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**To the Minister of Health, Welfare and Sport and
The inspector-general of the Netherlands Food and Consumer Product Safety Authority**

Advice from the Director of the Office for Risk Assessment and Research on ensuring the safety of food supplements

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Background

Large numbers of food supplements are available on the Dutch and European market. The market is growing and many consumers use food supplements. According to the Healthy Lifestyle Monitor from market research firm Multiscope, 41% of adult Dutch men and women used food supplements in 2022, spending 1.6 billion euros (Voeding Nu editorial team, 2023). This covers a wide range of products such as vitamins and minerals as well as herbal preparations.

The Office for Risk Assessment and Research (BuRO) of the Netherlands Food and Consumer Product Safety Authority (NVWA) has assessed the risk of a number of food supplements over the past few years. This mainly involved cases in which the intake of a food supplement resulted in serious health effects. In more general terms, there are concerns about the safety of food supplements because their composition is often unknown, legislation governing food supplements is limited and, as a consequence, the NVWA has few enforcement options.

Question

BuRO prepared this advisory report on its own initiative. The advice is, however, also a response to specific questions from the Ministry of Health, Welfare and Sport (VWS) regarding individual food supplements or substances in food supplements. The question put by BuRO is: What are the health risks of food supplements and how can we (better) ensure the safety of food supplements in the Netherlands?

Approach

The advice summarises previous risk assessments by BuRO, describes the statutory frameworks governing food supplements and considers when food supplements are subject to other legislation than food law.

In March 2023, a search was conducted in Scopus for relevant literature with ‘safety food supplement*’ in the title (190 results) and ‘nutrivigilance’ in the title (7 results). A more systematic literature study resulted in between tens and hundreds of thousands of publications about individual food supplements. Consequently, a more targeted search was conducted for general publications about the safety of food supplements and nutrivigilance.

Definitions

Food supplements are defined as: foods 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, ... designed to be taken in measured small unit quantities (Directive 2002/46/EC[1]).

A herbal preparation is a herbal substance, processed or unprocessed, which is intended for human use, including herbal extracts; a herbal substance is a substance consisting of plant material (Commodities Act Decree Herbal Preparations[2]).

A herbal medicinal product is defined as: any medicinal product, exclusively containing as active ingredients one or more herbal substances, one or more herbal preparations, or a combination of the two (Medicines Act[3] based on European Directive 2001/83/EC[4]).

Legislation

- Like all foods, food supplements in the Netherlands are subject to the General Food Law (Regulation (EC) no. 178/2002[5]) and the Dutch Commodities Act[6]. Important principles are that the manufacturer bears primary responsibility for the production of safe food and that no unsafe foods may be traded (Article 14). Possibly positive properties of the food supplements do not play a role in the risk assessment.
- There is legislation regarding maximum concentrations of contaminants, residues of pesticides, etc., with which food supplements must comply.
- If not consumed in significant amounts prior to 15 May 1997, a food is a 'novel food' according to Regulation (EU) 2015/2283[7].
- Regulation (EC) no. 1925/2006[8] contains an article about other substances than vitamins or minerals, subject to a prohibition or restriction, or which are under investigation by the European Community (Article 8). In the Netherlands, a number of herbs are prohibited on the basis of the Commodities Act Decree Herbal Preparations.
- Directive 2002/46/EC regulates which vitamins and minerals may be used in food supplements. The daily maximum amounts have not yet been determined.
- Consumers may not be misled by the labelling of foods. This applies to the properties of the food (for example composition), the attribution of unproven effects or properties, and the suggestion of special properties also present in other foods (Regulation (EU) no. 1169/2011[9]).

[1] Directive 2002/46/EC on the approximation of the laws of the Member States relating to food supplements.
[2] wetten.nl - Regeling - Warenwetbesluit Kruidenpreparaten - BWBR0012174 (overheid.nl)
[3] wetten.nl - Regeling - Geneesmiddelenwet - BWBR0021505 (overheid.nl)
[4] Directive 2001/83/EC on the community code relating to medicinal products for human use.
[5] Regulation (EC) no. 178/2002 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.
[6] wetten.nl - Regeling - Warenwet - BWBR0001969 (overheid.nl)
[7] Regulation (EU) 2015/2283, on novel foods, amending Regulation (EU) no. 1169/2011 of the European Parliament and the Council and repealing Regulation (EC) no. 258/97 of the European Parliament and the Council and Regulation (EC) no. 1852/2001 of the Commission.
[8] Regulation (EC) no. 1925/2006 on the addition of vitamins and minerals and of certain other substances to foods.
[9] Regulation (EU) no. 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers, amending Regulations (EC) no. 1924/2006 and (EC) no. 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the European Parliament and of the Council, Commission Directives 2002/67/EC and 2008/5/EC and Commission Regulation (EC) no. 608/2004.

- Regulation (EC) no. 1924/2006[10] regulates the use of health claims. Health claims must first be scientifically tested (by EFSA, European Food Safety Authority) before they are admitted to the market by the European Commission and the Member States.
- The Dutch Medicines Act states that a medicine is presented or administered as being suitable for recovering, improving or otherwise altering physiological functions in humans by bringing about a pharmacological, immunological or metabolic effect. Medicines must have a trading permit, unlike foods, are not always freely available, and must be accompanied by a patient information leaflet or package leaflet approved by the Medicines Evaluation Board (MEB). Risk-benefit assessments are made for medicines and (mild) adverse reactions can be accepted. The principle for foods is that they must be safe, and have no adverse health effects.
- Herbal medicinal products are subject to compulsory registration but are subject to a simplified registration procedure as compared with medicines. The effectiveness of traditional herbal medicinal products is assessed on the basis of prolonged use and experience.
- All actions involving substances covered by the Opium Act[11] are prohibited, unless an exemption has been granted. This is supervised by the Health and Youth Care Inspectorate (IGJ).
- If there are doubts about whether a product is subject to the Medicines Act, Opium Act or Commodities Act, the Medicines Act and Opium Act take precedence over the Commodities Act. In other words, if a product is not subject to the Medicines Act or Opium Act, it is deemed a food and is subject to the Commodities Act.

Hazard identification and hazard characterisation

- In the period 1991-2021, 823 herbal products were mentioned in 789 notifications about herbal medicinal products (n=229) and herbal preparations (n=594) by the Netherlands Pharmacovigilance Centre Lareb. Around 15% of the notifications related to adverse reactions, were assessed by Lareb as being serious (van Hunsel et al., 2022).
- Food supplements can contain (added and labelled or unlabelled) pharmacological active substances that are prohibited, or the safety of which has not been demonstrated.
- In 2021, the Dutch National Poisons Information Centre (NVIC) was consulted about 2298 cases of exposure to food supplements. These were cases of acute poisoning. The majority of information requests (38%) in the category 'food, drink, food supplements and drugs' related to food supplements. High-risk food supplements include high-dose vitamin D preparations, sedatives containing doxylamine, stimulating sport and weight loss products and selective androgen receptor modulators (SARMs) (Roelen et al., 2022). In 2022, NVIC was consulted about 2058 cases of human exposure to food supplements (Nugteren-van Lonkhuyzen et al., 2023).
- Via the European Rapid Alert System for Food and Feed (RASFF), between 1 January 2013 and 1 January 2023, 909 notifications were registered in the category 'Dietetic foods, food supplements and fortified foods' under 'food' (from a total of 11,492 notifications).
- Adverse reactions to food supplements that are generally reported, include headache, insomnia, nausea, vomiting, tachycardia, dizziness, heart palpitations and stomach complaints (Roelen et al., 2019). In serious cases, the ingestion of a food supplement can lead to organ failure or even death. These are acute health effects. Little is known about the chronic health effects.

[10] Regulation (EC) no. 1924/2006 on nutrition and health claims made on foods.
[11] wetten.nl - Regeling - Opiumwet - BWBR0001941 (overheid.nl)

Food supplements with herbs can have adverse reactions and interactions with other substances, for example in medicines[12].

Exposure estimate

- Over the past few decades, increasing numbers of people have started taking food supplements, including herbal preparations. In the Netherlands, in 1987/1988, 17% of respondents to the Dutch National Food Consumption Survey (DNFCS) used food supplements; in 2019-2021 this had risen to 56%.
- In 2019, in the Netherlands, 63% of respondents (15-70 years of age) surveyed by Motivaction regularly used food supplements and 37% occasionally. The most commonly consumed were multivitamins followed by vitamin D and magnesium (Motivaction, 2019).
- According to the Healthy Lifestyle Monitor from market research firm Multiscope, 41% of adult Dutch men and women used food supplements in 2022 (Voeding Nu editorial team, 2023).
- In 2022, 93% of respondents in EU Member States, including the Netherlands, used a food supplement with vitamins and/or minerals (Ipsos for Food Supplements Europe, 2022).
- In 2014, around 10% of men, 17% of women and 13% of children used herbal supplements (Jeurissen et al., 2018).
- More than one quarter of (recreational) sportsmen and women in the Netherlands used pre or post-workout supplements in 2020 (Razenberg-Gijsbers et al., 2021).

Risk characterisation

- Intakes above the known, tolerable upper intake levels for vitamins and minerals can result in negative health effects.
- Herbal preparations are often considered "natural". However, they can contain substances that have harmful effects on health.
- The composition of herbal preparations is often unknown and then the health risks cannot be assessed.
- Partly due to the often uncertain legal status and the absence of a (systematic) system of notifications, there is no complete picture of the health risks run by users of different types of food supplements.
- BuRO suggests to classify food supplements in 4 groups based on (likely) health risks: 1) food supplements with vitamins and minerals, 2) single herbal preparations, 3) composite food supplements with multiple active substances, and 4) food supplements that are actually novel foods or (herbal) medicinal products. This latter group also includes products sold as food supplements (or not labelled as food supplements but as "research chemicals" or with no label at all) that the consumer actually expects to have some effect (for example pre-workouts, SARMs, nootropics (substances that claim to improve mental performance), psychoactive herbs).

Ensuring the safety of food supplements

It is not possible to conduct a risk characterisation and risk assessment for the entire group of food supplements, given their varied composition and intake. In particular, quality requirements are absent for food supplements that contain plant material and added substances. Medicines must satisfy the statutory requirements of the harmonised European Pharmacopoeia. Also for novel foods, additives and flavourings, as well as for health claims, for example, European criteria for admission to the market have been laid down and all these products are subject to an admission procedure, including a safety assessment. The same does not apply to food supplements. The Netherlands is one of the few European Member States that has no notification or registration requirement for food

[12] See: Herbal preparations | Netherlands Nutrition Centre

supplements. Other European countries, for example, have opted for positive and/or negative lists of herbs that may or may not be used in food supplements. Lists of this kind may or may not be legally binding.

The purpose of a notification system is to obtain an overview of food supplements available on the Dutch market. The simplest system requires nothing more than the registration of a food supplement, while a more elaborate system could involve the assessment of a submitted safety dossier for each food supplement. In 2020, the Minister for Medical Care wrote to the Chairman of the Dutch House of Representatives that 'in a market in which new products and suppliers are constantly emerging, it is essential that the food safety authority is able to act effectively upon receiving signals, notifications and inspections of unsafe products'. A letter from the Ministers of Health, Welfare and Sport (VWS) and Agriculture, Nature and Food Quality (LNV) to the House of Representatives in March 2023, once again indicated that the efforts of the Netherlands are aimed at the establishment of harmonised specific legislation for food supplements, also on a European level. The letter went on, 'The introduction of a notification system for food supplements could further reinforce compliance and the supervision of safety. Part of the approach to food supplements is an investigation into the introduction of a notification system in the Netherlands. Many European countries already operate a notification system in which products first have to be registered before they can be placed on the market. ... Another key point for attention remains improving the communication about food supplements to businesses and consumers.'

On 7 December 2023, the NVWA launched a campaign on food supplements, primarily via social media and aimed at consumers, that emphasised the fact that the use of food supplements is not without risk. These risks were explained using a video, a news release and a podcast. The podcast discussed the risks of food supplements and the possible dilemmas for enforcement that result from existing legislation and regulations and the growing trade in these products (see: nvwa.nl/voedingssupplementen).

Advantages and disadvantages of a notification system

The main advantages of a notification system are as follows.

- Better ensuring the safety of food supplements on the Dutch market.
- Preventing introduction of food supplements to the market containing active pharmacological substances or medicines that represent a health risk.
- Transferring the burden of proof of safety to the manufacturer or seller. The manufacturer/seller is responsible for the safety of a food supplement and must be able to demonstrate that safety by means of a safety dossier. At present, the burden of proof to show that something is unsafe lies with the NVWA.
- Generating data about the safety of (substances in) food supplements.
- Providing honest information about food supplements to consumers because labels meet requirements and can be checked. Consumers can then make a more informed choice on the basis of the information available.
- The use of positive and negative lists of substances. It is also possible to rapidly assess whether the substances in question are novel foods or not admitted substances.
- The ability to supervise prohibited health claims.
- A (future) agreement on the safety assessment of food supplements.
- Contributing to the safety of food supplements in Europe through the timely exchange of information about high-risk food supplements (for example via RASFF notifications) with other European countries.
- Contributing to the assessment of substances which could be prohibited in Europe according to Regulation (EC) no. 1925/2006.

The main disadvantages of a notification system are as follows.

- A notification system requires a contribution by expert assessors. Nevertheless, a system could be established which contains known information, for example about medicines or novel foods.
- Additional costs for the government and the sector.

Countries that have introduced a notification system, with different levels of requirements, have not evaluated the effects of the introduction of these systems.

Conclusions

- The consumption of all types of food supplements is increasing.
- Contrary to the intake of substances from other foods, there is no or only very limited specific legislation for food supplements, in particular herbal preparations.
- Little, if anything, is known about the composition of many food supplements, in particular those containing plant materials, and no quality requirements have been laid down for herbal preparations. There is legislation governing food supplements with vitamins and minerals, and there are clear rules on which chemical forms of vitamins and minerals are permitted to be used. However, as yet, no maximum daily limits have been laid down in legislation.
- The use of all types of food supplements can represent a potential risk as a consequence of intrinsic substance properties, the properties of additives or interaction with other substances (for example medicines).
- Food safety and the ensuring of food safety are at a high level in Europe and the Netherlands, but food supplements and in particular those food supplements that contain multiple (bioactive) substances and herbal preparations represent an exception.
- There is no compulsory notification or registration of food supplements in the Netherlands, and the NVWA only has limited options for (quality and safety) checks. This represents a potential health risk for consumers.
- Member States are permitted to introduce a notification obligation in line with European legislation. According to European legislation, (herbal) medicinal products, novel foods, food additives, food flavourings, etc. are subject to compulsory notification and/or registration, prior to admission to the market.
- BuRO is unable to provide a detailed substantiation of the health risks of all food supplements because the necessary data are not available, and the group of food supplements is too diverse. It is also not possible to calculate, in advance, what the effect on the health of consumers will be when the safety of food supplements is better guaranteed. However, the many reported cases suggest that serious health effects can occur through the use of food supplements.
- BuRO has proposed a classification into 4 groups: a) food supplements with vitamins and minerals, b) single herbal preparations, c) composite food supplements, and d) food supplements that are actually novel foods or (herbal) medicinal products.
- A notification system offers a solution for better ensuring the safety of food supplements and improving the provision of information to consumers and businesses.

Uncertainties

The most important uncertainties in this advice are the absence of evaluations of established notification systems already in use, the impossibility of providing a detailed (scientific) substantiation of the health risks of food supplements, in particular in the long term, and the absence of a clear picture of costs and benefits.

Advice

In response to the question 'What are the health risks of food supplements and how can we (better) ensure the safety of food supplements in the Netherlands?', BuRO concludes and advises the following.

It is not possible to conduct a risk characterisation and risk assessment for the entire group of food supplements, given their varied composition and intake. The use of all types of food supplements has increased and the numerous reported cases indicate that serious health effects can occur through the consumption of food supplements. To obtain an overview of the food supplements present on the Dutch market and to prevent potentially harmful food supplements to be placed on the market, a notification system for food supplements is needed in the Netherlands, that will be able to protect consumers against potentially harmful health effects. Such a system must contain information about a food supplement, which is also accessible for consumers. In this way, consumers can make a (better) informed choice.

<u>To the Minister of Health, Welfare and Sport</u>

- Facilitate the introduction of a notification system for food supplements in the Netherlands by:
  - preparing legislation that regulates the compulsory registration of food supplements in the notification system by manufacturers, and
  - (commissioning) the development of a suitable database[13].
- Initiate or support a proposal for the introduction of an EU notification system.

<u>To the Inspector-General of the Netherlands Food and Consumer Product Safety Authority (NVWA)</u>

- Support the introduction and implementation of a notification system in the Netherlands and enforce on the basis of that notification system.

[13] In this process, use could be made of existing examples of databases in, for example, Denmark and France.

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1. Introduction

The first humans fed themselves by hunting and fishing, and eating what they could find in nature, such as seeds, nuts and fruits. As people started to farm the land, they became more dependent on what was available in the area in which they lived and what they could grow. Food quality and monitoring that quality date back to this period. In the Netherlands, during the Middle Ages, certain places acquired city rights and were made responsible for clerical tasks, legislation and the administration of justice. City councils started to take responsibility for inspecting goods and commodities such as meat, fish and bread with the aim of protecting consumers against poor and overpriced food[14]. The aim of the Commodities Act of 19 September 1919 was to promote the safety of foods by outlawing harmful and unsuitable foods, providing the public with information about what they were buying and tackling unfair trade practices.

Before the active substances we know today as medicines were identified, almost everyone in all parts of the world used herbal remedies to treat illness and disease. Herbal medicine was based on experience with and knowledge of herbs, but was not scientifically substantiated. The Chinese pharmacopoeia on herbal medicine, for example, dates back around 4800 years. In India, in ayurveda medicine, more than 700 medicinal plants were known thousands of years ago[15]. Numerous medicinal herbs from South America have now been described (for example by Van der Snoek, 2010). Indigenous Indian tribes used and continue to use plants and parts of plants as a source of medicine and food. One example of such a plant is stevia, which is used today as a sweetener in Europe.

In Medieval Europe, herbal medicine was mainly practised from monasteries with extensive herb gardens. A well-known 'toxicologist' from this period is Paracelsus (1493-1541) who studied herbs and their active substances. He also described the principle of homeopathic medicines. As far back as the 16th century, Paracelsus said: *'Sola dosis facit venenum'* ('the dose makes the poison'). Later, in the 19th century, apothecaries took over the role of the monasteries and succeeded in isolating substances from plants, and synthesising them chemically. This resulted in improved dosing, storability, purity, etc. Nevertheless, the effect of a plant which can contain multiple substances is not always the same as that of a purified substance, and thus herbal medicine (plant-based medicine or phytotherapy) continued to exist alongside regular medicine. In a number of countries, including Germany and France, phytotherapy is an integral part of regular medicine. In the Netherlands, herbal remedies are still prescribed by a number of naturopaths (practitioners of natural medicine) and physicians. In a thesis by AFH Hijmans from 1961 (entitled *Het zogenaamde werkzame bestanddeel van een drietal plantaardige geneesmiddelen*, referred to in [16]), it is stated that around 3000 medicinal plants are known to herbal medicine (of the alleged 400,000 or so plant species) but in practice the actual number is limited to around 200 medicinal herbs.

Today, the market offers numerous food supplements that contain herbs, which because of their (not always scientifically proven) possible beneficial effects are widely purchased by consumers. Over the last 30 years, the Dutch government has encouraged innovation in many fields, certainly including the fields of food, nutrition and health. However, legislation has not kept pace with the developments of foods. For example, there is still no legislation regarding

[14] The status of food safety | About the NVWA | NVWA
[15] History of herbal medicine (therapeutenkompas.nl)

maximum daily doses of vitamins and minerals or the admission of substances in food supplements.

2. Question

For many years, the Office for Risk Assessment and Research (BuRO) of the Netherlands Food and Consumer Product Safety Authority (NVWA) has been concerned about the safety of food supplements. These concerns are not exclusively restricted to cases in which the intake of a food supplement has resulted in serious health effects. In more general terms, there are concerns about the safety of food supplements because legislation governing food supplements is limited and, as a consequence, the NVWA has few enforcement options open. There is a huge variety of herbs and substances in food supplements, and businesses emphasise the (supposed) positive properties, while paying little attention to long-term and short-term safety. The Health Council of the Netherlands advises the intake of a number of vitamins in the form of a food supplement for certain population groups, but the range of food supplements, and in particular herbal preparations, is constantly growing, and is widely purchased by consumers. Partly in response to questions and regular consultation with, among others, the Ministry of Health, Welfare and Sport (VWS) and the National Institute for Public Health and the Environment (RIVM), all the experience and knowledge acquired has been brought together in an advice, aimed at better ensuring the safety of food supplements.

BuRO prepared this advisory report on its own initiative. The advice is, however, also a response to specific questions from VWS and risk assessments by BuRO and RIVM of individual food supplements or substances in food supplements.

The question put by BuRO is: What are the health risks of food supplements and how can we (better) ensure the safety of food supplements in the Netherlands?

3. Approach

In March 2023, a search was conducted in Scopus for relevant literature with 'safety food supplement*' in the title (190 results) and 'nutrivigilance' in the title (7 results). The advice also contains the experience acquired by BuRO over the past 15 years with food supplements and the legal frameworks.

A more systematic literature search in PubMed in January 2024 (search terms: ("safety"[Title/Abstract] OR "food supplement*"[Title/Abstract] OR "toxicity"[Title/Abstract] OR "adverse effect*"[Title/Abstract] OR "risk*"[Title/Abstract]) AND ((("diet"[MeSH Terms] OR "diet"[Title/Abstract] OR "dietary"[Title/Abstract] OR "supplement*"[Title/Abstract]) OR "multivitamin*"[Title/Abstract] OR "mineral s"[Title/Abstract] OR "minerals"[MeSH Terms] OR "minerals"[Title/Abstract] OR "mineral"[Title/Abstract]) OR "supplement*"[Title/Abstract]) OR ("botanic"[Title/Abstract] OR "botanical"[Title/Abstract] OR "botanically"[Title/Abstract] OR "botanicals"[Title/Abstract] OR "botanics"[Title/Abstract]) OR ("dietary supplements"[MeSH Terms] OR ("dietary"[Title/Abstract] AND "supplements"[Title/Abstract]) OR "dietary supplements"[Title/Abstract] OR ("herbal"[Title/Abstract] AND "supplement"[Title/Abstract]) OR "herbal supplement"[Title/Abstract])) generated almost 670,000 results, many about individual food supplements. The vast majority (311,000 publications) appeared in the last 20 years. Slightly more than 67,000 publications were meta analyses and (systematic) reviews. Therefore, a more targeted search was conducted for general publications about the safety of food supplements and nutrivigilance.

4. European and national legislation

Below follows a brief description of current food-related legislation. For a complete overview and additional information, see Appendix 1.

4.1 Foods

The Netherlands has the Commodities Act[16]. In 2002, the General Food Law (Regulation (EC) no. 178/2002[17]) came into force, and the European Food Safety Authority (EFSA) was established. In other words, there has only been harmonised legislation on food safety in Europe since 2002; the Regulations and Directives apply in all Member States of the European Union. In the event of a conflict with national legislation, a European Regulation takes precedence over the national law. An important principle is that the manufacturer bears responsibility for the production of safe food. The General Food Law applies to food and feeds. No unsafe food may be placed on the market (Article 14). Food is deemed unsafe if following regular preparation and consumption, the consumer can become sick or can expect negative effects on health in the short or long term. Article 14(8) also states that if a food conforms with the specific provisions applicable to that food, this shall not bar the competent authorities from taking appropriate measures to impose restrictions on it being placed on the market or to require its withdrawal from the market where there are reasons to suspect that, despite such conformity, the food is unsafe.

Moreover, if not consumed in significant quantities prior to 15 May 1997, a food can also be a novel food as intended in Regulation (EU) 2015/2283[18].

4.2 Prohibited or restricted substances

Regulation (EC) no. 1925/2006[19] contains an article about prohibited or restricted substances, and substances that are under investigation by the European Community (Article 8). The procedure provided for in Article 8 is followed when a substance other than vitamins or minerals, or an ingredient containing a substance other than vitamins or minerals, is added to foods or used in the manufacture of foods under conditions that would result in the ingestion of amounts of this substance exceeding those reasonably expected to be ingested under normal conditions of consumption of a balanced and varied diet and/or would otherwise represent a potential risk to consumers.

4.3 Food supplements

Food supplements are foods. They can contain different substances. Directive 2002/46/EC defines food supplements in Article 2 as follows: foods 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, namely forms such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquids, drop dispensing bottles and other forms of liquids and powders designed to be taken in measured small unit quantities; and nutrients are: vitamins and minerals. This definition has remained unchanged despite innovations and changing consumption patterns. Moreover, the definition is not sufficiently precise, so that it is multi-interpretable (EESC, 2021). Additionally, this Directive regulates which vitamins and minerals may be used in food supplements. Article 5 states that maximum amounts will be set, but this has not yet happened.

[16] wetten.nl - Regeling - Warenwet - BWBR0001969 (overheid.nl)
[17] Regulation (EC) no. 178/2002 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.
[18] Regulation (EU) 2015/2283, on novel foods, amending Regulation (EU) no. 1169/2011 of the European Parliament and the Council and repealing Regulation (EC) no. 258/97 of the European Parliament and the Council and Regulation (EC) no. 1852/2001 of the Commission.
[19] Regulation (EC) no. 1925/2006 on the addition of vitamins and minerals and of certain other substances to foods.

At present, EFSA is working on a revision of the tolerable upper intake levels, and these will probably be used in the (near) future to set maximum amounts in Europe. To date, therefore, in Europe legislation only exists that relates to the use of vitamins and minerals in the manufacture of food supplements. For the use of other substances than vitamins or minerals in the manufacture of food supplements, regulations contained in national legislation continue to apply. In Directive 2002/46/EC[20], specific provisions have, however, been included for statements on labels, which apply to all food supplements, irrespective of their composition.

4.4 Herbal preparations

In the Netherlands, the Commodities Act Decree Herbal Preparations[21] came into force in 2001. This decree defines a herbal preparation as a herbal substance, processed or unprocessed, which is intended for human use, including herbal extracts; a herbal substance is a substance consisting of plant material. The Commodities Act Decree Herbal Preparations imposes rules on the use of herbs in foods such as food supplements. One of the reasons for this was that the herbs were traded as food supplements (foods). Because the composition of a herbal preparation is often not (fully) known, the food safety authority is not able to automatically assume the safety of the herbal preparations on the market. Well-known examples of herbs used in food supplements are valerian, garlic, ginkgo and St. John's wort. The Commodities Act Decree Herbal Preparations states that herbal preparations may only contain herbal substances in amounts that are not harmful to public health and as such a number of substances are included that may not occur or only in limited amounts in herbal preparations. The legal status of herbal preparations is not harmonised in Europe.

The Commodities Act Decree Herbal Preparations is not applicable to kitchen herbs, spices and flavourings or the use of herbs in medicines and cosmetic products. Other regulations apply in these areas. Herbal preparations are not subject to any reporting or notification requirement; in other words, these preparations can be placed on the market without informing the government (NVWA). Besides a number of prohibited herbs, the Commodities Act Decree Herbal Preparations contains no specific quality requirements. However, Article 6 specifies that advice on use and dosage must be provided for herbal preparations.

Herbs (and other substances) generally have a physiological effect and are often taken for their (supposed) positive health effects. These products are subject to the General Food Law: they must be safe; any positive properties play no role in the safety assessment. Adverse reactions can sometimes mean that, for example, herbal preparations are assessed as "harmful". If a physiological effect becomes too great, a product can be close to becoming a (herbal) medicinal product (see Herbal medicinal products). To obtain a trading permit for a (herbal) medicinal product (essential for placing it on the market), an extensive risk-benefit assessment must first be carried out by the evaluating body (in the Netherlands, the Medicines Evaluation Board (MEB)).

4.5 Labelling

Consumers may not be misled by the labelling of foods. This applies to the properties of the food (for example composition, amount, shelf life) and the attribution of unproven effects or properties, and the suggestion of special properties also present in other foods. Article 9 of Regulation (EU) no.

[20] Directive 2002/46/EC on the approximation of the laws of the Member States relating to food supplements.
[21] wetten.nl - Regeling - Warenwetbesluit Kruidenpreparaten - BWBR0012174 (overheid.nl)

1169/2011[22] contains a list of mandatory particulars for prepacked foods, including a list of ingredients, a declaration of the quantity of ingredients and instructions for use if the food is difficult to use without instructions. Article 6 specifies that food supplements may not be labelled, presented or advertised as having the property to prevent, treat or cure human disease, nor may any suggestions of such properties be made in labelling, presentation or advertising. Mandatory elements of labels include the portion recommended for daily consumption, a warning against exceeding the daily recommended portion and the notification that food supplements may not be used as a substitute for a varied diet. In addition (Article 7), it may not be claimed or suggested in the labelling, presentation and advertising of food supplements that a balanced and varied diet in general is unable to provide appropriate amounts of nutrients.

4.6 Health claims

For many consumers, it is not entirely clear which foods are "healthy" and which food choices contribute to a healthy lifestyle. In the media, on websites, in vlogs and blogs, many health claims have been and continue to be made. In 2006, this resulted in a European regulation (Regulation (EC) no. 1924/2006[23]) which regulates the use of nutrition and health claims. Health claims must first be scientifically tested (by EFSA) before they are admitted by the European Commission and the Member States. From 2010 onwards, manufacturers have no longer been able to place claims on their packaging or make advertising statements that mislead consumers. A claim must always be linked to a nutrient or ingredient. The claims submitted for botanicals (herbal preparations) have been placed on hold and have not yet been assessed by EFSA. A small number of claims for herbs have been assessed and have received a negative assessment by EFSA. However, these claims and the claims that have been submitted may still be used until the European Commission has reached a definitive decision. This is often stated on the packaging but generally suggests to consumers a positive effect of the food supplement. The reason EFSA is no longer assessing the claims is that no agreement has yet been reached on the criteria to be applied.

4.7 Opium Act

Under the Opium Act[24], all activities involving products covered by the Opium Act are prohibited, unless an exemption has been granted. This is supervised by the Health and Youth Care Inspectorate (IGJ).

4.8 Medicines

The Dutch Medicines Act[25] is based on European Directive 2001/83/EC[26]. In the Dutch Medicines Act, a medicine is defined (in Article 1) as: a substance or set of substances or combination of substances which is intended to be administered or applied or is in any way presented as being suitable for:

1. treating or preventing a disease, defect, wound or pain in humans,
2. making a medical diagnosis in humans, or

[22] Regulation (EU) no. 1169/2011 on the provision of food information to consumers, amending Regulations (EC) no. 1924/2006 and (EC) no. 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the European Parliament and of the Council, Commission Directives 2002/67/EC and 2008/5/EC and Commission Regulation (EC) no. 608/2004.
[23] Regulation (EC) no. 1924/2006 on nutrition and health claims made on foods.
[24] wetten.nl - Regeling - Opiumwet - BWBR0001941 (overheid.nl)
[25] wetten.nl - Regeling - Geneesmiddelenwet - BWBR0021505 (overheid.nl)
[26] Directive 2001/83/EC of the European Parliament and the Council of 6 November 2001 on the community code relating to medicinal products for human use.

3. recovering, improving or otherwise altering physiological functions in humans by bringing about a pharmacological, immunological or metabolic effect.

There are two groups of medicines: prescription medicines (subject to medical prescription) and non-prescription medicines (not subject to a medical prescription - self-care medicines). In the Netherlands, the following supply channels exist:

- General sales;
- Pharmacy and drugstore only;
- Pharmacy only;
- Only via doctor's prescription.

In the determination of the supply channel (by the MEB), consideration is given to whether the user can use the product safely (concentration and dose of the active substance) and also whether the user is capable of making the right diagnosis and whether the chosen product is the right choice for dealing with the problem. The awarding of the supply channel status is therefore an additional safety guarantee and distinguishes medicines from freely available food supplements, to be used at personal discretion (Tiesjema et al., 2013a).

According to the Medicines Act, medicines must also have a patient information (package) leaflet assessed and approved by the MEB. In case of doubt as to whether an item is a medicine, an Opium Act product or a Commodities Act product, the Medicines Act and Opium Act take precedence over the Commodities Act[27].

4.9 Herbal medicinal products

A herbal medicinal product is defined in the Dutch Medicines Act as: any medicinal product, exclusively containing as active ingredients one or more herbal substances, one or more herbal preparations, or a combination of the two. This definition is identical to that in the European Directive 2001/83/EC.

In 2005, the European Medicines Act was supplemented with a simplified registration procedure for herbal medicinal products. Just like other medicines, herbal medicinal products are subject to compulsory registration. In other words, they can only be placed on the market following registration by the MEB. The statutory evaluation criteria employed by the MEB in this matter are: quality, efficacy and safety. For efficacy, an exception is made for herbal medicinal products with a long tradition in the European Union: the so-called traditional herbal medicinal products. For these products, the efficacy is not clinically tested but based on long-lasting use and experience.

In 2010, 14 products were registered in the Netherlands as traditional herbal medicinal products (Tiesjema et al., 2011). At present (21 January 2023) there are 48. In principle, the extracts are well described.

Traditional herbal medicinal products are only available from the pharmacy and drugstore. This represents an additional safety guarantee that these products enjoy as a medicine and which distinguishes them from freely available food supplements, to be used at personal discretion. Furthermore, traditional herbal medicinal products must be manufactured according to GMP[28], under which detailed rules exist for, among other things, the specifications of raw materials.

4.10 Conclusion on legislation

Food supplements are foods and must comply with existing laws and regulations on foods. In brief, this means that a food cannot be defined as a medicine or

[27] wetten.nl - Regeling - Warenwet - BWBR0001969 (overheid.nl)
[28] GMP or Good Manufacturing Practice is a quality assurance system for the pharmaceutical industry (GMP en kwaliteitsdefecten | College ter Beoordeling van Geneesmiddelen (cbg-meb.nl)).

Opium Act product, is not harmful, contains no or limited amounts of regulated substances, contains no novel foods that have not been admitted, is correctly labelled and only bears assessed and approved claims.

Looking at existing legislation on foods, it is clear that the legislation is focused mainly on foods already available on the market. There is no legal obligation to investigate the safety of foods before they are placed on the European market. One exception is legislation for novel foods. Before a novel food can be admitted to the European market, a dossier must first be submitted, and the risk assessed by EFSA. Assessment in advance prevents possibly harmful novel foods being placed on the European market. Similar legislation which examines potential harmful health effects in advance also exists for the admission or permission to place on the market various other products including (animal) medicines, food additives, pesticides and cosmetics.

5. Food or (herbal) medicinal product

In 2011, RIVM conducted research and reported on herbs as commodities or medicinal products (Tiesjema et al., 2011). Certain herbs such as Ginkgo biloba, St. John's wort and valerian were used both in foods and medicinal products in 2010. If a herbal preparation contains a specified effective dose, according to the Medicines Act, this product must be seen as a medicinal product. The question is from what dose this should apply. Medicines are intended for patients and foods (food supplements) for the general population (in principle healthy people). For medicines, risk-benefit considerations are made that do not apply to foods. The operating principle is that foods are safe.

In case of doubt as to whether something is a medicinal product or a food, the *Adviesgroep Statusbepaling grensvlak medische producten* (Advisory Group on determining the status at the interface of medical products) will decide[29].

6. Dangers of food supplements

A consumer who uses a food supplement to rectify a (supposed) nutrient deficiency or to tackle or prevent a disorder, expects the food supplement to deliver an effect, and should in fact have opted for a (herbal) medicinal product. A danger is that patients will turn to food supplements and herbs for a cure rather than attending a doctor.

An exploratory study by RIVM revealed that herbal preparations from Traditional Chinese Medicine (TCM) were used for every conceivable medical disorder (Hoving et al., 2014). With just a few exceptions, these products are not viewed today in the Netherlands as medicines, but as foods. As such they fall under the Commodities Act. RIVM noted that there is a stubborn misunderstanding among consumers that natural products such as herbs are safe. The study also revealed a major rise in the number of companies trading in products from Traditional Chinese Medicine and registered with the Chamber of Commerce in the period 1988-2013, increasing from a few in 1988 to more than 150 by 2013, and then to 194 by 2023 (reference date: 26 May 2023).

6.1 Reports on adverse reactions and incidents

Adverse reactions and incidents involving medicines and food supplements can be reported at several places in the Netherlands. Pharmacovigilance Centre Lareb is the Dutch centre for notification and knowledge regarding adverse reactions to medicines and food supplements. The Dutch Poisons Information Center (NVIC) is the centre of expertise for clinical toxicology in the Netherlands. Here, healthcare professionals can receive assistance in dealing with incidents. Notifications can

[29] Netherlands Government Gazette 2018, 37730 | Overheid.nl > Officiële bekendmakingen (officielebekendmakingen.nl)

also be made to NVWA, IGJ, Doping Authority Netherlands and the Customs Service.

Pharmacovigilance Centre Lareb

Table 1 provides an overview of the number of reports received each year by Lareb concerning adverse reactions to herbal preparations, vitamins, other supplements and other health products not registered as medicines. In 2022, the majority of reports related to (multi)vitamin preparations, often in relation to vitamin B6. The other complaints related to preparations with red yeast rice, Midalgan®, St. John's wort, valerian and supplements with phytoestrogens (Lareb, 2023). Between 1992 and 2015, a total of 451 reports were submitted (on average almost 20 reports a year).

Table 1. Total number of reports received by Lareb per year on adverse reactions to herbal preparations, vitamins, other supplements and other health products not registered as medicines (Lareb, 2023).

Year	**1992-2015**	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**
Number	451	76	95	115	141	133	125	131	109

Van Hunsel and Van Grootheest (van Hunsel & van Grootheest, 2013) analysed reports of suspected adverse reactions to herbal preparations as reported and registered in the Larab database in the period February 1991-March 2013. The Lareb database contained 336 reports of adverse reactions to herbal preparations. These included 247 individual preparations and a total of 221 different herbs. Of the 518 reported adverse reactions to herbal medicinal products, 55 were assessed as being serious. Van Hunsel et al. (van Hunsel et al., 2022) subsequently analysed reports of adverse reactions to herbal medicinal products and herbal supplements submitted between 1991 and February 2021 to the Pharmacovigilance Centre Lareb, on the basis of their legal status. The products were categorised according to the Herbal Anatomical Therapeutic Chemical Classification System. In total, up to February 2021, 789 reports of herbal medicinal products and herbal supplements were received by Lareb. Reports can relate to multiple products. Of these, 823 herbal products (229 registered medicinal products and 594 herbal preparations) were categorised as suspicious, with a total of 1727 adverse reactions. Of the 823 herbal products, 522 reports related to individual herbal products, 256 to combined products, 27 to vitamin products with herbal ingredients and 18 to product issues. Around 15% of reports related to serious adverse reactions.

Dutch Poisons Information Centre (NVIC)

In 2018, NVIC was consulted about 778 exposures to food supplements (excluding vitamins). The majority of questions (471 exposures) related to food supplements with a (claimed) sedative effect, primarily melatonin. In the category "Stimulating sport/weight loss products", there were 108 exposures. These food supplements represent the greatest health risk because they regularly contain prohibited substances (Roelen et al., 2019). Complaints or symptoms reported following ingestion of or overdosing with stimulating food supplements are nausea, vomiting, tachycardia, dizziness, restlessness and headache. In a number of cases, serious health effects were reported such as significantly raised blood pressure and cardiac arrhythmia.

In 2021, NVIC was consulted about 2298 exposures to food supplements (38% of the total 5993 exposures in the category "food, drink, food supplements and drugs"). The most often reported and as such possibly the most high-risk food supplements included high-dose vitamin D preparations, sedatives containing

doxylamine, stimulating sport and weight loss products and selective androgen receptor modulators (SARMs) (Nugteren-van Lonkhuyzen et al., 2022; Roelen et al., 2022). The majority of exposures to food supplements occurred in adults between 18 and 65 years of age. In 2022, NVIC was consulted about 2058 human exposures to food supplements, including high-dose vitamin D preparations, phenibut, stimulating sport and weight loss products, anabolic steroids and oestrogen-prohibiting preparations (Nugteren-van Lonkhuyzen et al., 2022). These are cases of acute intoxication.

RASFF

Via the European Rapid Alert System for Food and Feed (RASFF), a system for alerts relating to foods and feeds established with a view to safeguarding the exchange of information between Member States and enabling a rapid response by food safety authorities in the event of risks to public health as a consequence of the food chain, between 1 January 2013 and 1 January 2023, 909 notifications were registered in the category "Dietetic foods, food supplements and fortified foods" under "food" (from a total of 11,492 notifications). In 591 cases it concerned "food supplements".

Individual cases relating to pharmacological substances in food supplements

Over the past few years there have been various cases in which the intake of food supplements led to negative health effects. For example, in 2021, Lareb and NVIC received four reports about the herbal preparation Sulami®[30]. Following the intake of the supplement, the following symptoms, among others, were reported: headache, dizziness, insomnia, accelerated cardiac rhythm and reduced kidney function. Following analysis, the supplements were found to contain sibutramine and canrenone. In Europe, sibutramine was admitted as a medicine for the treatment of obesity. Due to serious adverse reactions to the medicine, such as increased risk of stroke, the authorisation was withdrawn. Canrenone is used as a diuretic (van de Koppel et al., 2023). After taking the herbal preparation Binahong Extra®, one person suffered Cushing's Syndrome caused by exposure to increased concentrations of the adrenal cortex hormone cortisol. Following analysis, the preparation was found to contain dexamethasone and paracetamol. Van Hunsel et al. described a case of a "natural" preparation for weight loss that turned out to contain sibutramine. After taking the herbal preparation Irem Naturel, the user suffered symptoms including dizziness, dryness of the mouth, increased heart rate and disorientation (van Hunsel et al., 2016).

In 2021, Lareb received 4 reports of an unexpected positive effect on joint pain from the use of the herbal preparation Montalin. Montalin is a herbal preparation from Indonesia which according to the label is 100% natural and helps with gout, stress, rheumatism, swelling of the legs and muscle stiffness. Analysis showed that in addition to herbs, Montalin also contained meloxicam and paracetamol (van de Koppel et al., 2022).

The cases of non-admitted substances in food supplements known to Lareb, NVIC or NVWA probably represent the tip of the iceberg. The long-term effects of many food supplements and herbal preparations are unknown. The question is whether a consumer will easily make the connection between negative health effects and the intake of a food supplement or herbal preparation. Even if a consumer were to do so, it is questionable whether the use of the food supplement would be reported when visiting a GP or emergency room. This will mainly take place upon

[30] The herbal preparation Sulami not only contained herbs but also a medicine for the treatment of obesity and a diuretic that helps to drain excess moisture. These products were illegally added and not reported on the packaging (NVWA waarschuwt voor afslankmiddel Sulami | Nieuwsbericht | NVWA).

the occurrence of acute effects and not in response to effects that take place following prolonged use.

Geller et al. used data from 63 emergency rooms in the US in the period 2004-2012 to investigate how many visits were the result of health effects related to food supplements. On the basis of 3667 cases, they estimated that 23,005 visits to emergency rooms each year were related to the taking of food supplements. This resulted in 2154 hospital admissions. Following correction for unintended ingestion by children, 31.8% of these visits to the emergency room related to micronutrients and 65.9% to herbs and other food supplements, in particular products for weight loss and extra energy (Geller et al., 2015).

7. Use of food supplements

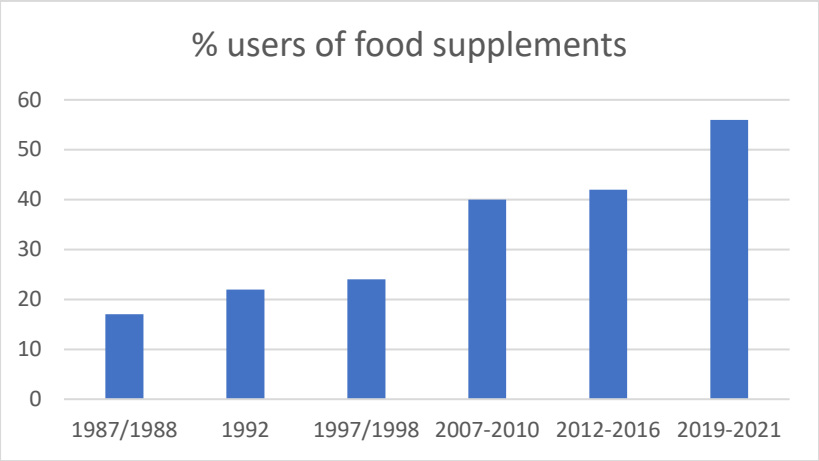

Figure 1. Percentage of users of food supplements in the Dutch National Food Consumption Surveys (Pajor, 2019; van Rossum et al., 2023).

Consumers are increasingly opting in favour of ease of use and health, in terms of their nutrition. The range of food supplements available with a particular recommendation (for example improved sports performance, improved concentration, assistance with weight loss, etc.) has grown considerably. Over the past few decades, increasing numbers of people have started taking food supplements, including herbal preparations. Figure 1 shows that the percentage of users of food supplements in the Netherlands, according to the Dutch National Food Consumption Surveys, has risen between 1987/1988 and 2019-2021 from 17% to 57% (Pajor, 2019; van Rossum et al., 2023). This is due to a number of different reasons, but the expansion of supply and the (often unapproved) recommendations have led growing numbers of consumers to believe that these supplements represent a good addition to their diet (van de Ven, 2016b). At the same time, the market tends to match consumer interest and demand (Pereira et al., 2017; Morgovan et al., 2019; The Portuguese Presidency, 2021; Vo Van Regnault et al., 2022). As a result of this growing interest, food supplements have become more widely available, in regular shops but also via the internet or the black market (Pereira et al., 2017).

In 2014, RIVM investigated the use of herbal supplements by screening a representative random sample of 75,100 Dutch adults and children. Then, 739 users in 8 different age and gender groups were further questioned. Around 10% of the men, 17% of the women and 13% of the children used herbal supplements. Around 600 different herbal supplements were reported, with 345 different herbs. The most commonly reported herbs were echinacea (*Echinacea purpura*), ginkgo (*Ginkgo biloba*), cranberry (V*accinium macrocarpon*), ginseng (*Panax ginseng*) and seaweed (mainly Spirulina and Chlorella) (Jeurissen et al., 2018).

In 2019, Motivaction concluded from an online survey of a nationally representative sample of 1113 Dutch people between the ages of 15 and 70 years old, that half of Dutch men and women were using food supplements; 63% on a regular basis and 37% occasionally. The most commonly consumed supplements were multivitamins, followed by vitamin D and magnesium. The other products in the top ten of most commonly used food supplements were vitamin C, vitamin B12, calcium, fish oil, iron, cranberry and vitamin B complex. In the age group 45-54 years of age, magnesium and vitamin C were taken more than average. Senior citizens opted more often for calcium, glucosamine, CBD oil and turmeric. Most notable was the fact that the majority of users based their decisions on information they had read or heard somewhere. Advice from friends and acquaintances also played an important role. The majority named as their reason for taking food supplements prevention, aimed at preventing possible complaints in the future (43%). One third took food supplements because they believed their intake of nutrients via their daily diet was insufficient, or to compensate for a less healthy lifestyle. Another group felt they had physical problems they could solve. The motto "It can't hurt to try" was adhered to by more than one-third of the user group, mostly men (Motivaction, 2019).

BuRO asked RIVM to conduct an investigation into pre- and post-workout supplements. These supplements are advised or taken to improve performance or to improve physical recovery following working out. For this purpose, in 2020, a questionnaire was distributed among more than 7000 amateur athletes who participated in a sport at least once a week. RIVM concluded that the use of workout supplements appeared to have become prevalent. In the Netherlands, more than one quarter of athletes consumed one or more supplements before or after exercise. They were most often used in fitness and strength sports, but also cycling and running. Men used more different products and also more often per week than women. Athletes between the ages of 25 and 34 years were the most common users. Around one in six persons were unaware of the ingredients in their sport supplements. This applied above all to women and young people (15 to 24 years of age). Around ten percent of the products used by the athletes surveyed, contained substances that could be harmful to their health. These concerned mainly supplements with different ingredients. The supplements can, for example, contain substances in too high dosages, substances that appear on the doping list (such as DMAA) or prohibited ingredients such as yohimbine. More than half of the users reported that the workout supplements were effective. Almost half had occasionally suffered adverse reactions, such as headache, insomnia, heart palpitations and stomach complaints. For a group of users, these adverse reactions were the reason to stop using them (Razenberg-Gijsbers et al., 2021).

Natuur- en gezondheidsProducten Nederland (NPN**,** trade association for manufacturers, raw material suppliers, wholesalers, importers and distributors of food supplements) reported in 2020 that around 66% of Dutch men and women above the age of 18 years used food supplements[31]. The food supplement market grew by 3.4% to 693 million euros. The best selling food supplement was vitamin D, purchased by 36% of supplement users. Total sales of herbal-based food supplements in the United States rose in 2016 by 7.7% compared with the previous year. Estimates suggest that consumers spent 7.452 billion dollars on herbal supplements in 2016, an increase of around 530 million dollars as compared with 2015 (Smith et al., 2017).

In 2022, 93% of respondents in EU Member States, including the Netherlands, had used a food supplement with vitamins and/or minerals (Ipsos for Food Supplements Europe, 2022).

[31] Market details food supplements | NPN (npninfo.nl)

According to the Healthy Lifestyle Monitor conducted by market research firm Multiscope, 41% of Dutch men and women used food supplements in 2022. The total amount spent on these products was 1.6 billion euros. The study was representative for the Dutch population; 5226 respondents of 18 years and older were consulted (Voeding Nu editorial team, 24 July 2023). This percentage is lower than reported in other studies. This may be due to the definition of food supplements used, and the understanding of the term by those interviewed.

In 2015, the food supplement market in Europe was worth more than 7.1 billion euros. For 2020, 9.5% growth (to 7.9 billion euros) was predicted, with Eastern European countries being the fastest growing markets (Morgovan et al., 2019).

One recent trend is the addition of plant material to drinks, such as beer and rum, as well as to (other) spirits. Plant (extracts) of hibiscus and cardamon have been added to rum, for example, and non-alcoholic gin has been placed on the market, containing pepper, mint, elderflower and elderberry, to imitate the taste of alcohol[32].

8. Food supplements and their risks

BuRO suggests dividing food supplements into 4 groups. This division is based on the existence of "traditional" food supplements (food supplements with vitamins and minerals, single herbal preparations) and products sold as food supplements (or not labelled as food supplements but as research chemicals or with no label at all) and which the consumer actually expects to have some effect (for example pre-workouts, SARMs, nootropics (substances that claim to improve mental performance) and psychoactive herbs). These are often composite food supplements and food supplements that are in fact novel foods or (herbal) medicinal products.
For an overview of the relevant risk assessments published by BuRO and publications from RIVM, see Appendix 2.

8.1 Food supplements with vitamins and minerals

Food supplements with vitamins and minerals intended to supplement the daily diet can contribute to growth, recovery and correct functioning of the body of individual humans who ingest insufficient amounts of these substances from their normal diet. As a rule, healthy people with a varied diet meet their need for vitamins and minerals. The likelihood of a deficiency is extremely small. Only special groups require additional nutrients. Babies (vitamins D and K), young children (vitamin D), women wishing to become pregnant (folic acid) and during pregnancy (vitamin D and folic acid), the elderly (vitamin D), people with a darker skin or people who spend too little time outside (vitamin D) and people who eat no animal products (vitamin B12) are advised to use food supplements[33]. It is a misunderstanding to believe that taking extra vitamins, minerals or trace elements above the recommended daily intakes is better for your health. The opposite is in fact the case. It can lead to negative health effects, such as when vitamin B6 intake is excessively high (BuRO, 2016). Directive 2002/46/EC specifies which substances are permitted in food supplements. EFSA is working on a revised version of a number of tolerable upper intake levels (ULs) for vitamins and minerals and these upper intake levels can then be used to estimate the risk represented by these food supplements.

[32] *Trends in dranken: van botanicals tot eetbare cocktails* (Trends in drinks: from botanicals to edible cocktails), vmt.nl
[33] *Heb ik extra vitamines en mineralen nodig?* (Do I need extra vitamins and minerals?) | Netherlands Nutrition Centre

8.2 Single herbal preparations

Many consumers assume that the use of herbal preparations will engender few or no health risks. However, even "natural" products may contain substances that have harmful health effects. There are many different herbal preparations on the market: from single extracts from the part of a plant to complex preparations with large numbers of ingredients, the composition of which is unclear. Herbal preparations are often used for (self-)medication or as a supplement to a treatment with regular medicines. A number of examples of interaction effects are: St. John's wort and turmeric bring about the accelerated decomposition of anti-cancer medicines and St. John's wort magnifies the effect of anti-depressants. Ginseng and ginkgo influence blood coagulation and caution is advised when taking blood-thinning medicines. Herbal preparations can strengthen or weaken the effect of medicines[34]. Sellers of these preparations often promise effects for which no scientific proof is available.

The composition and method of extraction of single herbal preparations, in other words extracts from (parts of) plants, are often known. These preparations have in many cases been available on the market for a long(er) period of time and are listed in the EFSA Compendium of Botanicals[35]. This is a database containing information about (substances in) plants. This database is also used to assist in the assessment of new plant-based foods or plant-based foods with a long tradition of use outside Europe but with no consumption history in the EU.

8.3 Composite food supplements

Today, there are many food supplements on the market that contain multiple substances, such as protein powders, an extract from one or more plants or a supplement with substances of vegetable origin such as seaweed, mosses and fungi to which natural or synthetic substances may or may not have been added, or a supplement comprising only synthetic substances. The precise composition of these food supplements is often unknown, and there is little knowledge of their interaction with medicines or other foods, although such interactions can occur. This group also includes food supplements with synthesised substances in which the manufacturer has searched for active substances, for example from old patents or (rejected) medicines. Examples include pre and post-workout supplements and nootropics or research chemicals.

To ensure that a food supplement actually does what it promises (for example promoting weight loss or improving erectile dysfunction), substances are added that are not declared on the label (Reeuwijk et al., 2014; van de Ven, 2016a; Dwyer et al., 2018). Therefore, consumers are unaware of what they are ingesting. This can result in a positive doping test, for example, as the use of performance-enhancing substances is forbidden in competitions (BuRO, 2021).

8.4 Food supplements that are actually novel foods or (herbal) medicinal products

If a food supplement is categorised by an expert as a (herbal) medicinal product or novel food, it must comply with the relevant procedures established for admission to the market. In other words, a manufacturer is required to submit a dossier that is assessed by EFSA or MEB respectively, before the supplement (be it a food or a (herbal) medicinal product) can be admitted to the market. This group also includes supplements that should in fact be covered by the Opium Act.

[34] https://www.voedingscentrum.nl/nl/service/vraag-en-antwoord/veilig-eten-en-e-nummers/is-de-combinatie-kruidenpillen-en-medicijnen-gevaarlijk-.aspx with reference to the NVWA website.
[35] Compendium of Botanicals | EFSA (europa.eu)

9. Ensuring the safety of food supplements

Food safety is at a high level in Europe and the Netherlands, but food supplements and in particular those food supplements that contain multiple (bioactive) substances and food supplements containing herbs (herbal preparations) represent exceptions. For the majority of people, herbal preparations have an innocent image, and they are often used because of their expected but generally unsubstantiated positive effects on health. Food supplements must be safe (as foods) but their safety and composition are not tested in the Netherlands by the government before they are placed on the market. This only takes place afterwards, if indications emerge that the ingestion of a food supplement represents a serious risk to health or if there are strong indications that it could represent a threat to public health. This also applies to food supplements with synthetic substances or combinations of substances.

The composition of food supplements, in particular those containing plant material, is often incompletely known and/or incorrectly indicated on the label. It is then difficult to carry out a risk assessment. No quality requirements have been laid down for herbal preparations. On the other hand, European and Dutch legislation does include prohibitions for a number of substances. However, starting materials, extraction methods, etc. are not specified, so that herbal preparations, even based on a single herb, may have different compositions. There is (limited) legislation on food supplements with vitamins and minerals; the permitted chemical forms of vitamins and minerals are laid down. As yet, however, the maximum amounts of vitamins and minerals permitted in food supplements have not been specified in Europe. Medicines must satisfy the statutory requirements of the harmonised European Pharmacopoeia. Consequently, the quality of medicines is identical in all European countries. For novel foods, additives and flavourings, as well as for health claims, criteria for admission have been laid down, and an admission procedure must be followed.

9.1 Past initiatives

In 2013, on behalf of NVWA-BuRO, RIVM produced an inventory, including by organising a workshop, of the possibilities for adapting (Dutch) legislation for herbal preparations in such a way that the safety and quality of the products can be better ensured. The question put to this workshop was, how can we best ensure the quality and safety of herbal supplements covered by the Commodities Act? The most significant problems identified in respect of herbal supplements were as follows (Tiesjema et al., 2013a).

1. No uniform legislation in Europe.
2. Uncertainties about the composition of a herbal supplement.
3. There is no list of products available on the market. The scale of the health problem is also not completely clear, or which products contribute to that problem. The scale of long-term effects on public health is also unknown. Only serious incidents are known.
4. There is insufficient knowledge of the risks and effect of herbs and herbal supplements both among manufacturers and retailers.
5. There is insufficient knowledge of the risks and effect of herbs and herbal supplements among consumers. Consumer perception is still that 'herbs are natural and therefore not harmful'. There is also a prevailing idea that only safe products are available on the market. Healthy diet is a focus of much attention. For example, the Netherlands Nutrition Centre recommends eating enough vegetables. It is possible that people who do not eat enough vegetables supplement their diet with food supplements because it appears to be an easy and in their eyes safe method. Among people who use (harmful) preparations due to a lack of knowledge, information provision may be helpful. However, there are also "believers" who will never be convinced of the possible hazards of herbs.

In 2013, RIVM observed that unlike for food additives and medicines, there is no registration and/or notification obligation for herbal preparations in the Netherlands. And this is still the case today. As a consequence, there is no clear knowledge of which herbal preparations are available on the market in the Netherlands. There are no specific quality requirements, starting materials and production processes are not laid down and there are no specific labelling requirements (Tiesjema et al., 2013a). The workshop identified three best options for amendments to legislation: introducing a notification or registration system, introducing a positive list, and expanding the negative (prohibited herbs) list in the Commodities Act Decree. The Netherlands was and still is one of the few European Member States that operates no notification or registration system for herbal supplements, or food supplements in general. Various other Member States have a notification obligation which ranges from submitting a label through to an extensive notification or registration obligation, including a safety and quality assessment before the supplement can be placed on the market (Vo Van Regnault et al., 2022).

9.2 Possible approach for classification and risk assessment of food supplements

RIVM has submitted a proposal (Tiesjema et al., 2011) for a guideline for assessing whether a herbal product is subject to the Commodities Act or is a medicinal product. The active dose is used as the starting point. In brief: if a product satisfies the presentation criterion and the administration criterion, it is subject to the Medicines Act. The presentation criterion is met if a therapeutical effect is claimed or the impression is raised that it has a therapeutic effect. The administration criterion relates to the effect; the potential function of the product in the body. If the above does not apply and it can then be concluded that the product has no active component (substance, extract or plant) that is also present in a registered medicine, the product is not subject to the Medicines Act, and is therefore subject to the Commodities Act. RIVM suggested taking the lowest minimum dose that appears on the packaging or in the package leaflet for a medicine or medicines as the active dose. RIVM concluded that 'If the product contains a dose that is equal to (or higher than) the minimum daily dose of the active substance/extract or herb in a registered medicine, it can be reasonably assumed that the product satisfies the administration criterion, and should therefore be subject to the Medicines Act' (Tiesjema et al., 2011). If in doubt, the *Adviesgroep Statusbepaling grensvlak medische producten* (Advisory Group on determining the status at the interface of medical products) can be consulted. If relating to a combination of active substances, for each active substance separately, the minimum recommended daily dose in the registered medicine must be compared with the maximum recommended dose in the food supplement.

Based on the EFSA guidance from 2009 (EFSA, 2009) and a proposal from RIVM (de Wit-Bos et al., 2019), BuRO produced a template for the risk assessment of a herbal preparation. The EFSA Scientific Committee proposed a framework in which a presumption of safety could be adopted for herbal preparations about which sufficient knowledge is available. In such cases, further testing is not necessary based on a long history of use whereby no health effects have occurred, and intake remained the same. The focus in the assessment must be on important groups of substances in the preparation and important substances in these groups. A dossier must also contain information about maximum concentrations of contaminants and the stability of the ingredients in the food supplement throughout its shelf life, intended use and recommended quantities etc. Any toxicological study must comply with international protocols, and interactions between substances must be investigated (EFSA, 2009; Speijers et al., 2010; Van den Berg et al., 2011). In 2020, BuRO formulated an internal working method for the evaluation of substances in food supplements. The operating principle is that regular foods contain bioactive substances but are not medicines.

9.3 Consultation between stakeholders and recent activities

For some time, regular consultations have taken place between NVWA Enforcement, RIVM, VWS and NVWA-BuRO about food supplements. Other parties occasionally attended (Doping Authority, IGJ). The result is a series of activities, including the drawing up of a list of high-risk substances (84 substances) and prohibited/undesirable substances in food supplements based on information from Belgium, Denmark, Italy and the Czech Republic. This list contains around 700 plants[36]. RIVM has issued proposals for the prioritisation of the assessment of herbs[37]. Discussions have been held with representatives of a number of European countries about their experiences with a notification system. The experiences turned out to be varied. None of the representatives consulted from the Member States reported having conducted an evaluation of their (national) notification system.

At the end of 2020, then Minister Van Ark (Minister for Medical Care) sent a letter to the Speaker of the House of Representatives about the approach to the safety of food supplements in the Netherlands (no. 258, Nutrition policy). In her letter, she remarked that in a market in which new products and suppliers are constantly emerging, it is essential that the supervisory authority is able to act effectively upon receiving signals, notifications and inspections of unsafe products. She further pointed out that unsafe substances in food supplements will be included in the Commodities Act and therefore prohibited ("negative list") as well as the intention to consider the possible introduction of a notification system for food supplements to be placed on the market in the Netherlands. The Minister also reported her wish for (more) harmonised European legislation on the safety of food supplements[38].

At the start of 2021, VWS asked BuRO to conduct risk assessments and prepare a guide for the way in which plant families from a longlist can be assessed, with a view to identifying a maximum permitted level for every plant family/active substance. BuRO considered a series of different approaches and existing initiatives (DACH list, Belgian Royal Decree[39] - a list of plants that are prohibited (list I) or restricted (list III), a list of "very high-risk substances", EFSA Compendium of Botanicals, EMA[40], NIH[41], American Botanical Council[42], etc.) and reached the conclusion that it was not possible to arrive at a classification according to the seriousness of health effects on the basis of the information available. A risk assessment on the basis of a plant family or plant species proved impossible due to the different extracts and plant parts used. It is not possible to assume a uniform risk assessment for all plant (species) within a family. Risk assessments must be carried out separately for each plant species. In other words: a case-by-case risk assessment is necessary for every herbal preparation. In August 2021, BuRO reported to VWS on the current status of all these efforts[43]. The Netherlands proposed using the DACH list (list drawn up by Germany (D), Austria (A) and Switzerland (CH)[44] as a means of submitting good, mutually harmonised risk assessments in the framework of European Regulation (EC) no.

[36] Report of NVWA Project Safety of Food supplements September, December 2020.
[37] Jeurissen S, Prioritization of botanicals used in plant food supplements, 2021.
[38] Letter to Parliament about the approach to safety of food supplements | Parliamentary Paper | Rijksoverheid.nl
[39] Royal Decree of 26 August 1997; https://www.health.belgium.be/nl/Node/24555
[40] European Medicines Agency | (europa.eu)
[41] Botanical Supplement Fact Sheets (nih.gov)
[42] Home - American Botanical Council (herbalgram.org)
[43] BuRO. Findings of the request for risk assessments from VWS, August 2021.
[44] https://www.bvl.bund.de/SharedDocs/Berichte/08_Stoffliste_Bund_Bundeslaender/stoffllisten_pflanzen_pflanzenteile.pdf?__blob=publicationFile&v=15.

1925/2006. The DACH list contains 170 harmful substances/plants (List A). Based on a decision tree, botanicals/substances can be placed on one of the three lists from Regulation (EC) no. 1925/2006 (List A: not recommended; List B: intake restriction; List C: uncertain (scientific uncertainty)). A working group of the Heads of (Food Safety) Agencies (HoA) is working on this. In advance of European rules, a list of botanicals will be added to the Commodities Act Decree Herbal Preparations (a negative list) in respect of which it has been determined that the health risks are sufficiently substantiated, with a risk assessment[45].

During its presidency of the European Union, in April 2021, Portugal organised a "High Level Conference on Food Supplements"[45]. This meeting offered representatives of competent authorities and other stakeholders an opportunity to share their opinion on the current state of affairs and on possible ways of improving the legal framework applicable to food supplements placed on the market in the European Union (the Portuguese Presidency, 2021). This meeting was followed by a publication of the European Economic and Social Committee (EESC) (EESC, 2021). Both parties concluded, among other things, that existing legislation on food supplements needed to be amended, in particular in respect of the definition of a food supplement, the setting of maximum concentrations of vitamins and minerals, the introduction of a compulsory national notification system for placing food supplements on the market and the establishment of a monitoring system for the negative effects of foods (nutrivigilance) (EESC, 2021; The Portuguese Presidency, 2021).

At the end of a workshop in October 2022 ('Food supplements vigilance systems in a public health perspective: the European context', held in Erice, Italy, 2-5 October 2022), the participants drew up a Manifesto. The aim of this manifesto is to increase awareness of the safe use of food supplements; to promote the establishment of a common European control system; to inform citizens and healthcare workers about the possible risks of the consumption of these products; and to promote the notification of possible harm (undesirable events) (Vo Van Regnault et al., 2022; Menniti-Ippolito et al., 2023).

In a letter from the Ministers of Health, Welfare and Sport (VWS) and Agriculture, Nature and Food Quality (LNV) to the Speaker of the Dutch House of Representatives of 22 March 2023 (no. 582, Food safety), it was once again indicated that the efforts of the Netherlands are aimed at the establishment of harmonised specific legislation for food supplements, also on a European level. The letter continues, 'The introduction of a notification system for food supplements could further reinforce compliance and the supervision of safety. Part of the approach to food supplements is an investigation into the introduction of a notification system in the Netherlands. Many European countries already operate a notification system in which products first have to be registered before they can be placed on the market. ...Another key point for attention remains improving the communication about food supplements for businesses and consumers.'

On 7 December 2023, the NVWA launched a campaign on food supplements, aimed primarily at consumers, which emphasised the fact that the use of food supplements is not without health risk. Over a one-week period, food supplements were highlighted through social media and other media channels. A video explained the method of monitoring and supervision; in a news release, information was provided about misleading claims for detox juices, and how they are being dealt with by the supervisory authority; and in a podcast, Martin Kooijman (NVWA-BED expertise) and emeritus professor Martijn Katan discussed the risks of food supplements and potential dilemmas for supervision as a result of current legislation and regulations and the growing trade in these products (see: nvwa.nl/voedingssupplementen).

[45] See: High Level Food Supplements Conference - YouTube.

The initiatives developed with a view to improving the safety of food supplements were aimed at identifying potentially harmful food supplements and drawing up a negative list. The identification and subsequent risk assessment of potentially harmful food supplements is a complex issue and calls for a case-by-case approach. Each individual food supplement, including herbal preparations, will have to be separately and individually assessed. This is a time-consuming process given the large number of (sometimes unknown) food supplements and herbal preparations available on the (European and) Dutch market. Moreover, risk assessments are currently being carried out by various European governments and EFSA, for example by drawing up a negative list, while the responsibility for placing safe food supplements on the market lies with the manufacturer.

It is not possible to conduct a risk characterisation and assessment for the entire group of food supplements, given their varied composition and intake. In particular, quality requirements are absent for food supplements that contain plant material and added substances. Medicines must satisfy the statutory requirements of the harmonised European Pharmacopoeia. Also for novel foods, additives and flavourings, as well as for health claims, for example, European criteria for admission have been laid down and all these products are subject to an admission procedure, including a safety assessment. The same does not apply to food supplements. The Netherlands is one of the few European Member States that has no notification or registration requirement for food supplements. Other European countries, for example, have opted for positive and/or negative lists of herbs that may or may not be used in food supplements. Lists of this kind may or may not be legally binding.

9.4 Purpose and advantages and disadvantages of a notification system

The purpose of a notification system is to acquire a clear picture of food supplements available on the Dutch market, and to assess a safety dossier that is submitted by the manufacturer, prior to admitting a food supplement to the Dutch market.

The main advantages of a notification system are as follows:

- Better ensuring the safety of food supplements on the Dutch market.
- Preventing introduction of food supplements containing active pharmacological substances or medicines to the market that represent a risk to health.
- Transferring the burden of proof of safety to the manufacturer or seller. The manufacturer/seller is responsible for the safety of a food supplement and must be able to demonstrate that safety by means of a safety dossier. At present, the burden of proof to show that something is unsafe lies with the NVWA.
- Generating data about the safety of (substances in) food supplements.
- Providing honest information about food supplements to consumers because labels meet requirements and can be checked. Consumers can then make a more informed choice on the basis of the information available.
- The use of positive and negative lists of substances. It is also possible to rapidly assess whether the substances in question are novel foods or not admitted substances.
- The ability to supervise prohibited health claims.
- A (future) agreement on the safety assessment of food supplements.
- Contributing to the safety of food supplements in Europe through the timely exchange of information about high-risk supplements (for example via RASFF notifications) with other European countries.
- Contributing to the assessment of substances which could be prohibited in Europe according to Regulation (EC) no. 1925/2006.

The main disadvantages of a notification system are as follows:

- A notification system requires a contribution by expert assessors. Nevertheless, a system could be established which contains known information, for example about medicines or novel foods.
- Additional costs for the government and the sector.

Countries that have introduced a notification system, with different levels of requirements, have not evaluated the effects of the introduction of these systems. A harmonised notification system at European level (equivalent to an existing assessment system for novel foods or medicines, for example) would be the best solution.

10. Conclusions

- The consumption of all types of food supplements is increasing.
- Contrary to the intake of substances from other foods, there is no or only very limited specific legislation for food supplements, in particular herbal preparations.
- Little, if anything, is known about the composition of many food supplements, in particular those containing plant materials, and no quality requirements have been laid down for herbal preparations. There is legislation governing food supplements with vitamins and minerals, and there are clear rules on which chemical forms of vitamins and minerals are permitted to be used. However, as yet, no maximum daily amounts have been laid down in law.
- The use of all types of food supplements can represent a potential risk as a consequence of intrinsic substance properties, the properties of additives or interaction with other substances (for example medicines).
- Food safety and the ensuring of food safety are at a high level in Europe and the Netherlands, but food supplements and in particular those food supplements that contain multiple (bioactive) substances and herbal preparations represent an exception.
- There is no compulsory notification or registration of food supplements in the Netherlands, and the NVWA only has limited options for (quality and safety) checks. This represents a potential health risk for consumers.
- Member States are permitted to introduce a notification obligation in line with European legislation. According to European legislation, (herbal) medicinal products, novel foods, food additives, food flavourings, etc. are subject to compulsory notification and/or registration, prior to admission to the market.
- BuRO is unable to provide a detailed substantiation of the health risks of all food supplements because the necessary data are not available, and the group of food supplements is too diverse. It is also not possible, in advance, to calculate the effect on the health of consumers when the safety of food supplements is better ensured. However, the many reported cases suggest that serious health effects can occur through the use of food supplements.
- BuRO proposes a classification in 4 groups: 1) food supplements with vitamins and minerals, 2) single herbal preparations, 3) composite food supplements, and 4) food supplements that are effectively novel foods or (herbal) medicinal products.
- A notification system offers a solution for better ensuring the safety of food supplements and improving the provision of information to consumers and businesses.

11. Uncertainties

The most important uncertainties in this advice are the absence of evaluations of established notification systems already in use, the impossibility of providing a detailed (scientific) substantiation of the health risks of food supplements, in particular in the long term, and the absence of a clear picture of costs and benefits.

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APPENDIX 1

Office for Risk Assessment & Research

Date
4 March 2024**Fout! Onbekende naam voor documenteigenschap.**

Our reference
TRCVWA/2024/1058EN**Fout! Onbekende naam voor documenteigenschap.**

European and national legislation

Foods

In 1979, the European Court of Justice pronounced the principle of mutual recognition within the EEC. In 1999, this resulted in a notice from the European Commission to the Council and the European Parliament about mutual recognition in the framework of the follow-up to the action programme for the internal market. Following a series of food scandals in Europe, the General Food Law (Regulation (EC) no. 178/2002) came into effect on 28 January 2002, and the European Food Safety Authority (EFSA) was established. In other words, there has only been harmonised legislation on food safety in Europe since 2002; the Regulations and Directives apply in all Member States of the European Union. In the event of a conflict with national legislation, a European Regulation takes precedence over the national law. Member States are at liberty to elaborate the directives. The General Food Law guarantees the safety of food for consumers. Important principles are that food law must as far as possible be based on scientific insights and evidence, and that the system must encompass all links in the food production and food distribution chain, the so-called "from farm to fork" principle. To guarantee the availability of high-level independent scientific knowledge, EFSA was established as the advisory body for the European Commission. Another important principle is that the producer bears primary responsibility for the production of safe food.

The General Food Law applies to foods and feeds. In article 2 food is defined as: any substance or product, whether processed, partially processed or unprocessed, intended to be, or reasonably expected to be ingested by humans. Article 7 describes the precautionary principle: 'In specific circumstances where, following an assessment of available information, the possibility of harmful effects on health is identified but scientific uncertainty persists, provisional risk management measures necessary to ensure the high level of health protection chosen in the Community may be adopted, pending further scientific information for a more comprehensive risk assessment.'

No unsafe foods may be placed on the market. Articles 14(2), (3) and (4) of the General Food Law state that food shall be deemed to be unsafe if it is considered to be a) injurious to health or b) unfit for human consumption. In determining whether any food is unsafe, regard shall be had: a) to the normal conditions of use of the food by the consumer and at each stage of production, processing and distribution and b) to the information provided to the consumer, including information on the label or other information generally available to the consumer concerning the avoidance of specific adverse health effects from a particular food or category of foods. In determining whether any food is injurious to health, regard shall be had: a) not only to the probable immediate and/or short-term and/or long-term effects of that food on the health of a person consuming it, but also on subsequent generations; b) to the probable cumulative toxic effects; c) to the particular health sensitivities of a specific category of consumers where the food is intended for that category of consumers. In other words, food shall primarily be deemed unsafe if following regular preparation and consumption of that food, the consumer can become sick, or can expect a negative effect on health, in the short or long term.

Article 14(8) also states that if a food conforms with the specific provisions applicable to that food, this shall not bar the competent authorities from taking appropriate measures to impose restrictions on it being placed on the market or to

require its withdrawal from the market where there are reasons to suspect that, despite such conformity, the food is unsafe.

Where Member States, the European Commission or EFSA have information about the existence of a serious direct or indirect risk to human health relating to a food, this shall be reported to the European Commission via the Rapid Alert System for Food and Feed (RASFF) (Article 50).

Table 2 provides an overview of European and Dutch food-related legislation.

Table 2. Overview of relevant European and Dutch legislation on food.

Regulation	**Description**
Regulation (EC) no. 178/2002[46]	General Food Law
Regulation (EC) no. 852/2004[47]	Food Hygiene Regulation
Regulation (EU) no. 2017/625[48]	Organisation of official controls
Regulation (EC) no. 2073/2005[49]	Microbiological criteria for foods
Regulation (EU) 2023/915[50]	Maximum level for certain contaminants in foods
Regulation (EC) no. 396/2005[51]	Maximum residue levels of pesticides
Regulation (EC) no. 1924/2006[52]	Nutrition and health claims made on foods
Regulation (EC) no. 1925/2006[53]	Addition of vitamins and minerals and other certain substances to foods
Regulation (EU) no. 2015/2283[54]	Novel foods

[46] Regulation (EC) no. 178/2002 of the European Parliament and the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety.
[47] Regulation (EC) no. 852/2004 of the European Parliament and of the Council of 29 April 2004 on the hygiene of foods.
[48] Regulation (EC) 2017/625 of the European Parliament and the Council of 15 March 2017 on official controls and other official activities performed to ensure the application of food and feed law, rules on animal health and welfare, plant health and plant protection products, amending Regulations (EC) no. 999/2001, (EC) no. 396/2005, (EC) no. 1069/2009, (EC) no. 1107/2009, (EU) no. 1151/2012, (EU) no. 652/2014, (EU) 2016/429 and (EU) 2016/2031 of the European Parliament and of the Council, Council Regulations (EC) no. 1/2005 and (EC) no. 1099/2009 and Council Directives 98/58/EC, 1999/74/EC, 2007/43/EC, 2008/119/EC and 2008/120/EC, and repealing Regulations (EC) no. 854/2004 and (EC) no. 882/2004 of the European Parliament and of the Council, Council Directives 89/608/EEC, 89/662/EEC, 90/425/EEC, 91/496/EEC, 96/23/EC, 96/93/EC and 97/78/EC and Council Decision 92/438/EEC (Official Controls Regulation) (Text with EEA relevance).
[49] Regulation (EC) no. 2073/2005 of the Commission of 15 November 2005 on microbiological criteria for foods (Text with EEA relevance).
[50] Regulation (EU) 2023/915 on maximum levels for certain contaminations in foods and repealing Regulation (EC) no. 1881/2006.
[51] Regulation (EC) 2023/915 of the Commission of 25 April 2023 on maximum levels for certain contaminations in foods and repealing Regulation (EC) no. 1881/2006.
[52] Regulation (EC) no. 1924/2006 of the European Parliament and the Council of 20 December 2006 on nutrition and health claims made on foods.
[53] Regulation (EC) no. 1925/2006 of the European Parliament and the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods.
[54] Regulation (EU) 2015/2283 of the European Parliament and the Council of 25 November 2015 on novel foods, amending Regulation (EU) no. 1169/2011 of the European Parliament and the Council and repealing Regulation (EC) no. 258/97 of the European Parliament and the Council and Regulation (EC) no. 1852/2001 of the Commission (Text with EEA relevance).

Directive 2002/46/EC[55]	Approximation of the laws of the Member States relating to food supplements
Commodities Act Decree on the addition of micronutrients to foods[56]	
Commodities Act Decree herbal preparations[57]	
Commodities Act Decree food supplements[58]	
Commodities Act Decree food supplements[59]	

As Table 2 shows, the majority of legislation is recent. In addition, regulations are regularly supplemented (consolidated). Commodity Act Decrees often follow European Regulations or Directives, are regularly adjusted and must be developed over time.

Before they are admitted to the European market by the European Commission and the Member States, new foods are assessed for safety by EFSA. This assessment includes composition, production process, nutritional and toxicological properties.

Food supplements

Food supplements may contain different substances. To date, in Europe, legislation only exists relating to food supplements with vitamins and minerals. Directive 2002/46/EC defines food supplements in Article 2 as follows: foods 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, namely forms such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquids, drop dispensing bottles and other forms of liquids and powders designed to be taken in measured small unit quantities; and nutrients are: vitamins and minerals. Moreover, this Directive regulates which vitamins and minerals may be used in food supplements. Article 5 states that maximum amounts will be set, but this has not yet happened. At present EFSA is working on a revision of the tolerable upper intake levels. These will probably also be used for setting maximum amounts for the addition of vitamins and minerals to foods (Regulation (EC) no. 1925/2006, Article 6).

Article 10 of Directive 2002/46/EC states that 'To facilitate efficient monitoring of food supplements, Member States may require the manufacturer or the person placing the product on the market in their territory to notify the competent authority of that placing on the market by forwarding it a model of the label used for the product'.

[55] Directive 2002/46/EC of the European Parliament and the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements (Text with EEA relevance).
[56] wetten.nl - Regeling - Warenwetbesluit Toevoeging micro-voedingsstoffen aan levensmiddelen - BWBR0008065 (overheid.nl)
[57] wetten.nl - Regeling - Warenwetbesluit Kruidenpreparaten - BWBR0012174 (overheid.nl)
[58] wetten.nl - Regeling - Warenwetbesluit voedingssupplementen - BWBR0014814 (overheid.nl)
[59] wetten.nl - Regeling - Warenwetregeling voedingssupplementen - BWBR0014903 (overheid.nl)

Substances prohibited or restricted

Regulation (EC) no. 1925/2006 contains an article about substances prohibited or restricted, or which are under investigation by the European Community (Article 8). The procedure provided for in Article 8 is followed where a substance other than vitamins or minerals, or an ingredient containing a substance other than vitamins or minerals, is added to foods or used in the manufacture of foods under conditions that would result in the ingestion of amounts of this substance greatly exceeding those reasonably expected to be ingested under normal conditions of consumption of a balanced and varied diet and/or would otherwise represent a potential risk to consumers. In the judgement of EFSA, the European Commission may:

a) if a harmful effect on health has been identified, the substance and/or the ingredient containing the substance shall:

   i) be placed in Annex III, Part A, and its addition to foods or its use in the manufacture of foods shall be prohibited;
   ii) be placed in Annex III, Part B, and its addition to food or its use in the manufacture of food shall only be allowed under the conditions specified therein;

b) if the possibility of harmful effects on health is identified but scientific uncertainty persists, the substance shall be placed in Annex III, Part C.

Food business operators, or any other interested parties, may at any time submit for evaluation to EFSA a file containing the scientific data demonstrating the safety of a substance listed in Annex III, Part C, under the conditions of its use in a food or in a category of foods and explaining the purpose of that use. EFSA shall inform without delay the Member States and the Commission of the submission and shall make the file available to them. Within four years from a date a substance has been listed in Annex III, Part C, a decision shall be taken, in accordance with the procedure referred to in Article 14(3) and taking into account the opinion of EFSA on any files submitted for evaluation as mentioned in paragraph 4 of this Article, to generally allow the use of a substance listed in Annex III, Part C, or to list it in Annex III, Part A or B, as appropriate.

At present, Part A comprises 6 prohibited substances. Part B (Restricted substances) comprises 3 substances and Part C (Substances currently under investigation by the Community) comprises 5 substances.

Herbal preparations

A herbal preparation is a herbal substance, processed or unprocessed, which is intended for human use, including herbal extracts; a herbal substance is a substance consisting of plant material. In the Netherlands, the Commodities Act Decree Herbal Preparations came into force in 2001. This decree imposes rules for the use of herbs in foods such as food supplements. One of the reasons for this was that the herbs were traded as food supplements (foods). Because the composition of a herbal preparation is not (fully) known, the supervisory authority is not able to automatically assume the safety of the herbal preparations on offer. Known examples of herbs used in food supplements are valerian, garlic, ginkgo and St. John’s wort. The Commodities Act Decree Herbal Preparations states that herbal preparations may only contain herbal substances in amounts that are not harmful to public health and as such a number of substances are included that may not occur or only in limited amounts in herbal preparations. However, the legal status of herbal preparations is not harmonised in Europe.

The Commodities Act Decree Herbal Preparations is not applicable to kitchen herbs, spices and flavourings or the use of herbs in medicines and cosmetic products. Other regulations apply in these areas. Herbal preparations are not subject to any reporting or notification requirement; these preparations can be

placed on the market without informing the government (NVWA). Besides a number of prohibited herbs, the Commodities Act Decree contains no specific quality requirements. However, Article 6 of the Commodities Act Decree Herbal Preparations specifies that advice on use and dosage must be provided for herbal preparations.

Labelling

Consumers may not be misled by the labelling of foods. This applies to the properties of the food (for example composition, amount, shelf life) and the attribution of unproven effects or properties, and the suggestion of special properties also present in other foods. Regulation (EU) no. 1169/2011, Article 9, contains a basic list of mandated particulars for prepacked foods: a. the name of the food; b. the list of ingredients; c. allergen labelling; d. quantitative declaration of ingredients; e. net quantity of the food; f. date of minimum durability or use by date; g. special storage conditions and/or conditions of use; h. the name or business name and address of the food business operator responsible; i. the country of origin or place of provenance; j. instructions for use where it will be difficult to make appropriate use of the food in the absence of such instructions; k. percentage by volume of alcohol with respect to beverages containing more than 1.2% by volume of alcohol; and l. nutritional value.

Moreover (Article 32), the designation of vitamins and minerals must be expressed as a percentage of reference intakes per 100 g or 100 ml laid down in point 1 of Part A of Appendix XIII. Article 6 specifies that food supplements may not be labelled, presented or advertised as having the property to prevent, treat or cure human disease, nor may any suggestions of such properties be made in labelling, presentation or advertising. Labelling must contain the following mandatory elements:

a) the name of the categories of nutrients or substances that characterise the product, or information relating to the nature of these nutrients or substances;
b) the portion of the product recommended for daily consumption;
c) a warning about exceeding the recommended daily portion;
d) the notice that food supplements may not be used as a substitute for a varied diet;
e) a warning that the product must be stored out of the reach of young children.

Article 7 states that it may not be claimed or suggested in the labelling, presentation and advertising in respect of food supplements that a balanced and varied diet in general is unable to provide appropriate amounts of nutrients.

Existing articles in law apply to all food supplements. However, in particular for herbal preparations, little is known about their composition, and the mandatory labelling elements for food supplements are generally not complied with.

For many consumers, it is not entirely clear which foods are healthy and which food choices contribute to a healthy lifestyle. In the media, on websites, in vlogs and blogs, many health claims have been and continue to be made. In 2006, this led to a European regulation (Regulation (EC) no. 1924/2006) that restricts the use of health claims. Health claims must first be scientifically evaluated (by EFSA) before they are allowed to be used by the European Commission and the Member States. From 2010 onwards, manufacturers have no longer been able to place claims on their packaging or make advertising statements that mislead consumers.

Opium Act

Under the Opium Act[60], all activities involving products covered by the Opium Act are prohibited, unless an exemption has been granted. This is supervised by the Health and Youth Care Inspectorate (IGJ).

Medicines

The Dutch Medicines Act[61] is based on European Directive 2001/83/EC[62]. According to this Directive, a medicine is defined as (Article 1): a) any substance or combination of substances presented for treating or preventing disease in human beings; or b) any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions.

In the Dutch Medicines Act and the European Directive, a medicine is defined as: a substance or combination of substances which is intended to be administered or applied or is in any way presented as being suitable for:

1. treating or preventing a disease, defect, wound or pain in humans,
2. making a medical diagnosis in humans, or
   recovering, improving or otherwise altering physiological functions in humans by bringing about a pharmacological, immunological or metabolic effect.

Directive 2001/83/EC, Article 70, describes two groups of medicines: prescription medicines (subject to medical prescription) and non-prescription medicines (not subject to a compulsory medical prescription - self-care medicines). The classification of self-care medicines is determined individually by each Member State of the European Union. In the Netherlands, the following supply channels exist:

- General sales (GS, medicines with a relatively very low potential risk);
- Pharmacy and drugstore only (PDO, medicines with a relatively low potential risk);
- Pharmacy only (PO, medicines with a relatively mild potential risk);
- Doctor's prescription only (PO).

In the determination of the supply channel (by the Medicines Evaluation Board (MEB)), consideration is given to whether the user can use the product safely (concentration and dose of the active substance) and also whether the user is capable of making the right diagnosis and whether the chosen product is the right choice for dealing with the problem. The awarding of the supply channel status is therefore an additional safety guarantee that these products enjoy as a medicine and which distinguishes them from freely available food supplements, to be used at personal discretion (Tiesjema et al., 2013a).

In addition, medicines must have a patient information (package) leaflet assessed and approved by the MEB. A patient information leaflet is derived from the summary of the product properties.

Regulations relating to the labelling and patient information leaflet for pharmaceutical products are also laid down in Directive 2001/83/EC and in the Medicines Act.

Article 1(6) of the Medicines Act states that 'if a product, in so far as relating to properties, satisfies both the definition of a medicine and the definition of a product in another legal regulation, this Act applies without prejudice in respect of

[60] wetten.nl - Regeling - Opiumwet - BWBR0001941 (overheid.nl)
[61] Directive 2001/83/EC of the European Parliament and the Council of 6 November 2001 on the community code relating to medicinal products for human use.
[62] wetten.nl - Regeling - Geneesmiddelenwet - BWBR0021505 (overheid.nl)

that product'. In other words, the Medicines Act takes precedence over the Commodities Act.

A product can be classified as a medicine either on the basis of its presentation (presentation criterion) or on the basis of its effect (administration criterion). The presentation criterion is met if a product claims a therapeutic effect in respect of disease, or on the basis of a presentation which gives the average consumer the impression that it has a therapeutic effect. The administration criterion relates to the effect; the potential function of the product in the human body, irrespective of the presentation of the product (Tiesjema et al., 2011). In its legal proceedings, the European Court (see below) suggested that if the properties of a medicine are not scientifically proven but also cannot be excluded, the product is not subject to the Medicines Act.

Rulings by the European Court of Justice on the administration criterion

In 2007, the European Court of Justice, in a ruling on garlic capsules, determined that the fact that a product has a physiological effect is insufficient to refer to that product as a medicine. The product must actually have a preventive or healing effect. A product (in this case garlic capsules) whose influence on physiological functions is not greater than the effects that the consumption of a reasonable amount of food (in this case garlic) could have on these functions, does not actually influence the metabolism and may therefore not be characterised as a medicine according to its effect[63]. In another case in 2009 (the Hecht-Pharma ruling[64]), the European Court of Justice concluded that there must be a 'significant recovery or significant improvement or alteration to physiological functions through the bringing about of a pharmacological, immunological or metabolic effect', if a product is to be referred to as a medicine according to its effect. The fact that one or more medicinal plants are ingredients in a product is therefore not sufficient to conclude that this product is capable of recovering, improving or altering physiological functions, or bringing about a pharmacological, immunological or metabolic effect, or that on that basis, a medical diagnosis may be made. It is possible that such a product will have no effect on the physiological functions or will bring about insufficient effect for it to be a medicine according to its effect, for example because of the minimum quantity of active substance. A subsequent ruling in 2009 discussed the question of whether a product that contains an active substance in a dose that is too low to be effective can nonetheless be a medicine because it can engender risks. The ruling of the European Court of Justice was that a product that contains a substance that has a physiological effect if used in a particular dose is no longer a medicine according to its effect if, given the dose of the active substance and under normal use, it delivers a health risk, without actually recovering, improving or altering physiological functions in humans[65] (Tiesjema et al., 2011).

The principle operated by the European Court of Justice is that if the efficacy cannot be determined with any degree of certainty, a product does not meet the administration criterion and can therefore not be a medicine according to its effect.

<u>Herbal medicinal products</u>

Herbal medicinal products, also known as phytotherapeuticals, are medicinal products which as their active components contain exclusively one or more herbal substances, one or more herbal preparations or a combination of one or more herbal substances and herbal preparations. A herbal medicinal product is defined in the Dutch Medicines Act as: any medicinal product, exclusively containing as

[63] Ruling of the Court of Justice EC in case C-319/05 dated 15-11-2007.
[64] Ruling of the Court of Justice EC in case C-140/07 dated 15-01-2009.
[65] Ruling of the Court of Justice EC in case C-27/08 dated 30-04-2009.

active ingredients one or more herbal substances, one or more herbal preparations, or a combination of the two. This definition is identical to that in the European Directive. For the application of the Medicines Act, herbal medicinal product is also understood to mean a medicinal product that, in addition to one or more herbal substances, one or more herbal preparations or a combination of one or more herbal substances or herbal preparations, also contains minerals or vitamins as active ingredients, the safety of which is guaranteed on the basis of sufficient evidence and the efficacy of the vitamins or minerals supplements the efficacy of the active herbal ingredients with regard to the specified indications.

In 2005, the European Medicines Act was supplemented with a simplified registration procedure for herbal medicinal products. Just like other medicines, herbal medicinal products are subject to compulsory registration. In other words, they can only be placed on the market following registration by the MEB. The statutory evaluation criteria used by the MEB in this matter are: quality, efficacy and safety. For efficacy, an exception is made for herbal medicinal products with a long tradition in the European Union: the so-called traditional herbal medicinal products. For these products, the efficacy is not clinically tested but based on long-term use and experience. In the provision of supporting arguments, it must be demonstrated that the product or an equivalent product has been in use in medical practice for at least 30 years, of which 15 years in the European Union. A link must also be demonstrated between the period of use and the claimed application. In providing evidence for the period of use, reference may also be made to an equivalent herbal medicinal product. Equivalent shall be taken to mean having the same active ingredients (irrespective of the additives used), an equivalent concentration and posology (dose), an identical or comparable intended effect and an identical or comparable method of administration. If the composition of the product is altered, this shall only be accepted if substances are removed and not added.

Pharmacopoeia

A pharmacopoeia is an official handbook issued by the government containing regulations governing the preparation of medicines for human and animal use and the requirements they must meet. The European Pharmacopoeia has legal authority in Dutch territory, for both human and veterinary medicines[66]. The European Pharmacopoeia contains monographs for raw materials, products and packaging materials. The raw material monographs relate both to active ingredients and additives of chemical, biological or semisynthetic origin. The Pharmacopoeia also describes general requirements for forms of administration such as tablets or inhalation preparations, but also, for example, for radiopharmaceuticals, vaccines and herbal teas. Medicines manufactured and used in Europe must meet the legal requirements of the European Pharmacopoeia.

There are also pharmacopoeias for herbs (for example 'Haagse Handschriften'). Searching the EMA (European Medicines Agency[67]) database yielded 3234 hits for "herbal monograph" and 354 for "monograph" in the category herbal. For traditional herbal medicinal products there is a guideline from the Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA).

Pharmacovigilance and nutrivigilance

After medicines are registered, their safety is monitored (pharmacovigilance). The aim of pharmacovigilance is to prevent harmful consequences of the use of medicines. The Health and Youth Care Inspectorate (IGJ) checks whether trading

[66] Wat is de Europese Farmacopee | RIVM)
[67] European Medicines Agency | (europa.eu)

permit holders comply with the legislation and regulations on pharmacovigilance in the Netherlands and in the EU. They do this by means of inspections[68].

In the Netherlands, adverse reactions to food supplements can be reported to Pharmacovigilance Centre Lareb. In 2022, Lareb announced having received a growing number of notifications about products that fall into the grey area of non-registered health-promoting products, including supplements (De Boer et al., 2022). At present, there is no structural approach on how to deal with the notifications of adverse health effects (De Boer et al., 2022).

[68] Farmacovigilantie (Phv) | Geneesmiddelen | Inspectie Gezondheidszorg en Jeugd (igj.nl)

APPENDIX 2

Risk assessments by the Office for Risk Assessment and Research (BuRO) and RIVM (including contributions from UM and Lareb)

Year	Substance/food	Reference
2023	Huperzia serrata	
	Withania somnifera	
	N-acetyl-cysteine (NAC)	
	Tabernanthe iboga	
	Tribulus terrestris	
	Mucuna pruriens	
2022	Risk assessment of (herbal preparations containing) Salvia divinorum	(Zwartsen, 2022)
	Shambala	(RIVM & WFSR, 2022)
	The use of workout supplements by athletes in the Netherlands	(Razenberg-Gijsbers et al., 2021)
	Dangerous herbal preparations for sale through online shops	(van de Koppel et al., 2022)
2021	Food supplements with pharmacologically active substances	(BuRO, 2021)
	Risk assessment of herbal preparations containing St John's wort	(de Wit et al., 2021)
	Nine prohibited stimulants found in sports and weight loss supplements: deterenol, phenpromethamine (Vonedrine), oxilofrine, octodrine, beta-methylphenylethylamine (BMPEA), 1,3-dimethylamylamine (1,3-DMAA), 1,4-dimethylamylamine (1,4-DMAA), 1,3-dimethylbut https://www.rivm.nl/publicaties/risk-assessment-of-caffeine-in-food-supplements	(Cohen et al., 2021)
2020	Advice on the health risks of food supplements containing black cohosh	(BuRO, 2020a)
	Health risks of breastfeeding tea	(BuRO, 2020b; RIVM & WFSR, 2020)
	Risk assessment of caffeine in food supplements	(Buijtenhuijs et al., 2020)
	Beta-fenethylamine (FEA), beta-methylfenethylamine (BMFEA) and N-beta-dimethylfenethylamine (N,N-DMFEA)	(RIVM, 2020a)
	Evaluation of halostachine	(RIVM, 2020b)
	Evaluation of higenamine	(RIVM, 2020c)
	Evaluation of hordenine	(RIVM, 2020d)
	Evaluation of icariin	(RIVM, 2020e)
	Assessment of isopropyloctopamine	(RIVM, 2020f)
	Evaluation of methylsynephrine	(RIVM, 2020g)

2019	Argyreia nervosa	(Chen & de Wit-Bos, 2019)
2018	MMS	(BuRO, 2018a)
	Synephrine	(BuRO, 2018b; Tiesjema et al., 2018)
	Sibutramine	(BuRO, 2018c)
	DMAA, DMBA, DMHA	(RIVM, 2018b)
	Weight loss products	(RIVM & WFSR, 2018)
	Supplement with synephrine, caffeine, DMHA (octrodrine) and yohimbine	(RIVM, 2018a)
	The stimulant higenamine in weight loss and sports supplements	(Cohen et al., 2019)
	Use and safety of doping and sport food supplements	(van den Berg et al., 2018)
2017	2,4-dinitrofenol	(BuRO, 2017)
	MMS	(RIVM, 2017)
	On the use of food supplements: Potential adverse effects	(Vrolijk, 2017)
	The vitamin B6 paradox: Supplementation with high concentrations of pyridoxine leads to decreased vitamin B6 function	(Vrolijk et al., 2017)
	Four experimental stimulants found in sports and weight loss supplements: 2-amino-6-methylheptane (octodrine), 1,4-dimethylamylamine (1,4-DMAA), 1,3-dimethylamylamine (1,3-DMAA) and 1,3-dimethylbutylamine (1,3-DMBA)	(Cohen et al., 2018)
2016	Vitamin B6	(BuRO, 2016)
	History full circle: 'Novel' sympathomimetics in supplements	(Rasmussen & Keizers, 2016)
	Iron supplements and magnesium peroxide: an example of a hazardous combination in self-medication	(Vrolijk et al., 2016)
	Pharmacologically effective red yeast rice preparations marketed as dietary supplements illustrated by a case report	(Venhuis et al., 2016)
	Pharmaceutical doses of the banned stimulant oxilophrine found in dietary supplements sold in the USA	(Cohen et al., 2017)
2015	Pyrrolizidine alkaloids	(de Wit et al., 2014)
	Vitamin B6	(RIVM, 2015)
	Hemorrhagic stroke probably caused by exercise combined with a sports supplement containing-methylphenylethylamine (BMPEA): A case report	(Cohen et al., 2015b)
	A synthetic stimulant never tested in humans, 1,3-dimethylbutylamine	(Cohen et al., 2015a)

	(DMBA), is identified in multiple dietary supplements	
	Interactions between herbs and medicines: St John's wort	(Tiesjema et al., 2013c)
	Post-launch monitoring of foods and supplements with Krill oil and oil from microalgae Schizochytrium sp.	(Brosens et al., 2014)
2014	A methamphetamine analog (N,alpha-diethyl-phenylethylamine) identified in a mainstream dietary supplement	(Cohen et al., 2014)
	Active pharmaceutical ingredients detected in herbal food supplements for weight loss sampled on the Dutch market	(Reeuwijk et al., 2014)
	The supplement-drug interaction of quercetin with tamsulosin on vasorelaxation	(Vrolijk et al., 2015)
	A cocktail of synthetic stimulants found in a dietary supplement associated with serious adverse events	(Venhuis et al., 2014)
	Identification and quantitation of N,alpha-diethylphenethylamine in preworkout supplements sold via the Internet	(Lee et al., 2014)
	Sildenafil and analogous phosphodiesterase type 5 (PDE-5) inhibitors in herbal food supplements sampled on the Dutch market	(Reeuwijk et al., 2013)
	Vitamin D: maximum enrichment levels for foods and maximum daily dosage for supplements: Scenario-based mathematical substantiation	(Verkaik-Kloosterman et al., 2013)
2013	Black Cohosh (Actaea racemose)	(RIVM, 2013)
	Adulterated sexual enhancement supplements: more than mojo	
2012	DMAA	(BuRO, 2012)
	Towards a decade of detecting new analogues of sildenafil, tadalafil and vardenafil in food supplements: a history, analytical aspects and health risks	(Venhuis & de Kaste, 2012)
2011	Geranamine	(RIVM, 2011)
	The identification of a nitrosated prodrug of the PDE-5 inhibitor sildenafil in a dietary supplement: a Viagra with a pop	(Venhuis et al., 2011)
	Assessment of health claims, content, and safety of herbal supplements containing Ginkgo biloba	(Fransen et al., 2010)
2010	Geranamine	(RIVM, 2010)

2009	46 prohibited herbs in Part II of the appendix to the Commodities Act Decree Herbal Preparations	(van de Bovenkamp et al., 2009a)
	Chelidonium majus	(van de Bovenkamp, 2009b)
	Pilocarpus jaborandi	(van de Bovenkamp, 2009a)
	Red rice	(Jeurissen, 2009)
	Trends in drug substances detected in illegal weight-loss medicines and dietary supplements. A 2002-2007 survey and health risk analysis	(Venhuis et al., 2009)
	Assessment of the health risks of 'prohibited herbs'	(van de Bovenkamp et al., 2009b)
2008	Monkshood (Aconitum napellus)	(van de Bovenkamp, 2008)
	Risk assessment of botanicals and botanical preparations intended for use in food and food supplement: emerging issues	(Rietjens et al., 2008)
2002	An epidemic of epileptic attacks after drinking herbal tea	(Johanns et al., 2002)
2000	Active components in food supplements	(Siemelink et al., 2000)

Other RIVM publications on food supplements and herbal preparations

2008	A database for supplements: needs and actions	(Buurma-Rethans et al., 2008)
2011	An overview of European and national legislation for herbal preparations	(Tiesjema et al., 2013a)
2011	Legislation for herbal supplements: options for alteration	(Tiesjema et al., 2013b)
2011	Herbs: Commodities or Medicines. Advice on the administration criterion	(Tiesjema et al., 2011)
2013	Interactions between herbs and medicines: St John's wort	(Tiesjema et al., 2013c)