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This work is dedicated to Acad. Victor Giurgiu at his 90th anniversary

Nutrivigilance a domain of excellence in food science Note I. Conceptual and applicative problems

Zeno Gârban[1,2]

[1]Former - Banat`s University of Agricultural Sciences and Veterinary Medicine "King Michael I of Romania" Timişoara, Faculty of Food Products Technology, Calea Aradului No. 119, RO-300645 Timişoara;
[2] Working Group for Xenobiochemistry, Romanian Academy-Branch Timişoara, Bd. M. Viteazu No. 24, RO-300223 Timişoara

Abstract

Nutrivigilance issues are currently addressing to distinct directions of theoretical and applied interest in food science. Basically, issues are targeted to: a) usual food products that may contain original nutrients and some chemical xenobiotics (their presence in such foods could be the consequence of deliberate inclusion – by additivation or accidental / illicit introduction - adulteration, pollutants); b) special processed foods (fortified foods – according to Regulation (EC) no. 1925/2006, food supplements according to Directive 2002/46/CE, novel foods - according to Regulation 2015/2283 /UE or foods for specific groups – Regulation (UE) no. 609/2013).

It should be noted that, in general, the idea of "vigilance" extends to food products, pharmaceuticals and cosmetics and - as a whole, aims to report undesired health effects with the evaluation of "adverse reactions".

This review presents general data on the concept of nutrivigilance and evolutionary aspects regarding the specifics of preventive measures. Also, in a broader framework, the specificity of the interdisciplinarity in nutrivigilance and the need to prevent harmful effects are discussed.

Keywords: nutrivigilance – interdisciplinary aspects; prevention; adverse effects

1. Introduction

Including various theoretic and applicative approaches, food science was constituted by extending knowledge referring to foods from the obtainment of raw material (of vegetal, animal, mineral origin) to preparing / processing food products for consumption and, also, to food safety.

From organisational point of view, at international level there is discussed about "food science and specific technology" as an assembly of topics of theoretical and applicative interest. There is known the "International Union of Food Science and Technology" (IUFoST).

Characteristic for food science is the high interdisciplinarity confirmed by the fact that it embodies diverse scientific concepts from chemistry, biochemistry, microbiology, gastronomy / gastrotechnie, chemical (food) engineering and food control.

2. Concept of nutrivigilance.

The general concept of vigilance (lat. vigilare - to supervise, to monitor, to guard, to keep an eye on) applied in pharmacology, cosmetology and, during last period, extended to nutrition, can be characterized as a distinct domain which reunites the scientific approach of those domains, as well as applicative problems. Theoretical aspects focus on the investigation of composition, reaction mechanisms, biologic-active effects a.o. Applicative aspects refer to detection, assessment of the so

Corresponding author: *e-mail:* zeno.garban@yahoo.com

called "safety profile" in order to prevent the appearance of adverse effects.

In the domain of nutrition, pharmacology and cosmetology scientific and applicative information aim at following the beneficial aspects of diverse products of food, pharmaceutic and cosmetologic interest. There also remain of interest the problems referring to possible harmful effects generated mainly by adverse reaction [1,2].

In a specific frame, collection and management of information involve the assessment of adverse effects in order to establish the safety profile, both at national and international level for each authorized product from the marketing perspective [3,4].

Monitoring of the "safety profile" is realized in steps using the information referring to adverse reactions, before using the product. There is also discussed about monitoring by assessing data regarding the "safety profile" after authorization. One can observe a control on products used for food, pharmaceutic, cosmetic purpose upstream – before authorizing, downstream – after use.

As to the concept of vigilance in relation with food, pharmaceutic and cosmetic products one has to consider, per primo - secondary effects considered as "foreseen effects".

These appear sometimes at normal doses (recommended for administration/use). Obviously, secondary effects are associated with known properties of ingredients. To these effects can be added, per secundo - unknown "adverse reactions", considered as "unforeseeable effects". These ones can be presumed to stay at the origin of conex disorders in relation with the administered/ consumed product.

In a larger context the "safety profile" for a certain processed product (of food, pharmaceutic, cosmetic interest) is more important. This is a "composite product" (obtained as a mix of diverse ingredients), presents a major interest for consumer`s safety. In this regard specific "vigilance measures" (nutri-vigilance, pharmacovigilance, cosmetovigilance) are necessary.

When analyzing the "safety profile" one has also to consider other specific criteria [5,6]. As example in this context are given the circumstances when multiple comorbidities exist and the applications of polytherapy for certain categories of population (elderly, children, pregnant women, patients with chronic renal or hepatic disorders etc.).

A peculiar aspect of nutrivigilance addresses "phytovigilance" – domain that consists in supervising the effects produced by the interaction between vegetal extracts of medical interest with diverse drugs, nutrients and also with ingredients of cosmetic products. Under this circumstances are discussed: herbal medicinal products, herbal food supplements, herbal cosmetics and/or medicinal plants [7].

This approach, as the authors mention, addresses, under the circumstances, pharmacovigilance, nutrivigilance, cosmetovigilance. Also, the mentioned authors refer to "addictovigilance" in case of the presence of vegetal extracts in diverse products, knowing that such extracts lead to addiction and sometimes target directly toxicovigilance [7]. For these reasons the study of toxicity (acute or chronic) and of the risk of interaction with diverse drugs is considered a necessity, with the recommendation of preliminary studies of pharmacokinetics and/or pharmaco-dynamics.

Referring to the vegetal extracts used in the obtainment of ingredients of food, pharmacologic interest or even of cosmetologic interest, one has to observe that these can contain a complex mixture of compounds. In such cases, through systematic investigations that follow the identification of "biologic active" constituents: of food interest (physiologic-active), pharmaceutic interest (pharmacologic-active), cosmetologic interest (toxicologic-active). This phenomenon can be explained by two situations: a) synergic effects – which potentiate each other; b) antagonic effects – the constituents have different (opposite) biologic active effects.

3. Evolutionary data regarding the specificity of preventive measures

In order to have an image over the wide problem of the history of the concept of vigilance related to food, pharmaceutic and cosmetic compounds, as well as over the theoretical and applicative problems involved, a short presentation is made.

The problem of vigilance is important for the safety of products use. If for drugs (where regulations are more severe) and cosmetics used by categories of persons, for foods the beneficiaries are from all categories of population.

At communitary level there are institutional forums with specific attributions for nutrivigilance, pharmacovigilance and cosmetovigilance.

3.1. Domain of nutrivigilance

The generic denomination of «nutrivigilance» integrates the problems regarding the investigation of the composition of ingredients of natural and processed food products, as well as the risk assessment related to undesirable effects.

Such effects are presented as harmful reactions that appear in conditions of normal use of a certain food or is the result of a non-conformal use as mentioned, as precaution, on the label.

From historical point of view in case of nutrients, of xenobiotics beside nutrients or use of unverified food ingredients, harmful effects appeared with serious consequences. Such a case (that appeared in the period 1945-1960) is represented by butter coloring with a substance with the trivial denomination "butter yellow". The chemical compound was 4-dimethyl-amino-azobenzene. Its use in butter coloring proved that it is a carcinogenic substance that produces liver cancer [8]. In time harmful, carcinogenic, mutagenic and teratogenic effects were discovered in different compounds which are present in foods or introduced without a thorough verification during food processing. Such situations fully attest the need to introduce nutrivigilance measures related to the presence of chemical xenobiotics beside nutrients.

Are considered serious the undesirable effects that need hospitalization or induce a functional incapacity (permanent or temporary), an eventually invalidity, a certain abnormality or a congenital malformation in conceptuses (teratogenic effects) or even death [9,10].

A remark of historical (informative) and applicative interest refers at the profession of dietitian. The oldest mentions regarding the concerns about diets have been found in Canada in the period 1902-1907. About 1920 the domain became of interest in United States, 1930 Japan, subsequently in Germany, Argentine and Netherland in 1935. In France the domain developed after 1940. First concerns were those of Lucie Randoin – researcher biologist in 1935. Subsequently in France have been elaborated "laws regarding the diet" and in 1945 was introduced the profile "specialist in rational diet". In 1948 professor Jean Trémolieres founded in Bichât hospital an experimental system of "dietary kitchen". In 1952 in "Hôtel Dieu" Hospital in Marseille was founded the first "Dietary Service". All these data of historic specificity are presented for the reason that by the development of food industry, the problem of dietetics diversified a lot and presents interest for nutrition and medicine [11].

Nutrivigilance regards all undesirable effects, more or less serious which have an unexpected impact on health: allergy, gastro-intestinal disorders, cutaneous reactions, heart disorders etc.

The approach of nutrivigilance from principles to applicative aspects has in view to report the increase of adverse events both for diverse processed food products, i.e. classical foods (of general use) and other groups of foods (e.g. food supplements, novel food etc.). This opinion formulated by Schmitz et al. [12] and Witt [13] shows the peculiar aspects of nutrivigilance in the context of extending the domain from normal food products (denominated by the authors natural) to special products such as food supplements. In this context could be also mentioned the approach of the problem of food industry products, revealing the role of xeno-biochemistry as a distinct direction [14].

In acceptance of Schmitz et al. [12], nutrivigilance is defined as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects related to the use of a food, dietary supplement, or medical food". Talking about foods as current products of food industry and about diverse food supplements, one can distinguish that a separation can be made between what we think [15] food products are (among which some containing chemical xenobiotics) and special processed food products (represented by food supplements, novel food, etc.).

Generally, nutrivigilance is following the detection and accountability of manufacturing and marketing of all food products.

3.2. Domain of pharmacovigilance

Under historical, evolutionary aspect it is mentioned that the first measures in the domain of pharmacovigilance have been taken once with the so called "thalidomide tragedy" (1961-1962). Thalidomide, a drug used as sedative during pregnancy in women, was proven to be harmful for conceptuses by the teratogenic effects. Under this situation monitoring procedures were introduced for the safety of human use drugs [9,14]. Diverse regulations were introduced by medical institutions

across Europe. By this purpose interest domains have been extended over other drugs.

Therefore medical staff (doctors, pharmacists) and also patients were asked to report "adverse reactions" to authorized institutions. In such a manner a certain transparency has been assured on the problem of adverse reactions.

Regarding the adverse reactions, scientific papers consider that these represent the 5th cause of in-hospital death. Also, there is considered that only 10-25% of adverse reactions are reported.

In Romania in the case of pharmacovigilance, the problems of this domain are of interest for the National Agency of Drug and Medical Devices (Agenţia Naţională a Medicamentului şi a Dispozitivelor Medicale), abbreviated - ANMDMR.

In the European Union the problem of pharmacovigilance is regulated by specific legislation. Report on secondary effects of drugs are usually made by doctors, pharmacists and, in some cases, patients.

At the level of the European Union the problems of pharmacovigilance are approached in compliance with Directive 2010/84/EU, Regulation (EU) No 1235/2010 by the European Medicines Agency (EMA). This Agency has extended attributions keeping connections with the authorities of member states.

3.3. Domain of cosmetovigilance

An overview on the domain of cosmetology and cosmetics shows their theoretic and applicative specificity. It is considered that the use of cosmetic products has three distinct objectives: decorative, conservative and corrective [16].

In cosmetology, considered as a scientific domain, chemical ingredients used in "cosmetic products" are investigated. By the applicative character cosmetics is of interest for maintaining the normality of targeted tissues: skin, hair, nails and oral cavity. There also is a conex domain of interest for therapeutic peculiarities known as cosmetopharmacology [17].

In general, a "cosmetic product", no matter the form of presentation (cream, gel, emulsion, lotion etc.) contains three categories of ingredients:

a) an active principle – substance that assures the efficiency of the product;

b) an excipient – the transporter of the active principle;

c) cosmetic additives – representing substances that act as preservatives, fresheners, dyes, pH stabilizer, emulsifier etc.

Cosmetovigilance is integrated to this domain aiming at a systematic focus on the possible undesirable effects of cosmetic products related to human health. Therefore following information is used: α) producers' declaration, e.g. undesirable effects; β) conex information e.g. misuse, allergies etc. In such situations information is registered and the incriminated product is analyzed/studied. The legal bases to follow the action of cosmetics is regulated in each country by specific laws. For example, in USA the federal law is represented by "Federal Food, Drug and Cosmetic Act" (acronym FD&C Act). In France, another example, undesirable effects are declared by a competent authority represented by "Agence Nationale de Sécurité du Médicament et des produits de *santé"* (acronym ANSM). In Romania cosmetic products are subject of Law 178/2000 which regulates diverse aspects in connection with cosmetics and, obviously cosmetovigilance.

It is interesting to mention that problems of cosmetology and cosmetics were of interest for mankind since Antiquity. Without giving details (although interesting under historical and scientific aspects), it is known that diverse ingredients have been used to obtain cosmetic products, in the form of mixtures, which often were complex and toxic. For example, there were used salts containing lead, mercury a.o. (in general metals with toxicogenic potential) and certain compounds with arsenic compounds content. Such substances were prepared as powders or mixed with fats (of vegetal or animal origin) and used for makeup, lotions etc.

4. Interdisciplinary specificity in nutrivigilance

In the domain of nutrivigilance one can approach two distinct direction of theoretic and applicative interest. The two directions address: 1) food products with content of chemical xenobiotics (deliberately accepted, occasionally or illicitly included – through food adulteration); 2) specific processed food products (containing various ingredients).

4.1. Nutrients and chemical xenobiotics

4.1.1. Aspects of food biochemistry

Biochemistry - in a wider context - is defined as the science which studies the composition and structure of chemicals naturally present in living organisms (bioconstituents) and the physico-chemical transformations which occur in these organisms, in space and time (nutrient metabolisation) involved in morphogenesis and energogenesis [18].

In figure 1 are presented the nutrients present in diverse food products.

Thus, biochemistry includes: a) static biochemistry (also referred to as descriptive biochemistry); b) dynamic biochemistry (biochemistry of biodegradation and biosynthesis metabolic processes).

For nutrients, the concept of "metabolisation", specific for dynamic biochemistry, is defining. The interactions which characterize these phases follow various "natural biochemical pathways" specific for physiology, and the resulting compounds are referred to as "metabolites". Metabolisation is characterized by two phases: α) catabolism; β) anabolism.

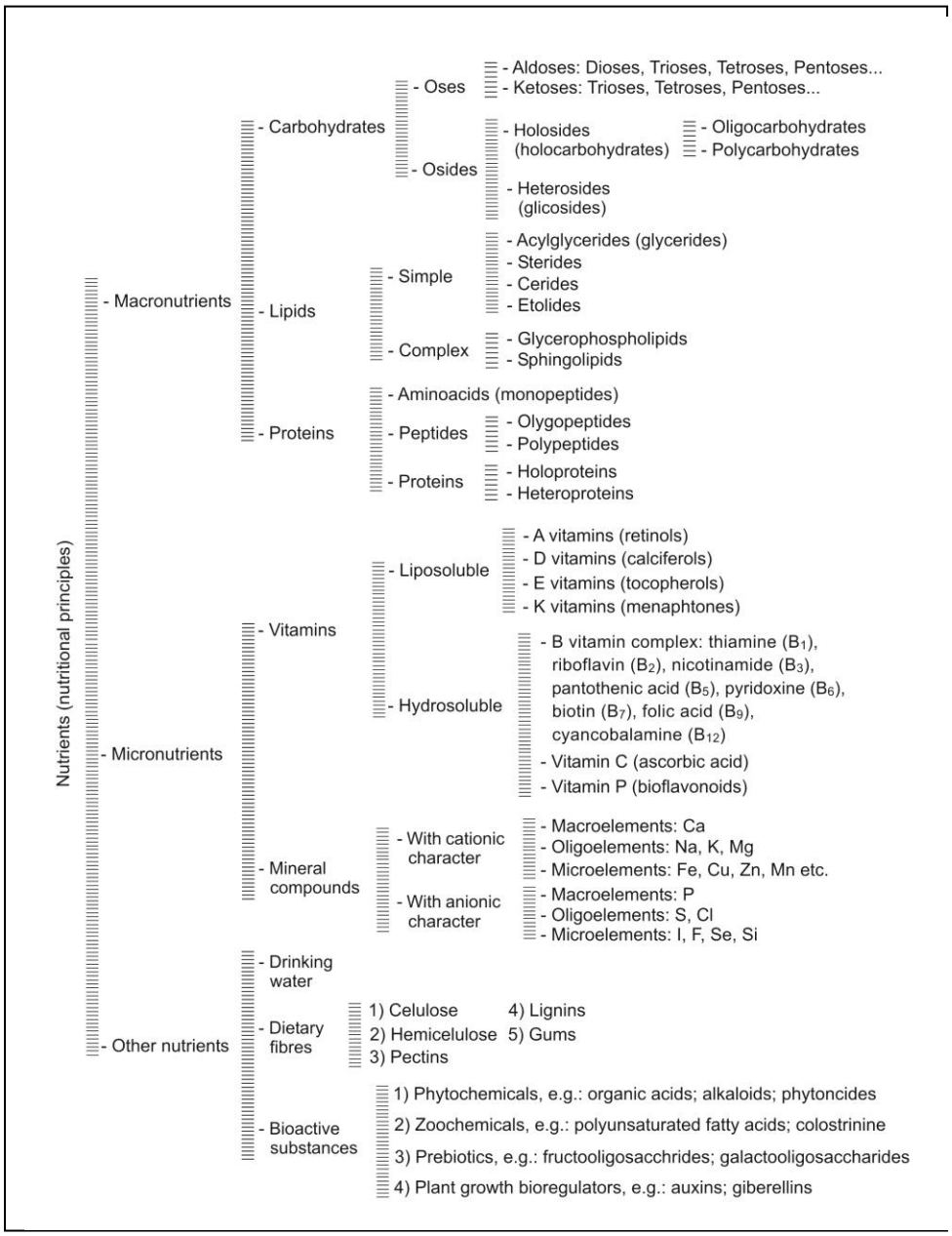

Figure 1. Nutrients present in food products – general presentation

4.1.2. Aspects of food xenobiochemistry

Xenobiochemistry - is defined as the science which studies the composition and structure of chemical xenobiotics and the physico-chemical transformations which they are exposed to in the organism, in time and space (biotransformation of xenobiotics). Figure 2 presents chemical xenobiotics detected in food products.

Also, a comparison may be made between the fields delimited within biochemistry which may be circumscribed in xenobiochemistry.

In xenobiochemistry - for rigorous and coherent explanation - we mutually agree on using the terms: a) static xenobiochemistry, *i.e.* descriptive xeno-biochemistry; b) dynamic xenobiochemistry, *i.e.* xenobiochemistry of the biotransformation processes.

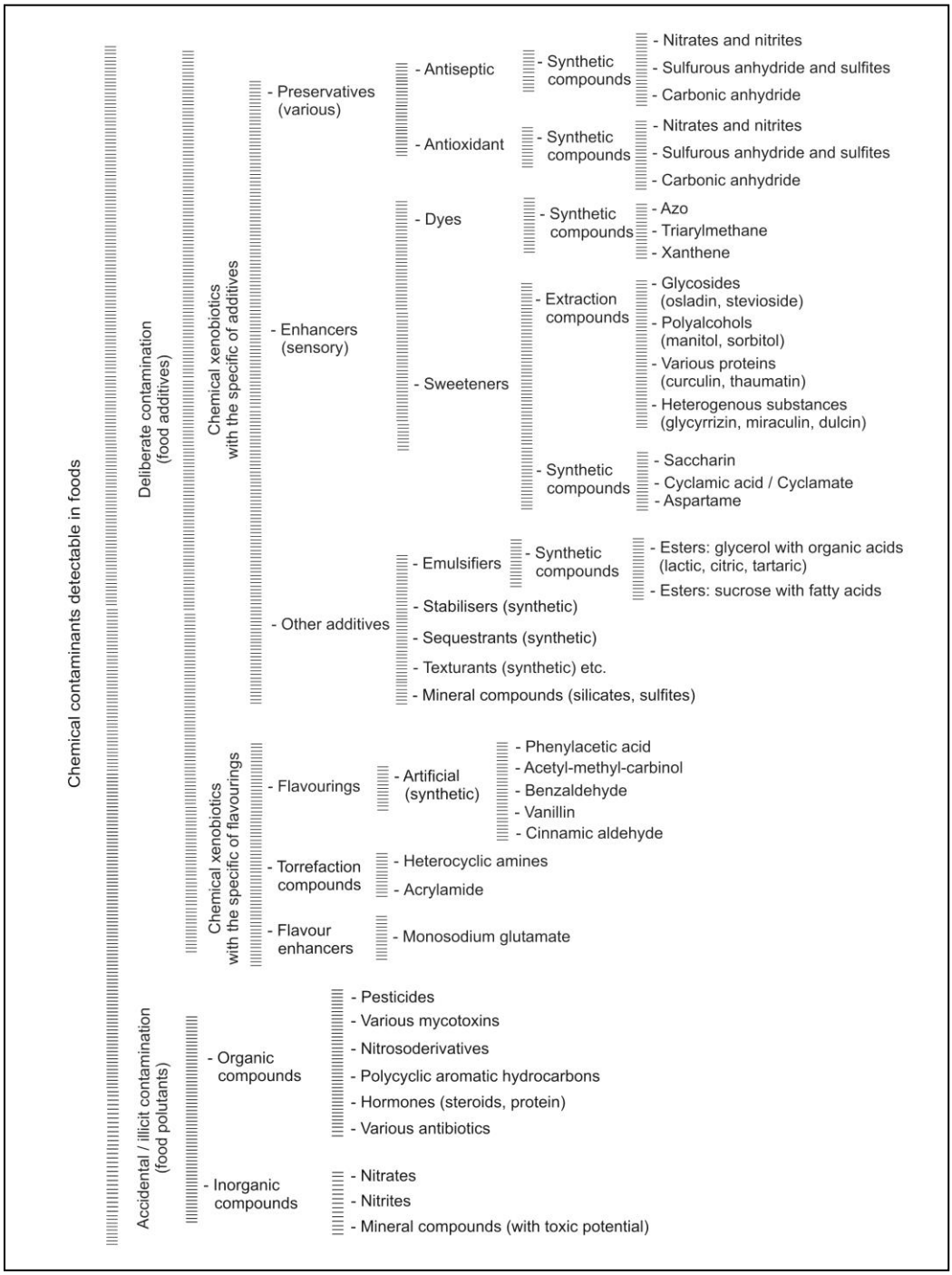

Figure 2. Main chemical xenobiotics detectable in food products

For chemical xenobiotics [19, 20] regardless if they belong to food contaminants, pharmaceutical products used for chemotherapy or specifically toxic substances (biocides), the defining concept is "biotransformation". The defining interactions for these phases – characteristic for xenobiochemistry - occur via "specific biochemical pathways" encountered in physiopathology (depending on the nature of the xenobiotic). The resulting compounds are referred to as "residual xenobioderivatives" [21].

This concept is specific for dynamic xenobiochemistry. In the case of biotransformation, there are also two phases which have been denominated as: α) xenobiodegradation; β) xeno-biosynthesis.

4.2. Specific processed food products

Among composite food products, in the extended acceptance of nutrivigilance domain, are included as above mentioned: 1) food supplements; 2) foods or beverages fortified with nutrients (vitamins and/or minerals) or with substances having nutritional or physiological roles (amino acids, botanical extracts), e.g. the so called "energizing" drinks; 3) novel food and novel food ingredients, e.g. phytosterols, noni juice; 4) food products intended for specific groups (infants and young children, weight reduction, specific medical purposes (patients suffering from food allergies)).

In France was conceived a certain "national device of nutrivigilance" coordinated by an institution founded (in 2009) on this purpose, i.e. „ l`**A**gence **N**ationale de **Sé**curité **S**anitaire de l`alimentation, de l`environnement et du travail". This institution is generally known by the acronym ANSES [22].

Assessment of undesirable effects is made in the frame of nutrivigilance on the basis of specific criteria. A first criterion recommended by ANSES (http://www.anses.fr./content/what-nutrivigilance) is represented by "producers' declaration" regarding possible undesirable effects. A second criterion consists in the contribution of specialists in health domain (doctors, pharmacists, dietitians etc.) in questioning consumers of daily use foods or special use foods (e.g. food supplements a.o.) regarding the observed effects [23, 24].

In this regard effects are mentioned in a "tele-declaration" on an event "signaling portal" or an "online form" can be used.

Data are transmitted to ANSES, and further on to a Ministry (in case of France, Ministry of Solidarity and Health). Depending on the effects observed, the number of registered cases and causal associations, ANSES can proceed to a thorough assessment of the risk associated with the intake of a certain food product or a certain ingredient. In general, ANSES considers that the tele-declarations referring to nutrivigilance are made by professionals in health domain (i.e. doctors, pharmacists, dietitians etc.) who can identify these effects in patients. It is also considered that other persons can make declarations as individuals and are invited to contact professionals from the health domain.

The assumed (declared) aim of nutrivigilance is that of improving consumers' safety by a rapid identification of possible adverse effects in consuming foods.

5. Conclusive data

In the body take place simultaneously physico-chemical transformations of interest for the metabolisation of nutrients – on "natural bio-chemical pathways" and for the biotransformation of xenobiotics – on "specific biochemical pathways". The latter are of interest for certain processes that evolve with physiopathologic specificity.

The issue of vigilance taken as a whole is studied in a broader connection, involving foods, pharmaceuticals and cosmetics. Evidently, in this situation, nutrivigilance, pharmacovigilance and cosmetovigilance are approached.

Obviously, when classifying food products in: a) usual food products; b) special processed food products (fortified foods, food supplements, novel foods, etc.) some interferences appear related to nutrivigilance.

Therefore, nutrivigilance can represent an efficient way to approach problems regarding undesired effects on health with the risk of generating side effects. For these reasons, continuous attention has been imposed in order to prevent harmful effects and to ensure food safety.

Compliance with Ethics Requirements. Authors declare that they respect the journal's ethics requirements. Authors declare that they have no conflict of interest and all procedures involving human / or animal subjects (if exist) respect the specific regulation and standards.

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