusing on the use of plants and EOs as presented in regulations other than those on veterinary medicinal products. Numerous assessments have already been published dealing with plants and EOs as part of their authorisations for use in human medicine or in the form of feed supplements and additives, for example. This stage resulted in the production of a list of data to be processed, obtained primarily from European agencies such as EFSA[94] and EMA[95], to be able to work on the identification stage.

The third stage involved working on the plants, herbal preparations and EOs most frequently mentioned during the hearings, for which the risks to consumers of food were assessed. This assessment also focused on specific and majority substances in EOs. This assessment of chemically defined substances aimed to refine the general assessment of the EOs.

Consumer risk was assessed based on the available data, supplemented by a literature search when necessary. At the end of the assessment, each plant, herbal preparation or EO was classified in one of the following categories:

- No concern for consumers of food derived from treated animals,
- Insufficient data to conclude as to whether there is any concern for consumers of food derived from treated animals.

There was another possible category, but it did not apply to any of the examples studied during this work:

[92] French research institute for organic farming
[93] Veterinary Phyto-Aromatherapy Network
[94] European Food Safety Authority
[95] European Medicines Agency

- Preparation of concern for consumers of food derived from treated animals, based on the available data.

Based on this work, a consumer risk assessment methodology for plants and herbal preparations including EOs is being proposed by the WG with a supporting two-step decision tree that can guide assessors throughout their assessments. This specific method classifies preparations into one of the following three categories:

- Preparation that can be used in veterinary medicine without any risk to consumers. These preparations must be included on a list in order to be authorised in medicinal products intended for food-producing animals. There may be restrictions on use, for example concerning routes of administration;
- Preparation considered as potentially of concern for consumers based on the available data (which means it cannot be used at the present time). A case-by-case assessment is necessary with the possibility of generating additional data or using the MRL approach;
- Preparation that cannot be used in veterinary medicine due to a risk to consumers.

As highlighted in the inventory of uses, and considering the traditional nature of phytotherapy and aromatherapy and the ways in which knowledge relating to them is currently passed on, there is sometimes a lack of precision with regard to the plant species (ambiguous common names, etc.), variety and CT used. The favoured preparations and conditions of use vary, according to the hearings. The WG considered the above when evaluating those uses that appeared the most common.

Unfortunately, there is frequently a lack of scientific data relating to plants and herbal preparations including EOs. Their chemical composition is often only partially defined. The lack of robust data (toxicological, PK, residue data, etc.) can impact the possibility of carrying out a consumer risk assessment. In general, substantial research work is needed to assess the efficacy, safety and benefit-risk ratio of phytotherapy and aromatherapy. It seems essential to acquire data on residues in particular when assessing consumer safety.

The information collected with regard to the DROMs[96] is not sufficient to have an overview of practices. The medical traditions and plants in these territories, which are different from those in metropolitan France, are associated with specific phytotherapy and aromatherapy practices in animal husbandry. Numerous overseas plants have been added to the list of medicinal plants in the French Pharmacopoeia. Furthermore, a large body of ethnobotanical and ethnopharmacological data is available for the DROMs. In the field, plants not considered as medicinal, and also toxic plants (whether or not they are included on list B of medicinal plants), may be used.

7.1 Recommendations

The MRL regulations are European. Implementing regulations are issued by the European Commission following opinions by EMA. The issue of the MRL status of plants and herbal preparations is therefore European and can only be managed at that level.

[96] French Overseas *Départements* and Regions

ANSES may present its report and opinion at European level to encourage a harmonised approach to this issue. The methodology set out in this report may be submitted to EMA, with the aim of including plants with no risk to consumers in Table 1 of Regulation (EU) No 37/2010 or on a new specific list that will need to be created. In parallel, a list of plants potentially of concern for consumers will need to be established. The priority list of EMA's HMPC[97] may be used for this. This list shows the plants assessed and mentions those species and preparations not meeting the definition of traditional use.

Studying the data available in other regulations will lead to the rapid extension of the list of plants that can be used in veterinary medicine for food-producing animals. The WG recommends also referring to toxicological data and considering the potential non-traditional nature of preparations.

The WG recommends monitoring practices and communicating about the classification of herbal preparations. It will be necessary to verify the identity and quality of the products used (PRMs[98]).

Monitoring through Total Diet Studies (TDSs) is recommended and should include, for example, some residue markers for plants.

In order to make up for the lack of data in the field of phytotherapy and aromatherapy in animal husbandry, research and development should be encouraged with support provided for research programmes whose priorities are the publication of:

- Toxicological data;
- Pharmacokinetic data on residues and metabolism;
- Consumption and exposure data;
- Data on the chemical compositions of the preparations used;
- Recommendations concerning new approach methodologies (NAMs), such as computational toxicology, new cell models, etc. (Efsa 2014a).

Inclusion on a roadmap of the French National Research Agency (ANR) is desirable with a definition of priority plants and herbal preparations.

The proposal of an appropriate approach for granting an MRL status for plants and herbal preparations, including EOs, and the assessment of their consumer safety, should be accompanied by an assessment of their efficacy and benefits, in particular as part of the Ecoantibio plan. Moreover, the continuation of this process and the promotion of phytotherapy and aromatherapy in animal husbandry cannot be dissociated from work aiming to consider the sustainability of plant resources and take into account production and supply chains, since this agricultural sector is dynamic in France.

[97] Committee on Herbal Medicinal Products
[98] Pharmaceutical raw materials

Lastly, it is desirable that professional organisations, directorates general (DGAL[99], DGS[100] and DGCCRF[101]) and various stakeholders in this field (veterinarians and farmers) continue to be jointly involved in work intended to facilitate the use of phytotherapy and aromatherapy medicinal products in animal husbandry.

Date of validation of the collective expert appraisal report by the Working Group and the Expert Committee: 19 October 2021

[99] Directorate General for Food
[100] Directorate General for Health
[101] Directorate General for Competition, Consumer Affairs and Fraud Control

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ANNEXES

Annex 1: Formal request letter

anses
agence nationale de sécurité sanitaire
alimentation, environnement, travail
Connaître, évaluer, protéger

Decision No 2020-096

INTERNAL REQUEST

The Director General of the French Agency for Food, Environmental and Occupational Health & Safety (ANSES),

Having regard to the Public Health Code, and in particular its Article L.1313-3 giving ANSES the prerogative to issue an internal request on any question with a view to accomplishing its missions,

Has decided the following:

Article 1. The French Agency for Food, Environmental and Occupational Health & Safety is issuing an internal request to conduct an expert appraisal whose characteristics are listed below.

1.1 Themes and objectives of the expert appraisal

State of knowledge on essential oils and plants of interest for phytotherapy and aromatherapy in food-producing animals aimed at establishing human health risk profiles.

1.2 Background of the internal request

This internal request follows on from the report on the "Inventory of alternatives to antibiotics aimed at reducing their use in animal husbandry" (Request No°2013-SA-0122) and from one of the conclusions of the report on the "Assessment of MA applications for herbal veterinary medicinal products" (Internal Request No 2014-SA-0081) concerning the primary challenge regarding the lack of an appropriate MRL status for the large majority of plants of interest in veterinary medicine.

Maximum residue limits (MRLs) are regulatory thresholds for residues of substances contained in veterinary medicinal products that are tolerated in foodstuffs from treated animals.

They are defined for a given substance, species and tissue, or foodstuff. They aim to guarantee a safe exposure level for consumers.

Concerning the classification of pharmacologically active substances administered to food-producing animals regarding maximum residue limits, Regulation (EU) No 37/2010 includes two tables:

- Table 1 corresponding to allowed substances (with possible use and/or species restrictions);
- Table 2 corresponding to prohibited substances (when no MRL can be set).

Some substances are considered, after assessment by EMA, as not falling within the scope of Regulation (EC) No 470/2009 with regard to MRLs. These are included on the "out of scope" list of EMA's Committee for Medicinal Products for Veterinary Use (CVMP) (EMA/CVMP/519714/2009). They include substances naturally occurring in the body and foodstuffs in the human diet that do not pose any risks to consumer health.

If a future herbal veterinary medicinal product is intended for food-producing animals, each essential oil or plant that it contains must be classified in Table 1 of the MRL Regulation or be included on the "out of scope" list. Therefore, the issue of the MRL status of essential oils and plants is fundamental for the phytotherapy treatment of food-producing animals, both when assessing MA application dossiers and when prescribing an extemporaneous herbal preparation (principle of the cascade, Art. L.5143-4 of the French Public Health Code).

In addition, the use of phytotherapy and aromatherapy is becoming more and more widespread on farms, in response to the development of organic agriculture and the decrease in the use of antibiotics (One Health, Ecoantibio plan).

However, the large majority of the commonly used essential oils and plants have not been assessed under Regulation (EC) No 470/2009 and therefore cannot currently be used in veterinary medicinal products intended for food-producing animals or be prescribed as part of an extemporaneous preparation by a veterinarian. Herbal products are often administered to animals in the form of complementary feed (containing additives).

Currently, only two herbal veterinary medicinal products intended for food-producing animals have an MA in France.

The development of phytotherapy/aromatherapy for food-producing animals requires a prior MRL assessment of these essential oils and plants (which is the responsibility of EMA), in order to guarantee a safe consumer exposure level. In a context where efforts are being made to control antimicrobial resistance and find therapeutic alternatives, and in response to the development of organic agriculture, possibilities for assessing hazards and risks to consumers therefore need to be reviewed to meet these expectations.

1.3 Questions on which the expert appraisal work will focus

It is important to note that in phytotherapy and aromatherapy, strict botanical identification of the plant used is a prerequisite. Indeed, depending on the species/plant part used, the geographic location, the season in which the plant is harvested, and the production process implemented, the resulting essential oil or other herbal preparation will not contain the same substances and therefore will not always have the same chemical composition or the same therapeutic capacities; its toxicity may even be different. For aromatherapy, chemical analyses of essential oils show that some contain a clear majority component and other minor substances. Others, however, are particularly complex and can contain over 100 compounds.

As a result, the conventional MRL assessment approach (according to the EU regulations on veterinary medicinal products) seems difficult, if not impossible, due to the complex and extremely varied quantitative and qualitative chemical composition of a given essential oil.

An internal request therefore seems necessary to assess the human health risks, especially for consumers of foodstuffs of animal origin, and to identify an assessment solution as an alternative to that applicable to MRLs, in order to consider the use of herbal health products as veterinary medicinal products for food-producing animals.

This work will focus on the state of knowledge on essential oils and plants of interest for phytotherapy and aromatherapy in food-producing animals aimed at establishing human health risk profiles thanks to:

- the possible use of data from the development of monographs for herbal medicinal products for human use;

- the possible use of data from other regulations, in particular on biocidal products and animal feed;

- the identification of essential oils and plants other than those already assessed by EMA, which do not fall within the scope of the MRL Regulation ("out of scope" list) and therefore do not pose any risks to consumer health;

- the identification of essential oils and plants whose toxicity is known in humans and for which it can therefore be considered they cannot be used in phytotherapy.

In its conclusion, this work may suggest alternative approaches that would be just as protective as the MRL principle.

This work will not examine the efficacy or the benefit/risk ratio of plants. It will be a first step before a comprehensive assessment of the human health risks associated with the identified essential oils and plants.

As part of public policy to facilitate access to herbal medicinal products, it is advisable to submit a request to EMA, on this basis of this work, to establish specific guidelines for veterinary phytotherapy medicinal products within a "herbal health products" theme, following the example of what EMA is doing in human medicine.

This work may also be useful to the European Commission when writing the report it is expected to present to the European Parliament and to the Council with regard to traditional herbal products used to treat animals in application of Article 157 of Regulation (EU) 2019/6 on veterinary medicinal products.

1.4 Estimated duration of the expert appraisal

September 2020 – June 2021

Article 2. An opinion will be issued and published by the Agency following completion of the work.

Signed in Maisons-Alfort on

Dr Roger Genet
Director General

Annex 2: Questionnaire used for the hearings

1- In what context do you use EOs/plants/herbal preparations on your production farms (e.g. plants as feed supplements, administered seasonally for a period of X for immune system stimulation)?

Questions regarding uses

2- Can you tell us what essential oils, plants and herbal preparations are used in cattle, from the most to the least commonly used?

For each EO, plant or herbal preparation mentioned, please specify:

- Main type of production animal treated: organic/conventional, meat/dairy, etc.
- Treated diseases (if possible, pathogens involved)
- Preventive, curative or metaphylactic use
- Dose
- Route of administration/area of application
- Treatment duration
- Treatment frequency (number of treatments/year)
- Treatment of all animals? Targeted or individual?

3- Can you tell us what essential oils, plants and herbal preparations are used in small ruminants from the most to the least commonly used?

For each EO, plant or herbal preparation mentioned, please specify:

- Main type of production animal treated: organic/conventional, meat/dairy, etc.
- Treated diseases (if possible, pathogens involved)
- Preventive, curative or metaphylactic use
- Dose
- Route of administration/area of application
- Treatment duration
- Treatment frequency (number of treatments/year)
- Treatment of all animals? Targeted or individual?

4- Can you tell us what essential oils, plants and herbal preparations are used in pigs from the most to the least commonly used?

For each EO, plant or herbal preparation mentioned, please specify:

- Main type of production animal treated: organic/conventional, etc.
- Treated diseases (if possible, pathogens involved)
- Preventive, curative or metaphylactic use
- Dose

- Route of administration/area of application
- Treatment duration
- Treatment frequency (number of treatments/year)
- Treatment of all animals? Targeted or individual?

5- Can you tell us what essential oils, plants and herbal preparations are used in poultry from the most to the least commonly used?

For each EO, plant or herbal preparation mentioned, please specify:

- Main type of production animal treated: organic/conventional, broiler chickens/laying hens, etc.
- Treated diseases (if possible, pathogens involved)
- Preventive, curative or metaphylactic use
- Dose
- Route of administration/area of application
- Treatment duration
- Treatment frequency (number of treatments/year)
- Treatment of all animals? Targeted or individual?

6- Can you tell us what essential oils, plants and herbal preparations are used in horses for human consumption from the most to the least commonly used?

For each EO, plant or herbal preparation mentioned, please specify:

- Main type of production animal treated: organic/conventional, etc.
- Treated diseases (if possible, pathogens involved)
- Preventive, curative or metaphylactic use
- Dose
- Route of administration/area of application
- Treatment duration
- Treatment frequency (number of treatments/year)
- Treatment of all animals? Targeted or individual?

7- Are you aware of other uses of EOs, plants or herbal preparations in other production animals (e.g. bees, fish, rabbits, etc.)?

8- If you use EOs, plants or herbal preparations, do you apply withdrawal periods?

Questions regarding "post-treatment"

9- Have you ever observed or learned of adverse effects occurring, following the use of EOs/plants/herbal preparations, in the treated animals, the farmer, or the person responsible for applying them to the animals?

10- Have you ever observed or learned of changes in the organoleptic properties of food derived from treated animals (e.g. odour of milk, difficulties with cheese-making technologies)?

Other questions

11- Why do you use EOs/plants/herbal preparations instead of proprietary veterinary medicinal products?

12- Where did you acquire your knowledge regarding the use of EOs/plants/herbal preparations to treat production animals (training, etc.)?

13- Where do you normally purchase EOs/plants/herbal preparations (purchasing offices, pharmacies, online, etc.)? Is the status of products important to you?

14- Do you favour certain suppliers for use in veterinary medicine? If so, which ones and why?

15- Do you request an analysis certificate to ensure the compliance of the EOs/plants/herbal preparations you purchase for the intended purpose?

16- Do you yourself prepare or purchase mixtures of EOs/plants/herbal preparations? If so, for each case, which ones?

17- If you prepare the mixtures yourself, what precautions do you take? In what conditions are they prepared? How do you label them?

Annex 3: Inventory from the hearings

- **Plants**

	Species (en)	Species	Plant part	Preparation type	Number of mentions	Convergence (%)
1	Wormwood	*Artemisia absinthium* L.	Aerial parts	Powder	1	*10.0*
2	Yarrow	*Achillea millefolium* L.	Flowering tops	-	2	*20.0*
3	**Garlic**	***Allium sativum* L.**	**Bulbs**	**Powder**	**8**	***80.0***
			Bulbs	**Hydrosol**		
			Bulbs	**Hydro-alcoholic extract**		
4	Lady's mantle	*Alchemilla xanthochlora* Rothm., (syn. *Alchemilla vulgaris* L.)	Aerial parts	-	1	*10.0*
5	Cashew	*Anacardium occidentale* L.	Bark	-	1	*10.0*
6	**(Common) mugwort**	***Artemisia vulgaris* L.**	**Aerial parts**	**Hydro-alcoholic extract**	**4**	***40.0***
7	**Artichoke**	***Cynara scolymus* L.**	**Leaves**	**Powdered plant**	**8**	***80.0***
8	Alder	*Alnus* sp.	Buds	Glycerine macerate	1	*10.0*
9	Elecampane	*Inula helenium* L.	Roots	-	2	*20.0*
10	Bamboo	Unspecified (*Bambusa vulgaris* Schrad.)	Stems	-	1	*10.0*
11	Burdock	*Arctium lappa* L.	Leaves and/or roots	-	2	*20.0*
12	Boldo	*Peumus boldus* Molina	Leaves	-	1	*10.0*
13	Boswellia (frankincense)	*Boswellia* sp.	Gum-oleoresin	-	1	*10.0*
14	Mullein	*Verbascum* sp.	Aerial parts	-	1	*10.0*
15	Restharrow	*Ononis spinosa* L.	Roots	-	1	*10.0*
16	Marigold	*Calendula officinalis L.*	Flower heads	-	1	*10.0*
17	Blackcurrant	*Ribes nigrum* L.	Leaves	-	2	*20.0*
18	**Milk thistle**	***Silybum marianum* (L.) Gaertn**	**Fruit**	**Dry plant or infusion**	**7**	***70.0***
				Standardised fluid glycerine extract	1	*10.0*
19	Sweet chestnut	*Castanea* sp.	Leaves	-	1	*10.0*
20	Oak	*Quercus robur* L., *Quercus* sp.	Bark	-	1	*10.0*

	Species (en)	Species	Plant part	Preparation type	Number of mentions	Convergence (%)
21	Chicory	*Cichorium intybus* L.	Underground parts	-	2	*20.0*
22	Couch grass	*Elytrigia repens* (L.) Desv. ex Nevski (syn. *Agropyron repens* (L.) Beauv.)	Underground parts	-	1	*10.0*
23	Comfrey	*Symphytum officinale* L. (syn. *S. consolida* Gueldenst ex Ledeb.)	Leaves and roots	-	1	*10.0*
24	Squash	*Cucurbita pepo* L. or *Cucurbita maxima* Lam.	Seeds	Hydro-alcoholic extract	1	*10.0*
25	Turmeric	*Curcuma domestica* Vahl (syn. *C. longa* L.)	Rhizomes	Powder or EO	3	*30.0*
26		Curcumin +/- piperine	-	-	1	10.0
27	Desmodium	*Desmodium adscendens* DC.	Aerial parts	Standardised fluid glycerine extract	1	*10.0*
28	**Echinacea**	***Echinaceae* sp.**	**Aerial parts/roots**	**-**	**5**	***50.0***
29	Dog rose	*Rosa canina* or other *Rosa* sp.	Pseudo fruit	-	1	*10.0*
30	California poppy	*Eschscholtzia californica* Cham.	Aerial parts	-	1	*10.0*
31	Fenugreek	*Trigonella foenum-graecum* L.	Seeds	Hydro-alcoholic extract	3	*30.0*
32	Male fern	*Dryopteris filix-mas* (L.) Schott (syn. *Aspidium filix-mas* (L.) Sw.)	Aerial parts	Powder	2	*20.0*
33	Raspberry	*Rubus idaeus* L.	Buds	Macerate	1	*10.0*
			Leaves	Powder	1	*10.0*
34	Ash	*Fraxinus* sp.	Leaves	-	2	*20.0*
35	Fumitory	*Fumaria* sp.	Aerial parts	-	2	*20.0*
36	Chaste tree	*Vitex agnus-castus* L.	Fruit	-	1	*10.0*

	Species (en)	Species	Plant part	Preparation type	Number of mentions	Convergence (%)
37	Gentian	*Gentiana lutea* L.	Roots	Powder	3	*30.0*
38	Ginger	*Zingiber officinale* Roscoe	Rhizomes	Hydro-alcoholic extract	1	*10.0*
39	Ginkgo	*Ginkgo biloba* L.	Leaves	-	1	*10.0*
			Leaves	Standardised fluid glycerine extract	1	*10.0*
40	Clove	*Syzygium aromaticum* (L.) Merr. & Perry (syn. *Eugenia caryophyllus* (Sprengel) Bull. & Harr.)	Cloves (flower buds)	-	1	*10.0*
41	Devil's claw	*Harpagophytum procumbens, H. zeiheri* (Burch.) DC. ex Meissn	Roots	-	1	*10.0*
42	Bay laurel	*Laurus nobilis* L.	Leaves	Hydrosol	2	*20.0*
43	Trefoil	*Lotus corniculatus* L.	Whole plant	-	1	*10.0*
44	Horse chestnut	*Aesculus hippocastanum* L.	Seeds	-	1	*10.0*
45	White horehound	*Marrubium vulgare* L.	Leaves, flowering tops	-	1	*10.0*
46	Lemon balm	*Melissa officinalis* L.	Leaves, flowering tops	-	1	*10.0*
47	St John's wort	*Hypericum perforatum* L.	Flowering tops	Oily macerate (external)	1	*10.0*
48	Blueberry	*Vaccinium myrtillus* L.	Leaves	-	1	*10.0*
49	Black cumin	*Nigella sativa* L.	Seeds	-	1	*10.0*
50	Hazel	*Corylus avellana* L.	Leaves	-	1	*10.0*
51	Walnut	*Juglans regia* L.	Leaves	-	1	*10.0*
52	Oregano	*Origanum vulgare* L.	Leaves, flowering tops	-	2	*20.0*
53	Java tea	*Orthosiphon stamineus* Benth.	Leaves and stem tips	-	2	*20.0*
			Leaves and stem tips	Standardised fluid glycerine extract	2	*20.0*
54	**Common nettle**	***Urtica dioica* L.**	**Leaves**	**-**	**6**	***60.0***
55	Papaya	*Carica papaya* L.	Leaves	-	1	*10.0*

	Species (en)	Species	Plant part	Preparation type	Number of mentions	Convergence (%)
56	Passion flower	*Passiflora incarnata* L. (syn. *P. edulis* Sims)	Aerial parts	-	1	*10.0*
57	Parsley	*Petroselinum crispum* (Mill.) Nyman ex A.W. Hill	-	Infusion	2	*20.0*
58	Mouse-ear hawkweed	*Hieracium pilosella* L.	Whole plant	-	1	*10.0*
59	Cayenne pepper	*Capsicum frutescens* L. (syn. *Capsicum annuum* L.)	Fruit	-	1	*10.0*
60	Scots pine	*Pinus sylvestris* L.	Buds	Standardised fluid glycerine extract	1	*10.0*
61	**Dandelion**	***Taraxacum officinale* (many synonyms)**	**Roots**	**Standardised fluid glycerine extract**	**10**	***100.0***
			Roots	**Powder**		
			Aerial parts	**Unprocessed**		
62	(Ribwort) plantain	*Plantago* spp.	Leaves	-	2	*20.0*
63	Tormentil	*Potentilla erecta* (L.) Raeusch. (syn. *P. tormentilla* Stokes)	Rhizomes	-	1	*10.0*
64	Field horsetail	*Equisetum arvense* L.	Aerial parts	Powder	1	*10.0*
65	Black radish	*Raphanus sativus* L. var. *niger* (Mill.) Kerner	Roots	Standardised fluid glycerine extract	1	*10.0*
66	Bearberry	*Arctostaphylos uva-ursi* (L.) Spreng	Leaves	-	1	*10.0*
67	Liquorice	*Glycyrrhiza glabra* L.	Underground parts	Standardised fluid glycerine extract	1	*10.0*
68	Meadowsweet	*Filipendula ulmaria* (L.) Maxim.	Flowering tops	-	2	*20.0*
69	Castor bean	*Ricinus communis* L.	Seeds	Oil	1	*10.0*
70	**Rosemary**	***Rosmarinus officinalis* L. (syn. *Salvia rosmarinus* Schleid)**	**Buds and leaves**	**-**	**5**	***50.0***
71	**Bramble**	***Rubus sp.***	**Leaves**	**-**	**4**	***40.0***
72	Purple loosestrife	*Lythrum salicaria* L.	Flowering tops	Hydro-alcoholic extract	2	*20.0*
73	Alfalfa	*Onobrychis* sp.	Aerial parts	-	1	*10.0*
74	Summery savory	*Satureja hortensis* L.	Leaves, flowering tops	-	2	*20.0*

	Species (en)	Species	Plant part	Preparation type	Number of mentions	Convergence (%)
75	Pink savory	*Satureja thymbra* L.	Aerial parts	-	1	*10.0*
76	Common sage	*Salvia officinalis* L.	Leaves	Powder or infusion	1	*10.0*
77	**Tansy**	***Tanacetum vulgare* L.**	**Flowering tops**	**-**	**4**	***40.0***
				Hydro-alcoholic extract	**1**	***10.0***
78	Common thyme	*Thymus vulgaris* L.	Leaves, flowering tops	Herbal tea, tincture	1	*10.0*
79	Valerian	*Valeriana officinalis* L.	Underground parts	-	1	*10.0*
80	Goldenrod	*Solidago gigantea* Ait.*, S. canadensis* L., *S. virgaurea* L.	Flowering tops	Powder	2	*20.0*

Preparation: if not specified: in unprocessed or powdered form.

- **Essential oils**

	Species (en)	Species	Family	Producing organ	Remarkable substances	Number of mentions	*Convergence (%)*
1	Yarrow	*Achillea millefolium* L.	Asteraceae	Flowering tops	-	1	*9.1*
2	Mugwort	*Artemisia vulgaris* L.	Asteraceae	Aerial parts	Thujone	2	*18.2*
3	Ajowan	*Carum copticum* L.	Apiaceae	Fruit	Thymol Carvacol	2	*18.2*
4	Garlic	*Allium sativum* L.	Liliaceae	Bulbs	Allyl sulfides	2	*18.2*
5	Aniseed	*Pimpinella anisum* L.	Apiaceae	Fruit	*Trans*-anethole	1	*9.1*
6	Basil	*Ocimum basilicum* L.	Lamiaceae	Leaves	Methyl chavicol Linalool	2	*18.2*
7	Boldo	*Peumus boldus* Molina	Monimiaceae	Fruit	Ascaridole	1	*9.1*
8	**Chinese or Ceylon cinnamon**	***Cinnamomum cassia* Blume or *Cinnamomum verum* J.S. Presl.**	**Lauraceae**	**Stem bark**	**Cinnamaldehyde Coumarin**	**6**	***54.5***
10	Cardamom	*Elettaria cardamomum* (L.) Maton	Zingiberaceae	Fruit	-	1	*9.1*
11	Carrot	*Daucus carota* L.	Apiaceae	Fruit?	-	2	*18.2*
12	Celery	*Apium graveolens* L.	Apiaceae	Fruit	Phthalides	1	*9.1*
13	Rock rose	*Cistus ladanifer* L.	Cistaceae	Flowering plant	Pinene Thujone (traces)	1	*9.1*
14	Lemon	*Citrus* x *limon* L.	Rutaceae	Zest	Limonene	2	*18.2*
15	Lemongrass	*Cymbopogon nardus* L.	Poaceae	Leaves	Citronellal	1	*9.1*
16	Turmeric	*Curcuma longa* L.	Zingiberaceae	Rhizomes	Sesquiterpenes	1	*9.1*
17	Cypress	*Cupressus sempervirens* L.	Cupressaceae	Branches	Pinene	2	*18.2*
18	Black spruce	*Picea mariana* (Mill.) Britton	Pinaceae	Leaves	Bornyl acetate	1	*9.1*
19	**Blue gum**	***Eucalyptus globulus* Labill. and related species**	**Myrtaceae**	Leaves	**Eucalyptol**	**7**	***63.6***
20	Lemon-scented gum	*Corymbia citriodora* Hook. (syn. *Eucalyptus citriodora* Hook)	Myrtaceae	Leaves	Citronellal	3	*27.3*
21	Wintergreen	*Gaultheria* sp.	Ericaceae	Leaves	Methyl salicylate	1	*9.1*

	Species (en)	Species	Family	Producing organ	Remarkable substances	Number of mentions	*Convergence (%)*
22	Ginger	*Zingiber officinale* Roscoe	Zingiberaceae	Rhizomes	Sesquiterpenes	3	*27.3*
23	Clove	*Syzygium aromaticum* (L.) Merr. & L.M. Perry	Myrtaceae	Cloves	Eugenol	4	*36.4*
24	Curry plant	*Helichrysum italicum* (Roth) G. Don	Asteraceae	Flowering aerial parts	Neryl acetate α-pinene Italidiones	2	*18.2*
25	**Bay laurel**	***Laurus nobilis* L.**	**Lauraceae**	**Leaves**	**Eucalyptol α-pinene**	**5**	***45.5***
26	True lavender (English lavender)	*Lavandula angustifolia* Mill.	Lamiaceae	Flowering tops	Linalool Linalyl acetate	1	*9.1*
27	Lavandin	*Lavandula x intermedia* Emeric ex Loisel. (unspecified clones)	Lamiaceae	Flowering tops	Linalool Linalyl acetate Eucalyptol	3	*27.3*
28	Aromatic litsea	*Litsea cubeba* (Lour.) Pers.	Lauraceae	Fruit	Citral	1	*9.1*
29	Lovage	*Levisticum officinale* Koch	Apiaceae	Roots	Phthalides	2	*18.2*
30	Manuka	*Leptospermum scoparium* J. R. Forster & G. Forster	Myrtaceae	Leaves	-	1	*9.1*
31	German chamomile	*Matricaria recutita* L.	Asteraceae	Flowering aerial parts	Sesquiterpenes	1	*9.1*
32	Melaleuca	*Melaleuca* sp.	Myrtaceae	Leaves / branches	Eucalyptol	1	*9.1*
33	Peppermint	*Mentha x piperita* L.	Lamiaceae	Leaves	Menthol Menthyl acetate Menthone	4	*36.4*
34	Wild bergamot	*Monarda fistulosa* L.	Lamiaceae	Leaves	Geraniol	1	*9.1*
35	Niaouli	*Melaleuca quinquenervia* Cav.	Myrtaceae	Leaves / branches	Eucalyptol	2	*18.2*
36	Oregano (mention with savory)	*Origanum* sp. / *Satureja* sp.	Lamiaceae	Flowering aerial parts	Thymol Carvacrol	1	*9.1*

	Species (en)	Species	Family	Producing organ	Remarkable substances	Number of mentions	*Convergence (%)*
37	**Common oregano**	***Origanum vulgare* L.**	**Lamiaceae**	Flowering aerial parts	**Thymol Carvacrol**	**6**	***54.5***
38	Spanish oregano (conehead thyme)	*Thymus capitatus* L. (syn. *Coridothymus capitatus* L.)	Lamiaceae	Flowering aerial parts	Thymol Carvacrol	1	*9.1*
39	**Palmarosa**	***Cymbopogon martinii* Roxb.**	**Poaceae**	**Leaves**	**Geraniol**	**5**	***45.5***
40	Patchouli	*Pogostemon cablin* (Blanco) Benth.	Lamiaceae	Leaves	-	1	*9.1*
41	Pelargonium (= bourbon geranium)	*Pelargonium* x *asperum* Ehrh. Ex Wild.	Geraniaceae	Leaves	Citronellol Geraniol	3	*27.3*
42	Pine	*Pinus* sp.	Pinaceae	Leaves / branches	Pinene	2	*18.2*
43	Douglas fir	*Pseudotsuga menziesii* (Mirbel) Franco	Pinaceae	Wood	Pinene Camphene	1	*9.1*
44	Ponderosa pine	*Pinus ponderosa* Douglas ex P. Lawson & C. Lawson	Pinaceae	Leaves / branches	Pinene Estragole	1	*9.1*
45	Scots pine	*Pinus sylvestris* L.	Pinaceae	Leaves / branches	Pinene	2	*18.2*
46	**Ravintsara**	***Cinnamomum camphora* L. var. Madagascar**	**Lauraceae**	**Leaves**	**Eucalyptol**	**5**	***45.5***
47	Rosemary	*Rosmarinus officinalis* L. (syn. *Salvia rosmarinus* Schleid.)	Lamiaceae	Aerial parts	Eucalyptol Camphor	1	*9.1*
48	Rosemary verbenone	*Rosmarinus officinalis* L. (syn. *Salvia rosmarinus* Schleid.)	Lamiaceae	Aerial parts	Eucalyptol Camphor	2	*18.2*
49	Eucalyptol rosemary	*Rosmarinus officinalis* L. (syn. *Salvia rosmarinus* Schleid.)	Lamiaceae	Aerial parts	Eucalyptol Camphor	2	*18.2*
50	Grand fir	*Abies grandis* (Douglas ex D.Don) Lindl	Abietaceae	Leaves / branches	Pinene	1	*9.1*
51	Savory (mention with oregano)	*Satureja* sp.	Lamiaceae	Flowering aerial parts	Thymol Carvacrol	1	*9.1*

	Species (en)	Species	Family	Producing organ	Remarkable substances	Number of mentions	*Convergence (%)*
52	Saro	*Cinnamosma fragrans* Baill.	Canellaceae	Leaves	Eucalyptol Pinene	1	*9.1*
53	Clary sage	*Salvia sclarea* L.	Lamiaceae	Leaves, flowering tops	Linalool Linalyl acetate	3	*27.3*
54	Tansy	*Tanacetum vulgare* L.	Asteraceae		Thujone	1	*9.1*
55	**Tea tree**	***Melaleuca alternifolia* Cheel**	**Myrtaceae**	**Leaves**	**Terpinen-4-ol**	**5**	***45.5***
56	Common thyme (CT linalool)	*Thymus communis* L.	Lamiaceae	**Leaves, flowering tops**	Linalool	2	*18.2*
57	**Common thyme**	***Thymus communis* L. / *Thymus satureioides* Coss. & Bal.**	**Lamiaceae**	**Leaves, flowering tops**	**Thymol Carvacrol Borneol**	**5**	***45.5***
58	Common thyme (CT thymol)	*Thymus communis* L.	Lamiaceae	**Leaves, flowering tops**	**Thymol**	2	*18.2*
59	Ylang-ylang	*Cananga odorata* J. D. Hook & T. Thompson	Annonaceae	Flowers	Benzoates	1	*9.1*

Annex 4: ANSES's list of plants of interest

- **List of plant parts of interest with an MRL status without restrictions**

Common name of the plant	Latin name	Part concerned	Form used
Common wormwood	*Artemisia absinthium*	Aerial parts	Powder/extracts
Common wormwood	*Artemisia absinthium*	Leaves or flowering tops	Green or after harvest
Yarrow	*Achillea millefolium*		Green or after harvest
Roman chamomile	*Chamaemelum nobile*	Flower heads	EO
Cinnamon	*Cinnamomum zeylinacum*	Bark of young twigs	EO
Cinnamon	*Cinnamomum zeylinacum*	Leaves	EO
Chinese cinnamon	*Cinnamomum cassia*	Leaves and young twigs	EO
Caraway	*Carum carvi*		
Lemon	*Citrus limon*		
Java citronella	*Cymbopogon winterianus*	Aerial parts	EO
Turmeric	*Curcuma longa*	Rhizomes	Extract
Eucalyptus	*Eucalypti aetheroleum*	Leaves or stems	EO
Lemon-scented gum	*Corymbia citriodora*	Aerial parts	EO
Blue gum	*Eucalyptus globulus*	Aerial parts	EO
Blue mallee	*Eucalyptus polybractea cryptonifera*		EO
Fennel	*Foeniculum vulgare*	Fruit	Powder/extract
Juniper	*Juniperus communis*	Branches	
Bay laurel	*Laurus nobilis*	Leaves	EO
West Indian lemongrass	*Cymbopogon citratus*		EO
Flax	*Linum usitatissimum*	Oil or seeds	
Marjoram	*Origanum majorana*	Leaves and flowering tops	EO
Thujanol marjoram	*Origanum majorana*	Flowering tops	EO
Lemon balm	*Melissa officinalis*	Aerial parts	Extract
Mint			EO
Peppermint	*Mentha* x *piperita*	Aerial parts	EO
Nettle	*Urtica dioica*	Leaves	Decoction
Palmarosa	*Cymbopogon martinii*	Aerial parts	EO
Cayenne pepper	*Capsicum annuum* L. var.	Dried ripe fruit	Oleoresin

	*minimum (*Miller) Heiser and small-fruit varieties of *Capsicum frutescens L.* (used as Cayenne pepper oleoresin)		
Cayenne pepper	*Capsicum annuum* L. var. *minimum* (Miller) Heiser and small-fruit varieties of *Capsicum frutescens* L.	Fruit	Extract
Rosemary	*Rosmarinus officinalis*	Aerial parts	EO
Rosemary verbenone	*Rosmarinus officinalis* (sb. verbenone)	Aerial parts	EO
Mountain savory	*Satureja montana*	Dried flowering tops	EO
Clary sage	*Salvia sclarea*	Fresh or dried flowering stems	EO
Elder	*Sambucus nigra*	Dried flowers	
Temulawak	*Curcuma xanthorrhiza*	Rhizomes	EO
Common thyme (with thymol)	*Thymus vulgaris* (*L. thymoliferum*)	Aerial parts	EO
Spanish thyme	*Thymus zygis*	Flowering tops	EO
Sweet thyme with linalool	*Thymus vulgaris linaloferum*		EO
Moroccan thyme	*Thymus serpylloides*	Aerial parts	EO
Thyme satureioides	*Thymus satureioides*	Aerial parts	EO

- **List of plants of interest with an MRL status and restrictions on use**

Common name of the plant	Latin name	Part concerned	Form used
Garlic	*Allium sativum*	Bulbs	EO
Garlic	*Allium sativum*	Bulbs	Extract
Garlic	*Allium sativum*	Bulbs	Fresh juice
Mugwort	*Artemisia vulgaris*	Leaves, flowering tops	
Arnica	*Arnica montana*	Flower heads	Tincture
Milk thistle	*Silybum marianum*	Leaves, fruit	
Comfrey	*Symphytum officinale*	Leaves	Extract
Cypress	*Cupressus sempervirens*	Branches	EO
Echinacea	*Echinacea purpurea*	Aerial parts, whole plant	Fresh juice/extract
Black spruce	*Picea mariana*	Needles	EO

Tarragon	*Artemisia dracunculus*	Aerial parts	EO
Ginkgo	*Ginkgo biloba*	Leaves	Extract
Clove	*Eugenia caryophyllus*	Dried floral buds = cloves	EO
Devil's claw	*Harpagophytum procumbens* and *H. zeyerii*	Rhizomes	Extract
Lavender	*Lavandula angustifolia*	Flowers, flowering tops	EO
Lavandin super	*Lavandula hybrida clone super*		EO
Niaouli	*Melaleuca viridiflora*		EO
Cineole niaouli	*If species: Melaleuca quinquenervia*	Young leafy twigs	EO
Onion	*Allium cepa*	Bulbs	Extract
Ravintsara	*Cinnamomum camphora ct cineole*	Leaves	EO
Goldenrod	*Solidago virgaurea*	Aerial parts	Green or after harvest

■ List of plants of interest without an MRL status

Common name of the plant	Latin name	Part concerned	Form used
Andrographis	*Andrographis paniculata*	Aerial parts	Extract
Artichoke	*Cynara sp*	Leaves	Extract
(Greater) burdock	*Arctium lappa*	Roots	Decoction
Basil	*Ocimum sp*	Aerial parts	EO
Cardamom	*Elettaria cardamomum*	Fruit	EO
Carrot	*Daucus carota*	Seeds or seeded plant	EO
Grey-leaved cistus	*Cistus albidus*		EO
Gum rock rose	*Cistus ladaniferus* CT pinene	Leafy branches	EO
Fenugreek	*Trigonella foenum-graecum*	Ripe seeds	
Male fern	*Dryopteris filix-mas*		
Ash	*Fraxinus*	Leaves	
American wintergreen	*Gaultheria procumbens*	Leaves	EO
Bourbon geranium	*Pelargonium asperum*		EO
Ginger	*Zingiber officinalis*		EO
Pomegranate	*Punica granatum*	Fruit	
Curry plant	*Helichrysum italicum*		EO
Litsea	*Litsea cubeba*	Aerial parts	EO

Aromatic litsea	*Litsea citrata*		EO
Lovage	*Levisticum officinale*	Roots	EO
Plume-poppy	*Macleaya cordata*		Extract
Manuka	*Leptospermum scoparium*	Aerial parts	EO
Tea tree	*Melaleuca alternifolia*	Leaves	EO
Walnut	*Juglans regia*	Leaves	
Oregano	*Origanum vulgare* or *Origanum compactum*	Aerial parts	EO
Pine		Branches	
Scots pine	*Pinus sylvestris*	Fresh leaves and branches	EO
Dandelion	*Taraxacum officinale*	Aerial parts and roots	
Pepper	*Piper nigrum*	Fruit	Extract
Field horsetail	*Equisetum arvense*	Aerial parts	Extract
Pueraria lobata	*Pueraria lobata, Pueraria montana* var. *lobata*	Vines	
Ravensara anisata	*Ravensara anisata*	Bark	EO
Meadowsweet	*Spirea ulmaria*	Flowers, flowering tops	Extract
Sainfoin	*Onobrychis viciifolia*	Aerial parts	Powder/extract
Bloodroot	*Sanguinaria canadensis*	Rhizomes	Extract
Willow	*Salix*	Bark	Extract
Wild thyme	*Thymus serpyllum*	Whole or fragmented dried flowering aerial parts	
Tansy	*Tanacetum vulgare*		Green or after harvest
Green tea	*Camellia sinensis*	Leaves	
Yucca	*Yucca schidigera*	Aerial parts	Extract

Annex 5: List of plants, herbal preparations and herbal substances included in Table 1 of Regulation (EU) No 37/2010

The "plant" substances listed in Table 1 (authorised use) are given below in alphabetical order.

These data have been extracted from Table 1 of COMMISSION REGULATION (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin.

N = 125

124 with "no MRL required" including one with an ADI

One with quantified MRLs (isoeugenol)

21 essential oils

41 substances for homeopathic use

Three for use as an excipient

Pharmacologically active substance	Animal species	Other provisions
Food additives (substances with a valid E number approved as additives in foodstuffs for human consumption)	All food-producing species	Only substances approved as additives in foodstuffs for human consumption, with the exception of preservatives listed in part C of Annex III to European Parliament and Council Directive 95/2/EC
Adonis vernalis	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias, at concentrations in the products not exceeding one part per hundred only
Aesculus hippocastanum	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding in the products not exceeding one part per ten only
Agnus castus	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding to the mother tincture and dilutions thereof only
Ailanthus altissima	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding to the mother tincture and dilutions thereof only
Allium cepa	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding to the mother tincture and dilutions thereof only
Aloe vera gel and whole leaf extract of *Aloe vera*	All food-producing species	For topical use only
Aloes, Barbados and Capae, their standardised dry extract and preparations thereof	All food-producing species	NO ENTRY

*Angelicae radix aetheroleum**	All food-producing species	NO ENTRY
*Anisi aetheroleum**	All food-producing species	NO ENTRY
Anisi stellati fructus, standardised extracts and preparations thereof	All food-producing species	NO ENTRY

Apocynum cannabinum	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias, at concentrations in the products not exceeding one part per hundred only For oral use only
Aqua levici	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias only
Arnica montana (arnicae flos and *arnicae planta tota)*	All food-producing species	For topical use only
Arnicae radix	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding in the products not exceeding one part per ten only
Artemisia abrotanum	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding to the mother tincture and dilutions thereof only
Atropa belladonna	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias, at concentrations in the products not exceeding one part per hundred only
Balsamum peruvianum	All food-producing species	For topical use only
Bellis perennis	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding to the mother tincture and dilutions thereof only
Bromelain	Porcine	NO ENTRY
Boldo folium	All food-producing species	NO ENTRY

Calendula officinalis	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding in the products not exceeding one part per ten only
Calendulae flos	All food-producing species	For topical use only
Camphora	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias, at concentrations in the products not exceeding one part per hundred only
Camphor	All food-producing species	External use only
Capsici fructus acer	All food-producing species	NO ENTRY
Cardiospermum halicacabum	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding to the mother tincture and dilutions thereof only
Carlinae radix	All food-producing species	For topical use only
*Carvi aetheroleum**	All food-producing species	NO ENTRY
*Caryophylli aetheroleum**	All food-producing species	NO ENTRY
Centellae asiaticae extractum	All food-producing species	For topical use only
Chrysanthemi cinerariifolii flos	All food-producing species	For topical use only ADI = 46 µg/kg
Cimicifugae racemosae rhizoma	All food-producing species	Do not use in animals producing milk for human consumption

Cinchonae cortex, standardised extracts and preparations thereof	All food-producing species	NO ENTRY
*Cinnamomi cassiae aetheroleum**	All food-producing species	NO ENTRY
Cinnamomi cassiae cortex, standardised extracts and preparations thereof	All food-producing species	NO ENTRY
*Cinnamomi ceylanici aetheroleum**	All food-producing species	NO ENTRY
Cinnamomi ceylanici cortex, standardised extracts and preparations thereof	All food-producing species	NO ENTRY
*Citri aetheroleum**	All food-producing species	NO ENTRY
*Citronellae aetheroleum**	All food-producing species	NO ENTRY
Condurango cortex, standardised extracts and preparations thereof	All food-producing species	NO ENTRY
Convallaria majalis	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias, at concentrations in the products not exceeding one part per thousand only
*Coriandri aetheroleum**	All food-producing species	NO ENTRY
Crataegus	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding to the mother tincture and dilutions thereof only
*Cupressi aetheroleum**	All food-producing species	For topical use only

Echinacea	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding to the mother tincture and dilutions thereof only. For topical use only. For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding in the products not exceeding one part per ten only.
Echinacea purpurea	All food-producing species	For topical use only
*Eucalypti aetheroleum**	All food-producing species	NO ENTRY
Eucalyptol	All food-producing species	NO ENTRY
Eucalyptus globulus	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding to the mother tincture and dilutions thereof only
Euphrasia officinalis	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding to the mother tincture and dilutions thereof only
Absinthium extract	All food-producing species	NO ENTRY
Cardamom extract	All food-producing species	NO ENTRY
Purified semi-solid extract from *Humulus lupulus* L. containing approximately 48% of beta acids (as potassium salts)	Bees	NO ENTRY

Pyrethrum extract	All food-producing species	For topical use only
*Foeniculi aetheroleum**	All food-producing species	NO ENTRY
Frangulae cortex, standardised extracts and preparations thereof	All food-producing species	NO ENTRY
Gentianae radix, standardised extracts and preparations thereof	All food-producing species	NO ENTRY
Ginkgo biloba	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias, at concentrations in the products not exceeding one part per thousand only
Ginseng	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding to the mother tincture and dilutions thereof only
Ginseng, standardised extracts and preparations thereof	All food-producing species	NO ENTRY
Hamamelis virginiana	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding in the products not exceeding one part per ten only
Hamamelis virginiana	All food-producing species	For topical use only
Harpagophytum procumbens	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding to the mother tincture and dilutions thereof only

Harunga madagascariensis	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias, at concentrations in the products not exceeding one part per thousand only
Hippocastani semen	All food-producing species	For topical use only
Hyperici oleum	All food-producing species	For topical use only
Hypericum perforatum[i]	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding to the mother tincture and dilutions thereof only
Isoeugenol	Fin fish	Muscle + skin = 6000 µg/kg ADI = 7.5 µg/kg
Jecoris oleum	All food-producing species	For topical use only
Juniperi fructus	All food-producing species	NO ENTRY
Lachnanthes tinctoria	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias, at concentrations in the products not exceeding one part per thousand only
*Lauri folii aetheroleum**	All food-producing species	NO ENTRY
Lauri fructus	All food-producing species	NO ENTRY
*Lavandulae aetheroleum**	All food-producing species	For topical use only

Lectin extracted from red kidney beans (*Phaseolus vulgaris*)	Porcine	For oral use only
Lespedeza capitata	All food-producing species	NO ENTRY
Lini oleum	All food-producing species	NO ENTRY
Lobaria pulmonaria	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding to the mother tincture and dilutions thereof only
Majoranae herba	All food-producing species	NO ENTRY
Matricaria recutita and preparations thereof	All food-producing species	NO ENTRY
Matricariae flos	All food-producing species	NO ENTRY
Medicago sativa extractum	All food-producing species	For topical use only
*Melissae aetheroleum**	All food-producing species	NO ENTRY
Melissae folium	All food-producing species	NO ENTRY
*Menthae arvensis aetheroleum**	All food-producing species	NO ENTRY
*Menthae piperitae aetheroleum**	All food-producing species	NO ENTRY
Menthol	All food-producing species	NO ENTRY
Millefolii herba	All food-producing species	NO ENTRY

*Myristicae aetheroleum**	All food-producing species	For use in newborn animals only
Okoubaka aubrevillei	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding to the mother tincture and dilutions thereof only
Phytolacca americana	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias, at concentrations in the products not exceeding one part per thousand only
Piceae turiones recentes extractum	All food-producing species	For oral use only
Polyoxyl castor oil with 30 to 40 oxyethylene units	All food-producing species	For use as excipient
Polyoxyl hydrogenated castor oil with 40 to 60 oxyethylene units	All food-producing species	For use as excipient
Oxidation products of *Terebinthinae oleum*	Bovine, ovine, caprine, porcine	NO ENTRY
Prunus laurocerasus	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias, at concentrations in the products not exceeding one part per thousand only
Quercus cortex	All food-producing species	NO ENTRY
Rhei radix, standardised extracts and preparations thereof	All food-producing species	NO ENTRY
Ricini oleum	All food-producing species	For use as excipient

*Rosmarini aetheroleum**	All food-producing species	NO ENTRY
Rosmarini folium	All food-producing species	NO ENTRY
Ruscus aculeatus	All food-producing species	For topical use only
Ruta graveolens	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias, at concentrations in the products not exceeding one part per thousand only
		Do not use in animals producing milk for human consumption
Salviae folium	All food-producing species	NO ENTRY
Sambuci flos	All food-producing species	NO ENTRY
Quillaia saponins	All food-producing species	NO ENTRY
Selenicereus grandiflorus	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias, at concentrations in the products not exceeding one part per hundred only
Serenoa repens	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding to the mother tincture and dilutions thereof only
Silybum marianum	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding to the mother tincture and dilutions thereof only
Sinapis nigrae semen	All food-producing species	NO ENTRY

Solidago virgaurea	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding to the mother tincture and dilutions thereof only
Strychni semen	Bovine, ovine, caprine	For oral use only at doses up to the equivalent of 0.1 mg strychnine/kg bw
Symphyti radix	All food-producing species	For topical use on intact skin only
Syzygium cumini	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding to the mother tincture and dilutions thereof only
Terebinthinae aetheroleum rectificatum*	All food-producing species	For topical use only
Terebinthinae laricina	All food-producing species	For topical use only
Thuja occidentalis	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias, at concentrations in the products not exceeding one part per hundred only
*Thymi aetheroleum**	All food-producing species	NO ENTRY
Thymol	All food-producing species	NO ENTRY
Tiliae flos	All food-producing species	NO ENTRY
Turnera diffusa	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding to the mother tincture and dilutions thereof only

Urginea maritima	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias, at concentrations in the products not exceeding one part per hundred only
		For oral use only
Urticae herba	All food-producing species	NO ENTRY
Virola sebifera	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias, at concentrations in the products not exceeding one part per thousand only
Viscum album	All food-producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding to the mother tincture and dilutions thereof only

Annex 6: The “therapeutic cascade”

Directive 2001/82/EC amended by Directive 2004/28/EC provides for and regulates the off-label use of veterinary medicinal products. It is transposed in France by Article L.5143-4 of the CSP which states that veterinarians must as a priority prescribe a veterinary medicinal product authorised for the species of animal in question and for the therapeutic indication mentioned in the MA.

Moreover, Article L.5143-4 of the CSP stipulates that when a veterinarian prescribes a medicinal product for food-producing animals, the substances with pharmacological action it contains must be among those listed in Table 1 of the Annex to Regulation (EU) No 37/2010.

Use of the principle of the “therapeutic cascade” requires prior verification of several points:

1) The veterinarian must check that there is no appropriate and available authorised (MA, TAU or import authorisation) medicinal product (withdrawal from the market by the holder or problem of supply by the holder),
2) For use in food-producing animals, the veterinarian must:
    - Make sure the substance is listed in Table 1 of Regulation (EU) No 37/2010 or included on the list of essential substances for equines[102]
    - Set a withdrawal period at least equal to the fixed withdrawal period (Annex 7).

The principle of the “therapeutic cascade” is described in Articles 112 to 115 of the new Regulation (EU) 2019/6.

Article 112 concerns non-food-producing animal species.

Veterinary medicinal products authorised in the relevant Member State or another Member State

for the same indication or for another indication

for the same species or another animal species

Medicinal products for human use

Extemporaneous preparations

Ability to use a veterinary medicinal product authorised in a third country for the same indication and same animal species

Case of animals of the equine species declared as not being intended for slaughter for human consumption

Article 113 concerns food-producing terrestrial animal species

Veterinary medicinal products authorised in the relevant Member State or another Member State

for the same indication or for another indication

[102] https://www.anses.fr/fr/system/files/ANMV-AMM-Substances-actives-equides-20310415.pdf

for the same or another food-producing terrestrial animal species

Veterinary medicinal products authorised in the relevant Member State or another Member State

for the same indication

for a non-food-producing animal species

Medicinal products for human use

Extemporaneous preparations

Ability to use a veterinary medicinal product authorised in a third country for the same indication and same animal species

No use of veterinary medicinal products authorised for food-producing aquatic species

The AS must be listed in Table 1 of Regulation (EU) No 37/2010.

Article 114 concerns food-producing aquatic species

Veterinary medicinal products authorised in the relevant Member State or another Member State

for the same indication or for another indication

for the same or another food-producing aquatic species

Veterinary medicinal products authorised in the relevant Member State or another Member State

for a food-producing terrestrial animal species

Medicinal products for human use

Extemporaneous preparations

Ability to use a veterinary medicinal product authorised in a third country for the same indication and same animal species

The AS must be listed.

Article 115 concerns fixed withdrawal periods

Annex 7: Fixed withdrawal periods

These are the withdrawal periods that should be applied when using the “therapeutic cascade”, which enables a medicinal product to be used outside the terms of the MA when no appropriate medicinal products are available. They are set out in Article L.5143-4 of the CSP.

According to Directive 2001/82/EC amended by Directive 2004/28/EC, the fixed withdrawal periods to be applied are as follows:

Meat and offal

- Mammals and poultry ≥ 28 days
- Fish ≥ 500 degree-days
- Horses ≥ 6 months

Milk ≥ 7 days

Eggs ≥ 7 days

These have been amended in Regulation (EU) 2019/6, which will enter into force as of 28 January 2022. Articles 112 to 115 describe the use of a medicinal product outside the terms of the MA. The fixed withdrawal periods to be applied are as follows:

Withdrawal periods for “meat & offal” from mammals/poultry/farmed game birds

- Longest withdrawal period for “meat & offal” x 1.5
- 28 days if the medicinal product is not authorised for food-producing animals
- One day if the medicinal product has a zero withdrawal period and is used in a different taxonomic family

Withdrawal periods for “milk”

- Longest withdrawal period for “milk” x 1.5
- Seven days if the medicinal product is not authorised for food-producing animals
- One day if the medicinal product has a zero withdrawal period

Withdrawal periods for “eggs”

- Longest withdrawal period for “eggs” x 1.5
- 10 days if the medicinal product is not authorised for food-producing animals

Withdrawal periods for aquatic species producing “meat”

- Longest withdrawal period for “meat & offal” x 1.5
- 25 degree-days if the highest withdrawal period for any animal species is zero
- Longest withdrawal period for “meat & offal” x 50 if terrestrial species (but < 500 degree-days)
- 500 degree-days if the medicinal product is not authorised for food-producing animal species

Withdrawal period for “meat and offal” from animals of the equine species: six months

Annex 8: List of plants, herbal preparations and herbal substances listed in Annex IV to Regulation (EC) No 396/2005 (November 2020)

Carvone

Equisetum arvense L.

Tea tree extract

FEN 560 (also called fenugreek or fenugreek powder)

Garlic extract

Geraniol

Laminarin

Mustard seed powder

Onion oil

Orange oil

Pepper

Citronellol

Clove oil, Eugenol

Rapeseed oil

Mint oil

Salix spp. *cortex*

Seaweed extracts

Sunflower oil

Thymol

Urtica spp.

Annex 9: List of biocidal products listed in Annex I of Regulation (EU) No 528/2012

(Z,E)-tetradec-9,12-dienyl acetate

Sodium acetate

(+)-tartaric acid

Acetic acid

Ascorbic acid

Citric acid

Lactic acid

Propionic acid

Baculovirus

Bentonite

Sodium benzoate

Citronellal

D-fructose

Carbon dioxide

Lavender oil

Linseed oil

Mint oil

Concentrated apple juice

Honey

Nitrogen

Oct-1-en-3-ol

Powdered egg

Webbing clothes moth pheromones

Saccharomyces cerevisiae

Iron sulphate

Vinegar

Annex 11: Tracking of report updates

Date	Page	Description of the change

Notes

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ISBN 979-10-286-0431-8 - Dépôt légal: avril 2022 - © Anses Éditions 2022 - Crédit photo : *Getty images*