HEADS OF FOOD SAFETY AGENCIES

HoA's first report on Food Supplements

IMPRINT

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Summary

The use of 'other substances' with a nutritional or physiological effect in food and/or food supplements is only partially harmonized within the EU. Only for substances listed in Annex III of Regulation (EC) No 1925/2006[1] on fortified foods and in the Regulation (EU) 2017/2470[2] on authorized novel foods a harmonization exists. It was determined that an agreed list of 'other substances' which should be prohibited or restricted in food supplements would be very beneficial to provide a higher level of consumer protection. This agreed list would also support a harmonized approach for regulation of food supplements due to the absence of a uniform risk management approach and in the view of the free movement of goods in the EU.

Therefore, the Heads of European Food Safety Agencies (HoA) established the working group "Food Supplements" (HoA WG FS), with members from 26 states, to agree on a common approach for the management and assessment of certain 'other substances'.
The members of the HoA WG FS collected information regarding the risks (including risk assessments), their assumed status as Novel Foods in accordance with Regulation (EU) 2015/2283[3] and other relevant aspects, for a total of 117 substances.
The HoA recommends achieving legal status in EU food law for any agreed substances via the 'Article 8 procedure' in Regulation (EC) No 1925/2006 and their addition to Annex III of the Regulation. Therefore, the substances for which sufficient scientific information was available were reviewed with regard to their eligibility for an 'Article 8 procedure'. It was concluded that a proposed list of 13 of the 117 substances should be prioritized as these are considered to pose a (possible) health risk to consumers, especially in the view of an enhanced intake via food supplements (daily dose) compared to the balanced and varied diet. The recommendation for an initiation of the 'Article 8 procedure' for these substances together with the underlying information could either be submitted by HoA or individual member states from the EU and EEA to EU COM, which may then initiate the 'Article 8 procedure'.
The HoA further recommends that substances assumed 'novel'[4] according to the available information (including national lists and RASFF notifications) should be forwarded by the HoA or the HoA

[1] Regulation (EC) No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods.
Online available: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32006R1925
[2] Commission Implementing Regulation (EU) 2017/2470 of 20 December 2017 establishing the Union list of novel foods in accordance with Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods. Online available: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32017R2470
[3] Regulation (EU) 2015/2283 of the European Parliament and of the Council of 25 November 2015 on novel foods, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001. Online available: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32015R2283
[4] In the entire report this term refers to substances, the HoA WG FS assumes to be novel and which are not authorized in accordance with Reg. (EU) 2015/2283.

WG FS to the EU COM (CAFAB[5] WG on Novel Food). Due to the large number, the substances should be grouped by priority before being submitted to the EU COM.

The recommendations of the HoA are in no way intended to duplicate or precede the work of corresponding working groups of EU COM or to prejudge their decisions. They are solely intended to support EU COM and EU/EEA-MS in determining appropriate EU legislative requirements.

The information compiled in this report follows the terms of reference established by HoA who oversee and conclude on the results of the accomplished work.

[5] CAFAB: Competent Authority Food Assessment Body

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1 Background on legal situation of the use of substances with a nutritional or physiological effect in food supplements

1.1 Legal framework

The use of certain other substances with a nutritional or physiological effect in conventional foods and food supplements (hereinafter referred to as food and/or food supplements) may be regulated by legislation of the European Union (EU) as well as national regulations.

1.1.1 EU legislation

In the EU food supplements are per definition foods and therefore all regulations applicable to food especially Regulation (EC) No 178/2002[6] (General Food Law Regulation) apply. According to this legislation, food has to be safe, which is the responsibility of the food business operator (FBO).

According to the Directive 2002/46/EC[7] (Food Supplements Directive), food supplements are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination. These substances comprise e. g. vitamins, minerals, amino acids, fibres, bacteria, fungi, plant extracts or other substances with a nutritional or physiological effect.
These other substances are defined in Article 2 (2) of Regulation (EC) No 1925/2006[8] (Fortified Food Regulation) as "substances other than vitamins and minerals with a nutritional or physiological effect" (hereinafter referred to as 'other substances').
The permitted vitamin and mineral substances that may be used in food supplements are defined in Annex I and II of Directive 2002/46/EC. For the use in foods, other than food supplements, the permitted vitamin and mineral substances are defined in Annex II of Regulation (EC) No 1925/2006. However, no common maximum levels for daily intake of vitamins and minerals have been established in the EU, yet.
The European Commission (EU COM) is currently developing a model for setting safe maximum levels for vitamins and minerals in food supplements and fortified foods.

According to Recital 8 of Directive 2002/46/EC, specific rules concerning 'other substances' with a nutritional or physiological effect' used as ingredients of food supplements should be specified at a later stage. However, the EU COM stated in 2008 that the community's legal instruments already provided sufficient legal basis for

[6] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. Online available: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32002R0178
[7] Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements. Online available: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32002L0046
[8] Regulation (EC) No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods.
Online available: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32006R1925

the regulation of 'other substances' and therefore did not consider it appropriate to lay down specific rules for substances other than vitamins or minerals for use in foodstuffs[9].

Further specific provisions for the regulation of 'other substances' are outlined in Article 8 of Regulation (EC) No 1925/2006 which provides a procedure to address the safety concerns associated with any substances other than vitamins and minerals used in food, including food supplements.
On its own initiative or on the basis of information provided by member states of the European Union and the European Economic Area (hereinafter referred to as EU/EEA MS), the EU COM may initiate the 'Article 8 procedure' in order to include a certain substance on a list to prohibit (Annex III Part A), restrict (Annex III Part B) or to put it under community scrutiny to be reviewed within four years (Annex III Part C). Although Regulation (EC) No 1925/2006 has been applicable since 1st July 2007, only nine substances are listed in Part A and B, and five substances in Part C of Annex III. Momentarily, five substances have currently been submitted for an 'Article 8 procedure' (berberine, *Garcinia cambogia* (accepted scientific name: *Garcinia cowa* Roxb. ex Choisy), alfa-lipoic acid and estragole together with *Foeniculum vulgare* Mill.).

In addition to Directive 2002/46/EC and Regulation (EC) No 1925/2006, Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods[10] (Novel Food Regulation) is applicable when it comes to the use of 'other substances' in food supplements.
Novel Food is defined as food that had not been used for human consumption to a significant degree in the EU before 15th of May 1997 and is falling under at least 1 of 10 categories mentioned in the regulation (e. g. foods consisting of, isolated from or produced from plants or their parts). The obligation to verify whether food intended to be placed on the EU market is 'novel' or 'not novel', lies with the FBO.
Any food which meets the definition of 'novel' falls under the scope of the Novel Food Regulation and needs a pre-market approval at EU level. Food supplements containing for instance a plant extract which is regarded 'novel' may not enter the market until the ingredient has been authorized by the EU COM.
The purpose of the legislation is to ensure the safety of food and food ingredients with no significant history of consumption in the EU. The Commission Implementing Regulation (EU) 2017/2470[11] (Union List of authorized Novel Foods) establishes a list of all the authorized Novel Foods in the EU, including their conditions of use, labelling requirements and their specifications.
This Regulation is amended following each new authorization.
Since Article 1 paragraph 3 (b) of Regulation (EC) No 1925/2006 states that this Regulation shall apply without prejudice to specific provisions laid down in Community legislation concerning Novel Foods and Novel Food ingredients, the specific directions of the Novel Food Regulation apply with priority.

[9] Report from the commission to the council and the European Parliament on the use of substances other than vitamins and minerals in food supplements. COM, 5.12.2008, COM(2008) 824 final. Online available: https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1563793210387&uri=CELEX:52008DC0824
[10] Regulation (EU) 2015/2283 of the European Parliament and of the Council of 25 November 2015 on novel foods, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001. Online available: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32015R2283
[11] Commission Implementing Regulation (EU) 2017/2470 of 20 December 2017 establishing the Union list of novel foods in accordance with Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods. Online available: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32017R2470

Besides this, the Novel Food Status catalogue[12] (NFSC) of the EU COM contains information made available to competent authorities on the status of some substances/of different foods as Novel Food. However, information in the NFSC is neither conclusive nor legally binding. Therefore, the status of a substance not listed in NFSC is not always apparent, for those listed it may be contested.
Implementing Regulation (EU) No 307/2012[13] specifies which requirements have to be fulfilled for substances being subjected to the 'Article 8 procedure'. According to Article 8, the substance has either to be added as an ingredient to foods or used in the manufacture of food. Therefore, Novel Foods would not meet this requirement for an 'Article 8 procedure'.

Certain 'other substances', if they are being added to food for technological purposes, e. g. for colouring or prolonging the shelf-life of the food, are subject to the provisions of Regulation (EC) No 1333/2008[14] (Food additive Regulation) and Regulation (EU) No 231/2012[15] (Food additive Specification Regulation). 'Other substances' with flavouring properties, in turn, are subject to the provisions of Regulation (EC) No 1334/2008[16] (Food flavourings Regulation). These regulations define the specifications (synonyms, definition and purity) and any restrictions linked with their use (maximal quantities and specific food categories to which these substances may be added). As a rule, the addition for technological purposes is either 'quantum satis' or in precisely specified small quantities. Adding the same substances for nutritional or physiological purposes however, is usually done in larger quantities.

1.1.2 National regulations

For 'other substances' with a nutritional or physiological effect which are not or not yet restricted at EU level specific national laws can be applied in EU/EEA MS ensuring a high level of consumer protection.
Currently, some EU/EEA MS and Switzerland have developed national policies or guidelines to authorize, prohibit or restrict the use of certain substances in food and/or food supplements.
Some EU/EEA MS and Switzerland have specific national laws in place for 'other substances ' than vitamins and minerals. However, many of these national legal instruments are based traditionally on 'expert opinions' only, and not on proper scientific risk assessments.
At the same time, some EU/EEA MS only have guidelines, that are not legally binding, and some EU/EEA MS have no regulations nor guidance at all.
This leads to a non-harmonized approach that uses a mix of guidelines, which may be based on varying assessment criteria in each EU/EEA MS.

[12] Novel Food Status catalogue of the EU COM: https://food.ec.europa.eu/safety/novel-food/novel-food-status-catalogue
[13] Commission Implementing Regulation (EU) No 307/2012 of 11 April 2012 establishing implementing rules for the application of Article 8 of Regulation (EC) No 1925/2006 of the European Parliament and of the Council on the addition of vitamins and minerals and of certain other substances to foods. Online available: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32012R0307
[14] Regulation (EC) No 1334/2008 of the European Parliament and of the Council of 16 December 2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods and amending Council Regulation (EEC) No 1601/91, Regulations (EC) No 2232/96 and (EC) No 110/2008 and Directive 2000/13/EC. Online available: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32008R1334
[15] Commission Regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council. Online available: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32012R0231
[16] Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives.
Online available: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32008R1333

1.1.3 Mutual recognition

Products that are not or not fully harmonized by European regulations are subject to the free movement of goods in accordance with Article 28 et seq. of the Treaty on the Functioning of the European Union[17] (TFEU; see in particular Article 34) and thus the principle of mutual recognition applies. The mutual recognition principle ensures market access for goods that are not or only partly subject to EU harmonization legislation. EU/EEA MS may not prohibit the sale of goods on their territory that do not fall under Union harmonization legislation but which have been lawfully marketed in another EU/EEA MS. This even applies if the good does not comply with the technical rules of the other country. However, there may be exceptions to this principle whenever public safety, health protection or the environment are concerned. Directive 2001/83/EC[18] of the European Parliament and of the Council applies where a product, taking into account all its characteristics, may fall within the definition of 'medicinal product' as laid down in Article 1(2) of that Directive. In that respect, in the case a EU/EEA MS classifies a product as a medicinal product in accordance with Directive 2001/83/EC, it may restrict placing on the market of that product in accordance with Union law.

Regulation (EU) 2019/515[19] applies to goods or aspects of goods that are not exhaustively covered by Union harmonization rules. The subject of the ordinance is, in particular, to describe the formal procedures of the mutual recognition.

In general products are on the market of EU/EEA MS without a proper risk assessment or pre-market assessment by authorities. However, the fact that a product is on the market does not necessarily mean that it is legal. Due to the principle of mutual recognition, it is often not possible to stop the sale of products containing substances of concern as long as the competent authority does not claim issues regarding public safety, health protection or the environment. With a harmonization of rules to regulate substances and goods containing these 'other substances' the need of mutual recognition for these substances would not be necessary any longer.

1.1.4 Challenges for competent authorities

For 'other substances' with a nutritional or physiological effect, only general food law and provisions under the general food law are applicable throughout the EU such as the Fortified Food Regulation, Novel Food Regulation, etc. As no additional effective regulations are in place for most 'other substances' their surveillance may pose challenges for the competent authorities.

The general requirement that all foods must be safe also applies to food supplements (Article 14 of Regulation (EC) No 178/2002) and is the primary responsibility of the FBO. However, based on Article 14 of Regulation (EC) No 178/2002 competent authorities may perform or initiate a risk assessment in order to evaluate the potential risk to consumers of foods or foods supplements. This will be done on a case-by-case basis, which is challenging and time consuming. Often information on hazard characterization and exposure is absent or limited and resources for scientific support cannot be provided.

[17] Consolidated version of the treaty on the functioning of the European Union. Online available: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:12012E/TXT:en:PDF

[18] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Online available: https://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX%3A02001L0083-20220101

[19] Regulation (EU) 2019/515 of the European Parliament and of the Council of 19 March 2019 on the mutual recognition of goods lawfully marketed in another Member State and repealing Regulation (EC) No 764/2008. Online available: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32019R0515

Unfortunately, the current framework of EU regulations in conjunction with national laws is not quite effective, neither for the food business operators (FBO), who want to place their products on several EU/EEA MS markets, nor for the authorities.

As outlined before, according to legislation non-authorized Novel Foods shall not be placed on the EU market. The responsibility lies with the FBO, but e. g. due to the often unknown status as a non-authorized Novel Food, competent authorities have to deal with the occurrence of such Novel Foods on the market.

Substances, other than vitamins and minerals may also be classified as medicinal in some EU/EEA MS because of the non-harmonized medicine legislation in the EU. This means that some substances may or may not be used in food supplements in different EU/EEA MS. This creates even more challenges for the FBO and for the food control authorities also in the context of mutual recognition.

1.1.5 Other factors affecting competent authorities

Infringements of EU food and feed legislation posing a direct or indirect risk to human health are reported through the Rapid Alert System for Food and Feed (RASFF) in accordance with Article 50 of Regulation (EC) No 178/2002. During recent years, several notifications and warnings concerning unsafe 'other substances' in food supplements (second most common reason for an alert) have been alerted via RASFF[20] underlining the fact, that regulation of these substances is insufficient or is not complied with.

Regulation (EU) 2023/915[21] (Contaminant Regulation, repealing Regulation (EC) No 1881/2006[22]) already sets maximum levels for some toxic substances originating from plants (e. g. hydrocyanic acid). However, in order to set further maximum levels within the framework of this regulation, monitoring data for the respective substances in foods are needed, which are often not present and difficult to collect. Thus, only a few substances that this working group has been working on could be suitable for inclusion in this regulation.

Attempts were made in the past to establish harmonized rules for the use of some 'other substances' throughout the EU. However, no consensual decision was reached.
Overall, there is a tremendous need to find common ways to manage or regulate these substances.

1.2 Establishment of the HoA Working group "Food Supplements" and its tasks

As outlined before, the use of 'other substances' with a nutritional or physiological effect in food and/or food supplements is only partially and not effectively harmonized within the EU apart from those listed in Annex III

[20] Annual report on RASFF notification 2022. Online available: https://food.ec.europa.eu/system/files/2023-08/acn_annual-report_2022.pdf
[21] Commission Regulation (EU) 2023/915 of 25 April 2023 on maximum levels for certain contaminants in food and repealing Regulation (EC) No 1881/2006. Online available: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32023R0915
[22] Commission Regulation (EC) No 1881/2006 of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs. No longer in force. Online available: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32006R1881

of Regulation (EC) No 1925/2006. In view of a uniform risk management approach in the EU, it is important to agree on a harmonized list of 'other substances' which should be prohibited or restricted in food supplements. Therefore, at the meeting of the Heads of European Food Safety Agencies (HoA) held in Dublin on March 28th in 2019 it was agreed to establish the working group "Food Supplements" (WG FS) to tackle this task. Terms of Reference (ToR) with a mandate to form a WG tackling this problem were established (see enclosed Attachment 'ToR of WG FS').

The main objective of the working group is to elaborate a common approach for the management and assessment of 'other substances' with a nutritional or physiological effect used in or as food and/or food supplements. For most other categories of substances including food additives, flavourings or contaminants the legal provisions are fully harmonized. The respective EU regulations provide maximum permitted quantities or maximum levels of these substances for different food groups. In addition, for permitted food improvement agents, chemical specifications for these substances are laid down in the current legislation, e. g. Regulation No. 231/2012.

At a national level, 18 (thereof 16 EU MS) of 26 members[23] of the HoA WG FS reported that they had drawn up positive and/or negative lists of 'other substances' which can or cannot be used in food and/or food supplements. However, those lists are not always legally binding. In some cases, the use of the substances in question is subject to compliance with technical conditions, such as maximum limits, type of extract or combination of ingredients.
Many substances mentioned on the national lists and their possible restrictions differ from state to state. However, some of the listed substances are assessed uniformly by several or most HoA WG FS members.
Therefore, harmonization could be initiated by drawing up a common negative list of 'other substances' which may not be used in food and/or food supplements based on the consensus of national lists and available risk assessments.
Eventually, suggested prioritized substances from this list could be included in Annex III Part A or B of Regulation (EC) No 1925/2006 leading to an increased legal certainty for the food business operators and facilitating the work of the competent authorities.
For this reason, the HoA WG FS first focussed on commonalities between the listings of the members of the working group and identified consistent assessments.

Based on the data available, the most feasible way seemed to be the approach to identify those substances which are not suitable for use in food and/or food supplements, primarily due to toxicity. Another argument for this approach is that such a list would provide the basis for harmonized measures to prohibit or restrict those substances which possess the highest potential to present a risk to the consumer.

[23] Members of the HoA WG FS, members which have national lists are underlined: Austria, Belgium, Bulgaria, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland.

Additionally, it could serve as a basis for further harmonization of substances assessed and managed differently between EU/EEA MS and Switzerland.

Thus, the first main objective of the WG was to identify substances which are possibly injurious to health and thus should be "prohibited or restricted in food and/or food supplements". ToR were adopted accordingly (see enclosed Attachment 'ToR of WG FS').

2 Accomplished milestones

2.1 Approach

The main objective of the HoA WG FS was to identify substances in food and/or food supplements that may lead to (concerns for) adverse health effects and therefore need to be prohibited or restricted (depending on dose and food matrix) regarding their use in food and/or food supplements. At first, the DACH-list[24] was used as a starting point. The DACH-list had been established by Germany (D), Austria (A) and Switzerland (CH) with the objective to provide all parties involved in the trade of goods with a decision guidance for the assessment of substances regarding their use as food or food ingredients.

The members of the HoA WG FS were asked to review 20 substances at a time. However, it became apparent that it is difficult to review all the substances as suggested. The members were not able to draw a conclusion on each substance as the underlying information (e. g. risk assessment) was often not available. It also became apparent that it would not be realistic to perform a risk assessment for each individual substance due to the large amount of time and resources needed and the general lack of data. Therefore, the members of the HoA WG FS decided to modify their approach.

First, existing risk assessments and other relevant contributions containing information on the possible health risks of the substances on the DACH-list were collected by asking members of the HoA WG FS to provide this information. Subsequently, members of the HoA WG FS submitted these to the HoA platform and added risk assessments for further relevant substances. Second, the subgroup 'risk assessment' was established for deciding on the best utilization of the collected information for enabling a prioritization of the substances regarding their suitability for an 'Article 8 procedure' under Regulation (EC) No 1925/2006. Currently, the subgroup consists of nine risk assessors[25].

In parallel to the work of the subgroup, the members of the HoA WG FS reviewed all available substances on the HoA platform regarding their status as a Novel Food. The members checked all information available to them (national lists, e-mail archives etc.) and assigned an assumed Novel Food status to each substance (Annex A) to the best of their knowledge. The assumed status will still have to be confirmed by the competent expert group on EU level (CAFAB[26] WG on Novel Food).
As outlined in section 1.1.1, substances that are considered Novel Foods cannot be legally put on the market unless they are authorized and included in the Union list. Authorized Novel Foods can be legally put on the market only in accordance with the conditions and specifications set in the Union list. Therefore, HoA WG FS considered these substances least relevant for further considerations by the HoA WG FS regarding a prohibition or restriction due to possible risks.

[24] See www.bvl.bund.de/stofflisten for detailed information and online availablitity.
[25] Risk assessors from Belgium, Estonia, France, Germany, the Netherlands, Sweden and Switzerland.
[26] CAFAB: Competent Authority Food Assessment Body

For an initiation of the 'Article 8 procedure' for prohibiting, restricting or putting substances under Community scrutiny in accordance with Regulation (EC) No 1925/2006 and Commission Implementing Regulation (EU) No 307/2012, the substance has to fulfil the following requirements (Table 1).

Table 1. Overview of the requirements needed in order to start an 'Article 8 procedure'.

Requirement	Yes	No
1. The substance is actually added to food products or used in the manufacture of food.		
2. Evidence demonstrating that the intake of the substance greatly exceeds normal intake from a balanced and varied diet and/or		
3. Evidence demonstrating a potential risk to consumers from consumption of the substance.		

Concerning question 1 (Q1) "Is the substance actually added to food products or used in the manufacture of food?" it was presumed that substances assumed to be 'not novel' or only 'not novel in food supplements' (not NFS) are actually being used in food and/or food supplements on the market and thus, the first requirement is met.
Substances assumed to be 'novel'[27] were given the lowest priority as they should presumably not be found on the market and thus not meet the first requirement. Therefore, the HoA WG FS decided a further review of these substances regarding the second and third requirements does not constitute a priority due to the above-mentioned restrictions linked with Novel Foods.

The HoA WG FS asked the subgroup 'risk assessment' to answer the second and third question (requirements) in order to prioritize the substances that might be suitable for an 'Article 8 procedure'. The subgroup 'risk assessment' agreed on a pragmatic approach for which only the information present on the HoA platform was used. Although the subgroup 'risk assessment' was aware that additional risk assessments (e. g. Monographs by European Medicines Agency (EMA)) and scientific literature might be present, it was decided to perform no additional literature search and to include no risk assessments that were not available on the HoA platform. Each substance was reviewed by two separate risk assessors, who discussed their findings and came to a common conclusion.

For question 2 (Q2) "Is there evidence demonstrating that the intake of the substance greatly exceeds normal intake from a balanced and varied diet?" one of the following answers was selected: "yes", "likely yes", "no" and "not possible to answer due to limited information".

The second option "likely yes" was chosen when there was limited information on dietary intake available on the HoA platform, but a quick search on the internet revealed that the substance is available in food supplements on the market in Europe. Thus, more research is needed to get an accurate overview of the intake. The intake of substances via food supplements leads to an intake of a concentrated dose of ingredients. It can be presumed that per definition the intake of food supplements leads potentially to higher plasma levels (above

[27] In the entire report this term refers to substances, the HoA WG FS assumes to be novel and which are not authorized in accordance with Reg. (EU) 2015/2283.

toxic threshold) compared with normal intake from a balanced and varied diet (with food matrix, throughout the day and not daily).

For question 3 (Q3) "Is there evidence demonstrating a potential risk to consumers from consumption of the substance?" one of the following answers was selected: "yes, due to risks", "yes, due to hazards", "no" and "not possible to answer due to limited information".

The first option "yes, due to risk" was chosen when a risk was identified in the risk assessment (based on hazard and exposure information, e. g. exposure > health-based-guidance-value (HBGV); however, exposure from food supplements may considerably differ between products (e. g. due to recommended dose) which affects the outcome of the risk assessment). In the cases where only hazard information was available, the second option ("yes, due to hazards") was chosen.

Substances assigned the highest priority regarding a needed regulation were the substances with the following answer combination: Q2 = "yes" or "likely yes" & Q3 = "yes, due to risk". Subsequently, the subgroup 'risk assessment' made short summaries of the substances with the highest priority in order to further substantiate the concerns and to identify substances with (possible) carcinogenic, mutagenic or reprotoxic properties.

In addition to the information directly available to the authorities (e-mail conversations, complaints, etc.), the HoA WG FS has sought out further sources from which information on the use of 'other substances' (with possible risks) in food can be obtained. In the RASFF, alerts are published when an authority, e. g. in the context of a monitoring program or during an inspection, finds a product that is legally not permissible, e.g. due to an ingredient. Possible reasons for an alert may include "unsafe ingredients" or "prohibited substances" or "unauthorized Novel Food ingredients". Therefore, all available RASFF alerts from 2017 until May 2022 on food supplements and fortified foods were collected and sorted by the reason of the alert (e. g. "unauthorized Novel Food ingredient"). Alerts were grouped based on identical reasons for an alert. For further analysis, only alerts due to "composition", "natural toxins" and "Novel Foods" were taken into account.

2.2 Results

2.2.1 Reviewed substances

The starting point of the review was a collection of 117 substances, which consisted of substances from the DACH-list and other substances suggested by the members of the HoA WG FS. Figure 1 provides an overview of the steps taken by the members of the HoA WG FS during the review of substances available on the HoA platform.

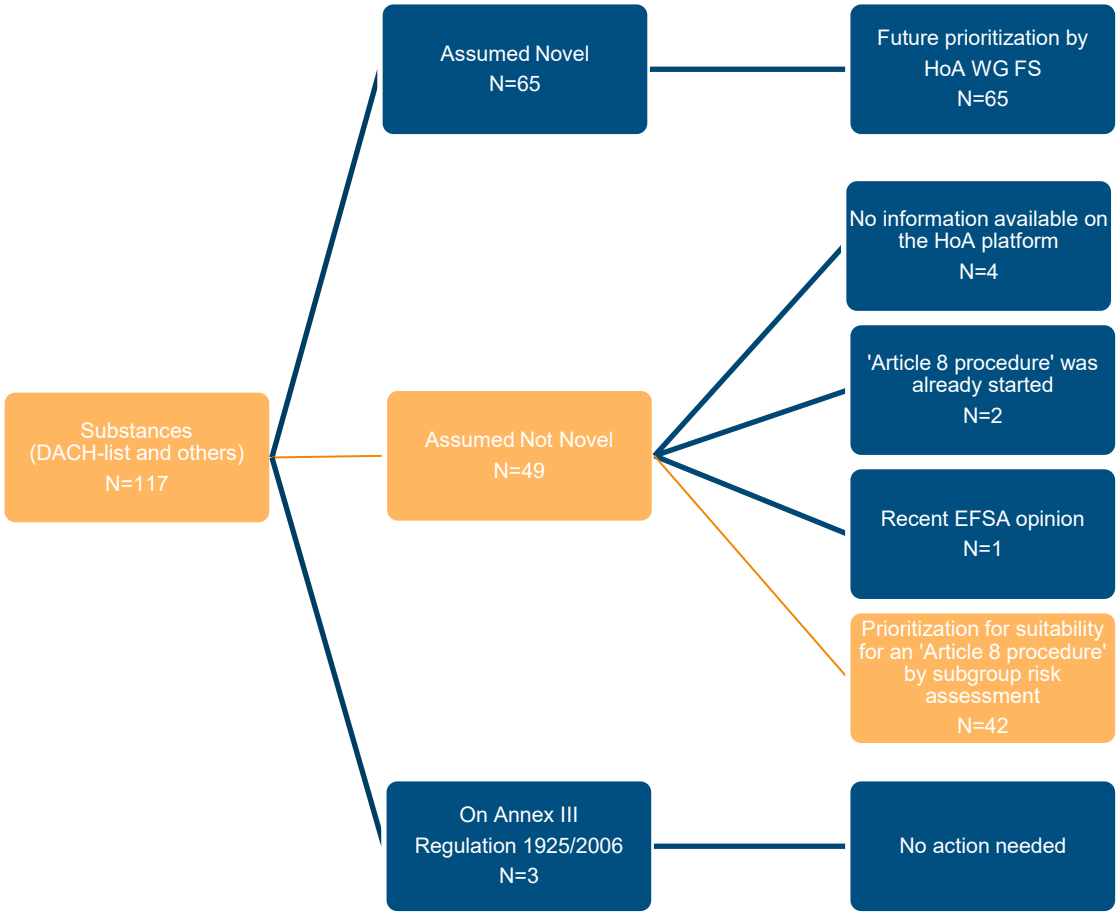

Figure 1. An overview of the steps taken by the members of the HoA WG FS during the review of substances present on the HoA platform. The orange boxes represent the route of the substances that were prioritized for suitability for an 'Article 8 procedure'.

Of the initial 117 substances, 65 substances were assumed to be 'novel', 49 were assumed to be 'not novel' or 'not NFS' by HoA WG FS to the best of their knowledge. In the meantime, 3 substances have already been included in Annex III of Regulation 1925/2006: *Monascus purpureus* (monacoline K) which is included in PART B and C as well as *Aloe ferox* and *Aloe vera*, both included in PART A. A complete overview of the reviewed substances and their status can be found in Annex A of this report. **The complete scientific names of each botanical substance including the corresponding author[28, 29] and the reviewed plant part or substance details, if specified, are stated in the overview in Annex A and Annex C, as well as in Table 2. In the continuous text as well as other tables and annexes however, they are omitted for pragmatic reasons.**

Some parts of *Angostura trifoliata*, *Annona muricata*, *Aquilegia vulgaris* and *Arnica montana* were considered 'not novel' by the HoA WG FS, but no risk information was available on the HoA platform. Therefore, these substances were not reviewed by the subgroup risk assessment.

[28] Authors according to https ://powo.science.kew.org
[29] In this report, the abbreviation "spp." refers to more than one not further defined species of the same genus.

Recently, the European Food Safety Authority (EFSA) has published an opinion regarding the dietary exposure to heavy metals and iodine intake via consumption of seaweeds and halophytes in the European population (EFSA, 2023). Iodine could be considered as a contaminant or a mineral but not as an 'other substance'. Therefore, iodine was not reviewed by the subgroup risk assessment, either.

EU COM has started an 'Article 8 procedure' for berberine and *Garcinia cambogia* (designated in the report with the accepted name *Garcinia cowa* Roxb. ex Choisy), already. Therefore, these substances were also not reviewed by the subgroup risk assessment.

Table 2 provides an overview of the 42 substances that were reviewed by the subgroup 'risk assessment' based on the information for these substances available on the HoA platform. It states the complete scientific name, including the author, and the assessed plant part or substance details, if specified. In addition, Annex B provides an overview of available EFSA opinions and monographs/assessment reports by EMA regarding the substances in Table 2. Only EFSA opinions on food were included. Opinions for health claims or feed were not considered. Furthermore, only EMA monographs/assessments on human use were included. No monographs/assessment regarding veterinary use were added.

Table 2. Overview of the substances reviewed by the subgroup 'risk assessment' and the available information on the HoA platform. Abbreviation RA stands for risk assessment.

Substance	Name of substance (as used in RA)	Substance details (as assessed in RA)	Available information on HoA platform
N-Acetyl-Cysteine	N-Acetyl-Cysteine	not applicable	(AECOSAN, 2015a; BLV, 2021)
Actaea racemosa L.	*Actaea racemosa* L.	rhizomes	(DTU, 2009; RIVM, 2013; BuRO, 2020)
Alisma plantago-aquatica L.	*Alisma plantago-aquatica* L. including *Alisma plantago-aquatica* L. ssp. orientale	fresh, dried rhizomes and various preparations thereof	(DTU, 2011b;2015)
Artemisia cina O.Berg	*Artemisia cina*	dried flower buds	(van de Bovenkamp et al., 2009)
Artemisia maritima L.	*Artemisia maritima*	dried flower buds, shoots and leaves	(van de Bovenkamp et al., 2009)
Carica papaya L.	*Carica papaya* L.	leaves	(FOD, 2020b)
Carlina acaulis L.	*Carlina* spp.	roots	(FOD, 2020e)
Chelidonium majus L.	*Chelidonium majus*	extracts of plant parts growing underneath and above the ground	(RIVM, 2009)
Cinnamomum verum J.Presl	*Cinnamomum verum* J.Presl	bark and essential oils thereof	(FOD, 2020c)
Coumarin in plant preparations	Coumarin	not applicable	(BfR, 2012b; ANSES, 2021)
Cucurbitacins in preparations of *Cucurbitaceae*	Extracts of *Cucurbitaceae* containing Cucurbitacins	roots, fruits	(Gry et al., 2006)

Substance	Name of substance (as used in RA)	Substance details (as assessed in RA)	Available information on HoA platform
Curcumin in *Curcuma* spp.-preparations	Curcuminoids and extracts of *Curcuma longa* L., *Curcuma xanthorrhiza* Roxb., *Curcuma zedoaria* (Christm.) Roscoe	rhizome and extracts thereof	(FOD, 2019; AESAN, 2020; BVL & BfArM, 2020; BfR, 2021; ANSES, 2022a)
Gentiana lutea L.	*Gentiana lutea* L.	roots, leaves	(DTU, 2022)
Ginkgo biloba L.	*Ginkgo biloba* L.	leaves	(Pelgrom et al., 2007)
Griffonia simplicifolia (Vahl ex DC.) Baill.	*Griffonia simplicifolia* (Vahl ex DC.) Baill.	no specific plant parts are mentioned in the RA	(FOD, 2004)
Huperzin A in *Huperzia serrata* Thunb.-preparations	Huperzin A	not applicable	(DTU, 2016)
Hypericum perforatum L.	*Hypericum perforatum* L.	aerial parts or dried flowering tops	(de Wit et al., 2019; DTU, 2019a)
Juglans regia L.	*Juglans regia* L.	whole plant excl. nuts	(van de Bovenkamp et al., 2009)
Lavandula angustifolia subsp. *angustifolia*	*Lavandula officinalis* Chaix	flowering tops and essential oils thereof	(FOD, 2020a)
Lepidium meyenii Walp.	*Lepidium meyenii* Walp.	root or germ stem (hypocotylene) or preparations thereof	(DTU, 2011a;2020a;2021)
Lycopus europaeus L.	*Lycopus europaeus* L.	no specific plant parts are mentioned in the RA	(van de Bovenkamp et al., 2009)
Melaleuca spp.-essential oils	*Melaleuca alternifolia* (Maiden & Betche) Cheel, *Melaleuca quinquenervia* (Cav.) S.T. Blake and *Melaleuca cajuputi* Maton & Sm. ex R.Powell	leaves and essential oils thereof	(ANSES, 2020)
Melatonin[30]	Melatonin	not applicable	(ANSES, 2018)
Mentha × piperita L.	*Mentha × piperita* L.	leaves and essential oils thereof	(FOD, 2021)
Morus alba L.	*Morus alba* L.	leaves, fruits, root bark and stem	(ZESPÓŁ DO SPRAW SUPLEMENTÓW DIETY, 2019)
Mutarda nigra (L.) Bernh.	*Brassica nigra*	roots, seeds and oil of the seeds	(van de Bovenkamp et al., 2009)
Ocimum basilicum L.	*Ocimum basilicum* L.	Essential oils of aerial parts	(FOD, 2022)
Ocimum tenuiflorum L.	*Ocimum tenuiflorum* L.	dried leaves	(DTU, 2019b)
Piper methysticum G.Forst.	*Piper methysticum* G.Forst.	roots	(van de Bovenkamp et al., 2009; ZESPÓŁ DO SPRAW SUPLEMENTÓW DIETY, 2021a)
Piperine*	Piperine	not applicable	(DTU, 2019c; ANSES, 2022b; ZESPÓŁ DO SPRAW SUPLEMENTÓW DIETY, 2022)

[30] See footnote 37 in Annex C.

Substance	Name of substance (as used in RA)	Substance details (as assessed in RA)	Available information on HoA platform
Podophyllum peltatum L.	*Podophyllum peltatum* L.	roots, rhizomes, resin	(van de Bovenkamp et al., 2009)
Rhodiola rosea L.	*Rhodiola rosea* L.	preparations of roots	(ZESPÓŁ DO SPRAW SUPLEMENTÓW DIETY, 2021b)
Rhododendron tomentosum (Stokes) Harmaja	*Ledum palustre* L.	no specific plant parts are mentioned in the RA	(van de Bovenkamp et al., 2009)
Salvia rosmarinus Spenn.	*Rosmarinus officinalis* L.	essential oils of aerial parts	(FOD, 2020d)
Solanum dulcamara L.	*Solanum dulcamara* L.	leaves, stems, roots, fruits	(van de Bovenkamp et al., 2009)
p-Synephrine in *Citrus* spp.-preparations*	*Citrus* spp. especially *Citrus* x *aurantium* L.	peel (epicarp and mesocarp) and other parts and extracts thereof	(Hammerling, 2012; ANSES, 2014; DTU, 2014a; Tiesjema et al., 2017; BuRO, 2018)
Tanacetum vulgare L.	*Tanacetum vulgare* or *Chrysanthemum vulgare*	leaves, flowers, stems and oil of leaves and flowering tops	(van de Bovenkamp et al., 2009)
Teucrium chamaedrys L.	*Teucrium chamaedrys* L.	no specific plant parts are mentioned in the RA	(van de Bovenkamp et al., 2009)
Tribulus terrestris L.	*Tribulus terrestris* L.	fruits, plant shoots and extracts thereof	(DTU, 2014b; AECOSAN, 2015b; ZESPÓŁ DO SPRAW SUPLEMENTÓW DIETY, 2021c)
Tryptophan	Tryptophan	not applicable	(AESAN, 2012)
Vinca minor L.	*Vinca minor* L.	no specific plant parts are mentioned in the RA	(van de Bovenkamp et al., 2009)
Withania somnifera (L.) Dunal	*Withania somnifera* (L.) Dunal	roots	(DTU, 2020b; ZESPÓŁ DO SPRAW SUPLEMENTÓW DIETY, 2020)

*A few risk assessments were initially added on the HoA platform, but later vanished for unknown reasons and therefore were not included in the review, being Bakhiya et al., 2017; Ziegenhagen et al., 2021.

2.2.2 Substances assumed to be 'novel'

Of the initial 117 substances 65 were assumed to be 'novel' to the best of the working group´s knowledge (Annex A).

HoA WG FS considered substances that were assumed to be 'novel' by the HoA WG FS with the lowest priority. As already mentioned, they should not be found on the market, as they are per definition not marketable without prior authorisation. If they are considered to be placed on the market, the Novel Food Regulation will apply primarily.

Due to the large number of substances, the HoA WG FS suggests to perform a prioritization of these substances before confirmation by CAFAB WG on Novel Food status is requested (see 3.2 and 3.3) and prior to further processing.

2.2.3 Prioritization of substances assumed to be 'not novel' or 'not NFS'

Of the initial 117 substances 49 were assumed to be 'not novel' or 'not NFS' to the best of the working group´s knowledge (Annex A).

The subgroup 'risk assessment' concluded that most of the available risk assessments on the HoA platform were of good quality and were written by risk assessors of reputable institutes. However, it was noted that some contributions contained limited information and were outdated. Overall, the assessments were considered suitable for priority setting and as a good starting-point for a final risk assessment of the selected substances by EFSA (presumably during the 'Article 8 procedure'). Eventually, the subgroup 'risk assessment' prioritized the 42 substances that were assumed to be 'not novel' or 'not NFS'.

Table 3 provides an overview of 13 substances with the highest priority; those are the substances considered to pose a (possible) risk to consumers and for which the intake via food supplements exceeds normal intake. The substances in Table 3 are listed alphabetically based on reply to Q2, consequently the order of these does not indicate a prioritization.

It has to be noted that substances which have not been prioritized in this review process, might still pose a risk to consumers. They may therefore be considered in future reviews.

For these 13 substances CAFAB WG on Novel Food has already been contacted and the status as 'not novel' or 'not NFS' has been confirmed.

Table 3. An overview of substances which were considered to be a risk for the consumer (yes to Q3) and to greatly exceed normal intake from a balanced and varied diet (yes or likely yes to Q2).

Substance	**Q2**		**Q3**
	Yes	**Likely yes**	**Yes, risk**
Coumarin in plant preparations	x		x
Curcumin in *Curcuma* spp.-preparations	x		x
Hypericum perforatum	x		x
Melaleuca spp.-essential oils	x		x
Melatonin*, [31]	x		x
Piperine	x		x
p-Synephrine in *Citrus* spp.-preparations	x		x
Tryptophan	x		x
Actaea racemosa		x	x
Lepidium meyenii		x	x
Ocimum tenuiflorum		x	x
*Tribulus terrestris***		x	x
*Withania somnifera****		x	x

*BfR has recently completed a risk assessment, which will be published in 2024 online. Information from this document was included in the detailed description of melatonin (Annex C).

**RIVM currently works on a risk assessment that will be published in 2024. This assessment is not finalized and therefore not included in this document.

***RIVM currently works on a risk assessment that will be published in 2024. Also ANSES works on a risk assessment that will be published in 2024. These assessments are not finalized and therefore not included in this document.

[31] See footnote 37 in Annex C.

Short summaries of these substances with more detailed information can be found in Annex C of this report. These summaries have been prepared following previous mandates from the EU COM to EFSA to initiate 'Article 8 procedures'. Of the substances from Table 3 Curcumin in *Curcuma* spp.-preparations, *Lepidium meyenii*, *Melaleuca* spp.-essential oils, *Ocimum tenuiflorum*, piperine, *Tribulus terrestris* and *Withania somnifera* exhibit (possible) carcinogenic, mutagenic or reprotoxic properties.

The 13 prioritized substances were also reviewed regarding existing permissions as food additives or food flavourings. Information on the findings can be found in Annex D of this report.

The Novel Food status of the remaining substances assumed to be 'not novel' or 'not NFS' will still have to be confirmed by CAFAB WG on Novel Food. Whether any regulations for their use as food additives or food flavourings exist, has not been reviewed yet.

Table 4 provides an overview of substances which raise concern based on their hazard characteristics and which (might) exceed normal intake from a balanced and varied diet. More information on exposure is needed in order to fulfil a risk assessment. The substances in Table 4 are listed alphabetically based on reply to Q2, consequently the order of these does not indicate a prioritization.

Table 4. An overview of substances which raise concern based on their hazard characteristics and which (might) exceed normal intake from a balanced and varied diet.

Substance	**Q2**			**Q3**
	Yes	**Likely yes**	**Not possible to answer due to limited information**	**Yes, hazard**
Juglans regia	x			x
Alisma plantago-aquatica		x		x
Carica papaya		x		x
Chelidonium majus		x		x
Gentiana lutea		x		x
Mutarda nigra		x		x
Solanum dulcamara		x		x
Tanacetum vulgare		x		x
Artemisia cina			x	x
Artemisia maritima			x	x
Cinnamomum verum			x	x
Ginkgo biloba			x	x
Huperzin A in *Huperzia serrata*-preparations*			x	x
Lycopus europaeus			x	x
Ocimum basilicum			x	x
Piper methysticum			x	x
Podophyllum peltatum			x	x
Rhododendron tomentosum			x	x
Teucrium chamaedrys			x	x
Vinca minor			x	x

*RIVM currently works on a risk assessment that will be published in 2024.

Table 5 provides an overview of the remaining substances which were reviewed. Based on the information available on the HoA platform, four substances (Q3 answered with 'no') were considered not being a risk for consumers. These four substances will therefore not undergo further prioritization in the HoA WG FS at this moment. For the other substances it was not possible to assess the risk due to the limited information available. The substances in Table 5 are listed alphabetically based on reply to Q3, consequently the order of these does not indicate a prioritization.

Table 5. An overview of the remaining substances which were reviewed.

Substance	**Q2**			**Q3**	
	Yes	**Likely yes**	**Not possible to answer due to limited information**	**No**	**Not possible to answer due to limited information**
Carlina acaulis			x		x
Cucurbitacins in preparations of *Cucurbitaceae*			x		x
Griffonia simplicifolia			x		x
Rhodiola rosea		x			x
Salvia rosmarinus		x			x
N-Acetyl-Cysteine*	x			x	
Lavandula angustifolia subsp. *angustifolia*	x			x	
Mentha × piperita		x		x	
Morus alba		x		x	

*RIVM currently works on a risk assessment that will be published in 2024.

2.2.4 RASFF notifications

The evaluation of the approx. 1500 RASFF alerts[32] on food supplements and fortified foods with regard to "composition", "natural toxins" and "Novel Foods" resulted in the selection of the following eight substances that had caused an alert before and at the same time had already been identified by the HoA WG FS: N-Acetyl-Cysteine (4 alerts), curcumin (14 alerts), huperzine A (17 alerts), melatonin (10 alerts), monacolin K (32 alerts), piperine (18 alerts), *p*-synephrine (19 alerts), *Tribulus terrestris* (3 alerts) and *Withania somnifera* (17 alerts). The presence of RASFF alerts for these substances identified by the HoA WG FS can additionally be considered as an evidence that they are actually used in food and/or food supplements on the market.

Other substances that caused alerts may be of interest to the HoA WG FS but have not been considered further yet, e. g. agmatine sulphate (101 alerts) and 1,3-dimethylamylamine (DMAA; 29 alerts). These could be included in future work within the HoA WG FS, if deemed important (see 3.3).

[32] RASFF alerts were taken into account from 1.1.2017 to 14.5.2022.

RASFF alerts also occurred due to already forbidden substances like Yohimbe bark, emodin and Ephedra herb (all in Annex III, Part A of Regulation (EC) No 1925/2006). The results of the evaluation can be found in the enclosed Attachment 'RASFF notifications'.

2.3 Conclusion of the review of substances

The 13 substances that are most eligible for an 'Article 8 procedure', as they are considered posing a risk to consumers and their intake through food supplements greatly exceeds normal intake from a balanced and varied diet, are the following: *Actaea racemosa,* Coumarin in plant preparations, Curcumin in *Curcuma* spp.-preparations, *Hypericum perforatum*, *Lepidium meyenii*, *Melaleuca* spp.-essential oils, melatonin[33], *Ocimum tenuiflorum*, piperine, *p*-Synephrine in *Citrus* spp.-preparations, *Tribulus terrestri*, tryptophan and *Withania somnifera* (Table 3).

Of these substances Curcumin in *Curcuma* spp.-preparations, *Lepidium meyenii*, *Melaleuca* spp.-essentials oils, *Ocimum tenuiflorum*, piperine, *Tribulus terrestris* and *Withania somnifera* exhibit (possible) carcinogenic, mutagenic or reprotoxic properties. Based on these properties the subgroup 'risk assessment' suggests, if necessary, to prioritize these substances over the other substances in Table 3 when starting an 'Article 8 procedure'.
Table 4 contains a list of substances which raise concern based on their hazard characteristics and which (might) exceed normal intake from a balanced and varied diet. The fact that these substances are not eligible for an 'Article 8 procedure' at the moment does not mean that there are no concerns. More information on hazard and exposure is needed in order to fulfil a risk assessment and to proceed with an 'Article 8 procedure'.

[33] See footnote 37 in Annex C.

3 Suggestion for next steps

As elaborated in the last paragraph the HoA WG FS has fulfilled the work mandate stated in the ToR (see enclosed Attachment 'ToR of WG FS') compiling a list of substances that based on existing risk assessments should be prohibited or restricted in food and/or food supplements.
Not included in the ToR, however, is neither the question in what way or through which legislation the use of these substances in food can be prohibited or restricted, nor which substances should be prioritized for such measures.

The recommendations of the HoA are in no way intended to duplicate or precede the work of corresponding working groups of EU COM or to prejudge their decisions. They are solely intended to support EU COM and EU/EEA-MS in determining appropriate EU legislative requirements.
The information compiled in this report follows the terms of reference established by HoA who oversee and conclude on the results of the accomplished work.

3.1 Possible ways to regulate substances assumed to be 'not novel' or 'not NFS'

Before further processing the CAFAB WG on Novel Foods should be enquired also for confirmation of the assumed status as 'not novel' or 'not NFS' of the non-prioritized substances. This could either be done by HoA or HoA WG FS.

The members of the HoA WG FS discussed by which means an implementation of measures on substances assumed to be 'not novel' or 'not NFS' by the EU COM could be realized.
Two approaches were discussed, being:

- Approach 1: The Heads of Food Safety Agencies hand over the recommendations of this report to EU COM. EU COM may initiate 'Article 8 procedures'.
- Approach 2: Individual EU/EEA MS hand over the report to EU COM. EU COM may initiate 'Article 8 procedures'.

Approach 1 was supported by the majority of the HoA WG FS (15 of 19 members participating at the vote, two members abstaining).
Approach 2 was supported by two members. Four additional members will support Approach 2, if the HoA is unable to hand over the recommendations of the report to EU COM (Approach 1).
Furthermore, four members indicated their basic commitment to hand over the report to the EU COM, if approach 2 is followed. In this case handing over the report would be representative on behalf of all members of the HoA WG FS.
Irrespective of the approach followed, all relevant information gathered by the HoA WG FS should be made available to EU COM and EFSA to accelerate the process of 'Article 8 procedures'.

The members of the HoA WG FS agreed to elaborate alternative options, in the case that 'Article 8 procedures' will not be achieved for some or all of the substances, provided that HoA supports this proposal (see 3.3).

3.2 Possible ways to handle substances assumed to be 'novel'

The substances that are assumed to be 'novel' could be forwarded by the HoA or by the HoA WG FS to the EU COM (CAFAB WG on Novel Food).
This way the classification as a Novel Food could be verified by the COM WG and a corresponding entry in the NFSC of the EU COM could be created. The publicly available NFSC, though not legally binding, provides the needed clarity to FBOs and competent authorities. In the case FBOs can provide information on the use of a certain substance in foods in the EU prior to 15th of May 1997 they can submit this information to EU/EEA MS or EU COM. Validation provided the entry in the NFSC would be adopted accordingly. Further handling of these substances by the HoA WG FS could then proceed as outlined in chapter 3.1.
Due to the large number of substances presumed to be 'novel', they should be submitted to the EU COM in clusters. Therefore, some prioritization should be suggested beforehand. This prioritization could be done - although not legally compliant (see 1.1.1., 1.1.4. and 2.2.1) - based on market availability in EU/EEA MS and Switzerland (e. g. RASFF-notifications, complaints and online searches) as these are the most urgent cases with doubt/incorrect information concerning the Novel Food status among FBOs. In case a substance is not on the market, it could be investigated whether the substance is prohibited or restricted on a national level.

Afterwards, the verified prioritized list with assumed Novel Foods could be forwarded to EU COM (CAFAB WG on E-Commerce) as a proposal for consideration in a future e-sweep project.

3.3 Proposals for further actions

With the submission and presentation of the report by HoA WG FS, HoA prolongs the mandate of the working group, as proposed by HoA WG FS. Therefore, HoA enjoins HoA WG FS to proceed its work congruent to the ToR and assigns new tasks, including prioritization of the substances for further processing. Further, HoA mandates HoA WG FS to continue identifying further substances, which shall due to their potential risk to human health either not or only with restrictions be added to foods/food supplements.

4 References

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ZESPÓŁ DO SPRAW SUPLEMENTÓW DIETY, 2020. w sprawie wyrażenia opinii dotyczącej stosowania Withania somnifera (L.) Dunal jako składnika suplementów diety.

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ZESPÓŁ DO SPRAW SUPLEMENTÓW DIETY, 2021b. w sprawie wyrażenia opinii dotyczącej stosowania preparatów z Rhodiola rosea jako składników suplementów diety.

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5 Annexes

Annex A

Table 6 provides and overview of the reviewed substances by the member of the HoA WG FS and the outcome of the review. The table continues on the next three pages.

Table 6. An overview of the substances reviewed by the members of the HoA WG FS regarding the assumed 'Novel Food Status' (specified for the plant part) including the outcome of the review.

Substance	Plant part(s) or substance details, if specified	Outcome of review, to be confirmed by CAFAB WG on Novel Food
Abrus precatorius L.	leaves, seeds	Assumed 'novel'
N-Acetyl-Cysteine (NAC)	not applicable	Assumed 'not novel' or 'not NFS'
Aconitum carmichaelii Debeaux	not specified	Assumed 'novel'
Aconitum kusnezoffii Rchb.	not specified	Assumed 'novel'
Aconitum napellus L.	all plant parts	Assumed 'novel'
Actaea racemosa L.	rootstocks/rhizomes	Assumed 'not novel' or **'not NFS'***
Actaea spicata L.	all plant parts, especially fruits and roots	Assumed 'novel'
Adenium spp.	all plant parts	Assumed 'novel'
Adonis vernalis L.	herb	Assumed 'novel
Aethusa cynapium L.	all plant parts	Assumed 'novel'
Agapanthus spp.	rhizomes, bulbs	Assumed 'novel'
Agrostemma githago L.	all plant parts, seeds	Assumed 'novel'
Aleurites spp.	all plant parts	Assumed 'novel'
Alisma plantago-aquatica L.	rhizomes and preparations thereof	Assumed 'not novel' or 'not NFS'
Alkanna tinctoria Tausch	roots	Assumed 'novel'
Aloe ferox Mill.	leaf juice/gel	On Annex III RE 1925/2006
Aloe vera (L.) Burm.f	leaf juice/gel	On Annex III RE 1925/2006
Amaryllis spp.	all plant parts	Assumed 'novel'
Anacyclus pyrethrum (L.) Lag.	roots	Assumed 'novel'
Anadenanthera spp.	seeds	Assumed 'novel'
Anamirta cocculus (L.) Wight & Arn.	fruits	Assumed 'novel'
Anchusa spp.	herb	Assumed 'novel'
Andromeda spp.	leaves, flowers	Assumed 'novel'
Anemone spp.	all plant parts	Assumed 'novel'
Angostura trifoliata (Willd.) T.S. Elias	all plant parts	Assumed 'not novel' or 'not NFS'
Annona muricata L.	leaves	Assumed 'not novel' or 'not NFS'
Antiaris toxicaria Lesch.	all plant parts	Assumed 'novel'
Aquilegia vulgaris L.	all plant parts	Assumed 'not novel' or 'not NFS'
Areca catechu L.	fruits	Assumed 'novel'
Argyreia nervosa (Burm. f.) Bojer	seeds	Assumed 'novel'
Arisaema spp.	rootstocks/rhizomes	Assumed 'novel'
Aristolochia spp.	all plant parts	Assumed 'novel'
Arnica chamissonis Less.	flowers	Assumed 'novel'
Arnica montana L.	not specified	Assumed 'not novel' or 'not NFS'

Substance	Plant part(s) or substance details, if specified	Outcome of review, to be confirmed by CAFAB WG on Novel Food
Artemisia cina O.Berg	flowers, fruits	Assumed 'not novel' or 'not NFS'
Artemisia maritima L.	all plant parts	Assumed 'not novel' or 'not NFS'
Arum spp.	all plant parts	Assumed 'novel'
Asarum canadense L.	rootstocks/rhizomes	Assumed 'novel'
Asarum europaeum L.	all plant parts	Assumed 'novel'
Aspidosperma quebracho-blanco Schltdl.	bark, wood	Assumed 'novel'
Atropa belladonna L.	all plant parts	Assumed 'novel'
Banisteriopsis caapi (Spruce ex Griseb.) C.V.Morton	bark, wood	Assumed 'novel'
Berberine in preparations of *Berberis vulgaris* L.	extracts from root, bark	Assumed 'not novel' or 'not NFS'
Bryonia alba L.	roots	Assumed 'novel'
Calliandra angustifolia Spruce ex Benth.	not specified	Assumed 'novel'
Carapichea ipecacuanha (Brot.) L.Andersson	roots	Assumed 'novel'
Carica papaya L.	leaves	Assumed 'not novel' or 'not NFS'
Carlina acaulis L.	roots	Assumed 'not novel' or 'not NFS'
Chamaeleon gummifer (L.) Cass.	all plant parts	Assumed 'novel'
Chelidonium majus L.	herb	Assumed 'not novel' or 'not NFS'
Cinnamomum verum J.Presl	bark, essential oils	Assumed 'not novel' or 'not NFS'
Citrullus colocynthis (L.) Schrad.	all plant parts	Assumed 'novel'
Colchicum autumnale L.	all plant parts	Assumed 'novel'
Convallaria majalis L.	herb	Assumed 'novel'
Convolvulus scammonia L.	roots	Assumed 'novel'
Coumarin in plant preparations	different parts depending on plant	Assumed 'not novel' or '**not NFS**'*
Croton tiglium L.	all plant parts	Assumed 'novel'
Cucurbitacins in preparations of *Cucurbitaceae*	not specified	Assumed 'not novel' or 'not NFS'
Curcumin in *Curcuma* spp.-preparations	esp. rhizomes	Assumed 'not novel' or '**not NFS**'*
Cytisus scoparius (L.) Link	all plant parts	Assumed 'novel'
Datura stramonium L.	all plant parts	Assumed 'novel'
Digitalis lanata Ehrh.	all plant parts	Assumed 'novel'
Digitalis purpurea L.	all plant parts	Assumed 'novel'
Dryopteris filix-mas (L.) Schott	all plant parts	Assumed 'novel'
Dysphania ambrosioides (L.) Mosyakin & Clemants	seeds	Assumed 'novel'
Garcinia cowa Roxb. ex Choisy	fruits	Assumed 'not novel' or 'not NFS'
Genista tinctoria L.	flowers	Assumed 'novel'
Gentiana lutea L.	roots	Assumed 'not novel' or 'not NFS'
Ginkgo biloba L.	leaves	Assumed 'not novel' or 'not NFS'
Griffonia simplicifolia (Vahl ex DC.) Baill.	esp. seeds	Assumed 'not novel' or 'not NFS'
Huperzin A in *Huperzia serrata* Thunb.-preparations	esp. aerial parts	Assumed 'not novel' or 'not NFS'
Hyoscyamus niger L.	all plant parts	Assumed 'novel'
Hypericum perforatum L.	herb flowers and leaves	Assumed 'not novel' or **'not NFS'*** Assumed **'not novel'** or 'not NFS'*

Substance	Plant part(s) or substance details, if specified	Outcome of review, to be confirmed by CAFAB WG on Novel Food
Iodine (Macroscopic Algae)	not applicable/not specified	Assumed 'not novel' or 'not NFS'
Ipomoea purga (Wender.) Hayne	all plant parts	Assumed 'novel'
Juglans regia L.	leaves, (green) fruits, seeds, skins	Assumed 'not novel' or 'not NFS'
Juniperus sabina L.	all plant parts	Assumed 'novel'
Lavandula angustifolia subsp. *angustifolia*	essential oils of flowering tops	Assumed 'not novel' or 'not NFS'
Leipidium meyenii Walp.	roots	Assumed '**not novel**' or 'not NFS'*
Lobelia inflata L.	all plant parts	Assumed 'novel'
Lycopus europaeus L.	herb	Assumed 'not novel' or 'not NFS'
Lysimachia arvensis (L.) U.Manns & Anderb.	herb	Assumed 'novel'
Mallotus philippensis (Lam.) Müll. Arg.	fruits	Assumed 'novel'
Mandragora officinarum L.	roots	Assumed 'novel'
Melaleuca spp.-essential oils	essential oils, leaves	Assumed 'not novel' or **'not NFS'***
Melatonin	not applicable	Assumed 'not novel' or '**not NFS**'*
Mentha × piperita L.	leaves (essential oil)	Assumed 'not novel' or 'not NFS'
Monacoline K (*Monascus purpureus*)	not applicable	On Annex III RE 1925/2006
Morus alba L.	leaves	Assumed 'not novel' or 'not NFS'
Mutarda nigra (L.) Bernh.	seeds	Assumed 'not novel' or 'not NFS'
Nerium oleander L.	leaves	Assumed 'novel'
Ocimum basilicum L.	herb, seeds	Assumed 'not novel' or 'not NFS'
Ocimum tenuiflorum L.	herb seeds	Assumed **'not novel'** or 'not NFS'* Assumed 'novel'
Pilocarpus jaborandi Holmes	leaves	Assumed 'novel'
Piper methysticum G.Forst.	rootstocks	Assumed 'not novel' or 'not NFS'
Piperine	not applicable	Assumed 'not novel' or **'not NFS'***
Podophyllum peltatum L.	roots, resin	Assumed 'not novel' or 'not NFS'
Pulsatilla pratensis (L.) Mill.	all plant parts	Assumed 'novel'
Pulsatilla vulgaris Mill.	all plant parts	Assumed 'novel'
Rauvolfia serpentina (L.) Benth. ex Kurz	roots	Assumed 'novel'
Rhodiola rosea L.	herb	Assumed 'not novel' or 'not NFS'
Rhododendron tomentosum (Stokes) Harmaja	herb	Assumed 'not novel' or 'not NFS'
Ricinus communis L.	seeds	Assumed 'novel'
Rubia tinctorum L.	roots	Assumed 'novel'
Salvia rosmarinus Spenn.	not specified, possibly aerial parts	Assumed 'not novel' or 'not NFS'
Scopolia carniolica Jacq.	all plant parts	Assumed 'novel'
Solanum dulcamara L.	esp. stems	Assumed 'not novel' or 'not NFS'
Strophanthus kombe Oliv.	not specified	Assumed 'novel'
Strychnos nux-vomica L.	seeds	Assumed 'novel'
p-Synephrine in *Citrus* spp.-preparations	esp. pulp and peel	Assumed 'not novel' or **'not NFS'***
Tanacetum vulgare L.	flowers, herb	Assumed 'not novel' or 'not NFS'
Teucrium chamaedrys L.	all plant parts	Assumed 'not novel' or 'not NFS'
Tribulus terrestris L.	fruits	Assumed 'not novel' or **'not NFS'***
Tryptophan	not applicable	Assumed 'not novel' or **'not NFS'***

Substance	**Plant part(s) or substance details, if specified**	**Outcome of review, to be confirmed by CAFAB WG on Novel Food**
Urginea maritima (L.) Baker	bulbs	Assumed 'novel'
Vinca minor L.	herb	Assumed 'not novel' or 'not NFS'
Withania somnifera (L.) Dunal	whole plant roots	Assumed 'not novel' or **'not NFS'** Assumed **'not novel'** or 'not NFS'*

* CAFAB WG NF has already been contacted to confirm the Novel Food Status (**bold = confirmed status)**.

Annex B

Table 7 provides an overview of available EFSA opinions and monographs/assessment reports by the European Medicines Agency (EMA) on the substances reviewed by the subgroup 'risk assessment'. Only EFSA opinions on food were included. No opinions for health claims or feed (additives) were considered for the table below. Furthermore, only EMA monographs/assessments on human use were included. Monographs/assessment regarding veterinary use were not considered for the table below.

Table 7. An overview of available EFSA opinions and monographs/assessment reports by EMA.

Substance	EFSA	EMA
N-Acetyl-Cysteine	Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) on a request from the Commission related to N-Acetyl-L-cysteine for use in foods for particular nutritional uses and in foods for special medical purposes | EFSA (europa.eu)	-
Actaea racemosa L.	-	Cimicifugae rhizoma - herbal medicinal product | European Medicines Agency (europa.eu)
Coumarin in plant preparations	Coumarin in flavourings and other food ingredients with flavouring properties - Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) | EFSA (europa.eu)	-
Curcumin in *Curcuma* spp.-preparations	Scientific Opinion on the re-evaluation of curcumin (E 100) as a food additive | EFSA (europa.eu)	Curcumae longae rhizoma | European Medicines Agency (europa.eu)
Gentiana lutea L.	-	Gentianae radix | European Medicines Agency (europa.eu)
Ginkgo biloba L.	-	Ginkgo folium | European Medicines Agency (europa.eu)
Hypericum perforatum L.	-	Hyperici herba | European Medicines Agency (europa.eu)
Juglans regia L.	-	Juglandis folium | European Medicines Agency (europa.eu)
Lavandula angustifolia subsp. *angustifolia*	-	Lavandulae aetheroleum | European Medicines Agency (europa.eu) Lavandulae flos | European Medicines Agency (europa.eu)
Melaleuca spp.-essential oils	-	Melaleucae aetheroleum | European Medicines Agency (europa.eu)

Substance	EFSA	EMA
Melatonin	-	Circadin | European Medicines Agency (europa.eu)
Mentha × piperita L.	-	Menthae piperitae aetheroleum | European Medicines Agency (europa.eu)
Ocimum basilicum L.	-	Public Statement on the use of HMP cont. estragole | HMPC (europa.eu) Public Statement on the use of HMP cont. methyleugenol | HMPC (europa.eu)
Ocimum tenuiflorum L.	Scientific Opinion on a Qualified Presumption of Safety (QPS) approach for the safety assessment of botanicals and botanical preparations | EFSA (europa.eu)	Public Statement on the use of HMP cont. estragole | HMPC (europa.eu) Public Statement on the use of HMP cont. methyleugenol | HMPC (europa.eu)
Piper methysticum G.Forst.	-	Piperis methystici rhizoma | European Medicines Agency (europa.eu)
Piperine	Scientific Opinion on Flavouring Group Evaluation 86, Revision 2 (FGE.86Rev2): Consideration of aliphatic and arylalkyl amines and amides evaluated by JECFA (65th meeting) | EFSA (wiley.com)	-
Rhodiola rosea L.	-	Rhodiolae roseae rhizoma et radix | European Medicines Agency (europa.eu)
Salvia rosmarinus Spenn.	Refined exposure assessment of extracts of rosemary (E 392) from its use as food additive | EFSA (europa.eu)	Rosmarini aetheroleum | European Medicines Agency (europa.eu)
Solanum dulcamara L.	-	Solani dulcamarae stipites | European Medicines Agency (europa.eu)
p-Synephrine in *Citrus* spp.-preparations	Safety of caffeine | EFSA (europa.eu)	-
Tribulus terrestris L.	-	Tribuli terrestris herba | European Medicines Agency (europa.eu)
Withania somnifera (L.) Dunal	-	Withaniae somniferae radix | European Medicines Agency (europa.eu)

Annex C

This Annex includes short summaries with more detailed information on the 13 substances of Table 3 in Chapter 2.2.3. Those are the substances considered to pose a (possible) risk to consumers and for which the intake via food supplements exceeds normal intake and are therefore prioritized. The summaries have been prepared following previous mandates from the EU COM to EFSA to initiate 'Article 8 procedures'. They could therefore serve as a template for new mandates from the EU COM to EFSA.

Actaea racemosa

Based on national risk assessment from the Netherlands, the HoA WG FS raised concerns regarding a potential risk to consumers linked to the consumption of foods containing preparations or extracts of *Actaea racemosa* L. (hereinafter referred to as *Actaea racemosa*) synonym *Cimicifuga racemosa* (L) Nutt.[34], rhizoma due to hepatotoxicity. Most important substances are triterpene glycosides, phenols and flavonoids. However, no toxicological data are available to link specific substances or groups of substances to the effects reported. In general, the intake of 40 mg *Actaea racemosa*, rhizoma per day (0.57 mg/kg body weight per day) for 6 months does not pose a risk for the consumer. This dose, however, may be largely exceeded with consumption of food supplements containing *Actaea racemosa*, as supplements on the market contain up to 2500 mg *Actaea racemosa*. However, possible idiosyncratic hepatotoxicity might occur in individuals at unknown intake. From this view point there is no safe dose. According to the European Medicines Agency *Actaea racemosa* rhizoma should not be taken for more than 6 months without medical advice. This concern leads to the following questions:

1. Is there a link between consumption of *Actaea racemosa*, rhizoma and/or preparations or extracts thereof and adverse effects on health including hepatoxicity?
2. What is the maximum level of total dietary exposure of *Actaea racemosa*, rhizoma unlikely to pose a risk of adverse health effects to humans?
3. What are possible subgroups of the general population that are more vulnerable or more sensitive to the adverse effects caused by *Actaea racemosa*?

Substance	Preparations or extracts of rhizome/rootstocks of *Actaea racemosa* L. Most important constituents are triterpene glycosides, phenols and flavonoids. Synonyms: *Cimicifuga racemosa* (L) Nutt, *Botrophis serpentaria* Raf., *Cimicifuga serpentaria* Pursh, *Macrotrys racemosa* (L.) Sweet, *Megotrys serpentaria* Raf., *Thalictrodes racemosa* (L.) Kuntze Common name: black cohosh
Medicinal use	Yes (HMPC, 2018a)
Most critical endpoint	Animal studies showed effects on bone marrow, thymus and liver. Worldwide severe cases of hepatotoxicity are reported. However they cannot be causally linked with the intake of *Actaea racemosa* L., rhizome (BuRO, 2020).
Toxicological reference point	Lowest observed adverse effect level of 62.5 mg *Actaea racemosa* L. /kg body weight was found in a 90-day study with mice (increased haematological parameters) (BuRO, 2020).

[34] The risk assessments always refer to the synonym *Cimicifuga racemose.*

Health Based Guidance Value	In general, the intake of 40 mg *Actaea racemosa* L., rhizome per day (0.57 mg/kg body weight per day) for 6 months does not pose a risk for the consumer. The margin of exposure is 110. However, possible individual idiosyncratic hepatotoxicity might occur at unknown intake. From this view point there is no safe dose (BuRO, 2020).
Exposure	Most extracts of *Actaea racemosa* L., rhizoma used in clinical trials are standardized and contain 40 mg *Actaea racemosa* L. rhizoma. However, on the internet supplements with 20 to 2500 mg *Actaea racemosa* L. rhizoma extract are available. These are probably not standardized (BuRO, 2020).
Remarks	According to the European Medicines Agency *Actaea racemosa* L. rhizoma should not be taken for more than 6 months without medical advice (HMPC, 2018a). Possible sensitive subgroups are (BuRO, 2020): - Patients with a history of liver injuries or disease. - Patients who receive or have received treatment for breast cancer or other hormone dependent tumours. - People who are hypersensitive to substances in *Actaea racemosa* L. rhizoma.

Coumarin in plant preparations

Based on national risk assessments from Germany and France, the HoA WG FS raised concerns regarding a potential risk to consumers linked to the consumption of foods containing coumarin due to hepatotoxicity. Some food supplements available on the market of the EU, especially those containing *Neolitsea cassia* (L.) Kosterm (synonym: *Cinnamomum cassia* (L.) J.Presl), lead to exposure exceeding the tolerable daily intake (TDI) derived by EFSA of 6 mg / day for a 60 kg adult (hepatotoxic effects) (EFSA AFC panel, 2008). This concern leads to the following questions:

1. Is there a link between consumption of coumarin or plant preparations containing coumarin and adverse effects on health?
2. What is the maximum level of total dietary exposure of coumarin or plant preparations containing coumarin unlikely to pose a risk of adverse health effects to humans (i.e. is the TDI still appropriate)?
3. What is the maximum level of exposure of coumarin or plant preparations containing coumarin via food supplements unlikely to pose a risk of adverse health effects to humans?
4. What are possible subgroups of the general population that are more vulnerable or more sensitive to the adverse effects caused by coumarin or plant preparations containing coumarin?

Substance	Coumarin is a natural aromatic compound found in certain plants such as *Neolitsea cassia* (L.) Kosterm (synonym: *Cinnamomum cassia* (L.) J.Presl, common name: Cinnamon; but also other *Cinnamomum* spp.), *Galium odoratum* (L.) Scop. (common name: sweet woodruff), *Dipteryx odorata* (Aubl.) Forsyth f. (common name: tonka bean) and *Melilotus officinalis* (L.) Lam. (common name: sweet clover). This list is not exhaustive. *Neolitsea cassia* (L.) Kosterm or preparations and extracts thereof are often used in FS and are particularly rich in coumarin. Also synthetically produced coumarin may be relevant.
Medicinal use	Two herbal medicinal products containing sweet clover have a marketing authorization in France: One for venotonic purposes (Esberiven Fort®) and the other as a sedative (Sedopal®) (ANSES, 2021).
Most critical endpoint	Hepatotoxic effects in animal studies. The liver toxicity of coumarin at high doses (> 25 mg/day in humans) was confirmed by the available toxicological data (BfR, 2012b; ANSES, 2021).

Toxicological reference point	NOAEL: coumarin dose of 10 mg/kg body weight per day (in a 2 years study with Beagle dogs: necropsies were observed at a coumarin dose of 25 mg/kg body weight per day but no effect at the dose of 10 mg/kg bw per day) (BfR, 2012b; ANSES, 2021).
Health Based Guidance Value	TDI is 0.1 mg/kg body weight by oral intake i.e. 6 mg/day for a 60 kg adult (hepatotoxic effects) (BfR, 2012b; ANSES, 2021).
Exposure	For the populations most exposed via food, exposure to coumarin through food consumption can be as much as 20 % of the TDI of 0.1 mg/kg body weight per day. On the market, dietary supplementation can range from 3 to 24 mg of coumarin per day. With these doses, the TDI of 0.1 mg/kg body weight per day (i.e. 6 mg/day for a 60 kg adult) may therefore be largely exceeded and a risk to human health cannot be ruled out (ANSES, 2021).
Remarks	According to ANSES, a limit of max 4.8 mg/day of coumarin intake by food supplements is needed in order to comply with TDI (this dose can be reached through daily consumption of food supplements containing around 1.6 g of cinnamon). A risk assessment encompassing all exposure routes, including also respiratory and dermal exposure, is not available yet (ANSES, 2021). Possible sensitive subgroups are: - Individuals with a history of liver disease. - Individuals taking medicines known to cause adverse liver effects.

Curcumin in *Curcuma* spp.-preparations[35]

Based on national risk assessments from Germany, France and Spain, the HoA WG FS raised concerns regarding a potential risk to consumers linked to the consumption of foods containing curcumin in *Curcuma* spp.-preparations or curcuminoids (often referred to as curcumin or curcumins) due to hepatotoxicity in humans and animals (at very high doses), although the mechanism is unknown. An acceptable daily intake (ADI) of 3 mg curcumin/kg body weight per day i.e. a maximum intake of 180 mg per day of curcumin for a 60 kg adult was derived by EFSA (based on reprotoxic effects). Some food supplements available on the market of the EU lead to exposures exceeding the ADI. Further, the established ADI is not appropriate for curcumin preparations with increased bioavailability. Also, curcumin is reported to interact with anticoagulant and anticancer drugs. This concern leads to the following questions:

1. Is there a link between consumption of curcumin or plant preparations or extracts containing curcumin without increased bioavailability and adverse effects on health?
2. Is there a link between consumption of curcumin or plant preparations or extracts containing curcumin with increased bioavailability and adverse effects on health?
3. What is the maximum level of total dietary exposure of curcumin or plant preparations or extracts containing curcumin, with and without increased bioavailability, unlikely to pose a risk of adverse health effects to humans?
4. What is the maximum level of total dietary exposure of curcumin or plant preparations or extracts containing curcumin in food supplements unlikely to pose a risk of adverse health effects to humans?
5. What are possible subgroups of the general population that are more vulnerable or more sensitive to the adverse effects caused by curcumin or plant preparations or extracts containing curcumin?

[35] The abbreviation "spp." refers to more than one not further defined species of the same genus.

Substance	Curcumin belongs to the curcuminoids, a class of plant secondary metabolites which also includes demethoxycurcumin, and bisdemethoxycurcumin. Curcuminoids are found in the rhizomes of various *Curcuma* species (e.g. *Curcuma longa* L., *Curcuma zanthorrhiza* Roxb., *Curcuma zedoaria* (Christm.) Roscoe). This list is not exhaustive. Curcumin is the principal curcuminoid (75-80 %) of *Curcuma longa* L. (turmeric). Commercial curcumin (spice) contains curcumin and the structurally analogous compounds. The available risk assessments often refer to curcuminoids as 'curcumin'. Also synthetically produced curcumin may be relevant.
Medicinal use	Medicinal uses for two species containing curcumin: *Curcuma longa* L. (synonym: *Curcuma domestica* Valeton) and for *Curcuma zanthorrhiza* Roxb. for their digestive properties (HMPC, 2014;2018b).
Most critical endpoint	Reprotoxicity: Wistar rodents study Hepatotoxicity: Case reports of hepatotoxicity have been reported in humans (and in animal studies, although doses used in animal studies were very high) but mechanism is unknown. In some of these cases analysis points to the use of curcumin in combination with other medicines, the use of multi-ingredient food-supplement or pre-existence of liver function problems. With regard to clinical trials conducted with curcumin: no hepatotoxicity reported (however, in many clinical trials, liver function was not assessed or reported) (ANSES, 2022a). Drug interaction highly suspected: interactions of curcumin have been reported with anticoagulant and anticancer drugs (ANSES, 2022a).
Toxicological reference point	NOAEL: 250-320 mg/kg in a reprotoxicity study with Wistar rodents (AESAN, 2020; BVL & BfArM, 2020; BfR, 2021; ANSES, 2022a).
Health Based Guidance Value	ADI: 3 mg curcumin/kg body weight per day i.e. a maximum intake of 180 mg per day of curcuminoids for a 60 kg adult (should only be used in view of curcumin preparations with no increased bioavailability) (AESAN, 2020; BVL & BfArM, 2020; BfR, 2021; ANSES, 2022a).
Exposure	The study of exposure to curcumin in the French population shows that this exposure through food is low. The estimated daily exposure to curcumin in the French population could be as high as 0.45 mg/kg body weight per day in adults and 0.77 mg/kg body weight per day in children (at the 95th percentile). EFSA exposure estimation: 0.2-0.6 mg/kg body weight per day. Food supplements on the French market generally provide 1 to 3 g of dry rhizome per day or 0.g to 1 g of curcumin per day. In Spain, "only 36 of the 106 supplements (34 %) provide information on its content, with 950 mg and 1.57 mg being the maximum and minimum daily amounts established, respectively". Increased exposure with formulations with improved bioavailability (ANSES, 2022a).
Remarks	According to ANSES, the ADI can be greatly exceeded when consuming a food supplement, especially if the bioavailability is modified. Due to the increased absorption of curcumin in the gastrointestinal tract and/or a reduced metabolization, a higher systemic bioavailability and thus in principle an increase in toxicity must be considered for these preparations. More research is needed, especially with regard to hepatotoxicity. The existing ADI for such products is not very conservative and may not ensure a sufficient level of protection for consumers. Novel Food status has to be considered for products with improved bioavailability. Warnings on the products have been mentioned in certain EU MS with regard to not use curcumin in case of liver or bile function problems, as well as to not use supplements in case of pregnancy, lactation or < 18 yr (FOD, 2019; AESAN, 2020; ANSES, 2022a).

Hypericum perforatum

Based on national risk assessments from Denmark and the Netherlands, the HoA WG FS raised concerns regarding a potential risk to consumers linked to the consumption of food supplements and herbal teas containing (preparations or extracts of) the herb of *Hypericum perforatum* L. (hereinafter referred to as *Hypericum perforatum*) due to phototoxicity and pharmacological effects that may occur. In addition, there are indications for genotoxicity, reprotoxicity and developmental toxicity with *Hypericum perforatum* and its constituents, however, the data are not sufficient to adequately conclude on those endpoints. From this view point, it is currently not possible to derive a safe dose level or health-based guidance value.

Based on the reported hypericin content of some food supplements containing *Hypericum perforatum* available on the market of the European Union, the estimated exposure to hypericin by consumers ranges from 1.4 to 41 µg/kg body weight per day for a 70 kg person. This estimated exposure exceeds the dose of 31 µg hypericin/kg body weight per day at which enhanced phototoxicity was observed in humans. This indicates that phototoxicity can occur when using food supplements with *Hypericum perforatum*. This concern leads to the following questions:

1. Is there a link between consumption of supplements (and herbal tea) containing *Hypericum perforatum* and adverse effects on health?
2. Has *Hypericum perforatum* genotoxic properties?
3. Is *Hypericum perforatum* able to induce reprotoxic effects and/or developmental toxicity?
4. What is the maximum level for acute (single dose) and chronic dietary exposure of supplements (and herbal tea) containing *Hypericum perforatum* unlikely to pose a risk of adverse health effects to humans?
5. What are possible subgroups of the general population that are more vulnerable or more sensitive to the adverse effects caused by *Hypericum perforatum*?

Substance	Supplements containing (preparations or extracts of) the herb of *Hypericum perforatum* L. Hypericin, pseudohypericin and hyperforin are generally thought to be the most relevant constituents for the pharmacological effects of *Hypericum perforatum* L. Hyperforin is the constituent related to drug interactions (de Wit et al., 2019). Synonyms: *Hypericum officinale* Gaterau, *Hypericum officinarum* Crantz, *Hypericum perforatum* var. *vulgare* Spenn., *Hypericum perforatum* subsp. *vulgare* (Spenn.) A.Fröhl., *Hypericum vulgare* Lam. Common name: St. John's wort
Medicinal use	Yes, see Hyperici herba | European Medicines Agency (europa.eu)
Most critical endpoint	Concerns are raised for the following endpoints (de Wit et al., 2019; DTU, 2019a): - Serious drug interactions mainly due to hyperforin. - Phototoxicity induced by hypericin. - Indications for genotoxicity, reprotoxicity and developmental toxicity. - Pharmacological effects may occur when exposure via supplements is in the same range as via herbal medicines.
Toxicological reference point	It is not possible to derive a toxicological reference point as for the most serious effects the data are not sufficient.

	For phototoxicity, a LOAEL of 31 µg hypericin/kg body weight per day in humans was identified.
Health Based Guidance Value	Not possible to derive health based guidance value for *Hypericum perforatum* L. or the main constituents, due to gaps in the toxicological data available (de Wit et al., 2019). EMA has established that for daily doses containing less than 1 mg hyperforin clinically relevant interactions are not reported (Hyperici herba | European Medicines Agency (europa.eu)).
Exposure	Based on the reported hypericin content of some food supplements containing *Hypericum perforatum* L. that are available in the Netherlands, the estimated exposure to hypericin by consumers ranges from 1.4 to 41 µg/kg body weight per day for a 70 kg person. The estimated exposure exceeds the dose of 31 µg hypericin/kg body weight at which enhanced phototoxicity was observed in humans. This indicates that phototoxicity can occur when using food supplements with *Hypericum perforatum* L.
Remarks	Adverse effects have been reported including dizziness, diarrhoea, skin reactions and psychiatric symptoms. Concerns about contamination with pyrrolizidine alkaloids (which are genotoxic carcinogens) (de Wit et al., 2019).

Lepidium meyenii

Based on a national risk assessment from Denmark, the HoA WG FS raised concerns regarding a potential risk to consumers linked to the consumption of foods containing *Lepidium meyenii* Walp. (hereinafter referred to as *Lepidium meyenii*), root or germ stem (hypocotylene) or its preparations due to effects on sex hormones, reproduction in rodents and hormonal effects on menopausal women. Most important substances are glucosinolates, macamides and imidazolalkaloids. However, no toxicological data are available to link specific constituents of *Lepidium meyenii* to the effects on the reproductive and endocrine systems, reported in experimental animals. A health based guidance value was not derived but DTU concludes based on human studies that doses of 2 g/day may have hormonal effect on menopausal women. This concern leads to the following questions:

1. Is there a link between consumption of *Lepidium meyenii*, root or germ stem (hypocotylene) or its preparations and adverse effects on health?
2. What is the maximum level of total dietary exposure of *Lepidium meyenii*, root or germ stem (hypocotylene) or its preparations unlikely to pose a risk of adverse health effects to humans?
3. What are, besides menopausal women, other possible subgroups of the general population that are more vulnerable or more sensitive to the adverse effects caused by *Lepidium meyenii*?

Substance	Roots or germ stems (hypocotylene) or preparations thereof of *Lepidium meyenii* Walp. Most important substances are glucosinolates, macamides and imidazolalkaloids (DTU, 2020a). Macamides (N-alkyl-amides) are considered as a group of substances that have bioactive properties and may be responsible for the effects attributed *to L. meyenii* (DTU, 2020a). Different phenotypes of *Lepidium meyenii* Walp. are typically referred to as yellow, red, violet and black maca. Maca preparations can have different compositions of plant constituents depending the plant variety, origin of the plant material as well as depending on the drying and extract-manufacturing process (DTU, 2020a).

	Synonyms: *Lepidium affine* Wedd., *Lepidium gelidum* Wedd., *Lepidium meyenii* var. *affine* Thell., *Lepidium meyenii* subsp. *gelidum* (Wedd.) Thell., *Lepidium meyenii* var. *gelidum* (Wedd.) Hosseus, *Lepidium meyenii* f. *rhombicum* Thell., *Lepidium meyenii* f. *rotundatum* Thell., *Lepidium peruvianum* G.Chacón, *Lepidium weddellii* O.E.Schulz Common name: Maca
Medicinal use	No
Most critical endpoint	Effects on sex hormones (mice, rats), male reproduction in animals (genitals, spermatogenesis, sperm count), female reproduction (sex hormones in rats/mice without ovaries), weight loss in male rats. Based on the animal studies described, it is not possible to establish a dose at which these effects are not seen (DTU, 2020a). Human studies: increase in estradiol in menopause women, some studies show effects and some do not on FSH, LH, PG - Effects in human individuals with metabolic syndrome in a randomised placebo controlled trial with dose 0.6 g dry root/day for 90 days (increased diastolic blood pressure in men and women and increased diastolic and systolic blood pressure in women) (DTU, 2020a).
Toxicological reference point	No NOAEL or LOAEL was established (DTU, 2020a).
Health Based Guidance Value	A HBGV was not derived and DTU considers that it is not possible to determine a dose from the described animal experiments where adverse effects can be ruled out. However, based on human studies, it cannot be excluded that 2 g of *Leipidum meyenii* Walp. per day as a food supplement may affect hormone levels in peri- and postmenopausal women (DTU, 2020a).
Exposure	The roots of the maca plant have long been consumed (history of use) as food in certain regions of South America, however no quantitative data is available (BfR, 2024 *in preparation*). Extracts from *Lepidium meyenii* Walp. roots as well as dried roots are marketed as food supplements. The daily doses of the extracts vary from 150 to 4000 mg (BfR, 2024 *in preparation*). A quick search on the internet revealed that supplements with *Leipidum meyenii* Walp. are available in Sweden. The recommended daily dose are for example 400 mg, 1 teaspoon to 1 tablespoon, or sold as powder with no given dose other than e. g. "mix powder with water or add it to a smoothie, salad or yoghurt"
Remarks	No toxicological data are available to link specific constituents of *Lepidium meyenii* Walp. to the effects on the reproductive and endocrine systems, reported in experimental animals. There are several human studies in which the aim has been to investigate *Leipidum meyenii* Walp.'s effects on sex hormones. DTU considers that it cannot be excluded that 2 g *Leipidum meyenii* Walp. per day may affect hormone levels in peri- and postmenopausal women (DTU, 2020a).

Melaleuca spp.-essential oils[36]

Based on a national risk assessment from France, the HoA WG FS raised concerns regarding a risk to consumers linked to the consumption of the essentials oils of the leaves and other parts of *Melaleuca alternifolia* (Maiden & Betche) Cheel, *Melaleuca quinquenervia* (Cav.) S.T. Blake and *Melaleuca cajuputi* Maton & Sm. ex R.Powell (hereinafter referred to as *Melaleuca alternifolia*, *Melaleuca quinquenervia*, *Melaleuca cajuputi*) as food supplements due to the presence of 1,8-cineol, methyleugenol and terpinene-4-ol. These substances might also be present in other plant-based foods or food supplements. 1,8 cineol has possible neurotoxic properties, the genotoxicity and carcinogenicity of methyleugenol have been demonstrated and terpinene-4-ol has effects on the reproductive system. This concern leads to the following questions:

<u>1,8-Cineol</u>

1. Is there a link between consumption of 1,8-cineol and adverse effects on health?
2. What is the maximum level of total dietary exposure of 1,8-cineol unlikely to pose a risk of adverse effects to humans?
3. What is the maximum level of total dietary exposure of 1,8-cineol in food supplements unlikely to pose a risk of adverse effects to humans?
4. What are possible subgroups of the general population that are more vulnerable or more sensitive to the adverse effects caused by 1,8-cineol?

<u>Methyleugenol</u>

1. Is there a link between consumption of methyleugenol and adverse effects on health?
2. What is the maximum level of total dietary exposure of methyleugenol unlikely to pose a risk of adverse effects to humans?
3. What is the maximum level of total dietary exposure of methyleugenol in food supplements unlikely to pose a risk of adverse effects to humans?
4. What are possible subgroups of the general population that are more vulnerable or more sensitive to the adverse effects caused by methyleugenol?

<u>Terpinen-4-ol</u>

1. Is there a link between consumption of terpinen-4-ol and adverse effects on health?
2. What is the maximum level of total dietary exposure of terpinen-4-ol unlikely to pose a risk of adverse effects to humans?
3. What is the maximum level of total dietary exposure of terpinen-4-ol in food supplements unlikely to pose a risk of adverse effects to humans?
4. What are possible subgroups of the general population that are more vulnerable or more sensitive to the adverse effects caused by terpinene-4-ol?

<u>*Melaleuca* spp.-essential oils</u>

1. Is there a link between consumption of essentials oils of *Melaleuca alternifolia, Melaleuca quinquenervia* and *Melaleuca cajuputi* as a food supplement and adverse effects on health?

[36] The abbreviation "spp." refers to more than one not further defined species of the same genus.

2. What is the maximum level of total dietary exposure of essentials oils of *Melaleuca alternifolia*, *Melaleuca quinquenervia* and *Melaleuca cajuputi* as a food supplement unlikely to pose a risk of adverse effects to humans?
3. What are possible subgroups of the general population that are more vulnerable or more sensitive to the adverse effects caused by essentials oils of *Melaleuca alternifolia*, *Melaleuca quinquenervia* and *Melaleuca cajuputi*?

Substance	1,8-cineol, methyleugenol and terpinen-4-ol present in essential oils of the leaves and other parts of *Melaleuca alternifolia* (Maiden & Betche) Cheel, *Melaleuca quinquenervia* (Cav.) S.T.Blake and *Melaleuca cajuputi* Powell (ANSES, 2020). *Melaleuca alternifolia* (Maiden & Betche) Cheel Synonyms: *Melaleuca linariifolia* var. *alternifolia* Maiden & Betche Common name: Tea tree *Melaleuca quinquenervia* (Cav.) S.T.Blake Synonyms: *Metrosideros quinquenervia* Cav., *Melaleuca leucadendra* var. *albida* Cheel, *Melaleuca leucadendra* var. *angustifolia* L.f., *Melaleuca leucadendra* var. *coriacea* (Poir.) Cheel, *Melaleuca maidenii* R.T.Baker, *Melaleuca smithii* R.T.Baker, *Melaleuca viridiflora* var. *angustifolia* (L.f.) Byrnes, *Melaleuca viridiflora* var. *rubriflora* Pancher ex Brongn. & Gris, *Metrosideros albida* Sieber ex DC., *Metrosideros coriacea* Poir. Common name: Broad-leaved Paperbark *Melaleuca cajuputi* Maton & Sm. ex R.Powell Synonyms: *Melaleuca saligna* (J.F.Gmel.) Reinw. ex Blume, *Melaleuca trinervis* Buch.-Ham., *Myrtus saligna* J.F.Gmel., *Pimentus saligna* (J.F.Gmel.) Raf.
Medicinal use	No
Most critical endpoint	1,8-cineol: possible neurotoxicity Methyleugenol: genotoxicity and carcinogenicity Terpinen-4-ol: reprotoxicity (ANSES, 2020)
Toxicological reference point	1,8-cineol: no toxicological reference point available due to the absence of precise toxicological studies. Methyleugenol: no toxicological reference point available due to genotoxicity and carcinogenicity. Terpinen-4-ol: a NOAEL of 250 mg/kg body weight (testicular and epididymal toxicity) (ANSES, 2020).
Health Based Guidance Value	1,8-cineol: as no toxicological reference point is available also no health based guidance value can be derived. Methyleugenol: no health based guidance value available due to genotoxicity and carcinogenicity. MOE-approach applies. Terpinen-4-ol: applying a safety factor of 100 to the NOAEL and an additional factor of 2 due to the short duration of the studies carried out, a corresponding maximum non-health ingestion of 1.2 mg/kg body weight per day was set for terpinen-4-ol by EFSA in 2012 (ANSES, 2020).
Exposure	There is no information regarding intake from a balanced diet: historical use has been described as external, not oral. *Melaleuca* essential oils are not usually used in food. Moreover, their oral intake as a food supplement is recent (ANSES, 2020).

Melatonin[37]

Based on national risk assessments from France and Norway, the HoA WG FS raised concerns regarding a potential risk to consumers linked to the consumption of food supplements containing melatonin/adult per day due to general (headaches, dizziness, drowsiness), cardiovascular, neurological, digestive and psychological symptoms in humans. Melatonin is an endogenous hormone in humans and also used as medicinal drug (EMA authorization for product containing 2 mg, see also Annex B). This concern leads to the following questions:

1. Is there a link between consumption of melatonin as a food supplement and adverse effects on health?
2. What is the maximum level of total and acute exposure of melatonin as a food supplement unlikely to pose a risk of adverse health effects to humans?
3. What are possible subgroups of the general population that are more vulnerable or more sensitive to the adverse effects caused by melatonin?

Substance	Melatonin Chemical name: N-acetyl-5-methoxytryptamine Also synthetically produced melatonin may be relevant.
Medicinal use	Yes Circadin and Melatonin Neurim: 2 mg prolonged release tablets (see also Annex B) Slenyto: 1-5 mg, mostly 2 mg/day, tablet
Most critical endpoint	Human: general (headaches, dizziness, drowsiness), cardiovascular, neurological, digestive and psychological symptoms (ANSES, 2018; VKM, 2021). Mainly based on ANSES nutrivigilance system; not only "healthy persons taking melatonin as a single ingredient in food supplements at proposed dose levels" (i.e. it included also cases with other food supplement ingredients, concomitant medication, medical history, overdoses in suicide attempts).
Toxicological reference point	Not possible to derive a toxicological reference point for children and adolescents. VKM identified a NOAEL of 0.005 mg/kg bw/day (90-day toxicity study in rats) and a NOEAL of 0.4 mg/kg bw/day (6-month repeated dose study in dogs) (VKM, 2021).
Health Based Guidance Value	No HBGV stated (ANSES, 2018). Recommendation not to exceed 2 mg melatonin per person per day (ANSES, 2018). VKM cannot conclude on the safety of 1 mg/day of melatonin for 3 months (VKM, 2021).
Exposure	Melatonin in food supplements is marketed in several EU MS. Melatonin is also an endogenous hormone. Melatonin is also known to be present in low amounts in food, but no dietary exposure data is currently available (BfR, 2024, *in preparation*).
Remarks	Favourable EFSA opinion for two health claims relating to melatonin in foodstuffs, requiring at least 0.5 mg or 1 mg of melatonin/portion, respectively (Commission Regulation (EU) No 432/2012). EMA advises against melatonin-intake by pregnant and breastfeeding women due to effects of melatonin on embryo-foetal development in rabbits and postnatal development in rats. Melatonin passes into breast milk. ANSES 2018 is mainly based on sufficiently documented nutrivigilance cases with likely causality, however most cases are with medical history, other food supplement ingredients, concomitant medication or overdoses (suicide attempts). ANSES considered the data from French pharmacovigilance and toxicovigilance systems as well as cases from other EU MS, Canada and the US FDA, to be too heterogeneous data (ANSES, 2018).

[37] In many MS there is an urgent need to e. g. determine the maximum daily dose of melatonin, or to restrict products aimed at children. However, as melatonin is considered medicinal in several MS, depending on e. g. the daily dose, the topic is highly complex. Thus, the HoA WG FS suggests to put further processing and submission of melatonin to the EU COM on hold for now.

Ocimum tenuiflorum

Based on a national risk assessment form Denmark, the HoA WG FS raised concerns regarding a potential risk to consumers linked to the consumption of foods containing preparations or extracts of *Ocimum tenuiflorum* L. (hereinafter referred to as *Ocimum tenuiflorum*), leaves extracts and other plant parts or preparations thereof due to effects on genitals in rabbits (possible reprotoxicity). This concern leads to the following questions:

1. Is there a link between consumption of *Ocimum tenuiflorum*, leaves extracts and other plant parts or preparations thereof and adverse effects on health?
2. What is the maximum level of total dietary exposure of *Ocimum tenuiflorum*, leaves extracts and other plant parts or preparations thereof parts unlikely to pose a risk of adverse health effects to humans?
3. What are possible subgroups of the general population that are more vulnerable or more sensitive to the adverse effects caused by *Ocimum tenuiflorum*?

Substance	Leaves and other plant parts (herb, flowers or seeds) and preparations or extracts thereof of *Ocimum tenuiflorum* L. Information on substances are not available in DTU 2019b. However, estragole and methyleugenol are present in leaves and methyleugenol in live plants according to the EFSA compendium of botanicals and ESCO 2009 (ESCO, 2009). Synonyms: *Geniosporum tenuiflorum* (L.) Merr., *Lumnitzera tenuiflora* (L.) Spreng., *Moschosma tenuiflorum* (L.) Heynh., *Ocimum flexuosum* Blanco, *Ocimum hirsutum* Benth, *Ocimum inodorum* Burm.f., *Ocimum monachorum* L., *Ocimum sanctum* L., *Ocimum sanctum* var. *cubensis* Gomes, *Ocimum sanctum* var. *hirsutum* (Benth.) Hook.f., *Ocimum scutellarioides* Willd. ex Benth., *Ocimum subserratum* B.Heyne ex Hook.f., *Ocimum tenuiflorum* f. *villicaulis* Domin, *Ocimum tomentosum* Lam., *Ocimum villosum* Roxb., *Plectranthus monachorum* (L.) Spreng. Common names: holy basil, Tulsi
Medicinal use	No
Most critical endpoint	Effects on genitals and fertility in rabbits (DTU, 2019b).
Toxicological reference point	Negative effects on the genitals and on fertility in rabbits at 100-300 mg dried leaves (DTU, 2019b).
Health Based Guidance Value	Factor of 14-41 (100-300 mg dried leaves/day gives 1.4-4.3 mg/kg body weight for an adult 70 kg). Normal praxis for biologically active substances is to use a factor of at least 100 when extrapolating from a No Observed Adverse Effect level, NOAEL, in experimental animals to humans. Therefore, DTU concludes that margin of safety of 14-41 is too small (DTU, 2019b).
Exposure	A quick search on the internet in Sweden learned that supplements with a recommended daily dose of 600-1380 mg *Ocimum tenuiflorum* L. are available. These are probably not standardized.
Remarks	DTU performed a risk assessment in 2012 (not available) with the conclusion that it is not possible to derive a safe dose of leaves extracts in food supplements. In 2019, DTU assessed documentation from a company on the safety of five food supplements. The submitted documentation did not change DTU's previous conclusion from 2012 (DTU, 2019b).

Piperine

Based on national risk assessments from Denmark, France, Germany and Poland, the HoA WG FS raised concerns regarding a potential risk to consumers linked to the consumption of food supplements containing piperine. The national risk assessments differ in critical endpoint in rodents (reproductive toxicity, elevated cholesterol plasma levels), point of departure, uncertainty factor and health based guidance value. Raised concerns lead to the following questions:

1. Is there a link between consumption of piperine and adverse effects on health?
2. Is there a link between consumption of isolated, highly piperine-enriched pepper extracts as bolus in food supplements and adverse effects on health?
3. What is the maximum level of total dietary exposure of piperine unlikely to pose a risk of adverse health effects to humans?
4. What is the maximum level of total dietary exposure of piperine in highly piperine-enriched pepper extracts as bolus in food supplements unlikely to pose a risk of adverse health effects to humans?
5. Does piperine increase the bioavailability of other ingredients in food supplements?
6. What are possible subgroups of the general population that are more vulnerable or more sensitive to the adverse effects caused by highly piperine-enriched pepper extracts as a bolus in food supplements?

Substance	Piperine Natural ingredient of *Piper nigrum* L. (black pepper), *Piper longum* L. and some other *Piper* species as well as *Aframomum melegueta* K.Schum (grains of paradise). Isolated, highly piperine-enriched pepper extracts (frequently ≥ 95 %) as bolus in food supplements (versus pepper for food seasoning or as flavouring agent) (Ziegenhagen et al., 2021). Chemical names: ((E,E)-piperine; IUPAC-name: (2E,4E)-5-(2H-1,3-benzodioxol-5-yl)-1-(piperidin-1-yl)penta-2,4-dien-1-one; CAS-No. 94-62-2; FEMA-No. 2909) Also synthetically produced piperine may be relevant.
Medicinal use	Yes
Most critical endpoint	Animal studies - Spermatogenesis and accompanying effects on male reproductive organs in rats (Ziegenhagen et al., 2021; ANSES, 2022b). - Elevated cholesterol plasma level in rats (EFSA CEF Panel, 2015; VKM, 2016b; DTU, 2019c).
Toxicological reference point	Different point of departures (PODs) by EFSA 2008/2011/2015/2016, JECFA 2005/2006, DTU 2019, VKM 2016 (EFSA CEF Panel, 2015; VKM, 2016b; DTU, 2019c; Ziegenhagen et al., 2021); none by ANSES 2022 (ANSES, 2022b). EFSA, DTU, VKM: NOAEL 5 mg/kg body weight per day from rat oral 90-day study (elevated cholesterol plasma level in male rats). BfR: LOAEL 10 mg piperine/kg body weight per day oral, several animal studies with rats and mice (male reproduction). ANSES: no POD identified, as in-depth clarification of reproductive toxicity is needed.
Health Based Guidance Value (HBGV)	Different HBGVs by the above mentioned authorities/committees differing in POD and UF:

	BfR: 2.3 mg piperine/person/day (70 kg bw, bolus; UF 300). DTU: 1.75 mg/person/day (70 kg bw; UF 200, including 2 for subchronic-chronic extrapolation). VKM: 3.5 mg/person/day (UF 100 to NOAEL). ANSES: none Max. allowed daily dose in food supplements: PL: max. 2 mg piperine/adult/day in food supplements excluding pregnant and lactating women (among others based on the above mentioned authorities/committees) (ZESPÓŁ DO SPRAW SUPLEMENTÓW DIETY, 2022).
Exposure	Piperine in food supplements is marketed in several EU MS. Exposure estimate for piperine from pepper in food preparations for male German population: mean 24-36 mg piperine/day and P95 64-96 mg piperine/day (Ziegenhagen et al., 2021). Piperine content in food supplements frequently ranges 5-30 mg/day with single products reaching 40 or 50-100 mg/day (Ziegenhagen et al., 2021).
Remarks	Piperine is also used and promoted to increase bioavailability of other ingredients in food supplements.

p-Synephrine in *Citrus* spp.-preparations[38]

Based on national risk assessments from Germany, France, the Netherlands, Sweden and Denmark, the HoA WG FS raised concerns regarding a potential risk to consumers linked to the consumption of foods containing *Citrus* spp.-preparations or extracts containing *p*-synephrine. *p*-Synephrine is a constituent of preparations or extracts of different *Citrus* species and especially of preparations or extracts of bitter orange (*Citrus* x *aurantium* L.), which are marketed as supplements for weight loss and enhancing athletic performance. The main health concern about *p*-synephrine use in food and sports supplements refers to its potential as a sympathomimetic to induce adrenergic (stimulant-related) adverse effects on the cardiovascular system. Animal and human studies, as well as numerous case reports, provide evidence for cardiovascular effects due to ingestion of high *p*-synephrine doses, especially in combination with caffeine and physical exertion. This concern leads to the following questions:

1. Is there a link between consumption of p-synephrine (e.g. from bitter orange extracts) as an ingredient of food supplements and adverse (cardiovascular) effects on health?
2. What is the maximum level for acute (single dose) and chronic dietary exposure of *p*-synephrine, as an ingredient of food supplements, unlikely to pose a risk of adverse health effects to humans?
3. What are possible subgroups of the general population that are more vulnerable or more sensitive to the adverse effects caused by *p*-synephrine (e.g. from bitter orange extracts) as an ingredient of food supplements?
4. What are recommendations for the possible high-risk groups, including individuals who deliberately take a lot of *p*-synephrine such as bodybuilders, athletes and people who want to lose weight and individuals who may be especially sensitive to the adverse effects, namely children, pregnant and lactating women and people taking medication for their blood pressure?

[38] The abbreviation "spp." refers to more than one not further defined species of the same genus.

Substance	*p*-Synephrine in *Citrus* spp.-preparations or extracts and especially preparations or extracts of *Citrus* x *aurantium* L. (common names: pummelo, Seville Orange, bitter orange). *p*-Synephrine (also referred to as synephrine) is an alkaloid with adrenergic activity and is a natural ingredient occurring in the pulp and peel (epicarp and mesocarp) of various citrus fruits (*Citrus spp.)* especially of bitter orange (*Citrus* x *aurantium* L.). *p*-Synephrine from bitter orange extracts is added to various products marketed as food, especially sports supplements and slimming products (Bakhiya et al., 2017). Also synthetically produced *p*-synephrine may be relevant.
Medicinal use	No, but synthetic *p*-synephrine has been on the market since the 1930s as a drug for the treatment of hypotension due to its sympathomimetic effect under the name Oxedrine or Sympatol® (BfR, 2012a).
Most critical endpoint	Animal studies on synephrine indicated acute cardiovascular effects as a critical toxicological endpoint. Animal studies involving oral administration clearly showed that supplementation with *p*-synephrine (in the form of *Citrus* x *aurantium* L. extract or as purified phytochemical) can lead to elevated blood pressure, and ingestion of synephrine in combination with caffeine can induce considerable cardiovascular effects with additional alteration of heart rate. The available mechanistic data indicate that effects of *p*-synephrine on the cardiovascular system are attributable to adrenergic stimulation. The scientific literature describes a number of cases of serious effects that were associated with the ingestion of preparations containing *p*-synephrine (case reports of ischemic stroke and cardiotoxicity including tachyarrhythmia, cardiac arrest, syncope, angina, myocardial infarction, ventricular arrhythmia, and death in otherwise healthy patients). Most cases involved preparations of *p*-synephrine, caffeine and other substances (BfR, 2012a; ANSES, 2014; Tiesjema et al., 2017).
Toxicological reference point	Animal studies do not allow the identification of a no observed adverse effect level (NOAEL), as the effects (on the cardiovascular system) were observed at all doses tested (BfR, 2012a).
Health Based Guidance Value	Currently no HBGV available. According to EFSA's Qualified Presumption of Safety (QPS) approach, *p*-synephrine intake is considered safe when consumed orally in amounts commonly found in foods. The BfR (Germany) recommends that supplements should provide no more than 6.7 mg of *p*-synephrine daily, which is equivalent to the median dietary intake from conventional foods in Germany, and is presumed to represent a safe intake of supplements (BfR, 2012a). The French ANSES concludes that intake levels of *p*-synephrine through food supplements must remain below 20 mg/day (ANSES, 2014). NL BuRO advises to set the maximum intake of *p*-synephrine from herbal preparations at 27 mg of *p*-synephrine per day (BuRO, 2018).
Exposure	The total daily intake of *p*-synephrine via conventional food, estimated for the German population under consideration of maximum concentrations of *p*-synephrine, amounts to 6.7 mg/day for average consumers and to 25.7 mg/day for high consumers (95th percentile). Estimations for the French population considering the maximum levels in citrus fruits yielded an average *p*-synephrine intake of 4.3 and 17.7 mg/day at the 95th percentile (BfR, 2012a; ANSES, 2014).
Remarks	Synephrine is frequently present in products in combination with caffeine and/or multiple herbal ingredients. The adverse effects of *p*-synephrine on the cardiovascular system may be enhanced when used in combination with other stimulants (such as caffeine).

	In its opinion on the risk assessment of caffeine (EFSA NDA Panel, 2015), EFSA was mandated to assess the risks for consumption of caffeine together with *p*-synephrine. EFSA concluded, that the question of whether or not *p*-synephrine modifies the acute cardiovascular effects of single doses of caffeine has not been adequately investigated in humans, particularly if consumed shortly before intense physical exercise, and therefore no conclusions could be drawn. *p*-Synephrine is considered a banned substance by the National Collegiate Athletic Association (NCAA)[39].

Tribulus terrestris

Based on national risk assessments from Spain and Denmark, the HoA WG FS raised concerns regarding a potential risk to consumers linked to the consumption of foods containing preparations or extracts of different parts of *Tribulus terrestris* L. (hereinafter referred to as *Tribulus terrestris*) due to possible genotoxic and estrogenic activity. In its natural form it contains various active substances, the most notable of which are steroidal saponins, β-carboline alkaloids, flavonoids and lignanamides. However, no toxicological data are available to link specific substances or groups of substances to the effects reported. In Spain supplements with high concentrations (250 and 1500 mg) *Tribulus terrestris* preparation or extract are on the market. This concern leads to the following questions:

1. Is there a link between consumption of *Tribulus terrestris* preparations or extracts and adverse effects on health?
2. What is the maximum level of total dietary exposure of *Tribulus terrestris* unlikely to pose a risk of adverse health effects to humans?
3. What are possible subgroups of the general population that are more vulnerable or more sensitive to the adverse effects caused by *Tribulus terrestris*?

Substance	Fruits, plant shoots and preparations or extracts thereof of *Tribulus terrestris* L. In its natural form it contains various active substances, the most notable of which are steroidal saponins, β-carboline alkaloids, flavonoids and lignanamides (AECOSAN, 2015b). Common names: puncture vine, Gokshura
Medicinal use	Yes? Tribuli terrestris herba are currently under review by EMA. There has been a call for data (see Tribuli terrestris herba | European Medicines Agency (europa.eu)).
Most critical endpoint	A clear critical endpoint cannot be identified. Clinical observations associate the intake of *Tribulus terrestris* L. with neuronal, hepatic and renal toxicity. These toxic effect are also seen in animal studies. *In vitro* studies indicated cytotoxicity as well as genotoxicity and estrogenic activity from *Tribulus terrestris* L. extracts (AECOSAN, 2015b).
Toxicological reference point	Not possible to derive a toxicological reference point.
Health Based Guidance Value	Not possible to derive a health based guidance value.
Exposure	In Spain supplements are on the market containing *Tribulus terrestris* extract between 250 and 1500 mg, which could lead to a daily intake between 250 and 9000 mg (AECOSAN, 2015b).

[39] See NCAA Banned Substances - NCAA.org

Tryptophan

Based on national risk assessments from Spain and Norway, the HoA WG FS raised concerns regarding a potential risk to consumers linked to the consumption of food supplements containing tryptophan in doses of 3 g/day and higher leading to adverse effects such as appetite suppression, nausea and vomiting, faintness, dizziness, drowsiness, tremor, fatigue, and headache. In the European Union supplements with high concentrations (500 to 1000 mg) of tryptophan are available on the market. In the Norwegian assessment it was concluded that in adults (≥ 18 years), adolescents and children, the intake of the specified doses (250, 300 and 450 mg/day) in food supplements may represent a risk of adverse health effects.

This concern leads to the following questions:

1. Is there a link between consumption of L-tryptophan and adverse effects on health?
2. What is the maximum level of total chronic dietary exposure of L-tryptophan unlikely to pose a risk of adverse health effects to humans?
3. What is the maximum level of exposure to L-tryptophan via food supplements unlikely to pose a risk of adverse health effects to humans?

Substance	Tryptophan is an essential amino acid that intervenes in protein synthesis and is the biochemical precursor of serotonin, melatonin, niacin and the coenzymes, NAD and NADP (AESAN, 2012). Chemical name: 2-amino-3-(1H-indol-3-yl) propionic acid Also synthetically produced Tryptophan may be relevant.
Medicinal use	No
Most critical endpoint	According to previous reports, short-term supplementation with L-tryptophan supplements in doses of 3 g/day and higher have led to adverse effects including appetite suppression, nausea and vomiting, faintness, dizziness, drowsiness, tremor, fatigue, and headache. A suspected, but not established, increased risk of cataract has also been reported. There is a lack of data concerning long-term supplementation (VKM, 2016a).
Toxicological reference point	Several doses associated with observed adverse effects have been referred to in the literature, the lowest being 3 g/day, which represents a LOAEL. A NOAEL of 2228 mg/day has been identified, based on monitoring of patients treated with tryptophan prescribed as an antidepressant in the UK who did not report side effects (VKM, 2016a).
Health Based Guidance Value	VKM will use 220 mg/day as a value for comparison in the risk characterisation of L-tryptophan. This value is based on the NOAEL described above and an uncertainty factor of 10.
Exposure	The Norwegian Food Safety Authority has requested a risk assessment of the doses 250 mg/day, 300 mg/day and 450 mg/day of L-tryptophan in food supplements for children 10 years and older, adolescents and adults (VKM, 2016a).
Remarks	The Scientific Committee concludes that, based on the information available to date and taking into account the considerations reflected in this report, the AESAN proposal of a maximum daily amount of 300 mg of L-tryptophan is acceptable from the safety point of view for use as a food supplement (AESAN, 2012; VKM, 2016a). VKM concludes that in adults (≥ 18 years), adolescents and children the specified doses 250, 300 and 450 mg/day L-tryptophan in food supplements may represent a risk of adverse health effects (AESAN, 2012; VKM, 2016a). It should not be consumed by pregnant women, or those individuals receiving treatment with antidepressants or who suffer from kidney failure.

	A crucial point is that adverse effects are exacerbated when tryptophan is administered in combination with antidepressant medications with serotonergic actions (i.e. which increase brain serotonin levels), including MAOIs, SSRIs, SNRIs tricyclic antidepressants and other drugs.

Withania somnifera

Based on a national risk assessment from Denmark, the HoA WG FS raised concerns regarding a potential risk to consumers linked to the consumption of supplements containing roots, herbs, flowers and preparations or extracts thereof of *Withania somnifera* (L.) Dunal (hereinafter referred to as *Withania somnifera*) due to (potential) effects on reproduction, thyroid hormones, acetylcholinesterase, the immune system and due to liver toxicity. The toxicity data are limited and not sufficient to derive a safe dose level or health-based guidance value. Besides in supplements, *Withania somnifera* is also used in herbal teas.

This concern leads to the following questions:

1. Is there a link between consumption of food supplements (and herbal teas) containing (preparations or extracts of) *Withania somnifera* and adverse effects on health?
2. What is the maximum level of total dietary exposure of *Withania somnifera* unlikely to pose a risk of adverse health effects to humans?
3. What are possible subgroups of the general population that are more vulnerable or more sensitive to the adverse effects caused by *Withania somnifera*?

Substance	Supplements and herbal teas containing roots, herbs, flowers and preparations or extracts thereof of *Withania somnifera* (L.) Dunal. Main constituents are withanolides and alkaloids (DTU, 2020b). Synonyms: *Alicabon somniferum* (L.) Raf., *Physalis somnifera* L., *Physaloides somnifera* (L.) Moench, *Hypnoticum somniferum* Rodr. ex Boiss., *Larnax morrisonii* (Dunal) Miers, *Physalis alpini* J.Jacq., *Physalis arborescens* Thunb., *Physalis flexuosa* L., *Physalis scariosa* Webb & Berthel., *Physalis somnifera* var. *communis* Nees, *Physalis somnifera* var. *flexuosa* (L.) Nees, *Physalis sugunda* Buch.-Ham. ex Wall., *Physalis tomentosa* Thunb., *Physalis villosa* Moench ex Steud., *Withania arborescens* Dunal, *Withania chevalieri* A.E.Gonç., *Withania kansuensis* Kuang & A.M.Lu, *Withania macrocalyx* (Chiov.) Chiov., *Withania microphysalis* Suess., *Withania morisonii* Dunal, *Withania mucronata* Chiov., *Withania obtusifolia* Täckh., *Withania sicula* Lojac., *Withania somnifera* var. *communis* (Nees) Dunal, *Withania somnifera* var. *flexuosa* (L.) Dunal, *Withania somnifera* var. *macrocalyx* Chiov., *Withania somnifera* subsp. *obtusifolia* (Täckh.) Abedin & al. Common names: Ashwagandha, winter cherry
Medicinal use	Yes, although EMA concluded that it was not possible to establish a community herbal monograph on traditional herbal medicinal products (Withaniae somniferae radix | European Medicines Agency (europa.eu)).
Most critical endpoint	Reported effects include (DTU, 2020b): - Effects on (male) reproduction via effects on levels of sex hormones. - Effects on thyroid hormones. - Inhibition of acetylcholinesterase. - Effects on the immune system. - Liver toxicity (based on case studies).
Toxicological reference point	N/A

Health Based Guidance Value	Not possible to derive HBGV for *Withania somnifera* (L.) Dunal. or the main constituents (DTU, 2020b).
Exposure	*Withania somnifera Withania somnifera* (L.) Dunal. in food supplements is marketed in several EU MS.
Remarks	There is information that women have used *Withania somnifera* (L.) Dunal. as an abortifacient; doses are not reported. Therefore, WHO advises not to use *Withania somnifera* (L.) Dunal. during pregnancy or lactation (DTU, 2020b). There are several RASFF notifications on *Withania somnifera* (L.) Dunal.; for example recent (March 2023) notifications by Denmark[40, 41, 42].

[40] https://webgate.ec.europa.eu/rasff-window/screen/notification/601523
[41] https://webgate.ec.europa.eu/rasff-window/screen/notification/602102
[42] RASFF Window - Notification detail (europa.eu)

Annex D

Result of the review of the 13 prioritized substances regarding existing permissions as food additives or food flavourings.

Coumarin in plant preparations

Coumarin is a phytotoxin and is categorized as an 'active principle'. These are undesirable naturally occurring substances that may not be used as flavourings. However, spices and other food ingredients with flavouring properties that may naturally contain such 'active principles' may be used.
Coumarin is included in Annex III Part A of Regulation (EC) No 1334/2008 in the list of "Substances which shall not be added as such to foods".
As the substance is naturally present in flavourings and food ingredients with flavouring properties or in certain ready-to-eat foods to which flavourings and/or food ingredients with flavouring properties have been added, coumarin may be present in certain foods at a specified maximum level[43].

According to Article 6(2) of Regulation (EC) No 1334/2008, without prejudice to Regulation (EC) No 110/2008, maximum levels of certain substances, naturally present in flavourings and/or food ingredients with flavouring properties, in the compound foods listed in Part B of Annex III shall not be exceeded as a result of the use of flavourings and/or food ingredients with flavouring properties in those foods. The maximum levels of the substances set out in Annex III shall apply to foods as marketed, unless otherwise stated. By way of derogation from this principle, for dried and/or concentrated foods which need to be reconstituted, the maximum levels shall apply to the food as reconstituted according to the instructions on the label, taking into account the minimum dilution factor.

Three Coumarin derivatives are also approved as flavouring substances without restrictions/exemptions and are listed in Annex I of Regulation (EC) No. 1334/2008:

- 3,4-Dihydrocumarin [Fl No. 13.009]
- 6-Methylcumarin [Fl No. 13.012]
- Octahydrocumarin [Fl No. 13.161]

Curcumin in *Curcuma* spp.-preparations

Curcumin (E 100) is listed as an approved food additive in Group III: "Colours with combined maximum limits" in Regulation (EC) No. 1333/2008. Curcumin is extracted mainly from *Curcuma*-species.

[43] Maximum levels of coumarin as listed in Annex III Part B of Regulation (EC) No 1334/2008: Traditional and/or seasonal bakery ware containing a reference to cinnamon in the labelling 50 mg/kg; Breakfast cereals including muesli 20 mg/kg; Fine bakery ware, with the exception of traditional and/or seasonal bakery ware containing a reference to cinnamon in the labelling 15 mg/kg; Desserts 5 mg/kg.

Hypericum perforatum

Hypericum perforatum L. is listed in Annex IV Part B of Regulation (EC) No 1334/2008 as a source material whose use is restricted in the production of flavourings and food ingredients with flavouring properties. According to Article 7(2) of Regulation (EC) No 1334/2008, flavourings and/or food ingredients with flavouring properties produced from the source materials listed in Part B of Annex IV may only be used under the conditions set out in that Annex. Flavourings and food ingredients with flavouring properties produced from *Hypericum perforatum* L. may only be used for the production of alcoholic beverage.

Piperine

Piperine [Fl No. 14.003] is listed as an approved flavouring substance in the Union list in Annex I Part B of Regulation (EC) No. 1334/2008 without any restrictions. Piperine is extracted mainly from *Piper nigrum* L.