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NUTRIVIGILANCE OF FOOD SUPPLEMENTS IN EUROPE

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CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
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REVIEW

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

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ABSTRACT

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

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

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1. Food supplements (FSs)

EU legislation

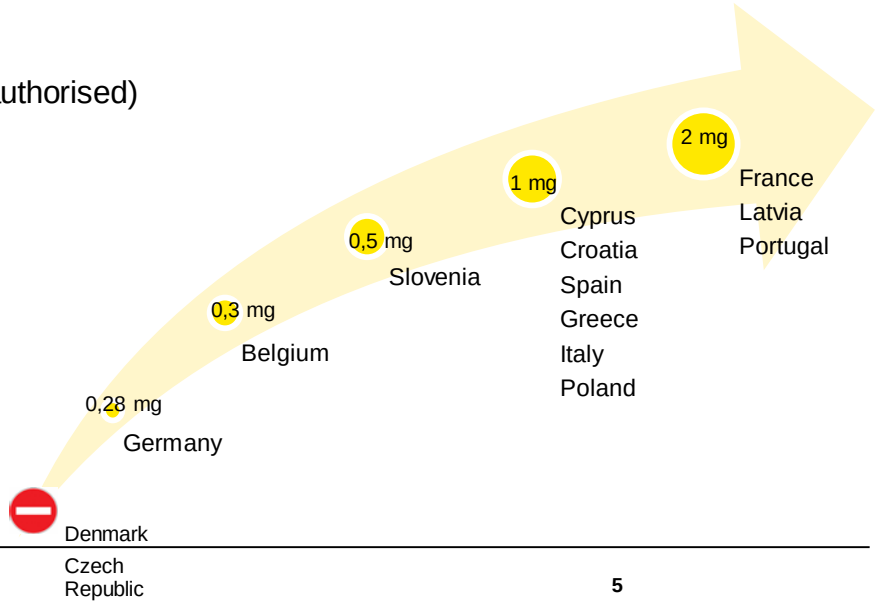
➢ **No harmonization of :**

- **FS compositions** : no positive or negative lists nor safety limits for most substances, plants, algaes…

Ex: regulatory status of melatonin in Europe (daily doses authorised)

An ingredient found acceptable in one European country may even be forbidden in another.

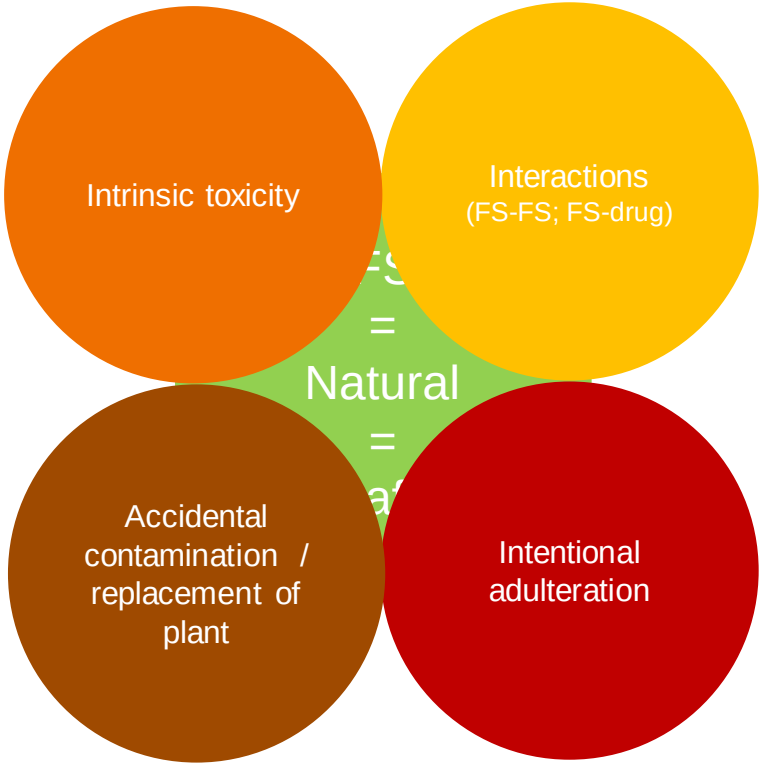
Despite this, they may be available all across Europe owing to the free cross-border movement and the internet.



EU legislation

- **No harmonization of :**
  - **FS compositions** : no positive or negative lists nor safety limits for most substances, plants, algaes…
  - **Pre-marketing obligations :** no common pre-market placement rules (20 EU countries established a notification system)
  - **Post-marketing surveillance.**
- **No pre-marketing efficacy studies** -> European claim regulation (claims on botanicals placed on hold)
- **No pre-marketing safety studies** -> the safety of the product is the responsibility of the manufacturer

Risks related to FSs

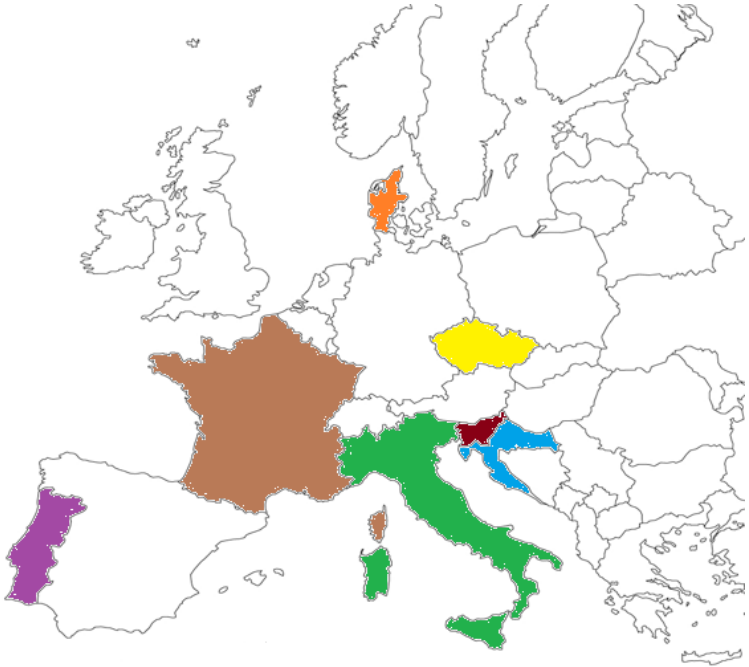


2. National vigilance systems for FSs

Denmark
Veterinary and Food Administration
73 reports (2014 –2020)

France
Anses
4863 reports (2009 - 2019)

Portugal
Ministry of Agriculture
136 reports (2014 – Mid 2020)



Czech Republic
National Institut of Public Health
37 reports (2015 – 2020)

Slovenia
National Institut of Public Health
107 reports (2016 - 2019)

Croatia
Institut of Public Health
6 reports (End of 2021 – mid 2022)

Italy
National Institut of Health
1480 reports (2002 – Mid 2020)

These systems aim to protect consumers by :

Early warning

- In case of serious effect (life-threatening) or near-miss
- Leads to the rapid implementation of management measures (market withdrawal…)

Risk assessment

- Help decision makers to implement management measures when needed (regulation, usage restriction, labelling obligation, market withdrawal…)
- Published on websites, scientific or general press
- Consumer information

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ANSES Opinion
Request No 2012-SA-0200

The Director General

Maisons-Alfort, 14 March 2014

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

on the risks associated with the presence in food supplements of *p*-synephrine or ingredients obtained from *Citrus* spp. fruits containing this substance

ANSES undertakes independent and pluralistic scientific expert assessments.
ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.
It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.

It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).

Its opinions are made public.
This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 14 March 2014 shall prevail.

On 6 August 2012, ANSES issued an internal request to conduct the following expert appraisal: Risks associated with the presence in food supplements of *p*-synephrine or ingredients obtained from *Citrus* spp. fruits containing this substance.

1. BACKGROUND AND PURPOSE OF THE REQUEST

The emergence in the general population of real or perceived overweight and obesity has led to a considerable increase in the consumption of food supplements claiming to reduce body fat and correct body composition. Some of these contain *p*-synephrine as well as other ingredients obtained from *Citrus* spp. fruits. In addition, given the recommendations to take regular physical exercise in order to combat overweight, some overweight subjects may combine consumption of these food supplements with physical exercise.

P-synephrine is found in the peel (epicarp and
and other species of *Citrus*.

Forty reports of adverse effects possibly rela
ingredient obtained from *Citrus* spp. fruits that
attention since its nutrivigilance scheme wa
admissible and contained enough information t
In this context, on 6 August 2012, ANSES iss
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within the nutrivigilance scheme.
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ORIGINAL ARTICLES AND REVIEWS

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Turmeric (*Curcuma longa* L.) food supplements and hepatotoxicity: an integrated evaluation approach

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Abstract

Introduction. Turmeric is the common name for the rhizome of *Curcuma longa* L. In the recent years, food supplements containing turmeric have been marketed and widely used by an increasing number of consumers. Spontaneous reports of suspected adverse reactions to food supplements are collected within the Phytovigilance system.

Methods. An ad hoc multidisciplinary group investigated the suspected cases of hepatotoxicity reported to the Italian Phytovigilance system associated with the assumption of turmeric food supplements with the methodology specific to pharmacovigilance as well as for the evaluation of the quality and safety of food supplements.

Results. A cluster of 28 spontaneous reports of acute hepatitis, mostly with cholestasis, associated with turmeric products were sent to the Italian Phytovigilance system in the first six months of 2019.
In all cases, except one, the causality assessment was at least possible. The suspected products were collected and analysed for the presence of drugs, heavy metals, aflatoxins, pesticides, synthetic dyes and pyrrolizidine alkaloids.

Conclusion. On the basis of the results of all the activities performed by multidisciplinary group, regulatory intervention was taken. This study highlights the importance of developing an integrated evaluation approach for the evaluation of the adverse effects associated with the use of food supplements.

Key words
- *Curcuma longa*
- food supplements
- adverse reactions
- food safety
- chemical analyses

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Raspberry ketone in food supplements – High intake, few toxicity data – A cause for safety concern?

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4-(4-hydroxyphenyl)-2-butanone
Food supplement
Weight loss
Threshold of toxicological concern
Margin of safety
Toxicity
Flavouring
Novel food
Natural

ABSTRACT

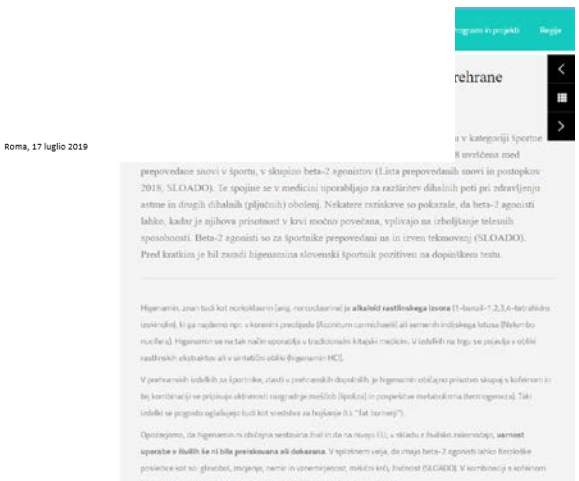
Raspberry ketone (4-(4-hydroxyphenyl)-2-butanone) is marketed on the Internet a
The recommended intake is between 100 and 1400 mg per day. The substance is n
raspberries (up to 4.3 mg/kg) and is used as a flavouring substance. Toxicological
ketone are limited to acute and subchronic studies in rats. When the lowest recom
raspberry ketone (100 mg) as a food supplement is consumed, it is 56 times the est
toxicological concern (TTC) of 1800 μg/day for Class 1 substances. The margin of saf
NOAEL of 280 mg/kg bw/day for lower weight gain in rats is 105 at 100 mg and
recommended doses are a concern taking into account the TTC and MOS. Investi
ketone in quantitative structure–activity relationship (QSAR) models indicated pot
fects and potential effects on reproduction/development. Taking into account the
plements, the compound's toxic potential should be clarified with further experin
the pure compound is regarded as novel food requiring authorisation prior to mar
ketone is not withdrawn from Internet sites from this country.

Centro Nazionale per la Ricerca e la Valutazione preclinica e clinica dei Farmaci

Dipartimento di Sicurezza Alimentare, Nutrizione e Sanità Pubblica Veterinaria

Segnalazioni di sospette reazioni avverse associate al consumo di integratori alimentari a base di curcuma: attività condotte dall'ISS

Roma, 17 luglio 2019



Similarities :

- Online reporting ;
- Voluntary based ;
- Reporters: healthcare professionals, manufacturers, consumers ;
- Under-reporting.

Reported cases

Unreported cases

- Insufficiently known systems
- Non-mandatory reporting
- Health professional is unaware that the patient is consuming FS (either because the question is not asked or because the patient does not mention it)
- FS not suspected by the consumer or health professional as they are considered "natural"

Differences :

- no harmonization of the data collection ;
- severity and causality assessment based on different methods.

3. Existing European systems for reporting on FSs safety

International Nutrivigilance network

Initiated in 2014 and driven by France

27 European countries + Brazil + Efsa (as an observer)

Aim: exchange of information on nutrivigilance

Monthly newsletter (n°94)

➡ No meetings due to lack of funding

Rapid alert system for food and feed (RASFF)

RASFF (1979) is a tool enabling the quick and effective exchange of information between Member States and the **European Commission** when risks to human and animal health are detected in the food and feed chain

Category of "dietetic foods, FSs and fortified foods"

Between 2003 and 2016 : only 13 RASFF notifications of adverse reactions related to this category

RASFF is not suitable for reporting FSs adverse effects.

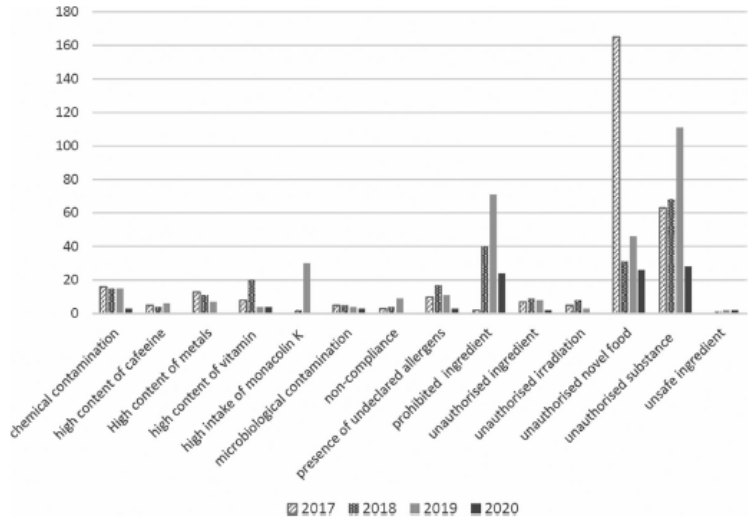


Figure 2. RASFF notifications from 2017 to 2020 in the category of "dietetic foods, FSs and fortified foods" according to the subject (European Commission 2021c). Besides the notifications reported in the table, subjects with less than five notifications are listed here: high content of nicotinic acid;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

Emerging risks exchange network (EREN)

Run by EFSA (2010)

“an emerging risk to human, animal and/or plant health is understood as a risk resulting from a newly identified hazard to which a significant exposure may occur or from an unexpected new or increased significant exposure and/or susceptibility to a known hazard”

Between 2016 and 2019 : 8 potentials issues concerning FSs were evaluated at EREN (6 considered as emerging issues)

Ex : Briefing note on hepatotoxicity associated with FSs containing Turmeric (Italy - 2019) -> follow-up unknown

(ID0412) Hepatoxicity associated with food supplements containing Turmeric

The Italian System for Phyto- and Nutri-Vigilance received 27 reports of hepatotoxicity associated with assumption of curcumin-containing supplements from December 2018 to June 2019. The concomitant use of drugs (mostly NSAIDs) was reported for 10/27, excluded for 7/27, the information was missing for 10/27. Some of the concomitant drugs are known or suspected to be hepatotoxic. Amongst the 10 cases with curcumin-drug association intake there were 2 cases of reported concomitant consumption of other supplements (not containing curcumin). The products involved were identified in 26/27 cases (one remained unidentified). The duration of use ranged from 8 days to 8 months (median 2 months). The reported hepatotoxicity was associated with a variety of products, in most cases having a high content of curcumin (50-1500 mg turmeric extract with 75-95% curcumin) often associated with other substances such as piperine (2.5-80 mg black pepper extract with 95% piperin) or in formulations that can increase absorption. The age of the cases ranged from 29 to 71 (median 55), 24/27 were females, 3/27 males. All but one were hospitalized with a diagnosis of acute hepatitis, most cases with cholestasis. In one case the hepatitis was diagnosed occasionally during a checkup. The declared reasons for using turmeric/curcumin supplements were weight loss, articular pain and osteoporosis. Some cases reported generic motivations like detoxification, supplementation and antioxidation. In 2010, the EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) re-evaluated curcumin (E 100) as a food additive. The ANS Panel established for curcumin an Acceptable Daily Intake (ADI) of 3 mg/kg body weight (bw)/day. Its exposure assessment was refined by EFSA in 2014.The intake of curcumin varied widely, in some cases also below the ADI of 3 mg/kg bw/day. However, the ADI is referred to life-long intake as a toxicological threshold, therefore, not to be used as a reference for toxic potential of short-term consumption of amounts above the ADI. EMA in its "Assessment report on Curcuma longa L., rhizome - EMA/HMPC/329745/2017" adopts the following warning related to the potential effect on bile secretion "Due to the nature of the potential effect on bile secretion it is not recommended to use C. longa preparations in case of obstruction of the bile duct, cholangitis, liver disease, gallstones and any other biliary diseases

Author	Classification[b]	New driver[c]	New hazard[c]	New/ increased exposure[c]	New/ susceptible group[c]	Recommendations of the emerging risk knowledge networks[d]
EREN-ITALY	Chemical hazard - New consumer trends	Y	N	Y	Y	**EREN recommendations** EFSA/BVL to consider a presentation for the 2020 workshop on Super foods in Berlin on emerging risks in food supplements

National vigilance systems for FSs could be a valuable source of information on emerging risks

4. The need for a European Nutrivigilance System

How to harmonize nutrivigilance systems in Europe ?

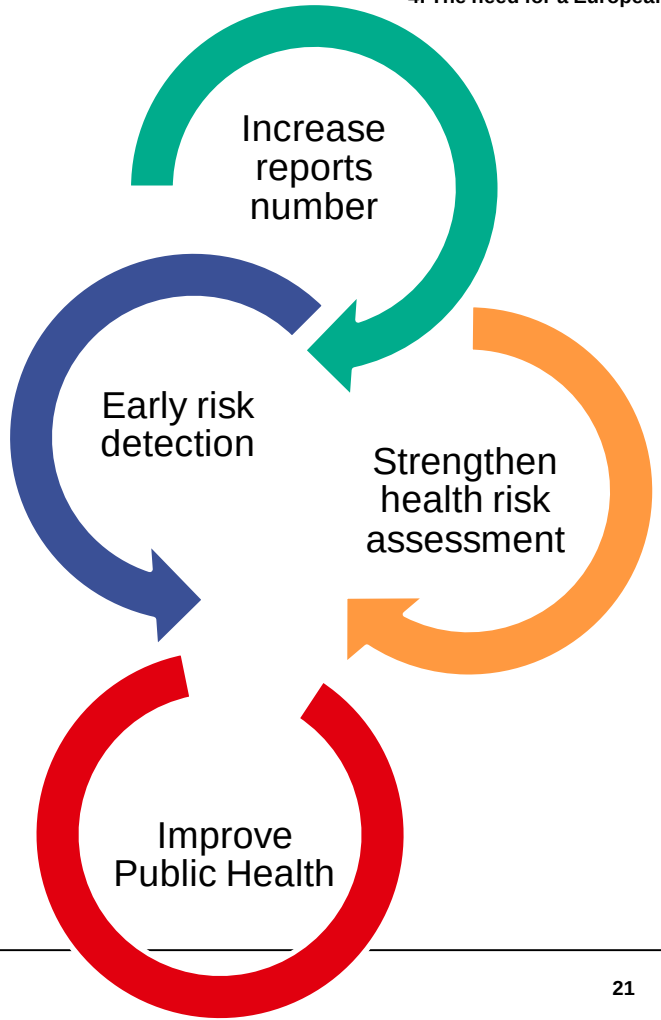
Harmonization of :

- nutrivigilance requirements in European countries ;
- data collection;
- severity and causality assessment methods.

➡ **Will allow to have a common understanding and to facilitate exchanges of information**

Common and centralized database ?
(ex: Eudravigilance for medicinal products)

What is expected from a European harmonized nutrivigilance system?



Final objective:

to improve public health by helping decision makers to implement management measures when needed and to set/adjust legal requirements at the European or country levels

A European harmonized nutrivigilance system will allow to achieve this objective more quickly and efficiently with less duplication of risk assessment

Thank you for your attention

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