**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.

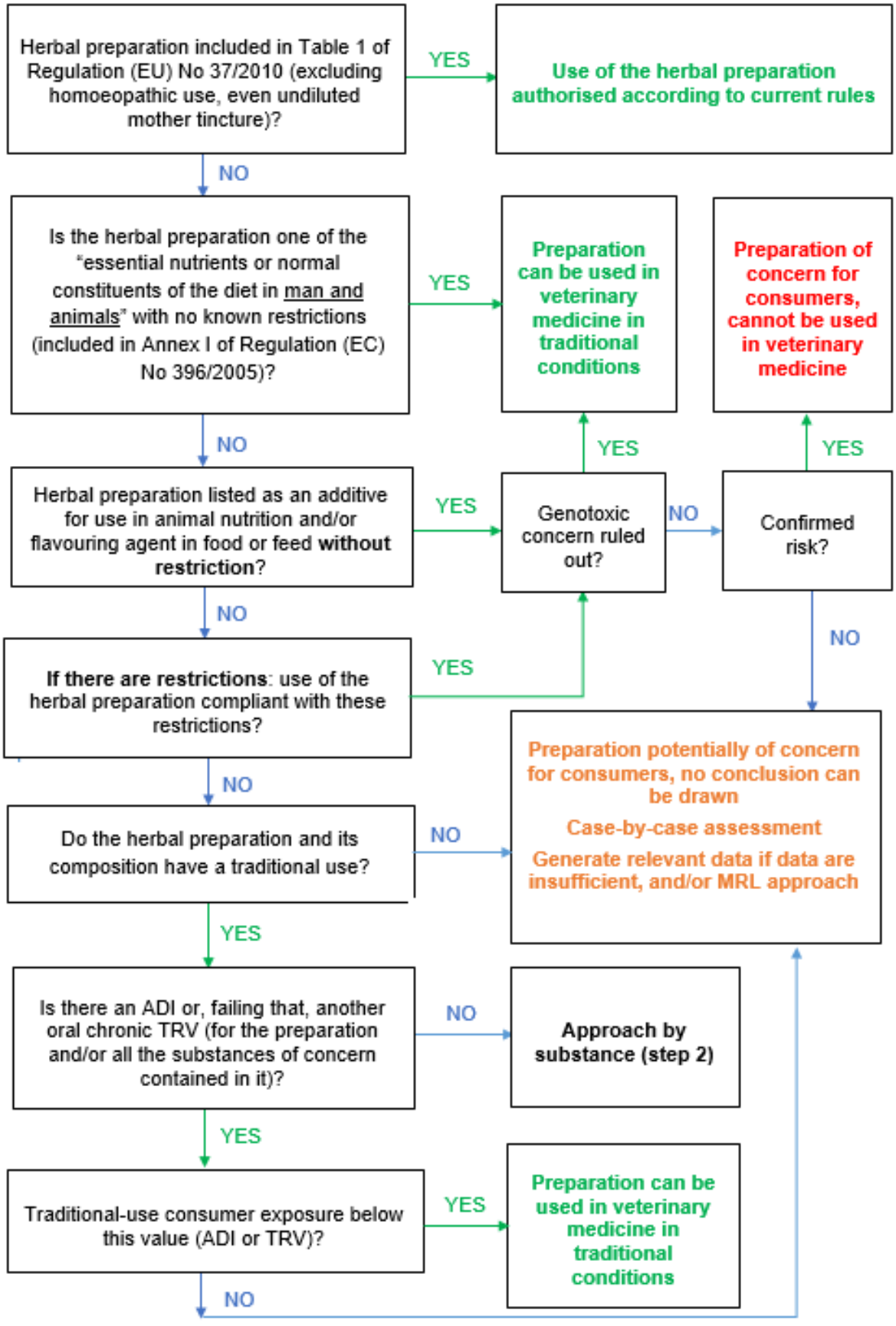


**Figure 1 : Decision tree for step 1 : overall approach (herbal preparations))**

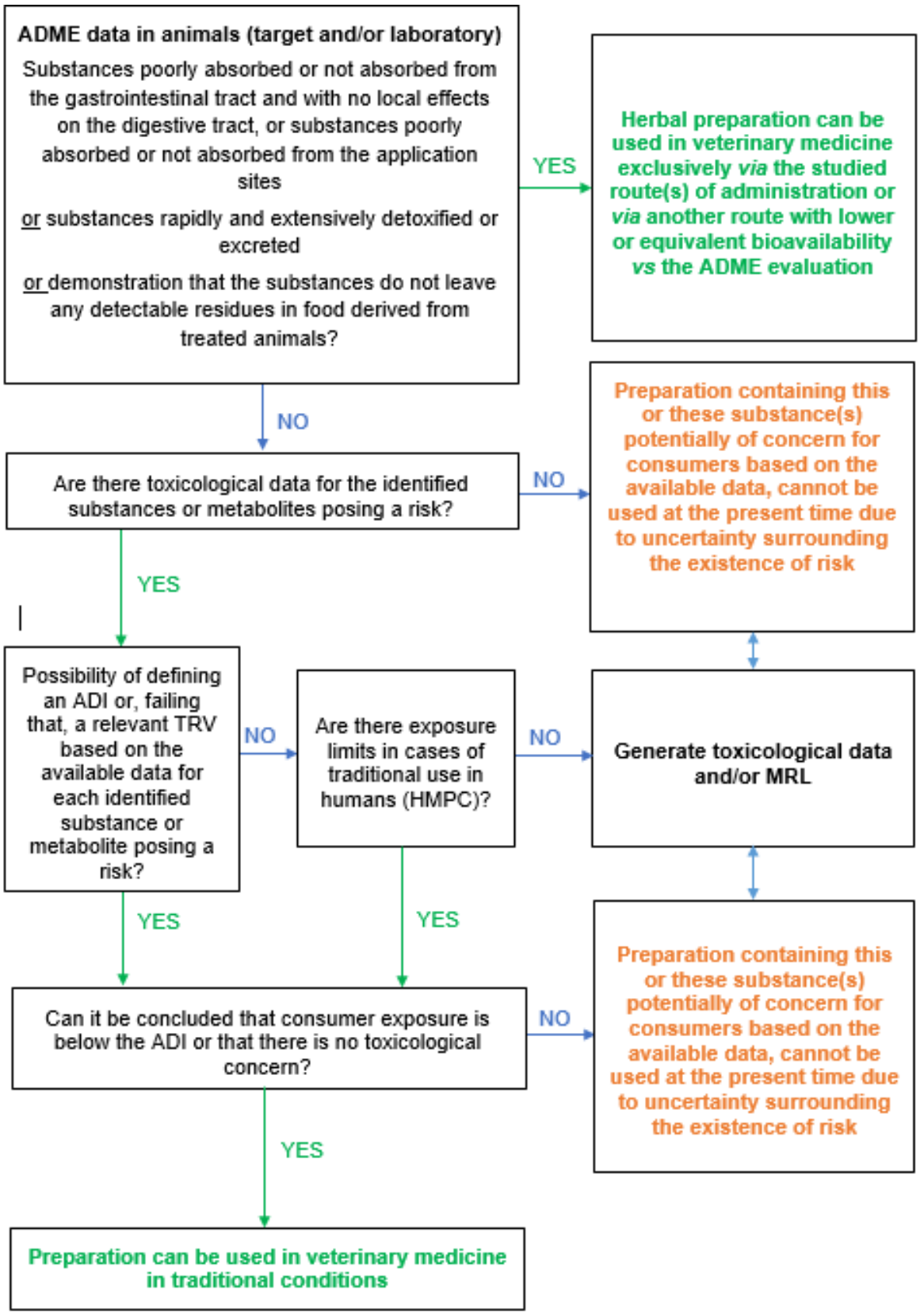


**Figure 2: Decision tree for step 2: approach by chemically defined substance when the overall approach is not possible**

### 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