



## OPINION PAPER

# FOOD SUPPLEMENTS: THE EUROPEAN REGULATION AND ITS APPLICATION IN FRANCE. THOUGHTS ON SAFETY OF FOOD SUPPLEMENTS

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### Abstract

The first definition of food supplements in France was established by decree 96-307 of April 10<sup>th</sup> 1996. In 2002, the European Community adopted a regulation for food supplements (European Directive 2002/46/CE June 10<sup>th</sup>). This was an important event in the regulation of food supplements. The European regulation was adopted in France, with some modifications, by decree 2006-352 of March 20<sup>th</sup> 2006. The European Regulation on food supplements is more defined than those for any other food types and is exemplary. The Regulation on addition of vitamins and minerals to food differs from the regulation on the addition of other substances such as amino acids, essential fatty acids, fibers, carbohydrates, various plant, and herbal extracts. While the Regulation includes vitamins and minerals to the positive list of supplements, other substances are included in the negative list of supplements. According to the Regulation, substances added to food supplements must have a nutritional or physiological effect. The increased use of food supplements led to the creation of a department specialized in the safety of food supplement. The safety of food supplements is a permanent concern for sanitary authorities. These authorities have recently combined scientific methodological approaches and a collective expertise to implement and monitor simple and useful rules that insure consumer's safety. Safety laws aim to protect the consumers of food supplements.

**Key words:** Safety, adverse effects, toxicology, dietary supplements, claim, complementary and alternative medicine, Nutriviigilance, European regulation, ANSES.

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### WHY SUCH AN INTEREST FOR FOOD SUPPLEMENTS IN FRANCE?

The first definition of food supplements in France was established by decree 96-307 of April 10<sup>th</sup>, 1996. This definition, by giving a first « official » existence to food supplements, promoted a more frequent use by French consumers. Today, food supplements are used by one third of French households. The food supplement market has created considerable media attention and financial stakes, as exemplified by the purchase of Oenobiol by Sanofi Laboratory; or by the partnership created by Nestlé and L'Oréal to promote Innéov Laboratories. Examples like these are abundant. However, one must keep in mind that food supplements have always been part of French culture and society, as exemplified by the traditional use of cod liver oil (intake of EPA and DHA omega 3 fatty acids, and vitamins A and D), brewer's yeast, royal jelly, etc.

Then why such a renewed interest for food supplements in France? Estelle Saget's journalistic article entitled « Are food supplements good for you ? » [Saget E., Les compléments alimentaires font-ils du bien ?] (L'Express, France February 11<sup>th</sup>, 2010) explains that the French love those products that are believed to improve their health, body shape, and beauty. Alongside of this renewed interest, the European Regulation that was established in 2002 further emphasized the need and use of food supplements,

with an obligation to change the national regulation. Its adoption in France, by a decree in 2006 [11], led to some modifications of the Regulation that included the possibility of using ingredients with physiological effects as well as the necessity of a clear acceptable product definition by the DGCCRF (General Direction for the competition, consumption and fraud prevention) prior to their commercialization, which mandated a formal process for authorization.

Consequently, the increased use of food supplements led to the creation of a department specialized in the evaluation of their safety and the publication of consumer alerts about product safety through the declaration of adverse side effects. The forms for adverse side effects are shown in figures 1 and 2. The setting in France of a similar vigilance to the drugs (i.e., pharmacovigilance) for nutrition supplements now exists; the general frame of « nutriviigilance » (<http://www.ansespro.fr/nutriviigilance/index.htm>) is within the AFSSA (now ANSES) according to the law "HPST" (<http://www.sante.gouv.fr/la-loi-hopital-patients-sante-et-territoires.html>).

The objectives of this European action, committed to regulating food supplements, were to bring benefits and increased safety for the consumer, and also to help create new products with evidence coming from research (with the concept of evidence-based nutrition) that fit within a more precise framework that regulates European indus-

tries involved in food supplementation.

The creation of the European regulation on nutritional or health claims responds to a need, created by a general use of « health » references associated to food products, and in particular to food supplements. The Regulation uses scientific reference texts such as PASSCLAIM to support its

contentions about food supplementation safety. The PASSCLAIM is a major publication and an example of collaborative work between scientists from academia and industry [5]. To summarize, a health claim must be 1) clearly justified, 2) based on accepted scientific evidence, and 3) should be well understood by the average consumer.



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Nom \*  ou cachet du déclarant

Adresse

Ville \*  Code postal \*

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Télécopie

Adresse électronique

**B - Données relatives au consommateur**

Nom \* (2 premières lettres)  Prénom (première lettre)  Age  OU Année de naissance (aaaa)

Sexe  Homme  Femme Grossesse en cours  oui  Non  Ne sait pas

Poids en Kg (Nombre entier)  Profession

Antécédents du consommateur  
 sans information

**C - Compléments alimentaires suspectés**

	Complément Alimentaire 1	Complément Alimentaire 2	Complément Alimentaire 3
Nom commercial*	<input style="width: 100%;" type="text"/>	<input style="width: 100%;" type="text"/>	<input style="width: 100%;" type="text"/>
Laboratoire - société	<input style="width: 100%;" type="text"/>	<input style="width: 100%;" type="text"/>	<input style="width: 100%;" type="text"/>
N° de lot	<input style="width: 100%;" type="text"/>	<input style="width: 100%;" type="text"/>	<input style="width: 100%;" type="text"/>
Usage - fonction Exemple : Pour mincir, pour rester en forme, ...	<input style="width: 100%;" type="text"/>	<input style="width: 100%;" type="text"/>	<input style="width: 100%;" type="text"/>
Type(s) (Plusieurs choix possibles)	<input type="checkbox"/> Vitamines - Minéraux <input type="checkbox"/> Plantes <input type="checkbox"/> Protéines-Acides Aminés <input type="checkbox"/> Ne sait pas <input type="checkbox"/> Autre	<input type="checkbox"/> Vitamines - Minéraux <input type="checkbox"/> Plantes <input type="checkbox"/> Protéines-Acides Aminés <input type="checkbox"/> Ne sait pas <input type="checkbox"/> Autre	<input type="checkbox"/> Vitamines - Minéraux <input type="checkbox"/> Plantes <input type="checkbox"/> Protéines-Acides Aminés <input type="checkbox"/> Ne sait pas <input type="checkbox"/> Autre

Figure 1. Related document for Adverse side effect reporting by health professionals, consumers and industry for health supplements in France.

	Complément Alimentaire 1	Complément Alimentaire 2	Complément Alimentaire 3
Lieu d'achat	<input type="radio"/> France <input type="radio"/> Hors France <input type="radio"/> Internet <input type="radio"/> Ne sait pas	<input type="radio"/> France <input type="radio"/> Hors France <input type="radio"/> Internet <input type="radio"/> Ne sait pas	<input type="radio"/> France <input type="radio"/> Hors France <input type="radio"/> Internet <input type="radio"/> Ne sait pas
Date du début de la consommation	/ /	/ /	/ /
Date de fin de la consommation	/ /	/ /	/ /
Dose de consommation (Exemple : 2 comprimés/jours)			
Réversibilité des effets à l'arrêt	<input type="radio"/> Oui <input type="radio"/> Non <input type="radio"/> Ne sait pas	<input type="radio"/> Oui <input type="radio"/> Non <input type="radio"/> Ne sait pas	<input type="radio"/> Oui <input type="radio"/> Non <input type="radio"/> Ne sait pas
Reprise de la consommation du produit	<input type="radio"/> Oui <input type="radio"/> Non <input type="radio"/> Ne sait pas	<input type="radio"/> Oui <input type="radio"/> Non <input type="radio"/> Ne sait pas	<input type="radio"/> Oui <input type="radio"/> Non <input type="radio"/> Ne sait pas
Si oui, l'effet indésirable est-il réapparu ?	<input type="radio"/> Oui <input type="radio"/> Non <input type="radio"/> Ne sait pas	<input type="radio"/> Oui <input type="radio"/> Non <input type="radio"/> Ne sait pas	<input type="radio"/> Oui <input type="radio"/> Non <input type="radio"/> Ne sait pas
<b>D - Description de l'effet indésirable</b>			
Date d'apparition des premiers effets	/ /	Durée de l'effet	
Description, et évolution *			
<b>E - Consommations associées important pour juger de l'imputabilité du complément alimentaire dans l'apparition de l'effet indésirable</b>			
Prise de produits associés dont médicaments ? (posologie, nom commercial...)			
<input type="checkbox"/> sans information			
Alcool	<input type="radio"/> Oui <input type="radio"/> Non <input type="radio"/> Ne sait pas	Quantité	
<b>F - Commentaires éventuels</b>			

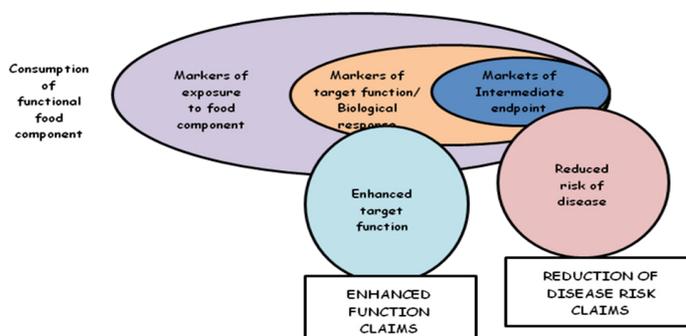
Figure 2. Related document for Adverse side effect reporting by health professionals, consumers and industry for health supplements in France.

THE « PASSCLAIM »

The PASSCLAIM, « the process of evaluation of the scientific support on claims about food products », is a plan of action which involves the collective thinking of hundreds of researchers. It provides the background and scientific criteria that are useful for the development of the European Regulation. It also aims at **an international scientific standard of a higher quality** for a coordinated and transparent evaluation of the evidence necessarily presented to the claim of any type of food. Peter Aggett [4] summarized the main evidence in the 2005 PASSCLAIM. That evidence must consistently be evaluated according to the following criteria : (1) characterization of the type

of food or dietary ingredient to which the invoked effects are attributed; (2) the data for humans, relying mostly on studies of intervention which represent target populations for the claim; (3) a dosage effect relationship; (4) the evidence allowing for definition of the confounding factors, such as the life-style, the way of consumption, the basic nourishment, and the dietary matrix, etc.; (5) an appropriate duration for the study; (6) a compliance measurement; and (7) strong and efficient statistics to verify the hypothesis. In addition, it is also important to use markers (i.e., biomarkers if available ) to evaluate the efficacy of the food supplements. These markers could be indicators for intermediate effects or final results. They have to be validated on a biological level, evaluated by a validated

method (insurance quality, BPL, etc.). Lastly, a global consistency and the complete evidence of published and un-published reports must be taken into consideration in the process of evaluation. These requirements are not easy to fulfill since there are always controversies associated with any claim. The evaluation is based on judgment of experts, with a balance on the strength of the claim, and a reasonable use of the applied criteria on an individual basis that takes into account the lack of knowledge and the possible necessity of additional knowledge and new data. The concept of PASSCLAIM was first planned by the FUFOSSE project (FUNCTIONAL FOODS SCIENCES IN EUROPE, 1999) combining scientific evidence with a matching health claim as is shown in figure 3 [2]. To define a claim that involves reducing a risk factor of a disease, there is a need to demonstrate a relationship between the food and the consumer's response to the food supplement. Example of intermediate markers include the reduction of LDL-cholesterol or the decrease of blood pressure, both strongly linked to the prevention of coronary and cardiovascular diseases (myocardial infarction, heart failure, total mortality and cardiovascular).



**Figure 3.** FUFOSSE Concept, scientific evidence and health claims (adapted from [2]).

## WHAT IS THE CURRENT STATUS OF REGULATION FOR FOOD SUPPLEMENTS IN EUROPE?

The status of food supplements was previously under the responsibility of each member of the European Union, wherein each country had its own laws or, in some cases, no laws. The European Commission wished to establish a European consensus for food supplements.

The main applicable regulations for food supplement are compiled in figure 4 (modified from the European Botanical forum).

The fact that food supplements are one of the more regulated among the different types of food needs to be emphasized. These regulations are numerous, comprising laws related to general foods, novel foods, specific food supplements, food hygiene, pesticides residues, contaminants, health claims, additives legislation, fortification, and labeling.

The former paperwork maze can be linked, for the food supplement, to the notion of « nutraceutical » because it is comparable to the general use of drugs (i.e., pharmaceutical) employed to improve health. However, it led to illegal exercise of their regulation in some European countries whereas in others, a national regulation prevailed. However, the treaty of Rome allowed for a complete freedom in the use of food supplements throughout Europe, according to the principle of mutual recognition.

Historically in France, the first mention defining food supplements dated from 1996 with the decree of April, 10<sup>th</sup> (synthesis article: Nutriform, special issue-food supplements as medical, Mach 2009, and www.synadiet.org). This decree defined *food supplements* as « *products designed to be ingested as supplement for daily food, in order to compensate for the real or supposed lack of daily intakes* ». Despite the actual definition, no texts gave a specific regulatory status to food supplements in France. Although sometimes associated to food supplement regulation, the old decree of April 15<sup>th</sup>, 1912 does not apply to modern food supplements. The **founding directive for food supplements** was adopted in Europe in 2002 (**European Directive 2002/46/CE June, 10<sup>th</sup>, 2002**). France was subsequently condemned in September 2005 by the European community Court for not adopting this directive. Finally, France adopted the directive according to the 2006-352 decree of March 20<sup>th</sup>, 2006.

This new regulation gives to food supplements a specific status and constitutes a major progress. According to the texts, food supplements are : « **food products which aim to complete the usual diet and which constitute a concentrated source of nutrients or of other substances having a nutritional or physiological effect on its own or combined on doses shapes, namely, the shapes of presentations such as gel capsules, pastilles, tablets pills, and other similar shapes, as powder bags, liquids phials, bottles with a dropper and other analogous shapes for liquids or powders preparations designed to be taken in small and measured quantities** ».

A major novelty is the **notion of physiological effects and properties** that affect the human body. However, this notion is linked to the broad definition of drugs, which can sometimes narrow the distinction between food supplements and drugs. Since it is difficult to define the physiological and physiopathological limits, two aspects that distinguish food supplements from drugs can be noted: 1) for the drug, the physiology is associated with a pharmacological effect (or immunologic and metabolic); and 2) a meaningful therapeutic activity (or therapeutic claim) is required for the drug. However, pharmacology is the science of the living organisms' response to chemical stimuli (according to H. Schmitt, *Éléments de Pharmacologie* (elements of pharmacology), Flammarion) and the question remains: do we need a new discipline that defines these innovations with food supplements, i.e., **supplementology**?

## THE EUROPEAN DIRECTIVE 2002/46/CE

### WHY SUCH A DIRECTIVE?

The directive was created to protect the consumer. This was necessary because of a number of factors, including the increasing numbers of food supplement products in the market, the diversity of the regulations used by each European member, the diverse life-style in European countries, the wide use of food supplements (i.e. vitamin D, iron, folic acid, vitamin B12), or the great number of ingredients in the composition of the food supplements.

The agreement between European members gives the condition for the use of nutrients (vitamins and minerals and their intake of substances). A positive list for the food supplements was created. Likewise, a specific label for food supplements was defined. The directive plans were to

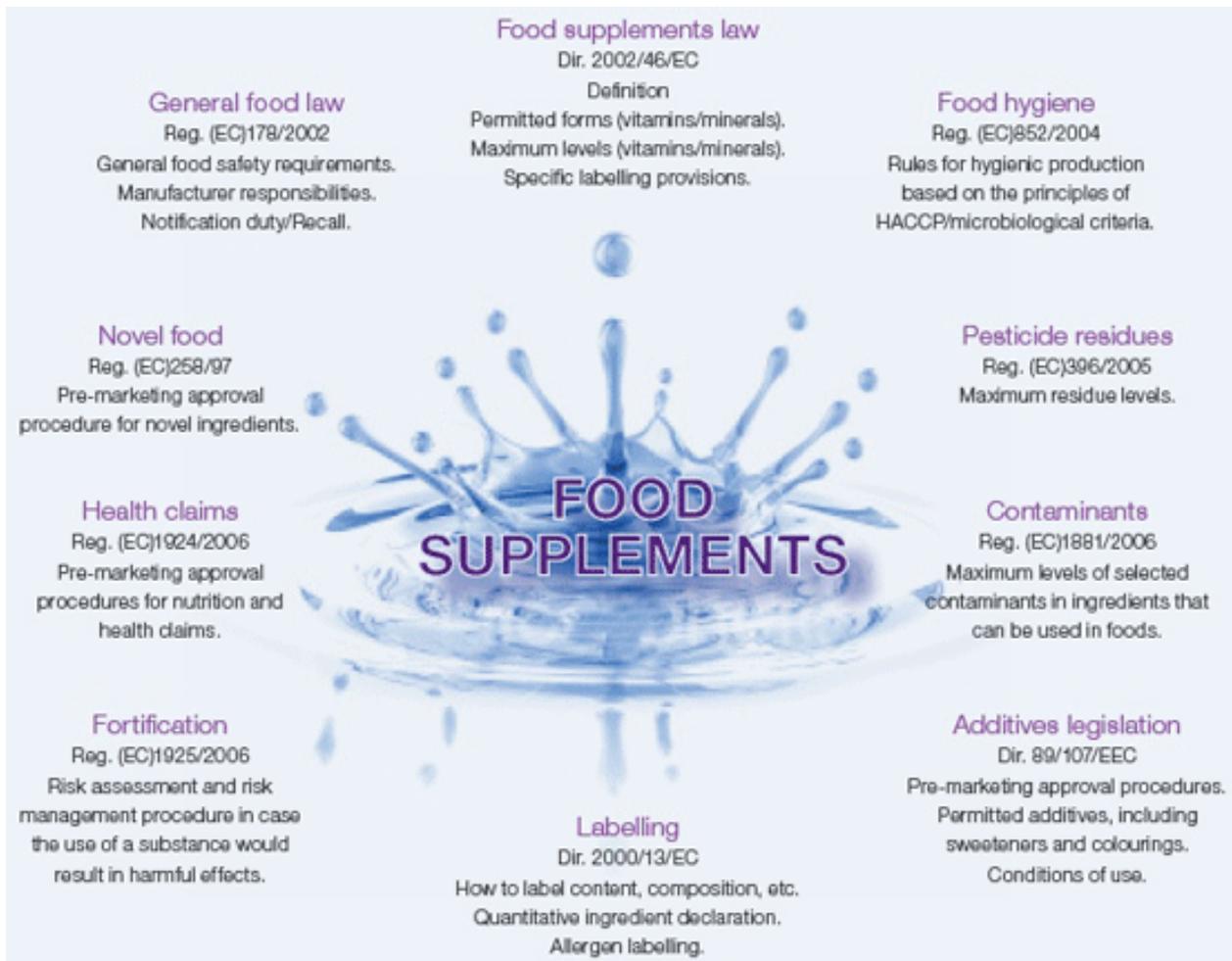


Figure 4. Main regulation applicable to food supplements in EC adapted from European Botanical Forum [8].

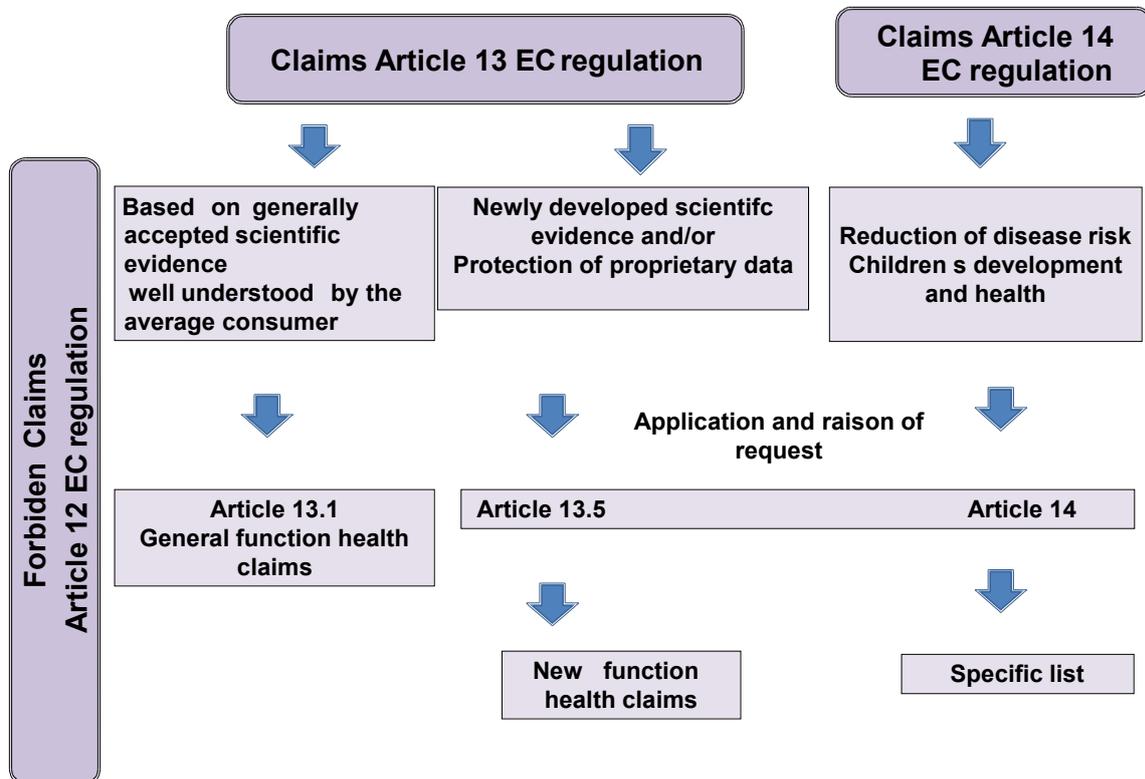


Figure 5. Health claims EC regulation.

eventually regulate other substances i.e., plants. However, these plans have been postponed by regulation 1137/2008 (appendix concerning the directive 2002/46/CE) in favor of the existing general procedures of regulatory modifications.

The harmonization in Europe of the use of vitamins and minerals (with the exception of the daily maximum quantities) lead to the publication of a positive list of 13 vitamins and 15 minerals that can be used in the making of food supplements (i.e., calcium, carbonate, chloride, citric acid, gluconate, orthophosphoric acid, hydroxide, and oxide).

The regulation policy facilitates marketing in every European member, labeling, connection to legislations, control of the products and, ultimately, the protection of the consumer.

#### **ADOPTION OF EUROPEAN DIRECTIVE 2006/352 DECREE OF MARCH, 20<sup>TH</sup> 2006**

In this decree article, the definition of food supplements is the same as in the European directive (article 2). It also contains the same list of vitamins and minerals to be used (article 5). The substances aimed at nutritional and physiological effects such as amino acids, essential fatty acids, probiotics, antioxidants are stated in article 6. There is also a list of 145 plants registered in pharmacopeia allowed for sale, out of the pharmaceutical circuit, by the decree 2008-841 (article 7).

In this decree, the authorization and notification processes are also defined. Thus, article 15 requires every food supplement to be declared to the DGCCRF at the same time as it is in the market, if it complies with the French regulation. Article 16 requires registration with the DGCCRF two months before the product is in the market when the food supplement contains an ingredient missing from the French list but authorized by one of the states of the European Union. The DGCCRF must reply within two months and may reject the product if there is a proof of a risk for human health. This decree represents a main advance for the manufacturer, the retailing groups, and food supplement consumers. Europe highly increased the claims used during the marketing of these products to further protect the consumer.

#### **CLAIMS**

The claim needs to be clearly defined. Every message or representation, non compulsory by virtue of the community or national legislation, representation such as images, graphic elements or symbols, regardless of its shape, which asserts, suggests or implies that a food product possesses some particular characteristics (regulation (EC) n° 1924/2006 of the European Parliament and of the December, 10th, 2006 council).

The regulation defined three distinct claims:

**The «nutritional claim»** includes every claim which asserts, suggests or implies that a food product possesses some nutritional properties beneficial for the energy (calorie value) it gives, given to a lower or a higher degree, or even do not give at all, and/or the same way; it also must indicate the nutrients or the other substances it contains, at a lower, or a higher proportion, as well as not containing any. Such claims are based on the analysis of the nutritional profile of the product, its energy value, its capacity to

provide or not provide a type of nutrient (ex. unsaturated fatty acids, foods with lower amounts of sugar, saturated fatty acids or sodium, etc.). They must be supported by concise scientific evidence. Thus, reports about Recommended Daily Amount (RDA) and a concise analysis of a substance are required to support a claim of the type « provides 30% of calcium RDA ».

**The «Health claim»** includes every claim that attests, suggests or implies the existence of a relation between a category of food products or one of its components and health. This claim makes reference to a state of a physiological well being in absence of disease(s). In this case, the claim is linked to the prevention and not to the therapeutic effect. This refers to the notion of physiological effect introduced by the 2002/46/CE European directive. These claims must be specific to a function or a product, supported by a scientific document which clearly describes the evidence of such a relationship. An example of such claim would be « Omega 3 fatty acids contribute to improved cardiovascular function ».

**The «Specific claim on reducing of the risk of disease»** includes every health claim that attests, suggests, or implies that the consumption of one category of food products, one food product or one of its components perceptibly reduces a risk of the development of the human diseases. This type of claim allows us to get closer to the frontier of therapeutics and drugs and this is where physiology and physiopathology become difficult to discern. It seems it has been difficult for the food supplement manufacturers to evolve at the frontiers of this type of claim.

Two types of health claims can be distinguished: one functional (article 13) and the other one specific (article 14) for food supplements. A rejection is registered according to article 12 and the use of this claim is forbidden and notified in EC. The definitions that are defined according to the articles 13 and 14 in figure 5 are identified according to three possibilities and usable lists of claims.

Considering the new rules that govern marketing and advertising of food supplements, the gathering of scientific evidence for a product becomes necessary. The safest way to acquire the evidence is by carrying out clinical trials that are double blind, controlled and randomized using appropriate placebo. This type of approach is unanimously accepted as the standard by the scientific community.

Randomized controlled tests (RCT) are the standard for therapeutic drug trials. However, it is still an experimental model. Currently, the same standard is required, every time, for studies supporting food supplements claims. As emphasized by Asp and Bryngelsson in 2008, observational studies for the generic claim result in a major methodology for the evidence [6]. Furthermore, pragmatic trials, closer to real life (naturalistic trials), which include observations of comparative cohorts and non randomized studies, can be relevant as reported by Vray et al. [25]. As recently outlined by Richardson [20], the scientific framework for health claims need to be reassessed. The “Proclaim” with a standardized approach proposed by Gallagher et al [13] should be considered. In the case of food supplements, the use of a placebo is not always justified. Indeed, a placebo is not always applicable for food studies, with the exception of novel foods, since foods are typically consumed at levels different from zero. An explanation is thus necessary to define the evidence on a case by

case basis. Clinical evidence for food supplements could be demonstrated by comparing a control group with very low intake to the appropriate dosage defined by the claim and/or by withdrawal trial like “Radiance” for the use and efficiency of digoxin in congestive heart failure [18].

### PROTECTION OF THE CONSUMER INTERESTS: THE PRECAUTIONARY PRINCIPLE

The food legislation (figure 4) introduced a new concept aimed at protecting the interests of the consumers: the precautionary principle. It was introduced after a series of health-related scandals that included use of growth hormone, contaminated blood, mad cow disease, avian influenza..., and the most recent examples of GMO (genetically modified organism) foods and influenza A. A report to the French Prime Minister, written by Philippe Kourilsky and Geneviève Viney on October 15<sup>th</sup>, 1999, defined the state of art for the precautionary principle. We need to remember, however, that we have to add to the precept of common sense « when in the doubt, don't do anything » and the principle: « do your best to act better », as shown in figure 6. The principle of precaution implies that research needs to be conducted to assess possible risks. This important point is sometimes overlooked [16, 17]. These elements bring out the consumer's awareness and some basis of how to choose the food. All this admits the prevention of illegal practices, and the falsification of food with an appropriate labeling approved for food supplements. A better future is still possible, with the implementation of traceability for food supplements according to the principles of the HACCP [24].

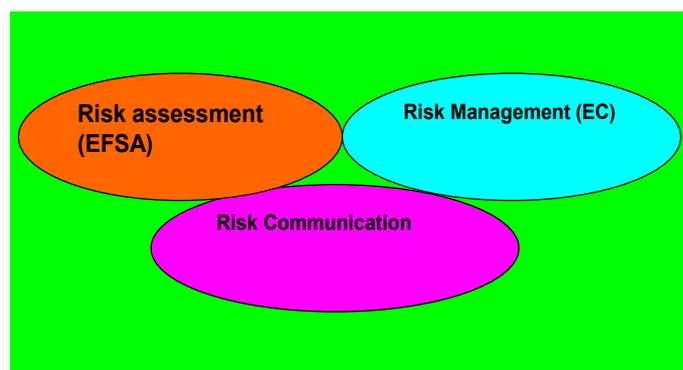
### THE SAFETY OF FOOD SUPPLEMENTS

We will first address the safety of food supplements. An article published in N° 464 of the French magazine “Que choisir” in November 2008 proposed a theory against food supplements in France. His title was « Vitamin C, omega 3, Slimness, food supplements phoney! and occasional health hazards (Vitamine C, oméga3, minceur, compléments alimentaires. Bidon! Et parfois dangereux pour la santé) ». The question that we wish to address here is « health hazard ». The outlined theory is that three families of food supplements are unsafe and that the efficiency of food supplements is questionable. We will use the experience acquired with the drug Ephedra, the principles of safety, and lastly the calculation of the limit of safety that allows protection the consumer. Our goal is to provide a comprehensive, objective and balanced scientific view of the two schools of thoughts: « the antis' and the pros' » food supplements. Ephedra is however an extreme example as it is not a nutrient rather it is a drug and so even though it has a nutrition connotation for weight loss. It is not the same as a supplement that contains vitamin A or iron.

**Are we in a serious crisis without any safety on food supplements reminiscent of the mad cow disease crisis and the bovine spongiform encephalopathy (BSE)?** The answer is no. Why? If we look for data on food supplements safety, publications on the death of people related to food supplement, with a risk of 0,0001 % are numerous (American data prepared by Ron Law). Data have shown that about half of the US population has been taking food supplements for several decades, and studies have re-

vealed two important facts: (1) the consumption of dietary supplements and nutrient-fortified foods are taken considerably above the recommended upper level of intake, and (2) drug-dietary-supplement interactions may occur in patients [21]. However, the severity of the potential interaction was classified as possible or probable (St John's wort and selective serotonin reuptake inhibitors; potassium and ACE inhibitors; and calcium and fluoroquinolones). In the case of Vitamin C, the potential for classification as a drug or food supplement exists. The intake of Vitamin C is complementary with the nutritional advised dietary intakes as 100 to 120 mg/day for food supplements, but very high for drugs with 500 mg/day, the risk (upper level) being 2000 mg of vitamin C [7]. Linus Pauling (the Nobel prize laureate for vitamin C) took 16 to 18 grams per day.

Exposure of consumers or patients to drug is not new. It responds to a demand of the society for health prevention or well being. In the 2008 activity report (page 4), a French trade union (Synadiet) reported that the expectation of the consumers of food supplements is to maintain a good health, complement their diet, avoid sub-deficiency (deficits), meet the needs of the body and create a source of well being. This is also a way, in France, to decrease health care expenditures covered by the national public health insurance system (social security). In the USA, the price of drugs is too high and medical prescription drug coverage is not as well developed than it is in France.



**Figure 6.** The 3 components for the food supplements risk analysis in the EC.

### THE EPHEDRA EXPERIENCE

To discuss the article (from Journalists) about food supplement published in « Que choisir », I will use as an example the history of the weight loss compound « ephedra ». This product that was listed among others in this publication is an interesting example of administration and management of the risks. After being in the market and evaluated as a risk, it was prohibited for use as a food supplement by the US FDA in 2004 [12].

**How did we evaluate the risk or the absence of risk of safety of this food supplement for the consumer?** This work was led by the US FDA from the data obtained from scientific articles regarding the word ephedrine in scientific database such as Pubmed, Toxnet, etc. The understanding of the mechanism of molecular action explaining the risk of toxicity (with a cause and effect relationship), and serious adverse effects (hospitalization reports, death with declarations of drug safety monitoring) called the attention to the sanitary branch. The website Health Canada (Santé Canada) recounted all these events for North America [22].

The question remains: “why did we wait until year 2004 to announce a prohibition on the use of ephedra, knowing the risks associated with its use since a significant number of publications had already appeared between 1993 and 2000” [14, 15]. In Europe, the branches of risk assessment have set up an efficient alerting system : i.e., the recent example with the Chinese melanin [10].

**The reading of the “Health Canada” public website for its facts is rich in information:** « *food supplements containing ephedra plant used by body-building enthusiasts and added to some additional supplements for weight lose, can lead to heart trouble, cardiovascular accident, and sometimes even death in people with otherwise good health. From the mid 90s, 54 deaths and at least 1000 cases of serious problem linked to the use of « ma huang », the Chinese name for ephedra, were reported in the United States. »... « Ephedra is usually used as a decongestant to ease breathing (in cold, flu, bronchitis, asthma, etc.), but also to lose weight and, in the case of athletes and body builders, to improve performances. Ephedra contains substances analogous to adrenalin, ephedrine and the pseudoephedrine, which stimulate the nervous system and the heart. »... «Based on the FDA and the American Association of Poison Control Centers’ data (AAPCC), the Public Citizen Health Research Group affirms that the use of ephedra is dangerous. From 1993 to 2000 in the United States, there were 800 reports of suspected unwanted effects of ephedra, including 81 deaths and 69 cerebral strokes and 62 cases of cardiac arrhythmia. In Canada, in October 2000, there were 60 declarations of this type, including two suicides. »...*

**The comment of “Health Canada” web site is:** «*it seems that the incidents were linked to the absence of clear directive on the recommended maximum daily doses and the aggressive marketing of the product »*. **In conclusion, the decision was made to prohibit the use of ephedra, but we can get a large amount of information for the future: which orientation for food supplement: prohibit, regulate or prevent?**

## THE PRINCIPLES OF SAFETY

The principles of safety are introduced by the remarks of food supplement advocates who stated the following:

- The **doses** of ephedra taken by consumers can be extremely **different** from what is indicated **on the label**. This is then a problem of labeling, but also of dosage and of the characteristics of the active ingredients.
- The simultaneous consumption of stimulants such as caffeine, which can be really dangerous. This brings up the problem of **interaction between molecules**, well known for drugs and the cause of numerous deaths.
- **Consumers were ill**. This is why the use of food supplements by patients needs a different status. The dosage of food supplements can be reduced to have a safety margin (balance between beneficial effects and toxic effects) more important, and contraindications for the patients with severe medical history.

These points belong to the current regulation to insure the safety of food supplements. This is the choice that was made with the publication of the 2002/46 directive. This last one defines the use of food supplement according to a system of unit dosage as criteria for food supplement, of

control of the making, and of the dosage (by its own laboratory). In addition, the food regulation forbids the use of health claim. Lastly, the analysis and the risk assessment combine different entities (sanitary branches, commissions, etc.) and is done according to the diagram in figure 6 [23]. The evaluation and the management of the risks are separated and it is the EFSA in the European Community (EC) that evaluates the safety of food supplement and gives scientific advice.

## THE SAFETY LIMITS

The methodology used by the EFSA, or AFSSA-ANSES for France, to establish the limits in the dosage for food supplements relies on scientific data. Each substance is defined by its chemical nature and its source or origins, data on consumption, its metabolic fate, and its biochemical characteristics. This data on safety are gathered from experimental, toxicological, clinical, and epidemiological evidences on drug safety monitoring data or on the possible existence of a decline in the consumption, and as well as opinions given by other committee or safety sanitary branches. The difficulty in the analysis is the existence of sufficient data in the international scientific database to establish limits in the dosage for safety.

In France, it is the DGCCRF (actor in the risk management) who which proposes a maximum daily dosage of use for an ingredient in food supplement tablet as example.

It is important to recognize that the safety of substance evaluations designed for food supplement was based on data on adults under «normal physiological condition ». However, they have been extrapolated to the category of pregnant or breast feeding women, children and the elderly [3]. Another difficulty can be the absence of data on healthy humans; since in many cases the data may have been obtained from unhealthy (sick) individuals.

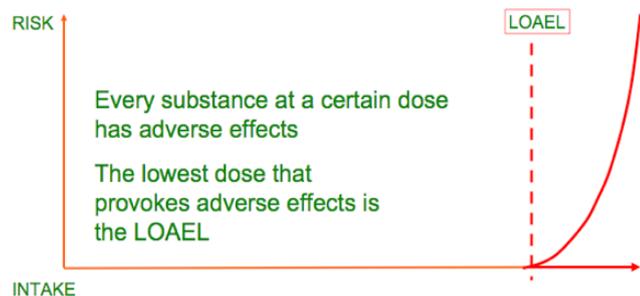
For vitamins and minerals, such as vitamin C, the safety limits are set based on the analysis of the risk with first the identification of the hazard (according to its seriousness) according to the intake of the food supplement (expressed as mg of substance/day): the higher the dose, the higher the risk. A scientific debate was recently organized in France [1]. As shown in figure 7, the parameter « LOAEL » (Lowest Observed Adverse Effect Level) representing the lowest dose without adverse effect can be determined. It corresponds to the dosage where there is risk. If this datum is obtained from a human in the ideal safety condition, this would be the maximum dosage not to be exceeded, which also takes into account the product intake in the consumer’s usual diet. If a dose without risk can be defined, we defined it as the NOAEL (No Observed Adverse Effect Level).

Figure 8 shows that the intake of the food supplement, defined by the NOAEL, is always lower than the LOAEL. For example, for food additives, this can be determined from experimental toxicology data including studies of one year chronic toxicity and a carcinogenic study during 2 years in rodents. This very long exposure allows to detect some risks of cancer and to extrapolate to human for a continuous use in human. In some cases, it has been impossible to establish this dosage (NOAEL, LOAEL). This has been the case for vitamins B1, B2, B12 for example, which do not have toxicity data [19]. A required safety testing for new ingredients (novel foods) in Europe requires a

90-day subchronic oral study in animals. A difference for an intermittent use (food supplement) and continuous use (food additives) merits to be explored.

Recently, some limits of safety for vitamins and minerals were reviewed for food supplements. It consists in defining an upper limit of safety (figure 7) with the UL (Upper Level). The limits correspond to the total intake of the nutrient by humans. As figure 7 shows, the lower limit is the recommended daily intake to avoid deficiencies in almost the whole population. The Upper Limit is then derived (by extrapolation) of the LOAEL or NOAEL and then dividing by an Uncertainty Factor (UF). This factor varies from 1 to more than 300 (300 is the result of an extrapolation from animal to human). It also depends on several other factors that include: (a) knowledge of the NOAEL or the LOAEL; (b) extrapolation of short exposure or long exposure (a few weeks study for human); (c) the scale of the effect to risk-intake curve between a low and a high dosage; (d) the inherent variability of the measurement (variation of the biological or clinical experimentation results); and (e) the variability of the response in humans.

These approaches allowed to obtain an accurate window (the closest limits in dotted lines on figure 8) corresponding to minima or maxima nutrient intake (or dose), minima in order to avoid the deficiencies and maxima in order to limit and control the excess or potential danger for the consumer.



#### LOAEL : Lowest Observed Adverse Effect Level

Figure 7. Relation between risk and intake for food supplements [23].

This upper limit based on risk of bleeding was calculated for omega-3 fatty acids (long chain fatty acids such as EPA and DHA as being higher than 3 g/day). The recommendation for the intake of these omega-3 fatty acids is between 0.3 and 0.5 g/day. The intakes were estimated to be lower than 0.5 g/day by the EFSA in 2005 [9]. This explains why for the omega-3 and in particular fish oil values do not represent a hazard for the consumer.

Among these 3 examples of food supplements, the problem of a more drug-like substance such as ephedra as a weight-loss product is now solved through prohibition of its use. For nutrients such as vitamin C, as for the omega-3, a sufficient amount of safety data and methodology of risk assessment has been collected, and all is needed is implementation and control through proper dosages related to upper limits.

In conclusion, the safety of food supplements remains a priority for health authorities. They can use scientific methodology and collective expertise which allow for monitoring and implementation of simple rules expressed as dosage and useful for the safety of the consumer.

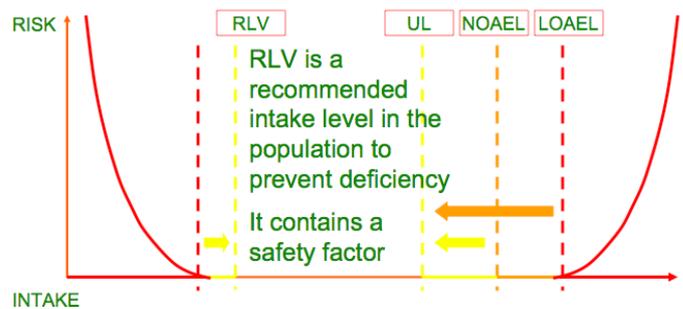


Figure 8. AJR/RDA Recommended Dietary Allowance, RLV reference labelling values, Upper levels and toxicological limits as NOAEL and LOAEL [23].

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