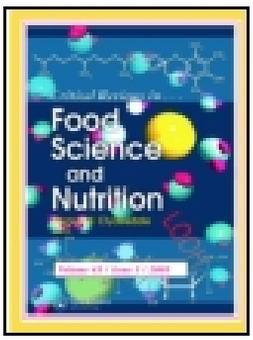

Critical Reviews in Food Science and Nutrition

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

The need for European harmonization of Nutrivigilance in a public health perspective: a comprehensive review

G. Vo Van Regnault, M. C. Costa, A. Adanić Pajić, A. P. Bico, S. Bischofova, U. Blaznik, F. Menniti-Ippolito, K. Pilegaard, C. Rodrigues & I. Margaritis

To cite this article: G. Vo Van Regnault, M. C. Costa, A. Adanić Pajić, A. P. Bico, S. Bischofova, U. Blaznik, F. Menniti-Ippolito, K. Pilegaard, C. Rodrigues & I. Margaritis (2021): The need for European harmonization of Nutrivigilance in a public health perspective: a comprehensive review, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2021.1926904

To link to this article: https://doi.org/10.1080/10408398.2021.1926904

Published online: 26 May 2021.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2021.1926904

Taylor & Francis
Taylor & Francis Group

REVIEW

The need for European harmonization of Nutrivigilance in a public health perspective: a comprehensive review

G. Vo Van Regnault[a], M. C. Costa[b,c,d], A. Adanić Pajić[e], A. P. Bico[f], S. Bischofova[g], U. Blaznik[h], F. Menniti-Ippolito[i], K. Pilegaard[j], C. Rodrigues[c,f], and I. Margaritis[a]

[a]French Agency for Food, Environmental and Occupational Health and Safety (ANSES), Maisons-Alfort, France; [b]Economy and Food Safety Standards Authority (ASAE), Lisboa, Portugal; [c]CBIOS – Universidade Lusófona's Research Center for Biosciences & Health Technologies, Lisboa, Portugal; [d]NICiTeS, Polytechnic Institute of Lusophony, Lisboa, Portugal; [e]Croatian National Institute of Public Health (CIPH), Zagreb, Croatia; [f]Directorate of Nutrition and Food Services, Directorate-General for Food and Veterinary (DGAV), Lisboa, Portugal; [g]Center for Health, Nutrition and Food – National Institute of Public Health in Prague, Czech Republic; [h]National Institute of Public Health Slovenia (NIJZ), Ljubljana, Slovenia; [i]Italian National Institute of Public Health, Rome, Italy; [j]National Food Institute, Technical University of Denmark, Kgs. Lyngby, Denmark

ABSTRACT

According to the European Union regulation, some countries have established a pre-market notification system for food supplements while others have not. As this regulation is unfulfilled, a notified and marketed food supplement ingredient in one country may be forbidden in another. Even though food supplements shall not be placed on the market if unsafe, some products may still expose the consumers to risks. The risk is increased by easier access due to worldwide dissemination fostered by the internet and free movement of goods in the European Union. The Rapid Alert System for Food and Feed and the Emerging Risks Exchange Network are described. To date, the European Union legislation does not include a provision to establish a dedicated vigilance system for food supplements (Nutrivigilance). Six European Union countries have nevertheless set up national systems, which are presented. The present lack of European Union data collection harmonization, does not allow easy cooperation between countries. This article advocates for creating a coordinated European Nutrivigilance System to detect and scrutinize adverse effects of food supplements. This, to help in directing science-based risk assessments and reinforce the science-based decision of policy makers to improve public health safety.

KEYWORDS:
Consumer protection; dietary supplement; emerging risk; food safety; food supplement; risk assessment

Introduction

Over the last few decades, the range of available foods supplements (FSs) has greatly expanded, with new products characterized by innovative ingredients and formats.

The FS (or dietary supplement as they are called in the United States) market has grown sharply in Europe and worldwide (ANSES 2017c; Binns, Lee, and Lee 2018; Garcia-Alvarez et al. 2014; Vargas-Murga et al. 2011). Moreover, the consumption of these products is becoming widely used by consumers aware of the impact of nutrition on health (Chaloupkova et al. 2020; Jeurissen et al. 2018), or expecting a functional effect, for example, on physical performance (Wardenaar et al. 2017; Sánchez-Oliver et al. 2020). Additionally, due to trade globalization and the underlying development of a transnational market on the internet, it is possible for consumers to order and import foods from other European Union Member States (EU MS) or countries outside the European Union (EU). This facilitates accessibility and consequently increases risks of exposure to products of non-verified quality.

Legally considered as food in Europe, FSs are subjected to the dispositions of the general food law laid down by the Regulation (EC) N° 178/2002 (European Parliament and the Council of the European Union 2002b). FSs are regulated by the European Directive 2002/46/EC (European Parliament and the Council of the European Union 2002a), which defines these products as "foodstuffs the purpose of which is to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in dose form." This directive specifies vitamins and minerals and their forms allowed in FSs but the maximum levels are not defined. Since it is a directive and not a regulation, EU MS have some latitude to implement the text, in particular on the modalities concerning marketing authorization (article 10) and maximum daily intake (article 5). Those, as well as post-marketing surveillance are the remit of EU MS.

Substances other than vitamins or minerals, including various plants and herbal extracts, can also be added to FSs. The conditions for the addition of substances to foodstuffs are subject to Regulation (EC) 108/2008 (European

CONTACT G. Vo Van Regnault gwenn.vovanregnault@anses.fr French Agency for Food, Environmental and Occupational Health and Safety (ANSES), Maisons-Alfort, France.

Parliament and the Council of the European Union 2008) of 15 January 2008 amending Regulation 1925/2006. They are subject to specific conditions according to whether they concern plants, plant extracts, or "certain other substances." In the case of certain other substances, the purpose of the evaluation is to establish progressively a negative list. Article 8 of this Regulation sets the possibility of a procedure at European Commission (EC) level allowing the restriction of such substances if they are found to present a risk upon risk assessment by the European Food Safety Authority (EFSA). The assessment procedure is initiated by the Commission or the EU MS. The procedure can end up classifying the substances into three categories: banned (A), restricted (B), and in the case of scientific uncertainty, those which are under Community control (C). When applied, the last scenario induces a 4-year use before assessment. To date, the European Commission has established a very short list of substances whose use in food is prohibited: *Ephedra* species and its preparations; yohimbe bark and its preparations originating from *Pausinystalia yohimbe* (K. Schum) Pierre ex Beille; aloe-emodin, emodin, danthron and all preparations in which these substances are present; preparations from the leaf of Aloe species containing hydroxyanthracene derivatives (European Parliament and the Council of the European Union 2015, 2019b; European Commission 2021a) or restricted: Trans fat; preparations from the root or rhizome of *Rheum palmatum* L., *Rheum officinale* Baillon and their hybrids containing hydroxyanthracene derivatives; preparations from the leaf or fruit of *Cassia senna* L. containing hydroxyanthracene derivatives; preparations from the bark of *Rhamnus frangula* L., *Rhamnus purshiana* DC. containing hydroxyanthracene derivatives (European Parliament and the Council of the European Union 2019a; European Commission 2021a). This is to be compared to the numerous reports of adverse effects, mostly for FSs with plant, plant preparations or certain other substances, published by EU MS food agencies. Even if some FSs with vitamins and minerals may give rise to adverse effects these are usually well-known. Whereas plants, plant extracts or certain other substances require risk assessments that are hampered by the fact that toxicological studies are usually very scarce or lacking, and assessments may require taking into account reported adverse effects and data on history of use. If case reports on adverse effects from EU MS vigilance systems are available, the diversity of approaches applied for determining causality may hinder a straightforward use of the data. Getting then back to the original notification and analyzing de novo the cases may prove extremely difficult. A uniformized system of vigilance in EU would significantly ease the process and make it more efficient in ensuring safety of FSs at EU level.

So even in presence of a European legislation, there is no harmonization of compositions for FSs (Bilia and Costa 2020). Thus, no positive or negative list nor safety limits are defined for most certain other substances, plants other organisms like algae, lichens, and fungi in FSs at the EU level, and each EU MS can define its own positive or negative lists. Nevertheless, as part of the free cross-border movement of goods, these products may be available in all European countries and worldwide. Melatonin is an example of differences in the regulatory status in Europe. Melatonin is authorized in FSs below a daily dose of 2 mg in France, Latvia, Portugal; 1 mg in Cyprus, Croatia, Spain, Greece, Italy, Poland; 0.5 mg in Slovenia; 0.3 mg in Belgium; 0.28 mg in Germany; while other countries, such as Denmark and the Czech Republic do not accept the use of melatonin in FSs (ANSES 2018; JAZMP 2019).

The Regulation 1925/2006 and the Directive 2002/46/EC do not require pre-marketing obligations prior to the commercialization of FSs. Nevertheless, both regulations make it possible for EU MS to require a notification before placing these products on the market. Concerning FSs, four Europeans countries (Austria, Netherlands, Slovenia, Sweden) do not have any pre-market placement rules, 20 European countries established a notification system and three (Croatia, Cyprus, Romania) set up an authorization system for certain special cases.

There is no pre-marketing efficacy studies mandatory for FSs, although these products are marketed under the European claim Regulation (European Parliament and the Council of the European Union 2006). A claim is a message that can be mentioned on food packages or in connection with a product (label, advertisement, web site), stating the health and/or nutritional benefits of a food or its ingredients. EFSA is in charge of assessing claims and the EC is responsible for authorization. Various claims for vitamin and minerals in FSs have been authorized (European Commission 2020a) but claims for botanicals (1500 claims) for which assessment methods still need to be defined by the EC, are placed on hold. Most non-business stakeholders and EU MS agreed that, in the current situation, which allows the continued use of unsubstantiated health claims for plants, reliable and adequate information to consumers is not ensured (European Commission 2020b). Indeed, it may be difficult to distinguish between FSs and medicinal products containing often the same plant substance(s) with similar properties claimed on the label. This creates distortions on the market perspectives of cause-effect relationships, safety criteria inconsistencies and lack of clarity for food business operators and consumers. Thus, it has to be considered that claims could mislead consumer and encourage an unnecessary use or misuse of FSs (Mariotti et al. 2010).

EU does not impose obligation to undertake pre-marketing safety studies for FSs, but it is the responsibility of the manufacturer to ascertain that a product is safe (European Parliament and the Council of the European Union 2002b). However, under certain conditions, FSs, often perceived as safe, can expose the consumers to risks. The number of adverse effects related to food supplements are unknown. It has been suggested that only 1% are reported (Binns, Lee, and Lee 2018).

The purpose of this article is to point out the importance of creating a harmonized and coordinated European Nutrivigilance System to detect and scrutinize adverse effects of FSs. The aim of the system is to explain what caused the

adverse effects, to increase scientific knowledge and to improve the public health safety since the collected data may lead to withdrawal of unsafe products from the market.

Risks related to FSs

Many articles report possible risks associated with the consumption of FSs (Dennehy, Tsourounis, and Horn 2005; Haller et al. 2008; Kothari, Patel, and Kim 2019; Morgovan et al. 2019; Patel et al. 2012; Smith and Dillon 2009; Restani et al. 2016). These adverse effects may be due to non-prohibited ingredients, to intentional adulteration, to unintentional contamination, or the combined effects of individual ingredients.

It seems essential to pool knowledge on product composition and adverse events reported in European countries, considering the free cross-border movement of FSs between EU MS, the easy access for consumers to FSs marketed worldwide, the increased consumption of FSs and the potential risks for consumers.

Risks related to non-prohibited ingredients

Non-prohibited ingredients may expose the consumer to a risk. The risk may be related to the ingredient itself, interactions with other ingredients or substances within the FS that may contain a mixture of ingredients or with other FSs or foods or drugs ingested concomitantly (Amadi and Mgbahurike 2018; Binns, Lee, and Lee 2018; Asher, Corbett, and Hawke 2017; Boullata 2005; de Boer, van Hunsel, and Bast 2015). Furthermore, the risk may be linked to an intrinsic toxicity of the ingredients, associated with the preparation of the product, the dosage or with the consumer sensitivity (Hudson et al. 2018; Navarro et al. 2017; Ronis, Pedersen, and Watt 2018). For instance, "red yeast rice," a red mold, mainly consisting of *Monascus purpureus*, grown on rice, is used in many FSs claiming to maintain a normal level of cholesterol. Red yeast rice contains monacolin K that has a chemical structure identical to lovastatin, the first commercially available statin on the market, and as an expected consequence has a similar risk profile of standard cholesterol lowering medicinal treatments. In fact, as statins, the use of this FS can expose consumers—especially those particularly susceptible due to genetic predispositions, pathologies or ongoing treatments—to risks (i.e., muscle and/or liver damage) (ANSES 2014b; Mazzanti et al. 2017; EFSA. 2018a).

Risks related to intentional adulteration or unintentional contamination

Many people opt for FSs as "natural" alternatives to drugs. Nevertheless, unscrupulous manufacturers may deliberately adulterate FSs with medicinal substances in order to increase their efficacy. Cases of adulteration of FSs by unauthorized active substances have been on the rise for several years (Rocha, Amaral, and Oliveira 2016; Zovko Končić 2018; Czepielewska et al. 2018). The FSs most frequently reported to be adulterated are weight-loss supplements, sexual performance enhancement supplements (ElAmrawy et al. 2016; Žuntar et al. 2018) and bodybuilding/athletic performance enhancement supplements (Garthe and Maughan 2018). For instance, various publications addressing contamination of fortified foods in general, and FSs for athletes, in particular highlight the presence of prohibited substances (mainly anabolic agents, or stimulants including obsolete medicinal agents like 1,3-dimethylamylamine (DMAA)) which may induce adverse reactions (i.e., myocardial infarction, arrhythmia or coronary artery diseases, hepatotoxicity, etc.) or/and result in positive anti-doping tests (ANSES 2016; Mathews 2018; Cohen 2014). Indeed, some of these substances are included in the Prohibited List published and revised annually by the World Anti-Doping Agency (WADA) (World Anti-Doping Agency 2021; UNESCO 2019). Even if some consumers buy FSs to improve their performance, they may not be aware of the adulteration of these products with not labeled drugs and the risks associated with the use. Given well-known adverse reactions associated with doping substances, which is one of the criteria for their prohibition, the prevention of adulteration of FSs and sport foods with these substances is an important public health issue. This was the concern underlying the European Committee for Standardization (CEN) document on doping prevention in sport (European Committee for Standardization 2020).

Furthermore, risk may occur from poor quality of FSs that may result in accidental contamination or overdose of toxic substances (Amster, Tiwary, and Schenker 2007; Ozdemir et al. 2013; MacFarquhar et al. 2010; Binns, Lee, and Lee 2018). For instance, several cases of replacement of harmless species of plants with toxic alternatives have been described (Van Den Berg et al. 2011; Abdullah et al. 2017; Martena et al. 2007).

Existing systems to detect risks related to FSs

The EC and the European Parliament coordinate systems for reporting on food safety including FSs safety, namely the Rapid Alert System for Food and Feed (RASFF) and the Emerging Risks Exchange Network (EREN) but the European legislation does not impose the creation of a dedicated vigilance system for FSs (Nutrivigilance). An overview of existing systems to detect risks related to FSs in EU is presented below.

National vigilance systems for FSs

In Europe, few countries have an autonomous vigilance system dedicated to FSs. Indeed, considering that no safety studies are mandatory before placing a FS on the market, six countries in Europe implemented a dedicated post-market surveillance system for FSs and some other specific foodstuffs: **Italy** (launched in 2002), **France** (2009), **Denmark** (2013), **Portugal** (2014), **Czech Republic** (2015), **Slovenia** (2016), and **Croatia** (2020). These systems are described below.

Table 1. Cases of adverse effects involving a FS with strong causality (very likely) and severity (very serious) from the French, Portuguese, and Slovenian Nutrivigilance Systems.

Main ingredients	Adverse effects
FRANCE	
Vitamins, minerals	Acute hepatitis
Vitamins, minerals	Acute hepatitis
Bifidobacterium lactis, B. longum, Lactobacillus acidophilus, L. paracasei, L. rhamnosus and *L. rhamnosus, L. paracasei, L. acidophilus, B. bifidum*	Infective endocarditis
Passiflora incarnata	Anaphylactic shock
Bauhinia variegata	Acute hepatitis
PORTUGAL	
Vitamins, minerals, and royal jelly	Edema, skin rashes, and allergic reaction
Vitamins and minerals	Anaphylactic shock
Passiflora incarnata, *Valeriana officinalis*, *Chamomilla recutita*, melatonin	Bowel obstruction
Tribulus terrestris	Azoospermia
Wheat protein hydrolysates, vitamins, minerals	Increased alanine aminotransferase, hepatotoxicity
SLOVENIA	
Triphala, yashtimandu, ashwaghanda, kanchanara	Acute hepatic failure
Guarana	Restlessness, increased heart rate, excessive sweating, headache, abdominal distension, increased urination
Guarana	Nausea, irregular and more intense heartbeat, tingling sensation in the chest
Cannabidiol	Disturbances of consciousness, tachycardia
Colloidal silver	Tremor, forgetfulness, argyria

Existing Nutrivigilance Systems are based on voluntary reports from health professionals, producers and consumers. Reported cases of adverse effects are processed by a specific protocol. For all these Nutrivigilance Systems, the analysis of information is the basis for preventive and corrective risk management measures implemented by the relevant authorities. These systems also support health promotion activities (education) and could as well trigger new scientific health risks assessments. Table 1 gives an overview of cases of adverse effects with strong causality and severity involving a FS. More data are available in Appendix.

The Italian Phytovigilance System

The Phytovigilance System, coordinated by the Italian National Institute of Health, collects spontaneous reports of suspected adverse reactions to FSs and preparations containing plants (such as cannabis for medical use). The surveillance system was activated in 2002 as a research project and became in 2012 a national system to support the Ministry of Health in monitoring safety of products of its regulatory competence.

Anyone observing a suspected adverse reaction associated with the above-mentioned products can report the reaction. A website (www.vigierbe.it) is available for online reporting. The coordinating center conducts the initial check activities. If information is incomplete, the reporter is contacted for filling in, if available, the missing data. For serious reactions, requiring hospitalization, clinical data and follow up of the patients are retrieved. Causality assessment is performed with a method adapted from the WHO causality assessment scale. The method takes into account: (1) event, results from laboratory tests and chronological data; (2) dechallenge; (3) rechallenge; (4) known pharmacological elements; (5) cause to effect plausibility; (6) alternative explanations for the reaction; (7) presence of adulterants/contaminants if suspected. A reaction can be defined as "Certain," "Probable/likely," "Possible," "Unlikely," "Unclassifiable" according to the different criteria satisfied (The Uppsala Monitoring Centre 2020). When necessary, a scientific committee (composed of experts in pharmacology, toxicology, pharmacognosy, phytotherapy, and botany) is consulted.

As to some results, from 2002 up to June 2020, 1480 reports related to FSs were included in the database. In 41% of the reports, drugs, FSs or other products were used concurrently. In 30% of the reports (n = 446), serious reactions were reported (life threatening events, hospitalization, death).

Many case reports were published (Bianchi et al. 2004; Menniti-Ippolito et al. 2008; Vitalone et al. 2012; Vannacci et al. 2011; Mazzanti et al. 2017); most of them related to hepatoxicity associated with different plants (green tea, *Chelidonium majus* L., *Cimicifuga racemosa* L.) Nutt. (synonym of *Actaea racemose* L.), *Garcinia cambogia* (Gaertn.) Desr. (synonym of *Garcinia gummi-gutta* L. Roxb.) (Mazzanti et al. 2009; Moro et al. 2009; Vannacci et al. 2009; Lapi et al. 2010; Gori et al. 2011; Crescioli et al. 2018; Lombardi et al. 2021). Safety issues related to quality problems of FSs were pointed out after the chemical analyses of FSs containing undeclared plants, such as species of *Rauwolfia* (Gallo et al. 2012), or an excess dose of vitamin D (Benemei et al. 2013).

Between 2002 and 2020, 116 reports concerning 212 suspected adverse reactions to FSs containing alpha-lipoic acid (also referred as ALA) were collected within the Italian phytovigilance system (Gatti et al. 2021). The most frequently reported effects were related to skin and subcutaneous tissue disorders, gastrointestinal disorders, and general disorders and administration site conditions. Ten cases of Insulin autoimmune syndrome, also known as Hirata disease, were collected within this system, as compared to only five previous cases reported worldwide. It is a life-threatening adverse

reaction to ALA-containing FS, leading to severe hypoglycemia. Although Hirata disease is well-recognized in Japan, the diagnosis and imputability to ALA remain challenging in the Western world. Overall, in 45 (38.8%) of the Italian cases the report was classified as serious (Gatti et al. 2021).

One of the last risk signals emerged in 2019 from a cluster of 28 reports (from November 2018 to June 2019) related to hepatitis, mostly cholestatic, associated with turmeric (*Curcuma longa* L.) containing FSs. To identify the substances potentially responsible for the adverse reactions observed, the suspected products were collected and analyzed. The analyses focused on the search of accidental contaminants, residues, and adulterants. In particular, the following classes of substances were checked: non-steroidal anti-inflammatory drugs (e.g., nimesulide), narcotic or psychotropic substances, heavy metals, aflatoxins, pesticides, pyrrolizidine alkaloids, and synthetic dyes (Menniti-Ippolito et al. 2020).

All these articles illustrate an intense assessment activity of different safety issues emerged from the surveillance system. During the years, the Ministry of Health issued several regulatory actions based on signals emerging from the surveillance.

The French Nutrivigilance System

France created in 2009 a Nutrivigilance System in order to identify the possible adverse effects of FSs, fortified food and beverage (FFBs), food for special dietary needs and novel foods and to reinforce consumer safety (except quality defects such as microbial contamination which is otherwise subjected to control). This Nutrivigilance System, coordinated by the French Agency for Food, Environmental and Occupational Health and Safety (ANSES) is based on voluntary reports from healthcare professionals (medical doctors, pharmacists, dieticians, etc.), FSs producers and consumers (ANSES 2021). A website (www.nutrivigilance-anses.fr) is available for online reporting.

The reports are recorded and analyzed by ANSES to determine the severity of the incident (low severity; mild; serious; very serious; lethal), the product's composition, the concordance with previous notifications, and so on. For each report, ANSES may contact the reporter again to try to obtain any missing information if necessary. Between 2009 and 2019, this Nutrivigilance System has registered 5355 reports of adverse effects, 4863 (91%) of which involved at least one FS (ANSES 2020).

Reports containing sufficient information are then submitted to a group of experts (composed of medical doctors), who analyze the likelihood of a link between consumption of the product and the adverse effect (causality assessment). In 2019, among the 1054 reports received, 454 (43%) were sufficiently documented to be analyzed (ANSES 2020). The method for assessing causality in Nutrivigilance was developed specifically by ANSES (ANSES 2019b). The causality takes into account chronological and etiological data (including possible interactions with other substances, in particular drugs). This score may be: excluded (I0), unlikely (I1), possible (I2), likely (I3), or very likely (I4). In 2019, the imputability was likely or very likely for 45% of reports and the severity was high (up to life-threatening or death) for 8.7% of reports (ANSES 2020).

ANSES may be required to initiate an alert procedure in case of a life-threatening case in which causality is strong (21 cases in 2019 (ANSES 2020)). This alert procedure allows a rapid action by the Ministry of Consumer Affairs in charge of the implementation of management measures.

The centralization of all FSs adverse effects reports in a dedicated Nutrivigilance System, allows ANSES to have a complete view of the adverse effects related to these products, to identify the related hazards to specific substances or products and perform appropriate risk assessment. These risk assessments, in the form of scientific opinions, are used for the governmental risk management. Additionally, these scientific opinions include recommendations that are published intended for healthcare professionals and consumers.

In this context, since 2009, ANSES has published on its website (www.anses.fr) sixteen opinions on a wide range of products monitored by Nutrivigilance, especially related to the risks associated with the consumption of certain components present in FSs (ANSES 2014a, 2014b, 2016, 2017a, 2017b, 2018, 2019a). These opinions highlight health risks for the general population or subgroups of the population, or under certain conditions of use and helps the risk manager to implement appropriate management measures. For instance, following the opinion on *p*-synephrine (ANSES 2014a), restrictions have been added in the French regulation setting out the list of plants authorized in FSs (French Ministry of the Economy and Productive Redress and the Digital Economy 2014). Taking into account the outcome of the opinion, these restrictions specify that for *Citrus aurantium* L. "Ingested *p*-synephrine should be less than 20 mg per recommended daily dose. Labeling must include a warning against use by children, pregnant or breastfeeding women and in case of antihypertensive treatment. Caffeine and caffeine sources are not allowed in FSs containing *Citrus aurantium* L."

The Danish Nutrivigilance System

The Danish Nutrivigilance System on FSs is a voluntary system established in December 2013 by the Danish Veterinary and Food Administration (DVFA), an agency under the Ministry of Food, Agriculture and Fisheries. Previously adverse events related to FSs were also reported, but the present system is specifically dedicated to FSs. From 2014 to 2020 DVFA received in total 73 reports (6–16 per year) on FSs suspected of having caused adverse effects. Thirty-tree reports concerned FSs with vitamins and minerals, 17 botanical ingredients, 16 vitamins, minerals, and botanicals, 4 vitamins, minerals, and certain other substances, 2 certain other substances, and 1 lactic acid bacteria. Physicians, consumers, or their relatives experiencing an adverse effect suspected caused by a FS may report it by filling in a form on the website of DVFA (https://www.foedevarestyrelsen.dk/Sider/forside.aspx). The filled in form contains contact

information, age, sex, weight, and height of the person experiencing the effect together with information on affliction by other illnesses, including allergies. The filled in form also collects information on the used FS (e.g., name, batch number), the daily intake, including an eventual exceeding of the intake recommended by the manufacturer, duration of intake, and concomitant intake of other FSs or medicines. Other information to fill in is description of the symptoms, results from clinical tests, and symptoms after cessation of intake and/or rechallenge. The vendor of a FS suspected of causing an adverse effect is contacted for collection of possible further adverse effects on the FS reported directly to the company. If considered necessary by DVFA, the collected information on the adverse effect and the ingredient list are sent to experts from the National Food Institute, Technical University of Denmark, for further assessment on causality, studying of which ingredients, that may have caused the effect by comparing with data published in scientific papers, toxicological data on individual ingredients, and so on.

Some risk assessments (in Danish) performed by the National Food Institute on substances or ingredients in FSs are published on the website of DVFA, for example, on DMAA, *Citrus aurantium* L. (synephrine), *Huperzia serrata* (Thunb.) Trevis., *Hypericum perforatum* L., *Polygonum multiflorum* Thunb., and *Tribulus terrestris* L. Other information found on this site is on the prohibited botanicals *Ephedra* spp. and yohimbe bark. Based on the reported adverse effects or risk assessments of certain ingredients, some papers or abstracts have been published, for example, on raspberry ketone (Bredsdorff et al. 2015), huperzine A (Bredsdorff and Pilegaard 2018), and on food supplements causing hepatotoxicity (Pilegaard 2011).

DVFA may take further actions dependent on the outcome of the causality assessment, the severity of effects, if more reports exist on adverse effects for the same FS, and/or identification of unsafe ingredients in the FS. Actions may be withdrawal of the FS, warnings to the Danish public, reports to RASFF, contacting countries where the FS is marketed via the Internet directly to consumers by homepages written in Danish, and/or what measures DVFA considers necessary.

The Portuguese Nutrivigilance system

The Portuguese System of notifications of adverse effects was implemented in 2014 under a voluntary approach by the Portuguese Competent Authority—Directorate General for Food and Veterinary (DGAV), in the Ministry of Agriculture. The form for the notification of adverse reactions is available on DGAV website: http://srvbamid.dgv.min-agricultura.pt/portal/page/portal/DGV/genericos?generico=10128953&cboui=10128953

From 2014 to mid-2020, DGAV received 136 notifications, however, only 23 cases with a causality were tracked as listed in Appendix from which 7 cases had "very serious" adverse effects which required a clinical evaluation to validate a cause-effect relationship. The symptoms were hepatotoxicity, severe renal failure, severe thrombocytopenia, anaphylactic shock, and hives in a baby.

The notifications were made by the food company operators (59%), pharmacists (28%), medical doctors/hospitals (5%), and consumers (7%). Most of the adverse effects were reported in women, 73% and 27% in men. One concerned a 4-month-old baby.

For many of the reported adverse effects (stomach pains and diarrhea, headaches, sleep disturbances and nightmares, arrhythmias, hypotension, weakness, itching, edema, rashes among others), a cause-effect relationship could not be determined. All of them were described as related to the intake of FSs according to the notification form. In the notification of adverse effects, reported non-conformities related to the lack of effectiveness (25) of the products were also included.

The Czech Nutrivigilance System

The Czech Nutrivigilance System, administered by the National Institute of Public Health – Center for Health, Nutrition and Food, was launched in the beginning of 2015.

Health professionals (27% of all cases reported) and the general public (73%) can, on a voluntary initiative, report adverse effects (except foodborne infectious diseases) of selected foods, especially those with not sufficiently known history of safe use (FSs, novel foods, etc.). A website (nutrivigilance.szu.cz) is available for online reporting.

From 2015 to 2020, the Czech Nutrivigilance System registered 111 reports of adverse effects, 37 (33%) of them were FSs. Most of the adverse effects affected women (56%). In 67% of all cases, the adverse effects concerned the gastrointestinal tract (nausea, abdominal pain, vomiting, abdominal cramps, diarrhea, constipation, bloating, heartburn, etc.). The second group of adverse effects that have been reported were skin reactions and allergic manifestations (rash, itching, burning of the skin, pimples, swelling, etc.), which were recorded in 11% of cases. The third most frequently reported group of symptoms (8%) was neuro/neuropsychological disorders. It was, for example, a drop in mood, or, conversely, excitation, nervousness, aggression, and so on. The remaining reports were symptoms in the area of the cardiovascular system (increased heart rate, higher blood pressure), insomnia, musculoskeletal pain, and so on.

The reports are collected and when necessary, the reporter is contacted to add missing information. The reports are analyzed in order to assess causality between the consumption of the product and the adverse effect. The causality assessment is based on six criteria used for the calculation of chronological score and a semiological (symptomatic) score. The level of causality is determined by a decision table containing the combinations of individual scores. The method offers five levels of causality assessment: very likely, likely, not clearly attributable, unlikely, and excluded.

If the causality is assessed as strong ("very likely" or "likely") and if the FS could endanger the health of

consumers, the report is forwarded to public health authorities (Ministry of Health; Regional Public Health Authorities) or to the control authorities for food (Czech Agriculture and Food Inspection Authority; State Veterinary Administration). These authorities can implement preventive and corrective measures to ensure safety for consumer health. A strong causality was determined in 23% of all reported cases (in case of FSs, the strong causality was determined in 40% of them) and no specific nationwide measure has been implemented yet. However, following reports, short news are published on the website (www.szu.cz) to inform consumers of the means to prevent adverse effects of foods, or FSs. For instance, news were published following reports of adverse effects after consumption of FSs with magnesium and vitamin B6; or with *Chlorella vulgaris*, *Chlorella pyrenoidosa* and *Spirulina*.

The Slovenian Nutrivigilance System

Slovenia established a Nutrivigilance System coordinated by the National Institute of Public Health Slovenia (NIJZ) in February 2016.

Nutrivigilance in Slovenia is using a voluntary approach of reporting adverse events (except foodborne infectious diseases) concerning foods (in particular: FSs, FFBs, foods for special dietary needs, and novel foods) or food ingredients. Reporting is open to all stakeholders who are aware of an adverse event (consumers, producers, pharmacists, medical doctors, other vigilance systems). A website (www.nijz.si/sl/nutrivigilanca) is available for online reporting.

These reports are analyzed by a group of experts from the NIJZ. Moreover, the NIJZ coordinates a Nutrivigilance network in Slovenia, which consists of national competent authorities and stakeholders (Ministry of Health, Health Inspectorate, Agency for Medicinal Products and Medical Devices, The Administration for Food Safety, Veterinary and Plant Protection, the Poison Control Center and the National Laboratory for Health, Environment and Food). Representatives from these institutions may be asked for advice or act as external experts if needed.

From 2016 to 2019, 113 reports were received, 38 (34%) of them were verified and submitted to the Expert Group. The severity of the adverse events is classified as mild (any change in well-being without clinical signs), serious (clinical signs or symptoms), and very serious (life-threatening conditions). Moreover, the possible association between the ingested food and the adverse events, are divided into very likely (if similar events already exist in the Nutrivigilance report database and/or are described in the scientific literature), likely (if similar cases exist in the scientific literature and the correlation can be physiologically explained to some extent), and less likely (no biological or physiological links between the ingredient and the reported effects).

Ninety-five percent of cases were related to the consumption of FSs, including FSs containing illegal ingredients such as cannabidiol (CBD) and colloidal silver, and only 5% to common foods (herbal tea for instance). Women (from 3 to 85 years of age) were more often associated with reported cases in Nutrivigilance (76% of FSs cases). The most frequently reported effects were hepatotoxicity, allergic reaction, disturbed heart function, abdominal pain, and fibromyalgia. The products were consumed for weight management, general health benefits, special conditions (pregnancy, infertility), blood cholesterol control, special dietary needs (sports nutrition, recovery from illness), joint pain, strengthening the immune system. The reports were received from consumers, hospital pharmacists, pharmacists, the national pharmacovigilance system, and medical doctors.

Between 2016 and 2019, eight events were considered very serious and 16 cases were classified as very likely.

Since 2016, NIJZ has published on its website opinions or warnings related to the risks associated with the consumption of certain foods, components present in FSs (as *Aloe vera* (L.) Burm. f., *Spirulina*, *Polygonum multiflorum* Thunb., *Glycyrrhiza glabra* L., Miracle mineral-MMS (solution of sodium chlorite "activated" with an acid), colloidal silver, high levels of vitamins etc.), or types of FSs (FSs for losing weight). These opinions are used by public health authorities to implement appropriate risk management measures. For instance, following the report of presence of octopamine and related unauthorized ingredients (vinpocetine, higenamine) in FS for sports, the Health Inspectorate has recently requested the withdrawal of them from the Slovenian market. In the first half of 2018, the Financial Administration of the Republic of Slovenia asked the Nutrivigilance network for cooperation due to information on the discovery of postal items containing the plant kratom (*Mitragyna speciosa* (Korth.) Havil.). At the request of the Ministry of Health, a rapid risk assessment was prepared, due to the public health risk, the substance was placed on the national list of illicit drugs and the products were withdrawn from the market.

The Croatian Nutrivigilance System

Until 2020, there was no targeted Nutrivigilance System in the Republic of Croatia that would collect data exclusively related to adverse effects on FSs. Adverse effects caused by FSs have been collected within the Pharmacovigilance System managed by The Croatian Agency for Medicinal Products and Medical Devices (HALMED).

In October 2020, the Nutrivigilance System was launched and managed by the Croatian Institute of Public Health (CIPH), at the Department of Food Supplements and Biologically Active Substances.

The main goal of the Nutrivigilance System is to prevent the risk of adverse effects after the use of FSs with regard to active ingredients, to report and compare national data with data reported to the RASFF, to monitor the safety of FSs and to improve consumer safety.

The Croatian Nutrivigilance System is based on voluntary reports from healthcare professionals (medical doctors, pharmacists, dieticians, etc.), FS manufacturers, and consumers.

CIPH will publish all data through the website (www.hzjz.hr/nutrivigilancija), newsletter, media, and so on, and

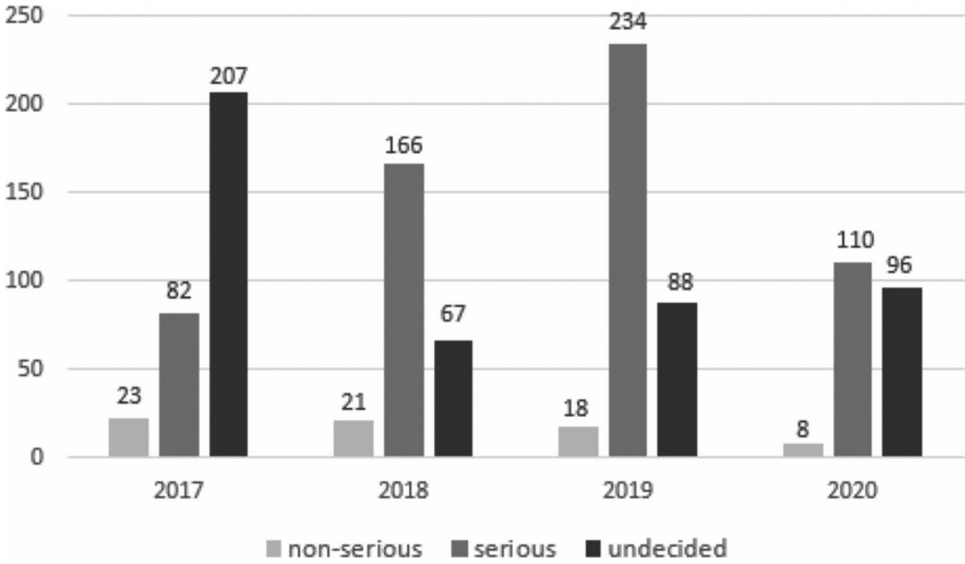

Figure 1. Total RASFF notifications in the category of "dietetic foods, FSs and fortified foods" from 2017 to 2020 (European Commission 2021c).

will provide education and implementation of public health measures in this area.

Existing European systems for reporting on FSs safety

It is evident that in most EU MS, no specific registration of adverse effects of FSs exist. In countries with dedicated Nutrivigilance Systems, there is no harmonization of the collection and the analysis of the data, which does not allow an easy cooperation and exchange between these countries. Albeit these limitations, there are interactive networks and dedicated platforms for exchange of information on safety of food, including FSs.

Rapid alert system for food and feed (RASFF)

To help ensure food safety, the European Union has since 1979 run the RASFF (European Commission 2021b). RASFF is a tool enabling the quick and effective exchange of information between EU MS and the EC when risks to human and animal health are detected in the food and feed chain. In recent years, the number of RASFF notifications in the category of "dietetic foods, FSs and fortified foods," related to unauthorized ingredients, has increased significantly, from 25 in 2003 to almost 200 in 2016 and almost 350 in 2019. An unauthorized ingredient means an ingredient that is not authorized, but also not prohibited. However, Czepielewska et al. (2018) stated that "between 2003 and 2016, there were only 13 RASFF notifications of adverse reactions related to 'dietetic foods, FSs and fortified foods' which indicates that RASFF is not entirely suitable for reporting FS adverse effects."

Interestingly, within the period from 2017 to 2020 (European Commission 2021c), there was a decrease in the number of RASFF notifications in the category of "dietetic foods, FSs and fortified foods," related to unauthorized composition, namely due to unauthorized substances and ingredients, unauthorized novel foods or high content of ingredients (vitamins, minerals/metals and other substances). Particularly, 306 notifications in 2017, 243 in 2018, 250 in 2019, and 214 in 2020. No adverse reactions are reported as such.

Since 2018, alerts on unsafe ingredients can also be found. The term "Unsafe ingredient" is used when the safety of the ingredient is not proven, mostly for lack of information, but also when, even if studies are available, safety is still not sufficiently proved. A prohibited ingredient means that there is a prohibition on the usage of this ingredient, for which a good example is *Yohimbe* extract or *Ephedra*.

In 2020, one alert related to the unsafe ingredient *Ptychopetalum* spp. in FSs from the Netherlands, Germany, France, and Austria (raised by Belgium) and another related to unsafe ingredient blue skullcap (*Scutellaria lateriflora* L.) in FS from the United States (raised by Spain). Also in 2019, two alerts related to unsafe ingredients: Hawaiian baby woodrose (*Argyreia nervosa* (Burm.f.) Bojer) in FSs from the Netherlands (raised by Germany), and holy basil (*Ocimum tenuiflorum* L. synonym *O. sanctum* L.) in FSs from the United Kingdom (raised by Denmark), as well as one case in 2018 related to the unsafe ingredient holy basil (*Ocimum sanctum*) in multi-vitamin FS from the United States, via the Netherlands (raised by Denmark).

A general picture of RASFF notifications in the category of "dietetic foods, FSs and fortified foods" is summarized, concerning the classification as not serious, serious, or undecided (Figure 1) and the subject (Figure 2).

Worthy of note, the concepts of unauthorized ingredient versus unauthorized substance: an ingredient is part of the product and may contain a mixture of substances (e.g., an extract of bark from yohimbe), while a substance is a chemical compound (like yohimbine) that can be found due to contamination, adulteration or for technical purposes. The most common unauthorized substances and ingredients reported in RASFF notifications between 2017 and the middle of 2020 are: DMAA; sildenafil and its analogues;

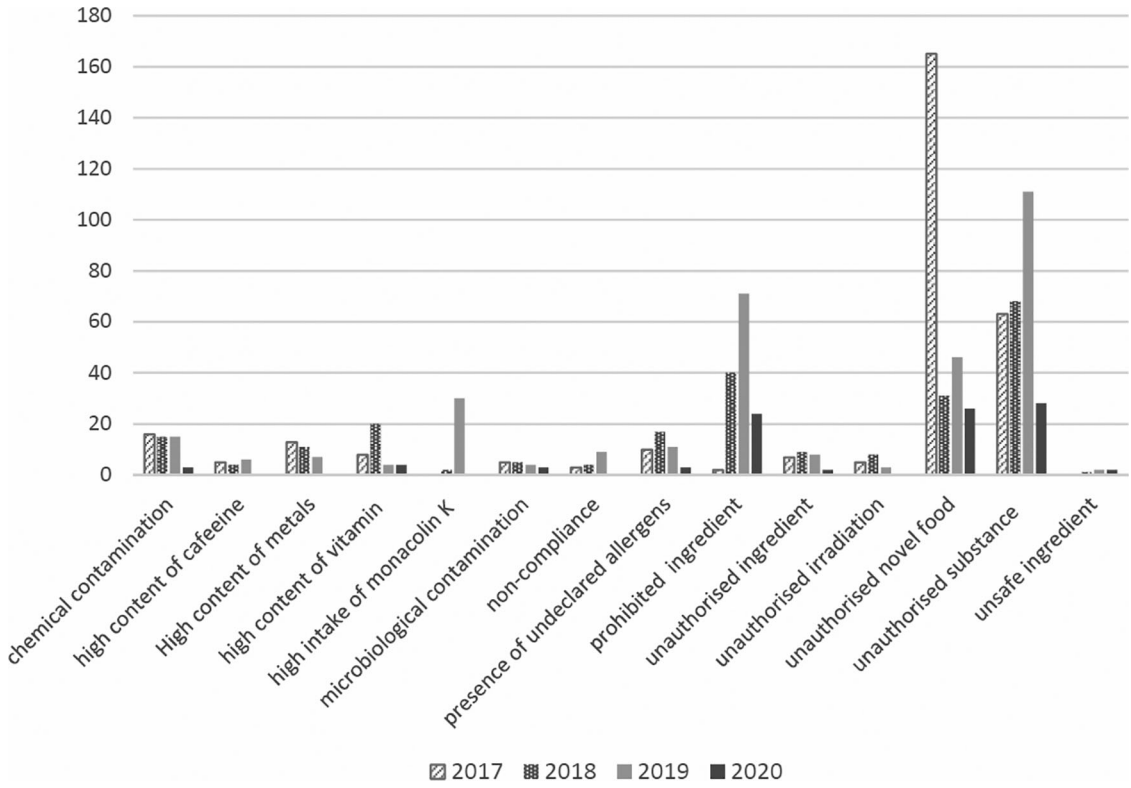

Figure 2. RASFF notifications from 2017 to 2020 in the category of "dietetic foods, FSs and fortified foods" according to the subject (European Commission 2021c). Besides the notifications reported in the table, subjects with less than five notifications are listed here: high content of nicotinic acid; high content of sorbic acid; high content of aloin; high content of hydroxy-citric acid; high content of iodine; high content of curcumin; and high intake of piperine.

tetrahydrocannabinol (THC); and yohimbine; represented more than 50% of all the unauthorized substances detected (Figure 3).

In 2017, *Ephedra*, a prohibited substance, was notified in a FS from unknown origin and in the first half of 2020, three notifications of another prohibited ingredient—Yohimbe bark extract, were also found in FSs from USA, UK, and the Netherlands.

Emerging risks exchange network

Established in 2010, the Emerging Risks Exchange Network (EREN) is an important part of a multifaceted emerging risk identification system operated by EFSA, providing a formal link with EU MS governments for cooperation on emerging risk identification in line with article 22(7) and 22(9) of the General Food Law (European Parliament and the Council of the European Union 2002b). According to the definition adopted by the Scientific Committee of EFSA in 2007, "an emerging risk to human, animal and/or plant health is understood as a risk resulting from a newly identified hazard to which a significant exposure may occur or from an unexpected new or increased significant exposure and/or susceptibility to a known hazard" (EFSA 2007).

An "emerging issue" can be defined as a food or feed safety risk that has very recently been identified and merits further investigation, and for which the information collected is still too limited to be able to assess whether it meets the requirements of an emerging risk. Thus, emerging issues are identified at the beginning of the emerging risks identification process as subjects that deserve further investigation and additional data collection. Emerging issues can include specific issues (e.g., a specific chemical substance or pathogen, or a specific susceptible group of the population), as well as general issues, called drivers (e.g., climate change), that could result in emerging risks (EFSA 2012).

The emerging risks identification process foresees that the EREN, as well as the Stakeholder Consultative Group on Emerging Risks (StaCG-ER), have three roles. Firstly, to raise new issues to the attention of EFSA and all participants in its emerging risks identification process. Secondly, to act as a pool of knowledge for emerging issues that EFSA brings to their attention and for which EFSA seeks more information, and thirdly, to provide expert consultation on whether an emerging issue merits further follow up. Following an exchange of information between the two groups and EFSA staff, the next step of the process is that these emerging issues are discussed at the Standing Working Group on Emerging Risks (SWG) that is composed of members of the EFSA scientific Panels and Scientific Committee. The SWG takes into consideration all the available information and recommends follow up actions for endorsement by the Scientific Committee (Costa et al. 2017; EFSA 2014).

EREN publishes annual activities reports. The last published report summarizes the EFSA's activities on emerging risks in 2019 (EFSA 2020b). In total, 17 potential emerging issues (all topics combined) were evaluated in 2019. Each issue was presented in the form of a standard briefing note and given a unique identifier (ID N°). When information

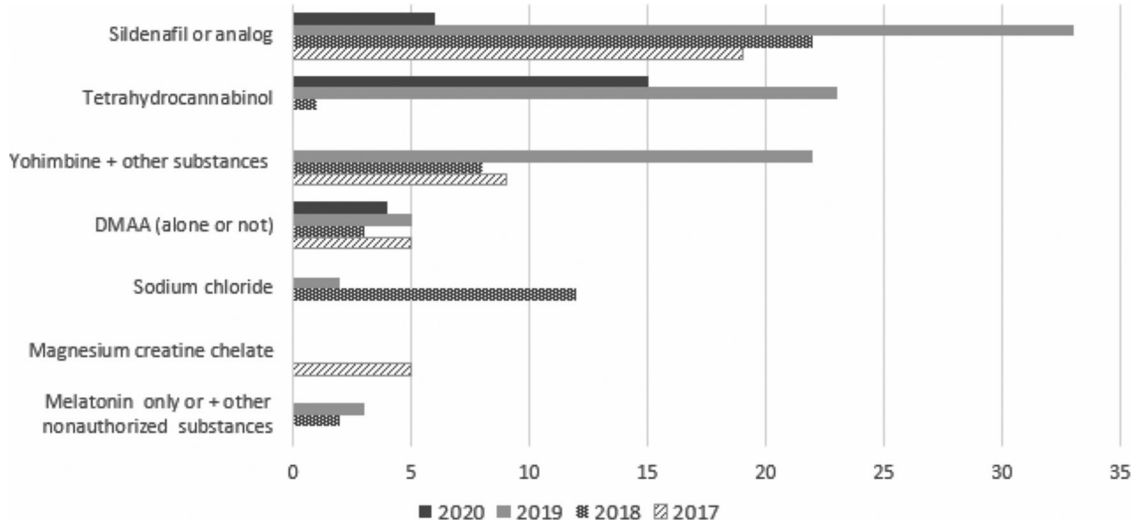

Figure 3. Most common unauthorized or prohibited substances and ingredients reported in RASFF notifications between 2017 and 2020. The presence of the following substances (with less than five notifications) were reported: 2-amino-6-methylheptane, 5-hydroxytryptophan, alpha-glyceryl phosphoryl choline, alpha-lipoic acid, arginine nitrate, beta-alanine and 2-hydroxyisocaproic acid, chlorate, D-glucosamine, dimethylethanolamine, E 127—erythrosine, evodiamine, *Hydrastis canadensis, Turnera diffusa*, isopropyloctopamine, lotus leaf extract (*Nelumbo nucifera*) and *Amaranthus cruentus*, magnesium amino acid chelate, N-acetylcysteine, sibutramine or analogue, synephrine, vanadyl sulfate + other substances, vinpocetine (substances with only one notification are not listed).

was available, the issues were classified according to six categories by hazard (the number of issues is shown in brackets) [microbiological hazard (9), chemical hazard (5), other (e.g., antimicrobial resistance and allergies) (2)] or driver identified [illegal activity , new consumer trends (6); new process or technology (2); climate change related, other]. The issues were assessed against a set of predefined criteria: new hazard; new or increased exposure; new susceptible group; and new driver. The criteria are based on the EFSA definition of emerging risk and emerging issue and have been described in detail in a previous report (EFSA 2012). Among the seventeen potential emerging issues evaluated in 2019, thirteen were considered as emerging issues [two of which concern FSs: (ID0409) Canabidiol and Canabidiol-containing products and (ID0412) Hepatoxicity associated with food supplements containing Turmeric] and four were not considered to be emerging issues or information was not available to reach a conclusion (EFSA 2020b). Between 2016 and 2019 eight potentials issues concerning food supplements were evaluated at EREN, six of them were considered as emerging issues (Table 2) (EFSA 2017, 2018b, 2019, EFSA 2020b).

In addition, 28 issues resulting from EU MS own horizon scanning activities were presented to EREN in 2019. These issues are brought forward for discussion as weak signals with the aim to collect further information from EREN experts and networks. In 2019 only one issue out of 28 presented was related to FSs : M0084 "Vitamin C supplements intake and increased risk of kidney stones" (EFSA 2020 b). In 2018, three issues were related to food supplements: "M0057 Chondroitin sulfate supplements linked to skin cancer growth"; M0058 "Certain iron supplements may influence the development of colon cancer"; M0082 "Experts issue warning over health supplements containing higenamine" (EFSA. 2019). But so far the outcome of the discussions of these four weak signals has not been published.

European Nutrivigilance network

In 2014, in order to bring the existing schemes together and raise awareness among other countries, France initiated exchanges with 13 EU MS. These contacts highlighted the interest for such a scheme and the need for harmonization and cooperation. Nowadays 27 European countries plus Brazil are involved in the Nutrivigilance network. Since 2014, the countries have continued their efforts by creating a jointly compiled newsletter. Due to lack of funding, no other meeting has taken place. Such network allows the exchange of information on Nutrivigilance and demonstrates that it is an important topic since almost all European countries expressed their interest in the subject and are members of the network.

The need for a European Nutrivigilance System

Even though RASFF collects data on occurrence of unsafe foods, including FSs or warn about finding of unauthorized constituents in foods, including FSs, RASFF is not dedicated to collection of adverse events in a harmonized manner in a single country or finding clusters of adverse effects more or less simultaneously in more countries. Mostly, RASFF will first be alerted when risk management has been performed.

Harmonized vigilance systems exist for some products as drugs with the EU pharmacovigilance system. Indeed, pharmacovigilance has successfully been developed and regulated in Europe (European Parliament and the Council of the European Union 2001, 2004, 2010a, 2010b, 2012a, 2012b) with a harmonized system for drug side effects coordinated by the EMA (European Medicines Agency) (EMA 2019). The collection and validation of reported drug side effects are decentralized at EU MS levels while risk assessments and decisions are made at EU level. The European harmonization of a pharmacovigilance system allows to streamline the

Table 2. Potential issues on FSs evaluated at EREN between 2016 and 2019 presented by Identifier Number (ID) (EFSA. 2017, 2018b, 2019, 2020b).

Year	Potential emerging risks	EREN conclusion / EREN recommendations /EFSA follow-up
2019	(ID0409) Canabidiol and Canabidiol-containing products	EREN conclusion: emerging issue EREN recommendations: EFSA to proceed to a risk assessment of CBD
2019	(ID0412) Hepatoxicity associated with food supplements containing Turmeric	EREN conclusion: emerging issue EREN recommendations: EFSA/BVL (German Federal Office of Consumer Protection and Food Safety) to consider a presentation for the 2020 workshop on Super foods in Berlin on emerging risks in FSs
2018	(ID0397) Anaphylaxis observed after consumption of FSs with royal jelly.	EREN conclusion: not an emerging issue EREN recommendations: To contact DG SANTE RASFF team and enquire if this kind of information would fall within the remit of RASFF notification system
2017	(ID 368) Risk associated with the use of black cohosh in FSs and tea	EREN conclusion: emerging issue EREN recommendations: 1. The evidence on hepatotoxicity is controversial. A systematic literature review of black cohosh possible health risks is recommended 2. A mapping exercise on the FS market authorization process at national level is necessary to identify possible emerging risks
2016	(ID 364) Adulterated food supplements on sale via internet	EREN conclusion: not an emerging issue Risk management issue and not part of EFSA remit on provision of risk assessment
2016	(ID 363) Piperine as an ingredient in FSs in the Portuguese market	EREN conclusion: emerging issue EREN recommendations: 1. EFSA should map the activities linked to FSs across the Member States. 2. EFSA should provide criteria to EREN on which FSs issues to focus in the future EFSA follow-up: Safety and efficacy of pyridine and pyrrole derivatives belonging to chemical group 28 when used as flavorings for all animal species (EFSA. 2016)
2016	(ID 362) Risks associated with the use of diosmin and hesperidin.	EREN conclusion: emerging issue EREN recommendations: 1. EREN members should continue to share their data from their national pharmacovigilance and national Nutrivigilance. 2 EFSA should consult EC for an update on the status of the relevant legislations. 3. EFSA should provide an update to EREN on its activities linked to botanicals. 4. EFSA should collaborate with Member States and EMA to develop a joint database to support risk assessment of FSs
2016	(ID 353) Risks associated with the use of green tea extracts in FSs	EREN conclusion: emerging issue EREN recommendations: 1. EREN should share data from their national intoxication centers linked to green tea extract. 2. EFSA should perform a survey on the content of green tea extracts sold in FSs via internet. EFSA follow-up: Scientific opinion on the safety of green tea catechin (EFSA ANS Panel 2018) Risks for human health related to the presence of pyrrolizidine alkaloids in honey, tea, herbal, infusions and FSs (EFSA CONTAM Panel 2017)

EU decision-making process on drug safety issues and to ensure the application of the measures to all medicines and to all EU MS.

Most EU MS register FSs adverse effects through an undedicated vigilance system or not at all. As described in the paper only six EU countries have created dedicated Nutrivigilance Systems for FSs and these systems face with an under-reporting-phenomenon. Nevertheless, if more than 1,000 reports of adverse effects related to FSs are received per year in France (67 million inhabitants) (ANSES 2020); it could be six time more at EU population scale (448 million inhabitants). The collection of adverse effects of FSs is an essential part of discovering unsafe FSs or ingredients in them to ensure public health safety. Pooling all these reports could allow to increase the reports number, to enhance the probability to detect a health risk earlier and to strengthen health risk assessments with more data on experienced adverse effects. Moreover, it could perhaps even reduce the duplication of risk assessments in different European countries. This should be facilitated by a common and centralized database. For instance, before finalizing each risk assessment, the French Agency for Food (ANSES) approached its European counterparts by means of EFSA Focal Points (EFSA 2020a) asking for national data on adverse effects likely to be associated with the consumption of the FS or ingredient assessed. For each application, several countries sent reports of adverse effects to ANSES. For example, following the analysis of 23 reports of adverse effects likely to be associated with the consumption of FSs containing glucosamine and/or chondroitin sulfate received between 2009 and 2018, ANSES issued a request with a view to identifying the potential health risks of these FSs (ANSES 2019a). Due to the solicitation of EFSA Focal Points, Germany sent 11 cases reported between 2003 and 2016 and Italy sent 17 cases reported between 2002 and 2016. If these cases had been pooled in one centralized database, the risks of these FSs could have been identified earlier.

Similarly, the more reports there are, the greater is the chance of identifying an adulterated or unsafe product meaning that this product can be withdrawn from the market earlier.

Moreover, such a system would also be a benefit to the FS industry since the more regulations diverge the more difficult it is for a manufacturer wishing to market its product in several EU MS to comply with the regulations. Harmonization of requirements in terms of Nutrivigilance would direct benefit the industry by increasing the safety of FSs marketed in EU and thereby consumer trust in the products.

Additionally, it will help the promotion of research cooperation and technology transfer in the field of chemical food analysis to unify definition of chemical and botanical analytical issues related to adverse effects analysis and prevention.

Furthermore, FSs produced in the USA as in all other countries worldwide are now accessible with a click. A robust framework for Nutrivigilance may therefore in future involve not only EC/European Parliament and EU MS authorities but also collaboration with, for example, US as well as competent authorities throughout all third countries.

Such a worldwide collaboration would strengthen the possibility of identifying potential safety concerns with FSs.

Conclusion

According to the European food regulation, it is the responsibility of the manufacturer to ascertain that a product is safe. Proving that a food is unsafe for the consumer falls within the competence of authorities (European Parliament and the Council of the European Union 2002b). Depending on the country, the main ingredients or substances found in FSs may be different. Some FSs or ingredients within them are known to induce adverse effects as, for example, observed in the adverse effects reported to the national Nutrivigilance Systems and RASFF. An ingredient found acceptable in one European country may even be forbidden in another. Despite this, FSs with these ingredients may be available all across Europe owing to the free cross-border movement or at the internet.

Thus, we advocate for creation of a coordinated Nutrivigilance System allowing for: (1) early identification of some emerging risks in the field of FSs, (2) harmonization of the collection and analysis of adverse effects related to components of FSs to have a common understanding and to facilitate exchanges of information, and (3) help decision makers to implement management measures when needed (regulation, usage restrictions, market withdrawal, etc.) and to set/adjust legal requirements at the European or country levels.

Over time, this approach is foreseen to lead to enhanced product safety for FSs and to result in better protection of public health.

Acknowledgments

The authors thank their respective colleagues in their Member State for fruitful exchanges of information within EFSA focal points. Also, since the part of the data reported in this paper was provided either by national authorities and by the EFSA reports, within the auspices of EU MS and the EU budget, the authors would like to thank all colleagues ensuring that the food safety authorities and agencies function effectively and efficiently, deliver their mandates as defined in the founding Regulations and work together to meet the expectations of European and national institutions, stakeholders and the public.

Disclosure statement

The authors are not aware of any affiliations, memberships, funding, or financial holdings that may be perceived as affecting the objectivity of this review.

Abbreviations

ALA	Alpha-lipoic acid
ANSES	French Agency for Food, Environmental and Occupational Health and Safety
CBD	Cannabidiol
DMAA	1,3-dimethylamylamine
DGAV	Portuguese Directorate-General for Food and Veterinary
DVFA	Danish Veterinary and Food Administration
EFSA	European Food Safety Authority
EMA	European Medicines Agency
EREN	Emerging Risks European Network
EC	European Commission
EU	European Union
EU MS	European Union Member States
FS	Food Supplement
FFB	Fortified Food and Beverage
NIJZ	National Institute of Public Health Slovenia
RASFF	Rapid Alert System for Food and Feed
SWG	Standing Working Group on Emerging Risks.

References

Abdullah, R., L. N. Diaz, S. Wesseling, and I. M. C. M. Rietjens. 2017. Risk assessment of plant food supplements and other herbal products containing aristolochic acids using the margin of exposure (MOE) approach. *Food Additives and Contaminants - Part A Chemistry. Analysis, Control, Exposure and Risk Assessment* 34 (2):135–44.

Amadi, C. N., and A. A. Mgbahurike. 2018. Selected food/herb-drug interactions: Mechanisms and clinical relevance. *American Journal of Therapeutics* 25 (4):e423–e433. doi: 10.1097/MJT.0000000000000705.

Amster, E., A. Tiwary, and M. B. Schenker. 2007. Case report: Potential arsenic toxicosis secondary to herbal kelp supplement. *Environmental Health Perspectives* 115 (4):606–8. doi: 10.1289/ehp.9495.

ANSES. 2014a. *Risks associated with the presence in food supplements of p-synephrine or ingredients obtained from Citrus spp. fruits containing this substance. Opinion of the French Agency for Food, Environmental and Occupational Health & Safety. French Agency for Food*. Maisons-Alfort: Environmental and Occupational Health & Safety.

ANSES. 2014b. *Risks associated with the presence of red yeast rice in food supplements. Opinion of the French Agency for Food, Environmental and Occupational Health & Safety. French Agency for Food*. Maisons-Alfort: Environmental and Occupational Health & Safety.

ANSES. 2016. *Risks associated with the consumption of food supplements for athletes seeking to develop muscle or reduce body fat. Opinion of the French Agency for Food, Environmental and Occupational Health & Safety. French Agency for Food*. Maisons-Alfort: Environmental and Occupational Health & Safety.

ANSES. 2017a. *Endocrine and metabolic risks related to the intake during pregnancy of vitamin D and iodine through food supplements involved in cases of nutrivigilance. Opinion of the French Agency for Food, Environmental and Occupational Health & Safety. French Agency for Food*. Maisons-Alfort: Environmental and Occupational Health & Safety.

ANSES. 2017b. *Risks associated with the consumption of food supplements containing spirulina. Opinion of the French Agency for Food, Environmental and Occupational Health & Safety. French Agency for Food*. Maisons-Alfort: Environmental and Occupational Health & Safety.

ANSES. 2017c. *The third individual and national survey on food consumption (INCA3 survey). Opinion of the French Agency for Food, Environmental and Occupational Health & Safety. French Agency for Food*. Maisons-Alfort: Environmental and Occupational Health & Safety.

ANSES. 2018. *Risks associated with the consumption of food supplements containing melatonin. Opinion of the French Agency for Food, Environmental and Occupational Health & Safety. French Agency for Food*. Maisons-Alfort: Environmental and Occupational Health & Safety.

ANSES. 2019a. *Risks associated with the consumption of food supplements for joint conditions containing glucosamine and/or chondroitin sulphate. Opinion of the French Agency for Food, Environmental and Occupational Health & Safety. French Agency for Food.*

ANSES. 2019b. *Updating the method for determining causality in reports of adverse effects in nutrivigilance. Opinion of the French Agency for Food, Environmental and Occupational Health & Safety*. Maisons-Alfort: Environmental and Occupational Health & Safety.

ANSES. 2020. *National nutrivigilance scheme review in 2019*. Maisons-Alfort: Environmental and Occupational Health & Safety.

ANSES. 2021. Everything you need to know about the nutrivigilance scheme. Accessed February 9. https://www.anses.fr/en/content/everything-you-need-know-about-nutrivigilance-scheme.

Asher, G. N., A. H. Corbett, and R. L. Hawke. 2017. Common herbal dietary supplement-drug interactions. *American Family Physician* 96 (2):101–7.

Benemei, S., E. Gallo, E. Giocaliere, G. Bartolucci, F. Menniti-Ippolito, F. Firenzuoli, A. Mugelli, and A. Vannacci. 2013. It's time for new rules on vitamin D food supplements. *British Journal of Clinical Pharmacology* 76 (5):825–6. doi: 10.1111/bcp.12134.

Bianchi, A., P. Cantù, F. Firenzuoli, G. Mazzanti, F. Menniti-Ippolito, and R. Raschetti. 2004. Rhabdomyolysis caused by *Commiphora mukul*, a natural lipid-lowering agent. *Annals of Pharmacotherapy* 38 (7-8):1222–5. doi: 10.1345/aph.1D486.

Bilia, A. R., and M. d C Costa. 2021. Medicinal plants and their preparations in the European market: Why has the harmonization failed? The cases of St. John's wort, valerian, ginkgo, ginseng, and green tea. *Phytomedicine : international Journal of Phytotherapy and Phytopharmacology* 81:153421 doi:10.1016/j.phymed.2020.153421. PMC: 33291029

Binns, C. W., M. K. Lee, and A. H. Lee. 2018. Problems and Prospects: Public Health Regulation of Dietary Supplements. *Annual Review of Public Health* 39:403–20. doi:10.1146/annurev-publhealth-040617-013638. PMCID:29272167

Boullata, J. 2005. Natural health product interactions with medication. *Nutrition in Clinical Practice* 20 (1):33–51. doi: 10.1177/011542650502000133.

Bredsdorff, L., and K. Pilegaard. 2018. Concern for adverse effects of huperzine a when sold as an ingredient in food supplements. *Toxicology Letters* 295:S145. doi: 10.1016/j.toxlet.2018.06.735.

Bredsdorff, L., E. B. Wedebye, N. G. Nikolov, T. Hallas-Møller, and K. Pilegaard. 2015. Raspberry ketone in food supplements - High intake, few toxicity data - A cause for safety concern? *Regulatory Toxicology and Pharmacology* 73 (1):196–200. doi: 10.1016/j.yrtph.2015.06.022.

Chaloupkova, P., M. Petrtyl, V. Verner, and L. Kokoska. 2020. Dietary supplements versus functional foods: Consumers' attitudes to their consumption. *British Food Journal* 122 (12):3853–68. doi: 10.1108/BFJ-10-2019-0767.

Cohen, P. A. 2014. Hazards of hindsight - Monitoring the safety of nutritional supplements. *New England Journal of Medicine* 370 (14):1277–80. doi: 10.1056/NEJMp1315559.

Costa, M. C., T. Goumperis, W. Andersson, J. Badiola, W. Ooms, S. Pongolini, C. Saegerman, M. Jurkovic, P. Tuominen, E. Tsigarida, et al. 2017. Risk identification in food safety: Strategy and outcomes of the EFSA emerging risks exchange network (EREN), 2010-2014. *Food Control* 73:255–64. doi: 10.1016/j.foodcont.2016.04.045.

Crescioli, G., N. Lombardi, A. Bettiol, E. Marconi, F. Risaliti, M. Bertoni, F. Menniti Ippolito, V. Maggini, E. Gallo, F. Firenzuoli, et al. 2018. Acute liver injury following *Garcinia cambogia* weight-loss supplementation: Case series and literature review. *Internal and Emergency Medicine* 13 (6):857–72. doi: 10.1007/s11739-018-1880-4.

Czepielewska, E., M. Makarewicz-Wujec, F. Różewski, E. Wojtasik, and M. Kozłowska-Wojciechowska. 2018. Drug adulteration of food supplements: A threat to public health in the European Union? *Regulatory Toxicology and Pharmacology* 97:98–102. doi: 10.1016/j.yrtph.2018.06.014.

de Boer, A., F. van Hunsel, and A. Bast. 2015. Adverse food-drug interactions. *Regulatory Toxicology and Pharmacology* 73 (3):859–65. doi: 10.1016/j.yrtph.2015.10.009.

Dennehy, C. E., C. Tsourounis, and A. J. Horn. 2005. Dietary supplement-related adverse events reported to the California Poison Control System. *American Journal of Health-System Pharmacy* 62 (14):1476–82. doi: 10.2146/ajhp040412.

EFSA ANS Panel. 2018. Scientific opinion on the safety of green tea catechins. *Efsa Journal* 16 (4):5239, 89pp.

EFSA CONTAM Panel. 2017. Statement on the risks for human health related to the presence of pyrrolizidine alkaloids in honey, tea, herbal infusions and food supplements. *EFSA Journal* 15 (7):4908, 34pp.

EFSA. 2014. Update on EFSA's activities on Emerging Risks 2012-2013. Parma, Italy: European Food Safety Authority. EFSA Supporting Publication 2014-EN-585.

EFSA. 2016. Scientific opinion on the safety and efficacy of pyridine, pyrrole, and quinoline derivatives belonging to chemical group 28 when used as flavourings for all animal species. *EFSA Journal* 14 (2):4390,19pp.

EFSA. 2017. Technical report on EFSA's activities on emerging risks in 2016. Parma, Italy: European Food Safety Authority. EFSA Supporting Publication EN-1336.

EFSA. 2018a. Scientific opinion on the safety of monacolins in red yeast rice. *EFSA Journal* 16 (8):5368, 46pp.

EFSA. 2018b. Technical report on EFSA's activities on emerging risks in 2017. Parma, Italy: European Food Safety Authority. EFSA Supporting Publication 2019: EN-1522.

EFSA. 2019. Technical report on EFSA's activities on emerging risks in 2018. Parma, Italy: European Food Safety Authority. EFSA Supporting Publication 2019:EN-1704.

EFSA. 2020a. Focal Point members and observers. Parma, Italy: European Food Safety Authority. Accessed August 5. https://www.efsa.europa.eu/en/people/fpmembers.

EFSA. 2020b. Technical report on EFSA's activities on emerging risks in 2019. Parma, Italy: European Food Safety Authority. EFSA Supporting Publication 2020:EN-1924.

EFSA. 2007. Definition and description of "emerging risks" within the EFSA's mandate (adopted by the Scientific Committee on 10 July 2007). Parma, Italy: Scientific Committee and Advisory Forum unit. EFSA/SC/415 Final.

EFSA. 2012. Toward a methodological framework for emerging risk identification. Parma, Italy: European Food Safety Authority. Supporting publication 2012-EN-243.

ElAmrawy, F., G. ElAgouri, O. Elnoweam, S. Aboelazayem, E. Farouk, and M. I. Nounou. 2016. Adulterated and counterfeit male enhancement nutraceuticals and dietary supplements pose a real threat to the management of erectile dysfunction: A global perspective. *Journal of Dietary Supplements* 13 (6):660–93. doi: 10.3109/19390211.2016.1144231.

EMA. 2019. Pharmacovigilance: Overview. Accessed August 2. https://www.ema.europa.eu/en/human-regulatory/overview/pharmacovigilance-overview.

European Commission. 2020a. EU Register of nutrition and health claims made on foods. Accessed September 22. http://ec.europa.eu/food/safety/labelling_nutrition/claims/register/public/?event=register.home.

European Commission. 2020b. Staff working document evaluation of the Regulation (EC) No 1924/2006 on nutrition and health claims made on foods with regard to nutrient profiles and health claims made on plants and their preparations and of the general regulatory framework for their use in foods {SWD(2020) 96 final}. Brussels, Belgium: European Commission.

European Commission. 2021a. Commission Regulation (EU) 2021/468 of 18 March 2021 amending Annex III to Regulation (EC) No 1925/2006 of the European Parliament and of the Council as regards botanical species containing hydroxyanthracene derivatives. Official Journal of the European Union L 96:*L* 96:6–8. Brussels, Belgium: European Commission.

European Commission. 2021b. RASFF - Food and Feed Safety Alerts. Accessed February 19. https://ec.europa.eu/food/safety/rasff_en.

European Commission. 2021c. RASFF Portal. Accessed January 19. https://webgate.ec.europa.eu/rasff-window/portal/?event=SearchForm&cleanSearch=1.

European Committee for Standardization. 2020. Doping prevention in sport — Good development and manufacturing practices aimed at preventing the presence of prohibited substances in food intended for sportspeople and food supplements, EN 17444. Brussels: European Committee for Standardization.

European Parliament and the Council of the European Union. 2001. Directive 2001/83/EC of 6 November 2001 on the Community code relating to medicinal products for human use. Official Journal of the European Communities L 311:67-128. Brussels, Belgium: European Parliament and the Council of the European Union.

European Parliament and the Council of the European Union. 2002a. Directive 2002/46/EC of 10 June 2002 on the Approximation of the Laws of the Member States Relating to Food Supplements, Official

Journal of the European Communities L 183:51-57. Brussels, Belgium: European Parliament and the Council of the European Union.

European Parliament and the Council of the European Union. 2002b. Regulation (EC) No 178/2002 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. Official Journal of the European Communities, L 31:1-24. Brussels, Belgium: European Parliament and the Council of the European Union.

European Parliament and the Council of the European Union. 2004. Regulation (EC) No 726/2004 of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. Official Journal of the European Union L 136:1-33. Brussels, Belgium: European Parliament and the Council of the European Union.

European Parliament and the Council of the European Union. 2006. Regulation (EC) No 1924/2006 of 20 December 2006 on nutrition and health claims made on foods. Official Journal of the European Union, L 404:9-25. Brussels, Belgium: European Parliament and the Council of the European Union.

European Parliament and the Council of the European Union. 2008. Regulation No 108/2008 of 15 January 2008 amending Regulation (EC) No 1925/2006 on the addition of vitamins and minerals and of certain other substances to foods. Official Journal of the European Union L 39:11-13. Brussels, Belgium: European Parliament and the Council of the European Union.

European Parliament and the Council of the European Union. 2010a. Directive 2010/84/EU of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use. Official Journal of the European Union, L 348:74-99. Brussels, Belgium: European Parliament and the Council of the European Union.

European Parliament and the Council of the European Union. 2010b. Regulation (EU) No 1235/2010 of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products. Official Journal of the European Union, L 348: 1-16. Brussels, Belgium: European Parliament and the Council of the European Union.

European Parliament and the Council of the European Union. 2012a. Directive 2012/26/EU of 25 October 2012 amending Directive 2001/83/EC as regards pharmacovigilance. Official Journal of the European Union, L 299:1-4. Brussels, Belgium: European Parliament and the Council of the European Union.

European Parliament and the Council of the European Union. 2012b. Regulation (EU) No 1027/2012 of 25 October 2012 amending Regulation (EC) No 726/2004 as regards pharmacovigilance. Official Journal of the European Union, L 316:38-40. Brussels, Belgium: European Parliament and the Council of the European Union.

European Parliament and the Council of the European Union. 2015. Regulation (EU) 2015/403 of 11 March 2015 amending Annex III to Regulation (EC) No 1925/2006 of the European Parliament and of the Council as regards Ephedra species and Yohimbe (Pausinystalia yohimbe (K. Schum) Pierre ex Beille). Official Journal of the European Union, L 67:4-5. Brussels, Belgium: European Parliament and the Council of the European Union.

European Parliament and the Council of the European Union. 2019a. Regulation (EU) 2019/649 of 24 April 2019 amending Annex III to Regulation (EC) No 1925/2006 of the European Parliament and of the Council as regards trans fat, other than trans fat naturally occurring in fat of animal origin. Official Journal of the European Union, L 110:17-20. Brussels, Belgium: European Parliament and the Council of the European Union.

European Parliament and the Council of the European Union. 2019b. Regulation (EU) 2019/650 of 24 April 2019 amending Annex III to Regulation (EC) No 1925/2006 of the European Parliament and of the Council as regards Yohimbe (Pausinystalia yohimbe (K. Schum) Pierre ex Beille). Official Journal of the European Union, L 110:21-22. Brussels, Belgium: European Parliament and the Council of the European Union.

French Ministry of the Economy, Productive Redress and the Digital Economy. 2014. Arrêté du 24 juin 2014 établissant la liste des plantes, autres que les champignons, autorisées dans les compléments alimentaires et les conditions de leur emploi. Journal officiel n°0163 texte n° 26 du 17 juillet 2014. On line https://www.legifrance.gouv.fr/jo_pdf.do?id=JORFTEXT000029254516.

Gallo, E., E. Giocaliere, S. Benemei, A. R. Bilia, A. Karioti, A. Pugi, M. di Pirro, F. Menniti-Ippolito, G. Pieraccini, L. Gori, et al. 2012. Anything to declare? Possible risks for patients' health resulting from undeclared plants in herbal supplements. *British Journal of Clinical Pharmacology* 73 (3):482–3.

Garcia-Alvarez, A., B. Egan, S. De Klein, L. Dima, F. M. Maggi, M. Isoniemi, L. Ribas-Barba, M. M. Raats, E. M. Meissner, M. Badea, et al. 2014. Usage of plant food supplements across six European countries: Findings from the plantlibra consumer survey. *PLoS One* 9 (3):e92265. doi: 10.1371/journal.pone.0092265.

Garthe, I., and R. J. Maughan. 2018. Athletes and supplements: Prevalence and perspectives. *International Journal of Sport Nutrition and Exercise Metabolism* 28 (2):126–38.

Gatti, M., I. Ippoliti, E. Poluzzi, I. C. Antonazzo, P. A. Moro, U. Moretti, F. Menniti-Ippolito, G. Mazzanti, F. D. Ponti, and E. Raschi. 2021. Assessment of adverse reactions to α-lipoic acid containing dietary supplements through spontaneous reporting systems. *Clinical Nutrition* 40 (3):1176–85. doi: 10.1016/j.clnu.2020.07.028.

Gori, L., P. Galluzzi, V. Mascherini, E. Gallo, F. Lapi, F. Menniti-Ippolito, R. Raschetti, A. Mugelli, A. Vannacci, and F. Firenzuoli. 2011. Two contemporary cases of hepatitis associated with *Teucrium chamaedrys* L. decoction use. Case reports and review of literature. *Basic & Clinical Pharmacology & Toxicology* 109 (6):521–6. doi: 10.1111/j.1742-7843.2011.00781.x.

Haller, C., T. Kearney, S. Bent, R. Ko, N. Benowitz, and K. Olson. 2008. Dietary supplement adverse events: Report of a one-year poison center surveillance project. *Journal of Medical Toxicology* 4 (2): 84–92.

Hudson, A., E. Lopez, A. J. Almalki, A. L. Roe, and A. I. Calderón. 2018. A review of the toxicity of compounds found in herbal dietary supplements. *Planta Medica* 84 (9-10):613–26.

JAZMP. 2019. Posodobljeno strokovno mnenje glede hormona melatonina in njegove uporabe v izdelkih, ki niso zdravila [Updated expert opinion on melatonin and its use in non-medicinal products]. *Opinion of the Agency for Medicinal Products and Medical Devices of the Republic of Slovenia*. https://www.jazmp.si/fileadmin/datoteke/dokumenti/SRZHPD/Melatonin_strokovno_mnenje-2019-12-19.pdf

Jeurissen, S. M. F., E. J. M. Buurma-Rethans, M. H. Beukers, M. Jansen-Van Der Vliet, C. T. M. Van Rossum, and R. C. Sprong. 2018. Consumption of plant food supplements in the Netherlands. *Food and Function* 9 (1):179–90. doi: 10.1039/c6fo01174h.

Kothari, D., S. Patel, and S. K. Kim. 2019. Probiotic supplements might not be universally-effective and safe: A review. *Biomedicine and Pharmacotherapy* 111:537–47.

Lapi, F., E. Gallo, E. Giocaliere, M. Vietri, R. Baronti, G. Pieraccini, A. Tafi, F. Menniti-Ippolito, A. Mugelli, F. Firenzuoli, et al. 2010. Acute liver damage due to *Serenoa repens*: A case report. *British Journal of Clinical Pharmacology* 69 (5):558–60.

Lombardi, N., G. Crescioli, V. Maggini, I. Ippoliti, F. Menniti-Ippolito, E. Gallo, V. Brilli, C. Lanzi, G. Mannaioni, F. Firenzuoli, et al. 2021. Acute liver injury following turmeric use in Tuscany: An analysis of the Italian Phytovigilance database and systematic review of case reports. *British Journal of Clinical Pharmacology* 87 (3):741–53. doi: 10.1111/bcp.14460.

MacFarquhar, J. K., D. L. Broussard, P. Melstrom, R. Hutchinson, A. Wolkin, C. Martin, R. F. Burk, J. R. Dunn, A. L. Green, R. Hammond, et al. 2010. Acute selenium toxicity associated with a dietary supplement. *Archives of Internal Medicine* 170 (3):256–61. doi: 10.1001/archinternmed.2009.495.

Mariotti, F., E. Kalonji, J. F. Huneau, and I. Margaritis. 2010. Potential pitfalls of health claims from a public health nutrition perspective. *Nutrition Reviews* 68 (10):624–38.

Martena, M. J., J. C. A. Van Der Wielen, L. F. J. Van De Laak, E. J. M. Konings, H. N. De Groot, and I. M. C. M. Rietjens. 2007. Enforcement of the ban on aristolochic acids in Chinese traditional herbal preparations on the Dutch market. *Analytical and Bioanalytical Chemistry* 389 (1):263–75. doi: 10.1007/s00216-007-1310-3.

Mathews, N. M. 2018. Prohibited contaminants in dietary supplements. *Sports Health* 10 (1):19–30.

Mazzanti, G., F. Menniti-Ippolito, P. A. Moro, F. Cassetti, R. Raschetti, C. Santuccio, and S. Mastrangelo. 2009. Hepatotoxicity from green tea: A review of the literature and two unpublished cases. *European Journal of Clinical Pharmacology* 65 (4):331–41.

Mazzanti, G., P. A. Moro, E. Raschi, R. Da Cas, and F. Menniti-Ippolito. 2017. Adverse reactions to dietary supplements containing red yeast rice: Assessment of cases from the Italian surveillance system. *British Journal of Clinical Pharmacology* 83 (4):894–908.

Menniti-Ippolito, F., I. Ippoliti, A. A. Pastorelli, I. Altieri, F. Scalise, B. De Santis, F. Debegnach, C. Brera, R. Pacifici, S. Pichini, et al. 2020. Turmeric (*Curcuma longa* L.) food supplements and hepatotoxicity: An integrated evaluation approach. *Annali Dell'Istituto Superiore di Sanita* 56 (4):462–9.

Menniti-Ippolito, F., G. Mazzanti, C. Santuccio, P. A. Moro, G. Calapai, F. Firenzuoli, A. Valeri, and R. Raschetti. 2008. Surveillance of suspected adverse reactions to natural health products in Italy. *Pharmacoepidemiology and Drug Safety* 17 (6):626–35.

Morgovan, C., S. Ghibu, A. M. Juncan, L. L. Rus, A. Butucă, L. Vonica, A. Muntean, L. Moş, F. Gligor, and N. K. Olah. 2019. Nutrivigilance: A new activity in the field of dietary supplements. *Farmacia* 67 (3):537–44. doi: 10.31925/farmacia.2019.3.24.

Moro, P. A., F. Cassetti, G. Giugliano, M. T. Falce, G. Mazzanti, F. Menniti-Ippolito, R. Raschetti, and C. Santuccio. 2009. Hepatitis from Greater celandine (*Chelidonium majus* L.): Review of literature and report of a new case. *Journal of Ethnopharmacology* 124 (2): 328–32. doi: 10.1016/j.jep.2009.04.036.

Navarro, V. J., I. Khan, E. Björnsson, L. B. Seeff, J. Serrano, and J. H. Hoofnagle. 2017. Liver injury from herbal and dietary supplements. *Hepatology* 65 (1):363–73. doi: 10.1002/hep.28813.

Ozdemir, B., I. Sahin, H. Kapucu, O. Celbis, Y. Karakoc, S. Erdogan, and Y. Onal. 2013. How safe is the use of herbal weight-loss products sold over the Internet? *Human & Experimental Toxicology* 32 (1):101–6.

Patel, D. N., W. L. Low, L. L. Tan, M. M. B. Tan, Q. Zhang, M. Y. Low, C. L. Chan, and H. L. Koh. 2012. Adverse events associated with the use of complementary medicine and health supplements: An analysis of reports in the Singapore Pharmacovigilance database from 1998 to 2009. *Clinical Toxicology* 50 (6):481–9.

Pilegaard, K. 2011. Cases of hepatotoxicity after intake of food supplements in Denmark 2009–2010. *Toxicology Letters* 205:S50. doi: 10.1016/j.toxlet.2011.05.196.

Restani, P., C. D. Lorenzo, A. Garcia-Alvarez, M. Badea, A. Ceschi, B. Egan, L. Dima, S. Lüde, F. M. Maggi, A. Marculescu, et al. 2016. Adverse effects of plant food supplements self-reported by consumers in the PlantLIBRA survey involving six European countries. *PLoS One* 11 (2):e0150089. doi: 10.1371/journal.pone.0150089.

Rocha, T., J. S. Amaral, and M. B. P. P. Oliveira. 2016. Adulteration of dietary supplements by the illegal addition of synthetic drugs: A review. *Comprehensive Reviews in Food Science and Food Safety* 15 (1):43–62.

Ronis, M. J. J., K. B. Pedersen, and J. Watt. 2018. Adverse effects of nutraceuticals and dietary supplements. *Annual Review of Pharmacology and Toxicology* 58 (1):583–601. doi: 10.1146/annurev-pharmtox-010617-052844.

Sánchez-Oliver, A. J., R. Domínguez, P. López-Tapia, F. M. Tobal, P. Jodra, J. J. Montoya, E. J. Guerra-Hernández, and J. J. Ramos-Álvarez. 2020. A survey on dietary supplement consumption in amateur and professional rugby players. *Foods* 10 (1):7. doi: 10.3390/foods10010007.

Smith, A., and J. Dillon. 2009. Acute liver injury associated with the use of herbal preparations containing glucosamine: Three case studies. *Case Reports* 2009 (sep02 1):bcr0220091603–bcr0220091603. doi: 10.1136/bcr.02.2009.1603.

The Uppsala Monitoring Centre. 2020. The use of the WHO-UMC system for standardised case causality assessment. Accessed November 6. https://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf

UNESCO. 2019. International Convention against Doping in Sport 2005 Accessed May 9. http://portal.unesco.org/en/ev.php-URL_ID=31037&URL_DO=DO_TOPIC&URL_SECTION=201.html.

Van Den Berg, S. J. P. L., L. Serra-Majem, P. Coppens, and I. M. C. M. Rietjens. 2011. Safety assessment of plant food supplements (PFS). *Food and Function* 2 (12):760–8.

Vannacci, A., F. Lapi, E. Gallo, M. Vietri, M. Toti, F. Menniti-Ippolito, R. Raschetti, F. Firenzuoli, and A. Mugelli. 2009. A case of hepatitis associated with long-term use of *Cimicifuga racemosa*. *Alternative Therapies in Health and Medicine* 15 (3):62–3.

Vannacci, A., A. Paoletti, E. Gallo, S. Benemei, M. Vietri, F. Lapi, R. Volpi, F. Menniti-Ippolito, L. Gori, A. Mugelli, et al. 2011. Interactions between natural health products and oral anticoagulants: Spontaneous reports in the Italian surveillance system of natural health products. *Evidence-Based Complementary and Alternative Medicine* 2011:1–5. doi: 10.1155/2011/612150.

Vargas-Murga, L., A. Garcia-Alvarez, B. Roman-Viñas, J. Ngo, L. Ribas-Barba, S. J. P. L. Van Den Berg, G. Williamson, and L. Serra-Majem. 2011. Plant food supplement (PFS) market structure in EC Member States, methods and techniques for the assessment of individual PFS intake. *Food and Function* 2 (12):731–9.

Vitalone, A., F. Menniti-Ippolito, R. Raschetti, F. Renda, L. Tartaglia, and G. Mazzanti. 2012. Surveillance of suspected adverse reactions to herbal products used as laxatives. *European Journal of Clinical Pharmacology* 68 (3):231–8. doi: 10.1007/s00228-011-1128-y.

Wardenaar, F. C., I. J. M. Ceelen, J. W. Van Dijk, R. W. J. Hangelbroek, L. Van Roy, B. Van Der Pouw, J. H. M. De Vries, M. Mensink, and R. F. Witkamp. 2017. Nutritional supplement use by Dutch elite and sub-elite athletes: Does receiving dietary counseling make a difference? *International Journal of Sport Nutrition and Exercise Metabolism* 27 (1):32–42.

World Anti-Doping Agency. 2021. Prohibited list 2021. Accessed February 7. https://www.wada-ama.org/en/content/what-is-prohibited.

Zovko Končić, M. 2018. Getting more than you paid for: Unauthorized natural substances in herbal food supplements on EU market. *Planta Medica* 84 (6-7):394–406.

Žuntar, I., A. Krivohlavek, J. Kosić-Vukšić, D. Granato, D. Bursać Kovačević, and P. Putnik. 2018. Pharmacological and toxicological health risk of food (herbal) supplements adulterated with erectile dysfunction medications. *Current Opinion in Food Science* 24:9–15. doi: 10.1016/j.cofs.2018.10.012.

Appendix: An overview of cases of adverse effects involving FSs with strong causality reported to the Czech, French, Portuguese, and Slovenian Nutrivigilance Systems

Main ingredients	Sex	Age	Adverse effects	Severity	Causality
CZECH REPUBLIC					
Vitamins and minerals	M	30	Tongue swelling, rash	Moderate	Likely
Vitamins and minerals	F	25	Abdominal cramps, abdominal pain, flatulence	Mild	Likely
Vitamins, minerals	F, M	18, 10	Rash, diarrhea, Headache	Moderate	Likely
Mg, vitamin B6	M	65	Flatulence, abdominal cramps	Mild	Likely
Mg, vitamin B6	F	40	Cramps, diarrhea	Moderate	Likely
Mg, vitamin B1, B6, B12, folic acid	F	28	Cramps, diarrhea	Moderate	Likely
Mg	M	39	Tongue irritation	Mild	Likely
Mg	M, F	47, 44	Flatulence, cramps, diarrhea	Mild	Likely
Ala-lipoic acid, vitamins	F	54	Strong and irregular heartbeat	Moderate	Likely
Lutein	F	41	Body rash	Moderate	Likely
Chlorella	F	31	Constipation, abdominal cramps	Mild	Likely
Chlorella	F	34	Gastrointestinal bleeding	Moderate	Likely
Cat's claw	F	50	Stomach discomfort	Mild	Likely
Valeriana officinalis, *Melissa officinalis*, *Passiflora incarnata*, *Humulus lupulus*, *Matricaria recutita* L.	F	59	Excitation, nausea, blurred vision	Moderate	Likely
Tribulus terrestris	M	65	Headache, stomach pain, increased heart rate, nervousness, mental disorder	Moderate	Likely
5-alpha-hydroxy laxogenin	M	33	Aggression, memory and concentration problems	Moderate	Likely
L-methionine, L-cysteine, biotin, vitamins, minerals	F	45	Dizziness	Mild	Likely
Lactobacillus casei, *L. rhamnosus*, *L. acidophilus*, *L. plantarum*, *L. fermentum Bifidobacterium breve*, *B. longum*, *B. bifidum*, *Lactococcus lactis* ssp. Lactis, *Streptococcus thermophilus*	M	33	Nausea, abdominal pain, vomiting	Mild	Likely
FRANCE					
Vitamins, minerals	F	29	Acute hepatitis	Very serious	Very likely
Vitamins, minerals	F	36	Acute hepatitis	Very serious	Very likely
Propolis, honey	F	23	Anaphylactic shock	Lethal	Likely
Pollen, *Crocus sativus* L.	F	39	Pruritus, dyspnea, tachycardia, edema	Serious	Likely
Bifidobacterium lactis, *B. longum*, *Lactobacillus acidophilus*, *L. paracasei*, *L. rhamnosus* and *L. rhamnosus*, *L. paracasei*, *L. acidophilus*, *B. bifidum*	F	66	Infective endocarditis	Very serious	Very Likely
Ispaghula, probiotics (*Lactobacillus bulgaricus*, *L. acidophilus*, *L. lactis*, *L. casei*, *Streptococcus thermophilus*, inulin, glutamine, *Aloe vera*, *Taraxacum officinale*, *Arctium lappa*, *Fumaria officinalis*, *Cynara scolymus*, Curcuma, papain	F	87	Acute pulmonary edema	Very serious	Likely
25 ingredients*	F	71	Acute hepatitis and death	Lethal	Likely
Passiflora incarnata	F	66	Anaphylactic shock	Very serious	Very likely
Acerola	F	26	Migraine	Serious	Likely
Bauhinia variegate	F	59	Acute hepatitis	Very serious	Very likely
Chitosan, kola nut caffeine, Fucus, Chrome	M	33	Acute renal failure	Very serious	Likely
L-arginine, L-lysine, L-glycine, L-tyrosine, taurine, L-phenylalanine, creatine, beta-alanine, inositol, betaine, choline, beetroot, caffeine, vitamins, *Vitis vinifera*, *Piper nigrum*, Amla	M	42	Amnesia, asthenia, headache, motor deficit	Serious	Likely
Lemon bioflavonoids, red vine, grape, hamamelis, red myrtle essential Oil, Ginkgo biloba, bromelain, vitamins, Se, lactoferrin	F	86	Pancytopenia	Very serious	Likely
Red yeast rice	F	58	Myalgia	Serious	Likely
Fish oil	M	46	Cerebellar intraparenchymal hematoma	Very serious	Likely
PORTUGAL					
Vitamins and minerals	F	52	Anaphylactic shock	Very Serious	Very likely
Vitamins, plant extracts	F	57	Abdominal pain, vomiting, shortness of breath and fever	Mild	Likely
Vitamins, minerals and royal jelly	M	2	Edema, skin rashes, allergic reaction	Very serious	Very likely
Honey, royal jelly, Quina, vitamins	F	Child	Severe renal failure	Very serious	Possible
Zingiber officinale, vitamins, minerals	F	–	Abdominal pain, vomiting, nausea	Mild	Likely
Silybum marianum, Cynara scolymus, Taraxacum officinale, Peumus boldus	F	–	Severe thrombocytopenic purpura	Very Serious	Possible

(*continued*)

Continued.

Main ingredients	Sex	Age	Adverse effects	Severity	Causality
Vaccinium macrocarpon, lactoferrin, fruit-oligosaccharides	M	54	Diarrhea, abdominal pain	Serious	Likely
Plants extracts	F	33	Hepatic failure	Serious	Possible
Silybum marianum, Cynara scolymus, Taraxacum, broccoli, choline, vitamin C, *Fumaria officinalis*, *Mentha piperita*	F	36	Acute hepatic failure	Very serious	Likely
Passiflora incarnata, Valeriana officinalis, Chamomilla recutita, melatonin	M	–	Bowel obstruction	Very serious	Very likely
Melatonin, passiflora, California poppy, melissa, vitamin B6	F	68	Loss of consciousness, headache	Serious	Very likely
Melatonin, passiflora, California poppy, melissa	F	–	Loss of consciousness, general discomfort	Mild	Likely
Melatonin, passiflora, California poppy and melissa	F	67	General discomfort	Mild	Very likely
Melatonin, passiflora, valerian, vitamin B6, California poppy	F	41	Chest pain, palpitations, headache, heart rhythm disorders	Mild	Likely
Tribulus terrestris	M	35	Azoospermia	Very serious	Very likely
Bacopa, omega-3, L-arginine, B vitamins, coenzyme Q10, resveratrol, amino acids, Mn	M	69	Hyperglycemia	Serious	Very likely
Amino acids, vitamins, *Bacopa monniera*, Panax ginseng, Ginkgo biloba	F	42	Sedation like reaction	Mild	Likely
Wheat protein hydrolysates, vitamins, minerals	F	58	Increased alanine aminotransferase	Serious	Very likely
Wheat protein hydrolysates, vitamins, minerals	F	72	General discomfort, migraine, nausea	Mild	Likely
Wheat protein hydrolysates, minerals, vitamins	F	54	General discomfort, migraine, nausea	Mild	Likely
Probiotics	M	4 mo.	Hives	Serious	Possible
Probiotics	–	15 d.	Blood in the feces	Serious	Possible
Lactobacillus reuteri SLOVENIA	M		Stomach-aches, diarrhea, headaches,	Mild	Likely
Vitamins, amino acids, minerals	F	83	Hyperthyroidism	Very serious	Likely
Mg	F	62	Diarrhea	Mild	Very likely
Vitamins, selenium, damiana, green tea, Glycyrrhiza glabra, diosgenin, omega-3 fatty acids	F	28	Diarrhea	Mild	Very likely
Vitamins, selenium, damiana, green tea, Glycyrrhiza glabra, diosgenin, omega-3 fatty acids	F	39	Diarrhea	Mild	Very likely
Red yeast rice and Collagen	F	70	Urticaria	Mild	Very likely
Chitosan, red yeast rice, citrus bioflavonoids, *Cynara scolymus*, vitamin C	F	55	Fibromyalgia	Serious	Very likely
Aloe vera gel	F	64	Rise in liver enzymes	Serious	Very likely
Triphala, yashtimandu, ashwaghanda, kanchanara	F	44	Acute hepatic failure	Very serious	Very likely
Plantago psyllium	F	43	Bone pain, foggy vision, digestive troubles, asthenia, yellowing of the oral cavity	Serious to very serious	Less likely in relation to an ingredient, likely if toxic elements, (mycotoxins) are present
Silybum marianum, probiotics	F	44	Urticaria	Mild	Likely
Guarana	M	18	Restlessness, increased heart rate, excessive sweating, headache, abdominal distension, increased urination	Very serious	Very likely
Guarana	M	23	Nausea, irregular and more intense heartbeat, tingling sensation in the chest	Very serious	Very likely
Garcinia cambogia, green coffee, chromium	M	85	Abdominal pain, ulcer	Very serious	Likely
Cannabidiol	F	3	Disturbances of consciousness, tachycardia	Very serious	Very likely
Conjugated linoleic acid	F	44	Tachycardia	Serious	Likely
Colloidal silver	M	39	Tremor, forgetfulness, argyria	Very serious	Very likely
Coenzyme Q10	M	77	Heart rhythm disorders	Serious	Very likely

F: female; M: male; FS: food supplement; mo.: months; d.: days.

*Ingredients were: red yeast rice, *Olea europea, Rheum palmatum, Hibiscus sabdariffa, Cola acuminata, Garcinia cambogia, Moringa oleifera, Opuntia ficus-indica, Commiphora mukul, Coleus forskohlii, Coffea arabica, Lentinula edodes, Crataegus oxyacantha, Rhodiola rosea, Eleutherococcus senticosus, Cassia mimosides, Orthosiphon stamineus, Cyclanthera pedata, Aristotelia chilensis, Ribes nigrum,* Mg, Zn, Cr, marine collagen, water.