Functional foods - from natural to “pharma” foods

U5

Enriched foods
Novel foods

Food supplements
Nutraceuticals

Special medical foods

Functional foods

U5

European Commission Concerted Action on Functional Food Science in Europe considers foods to be functional if it is satisfactorily demonstrated to beneficially affect one or more target functions in the body beyond adequate nutritional effects in a way that is relevant to either an improved state of health and well-being or a reduction of disease risk. Functional foods must remain foods and demonstrate their effects when consumed in daily amounts that can be normally expected.

In practice, a functional food can be:

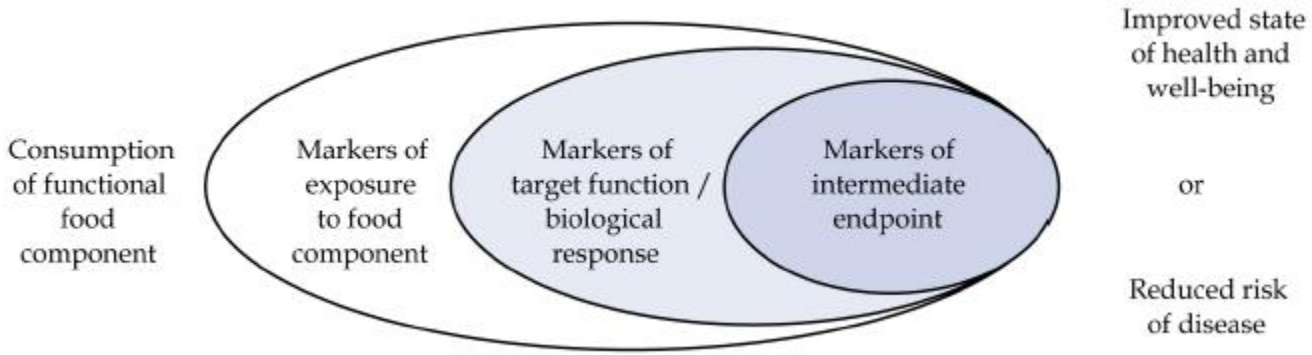
- an unmodified natural food;
- a food in which a component has been enhanced through special growing conditions, breeding or biotechnological means;
- a food to which a component has been added to provide benefits;
- a food from which a component has been removed by technological or biotechnological means so that the food provides benefits not otherwise available;
- a food in which a component has been replaced by an alternative component with favourable properties;
- a food in which a component has been modified by enzymatic, chemical or technological means to provide a benefit;
- a food in which the bioavailability of a component has been modified;
- or a combination of any of the above.

Table 3 Categories of functional foods and nutraceuticals

Category	Example
Basic Foods	Carrots (containing the anti-oxidant beta-carotene)
Processed Foods	Oat bran cereal
Processed Foods with Added Ingredients	Calcium-enriched fruit juice
Food enhanced to have more of a functional component (via traditional breeding, special livestock feeding or genetic engineering)	Tomatoes with higher levels of lycopene (an antioxidant carotenoid)
	Oat bran with higher levels of beta glucan
Isolated, purified preparations of active food ingredients (dosage form)	Isoflavones from soy
	Beta glucan from oat bran

In developing a functional food

U5



The use of markers to link food consumption to health outcomes

In the last few years the regulation of nutrition and health claims has been one of the top food-related themes discussed in Europe. Regulation covering these areas was indeed required. Protecting consumers against misleading claims, along with the harmonisation of the European market, were the key issues that needed to be addressed. The regulation targets functional foods, a concept which emerged in Japan about 20 years ago to reduce the escalating health care costs with a category of foods offering potential health benefits, although from a different perspective. It was decided that the use of pre-approved evidence-based health claims on food labels would serve us best and in the ensuing time there has been a focus on creating a list of approved claims. In such a system, functional foods are basically defined by the limitations and the opportunities for the use of claims.
A detailed examination of all the concerns raised by the EFSA in its published opinions, together with some additional advice about expectations related to the scientific substantiation of health claims, should result in the improved quality of clinical testing for bioactive components and functional foods.

In developing a functional food based on botanicals

U5

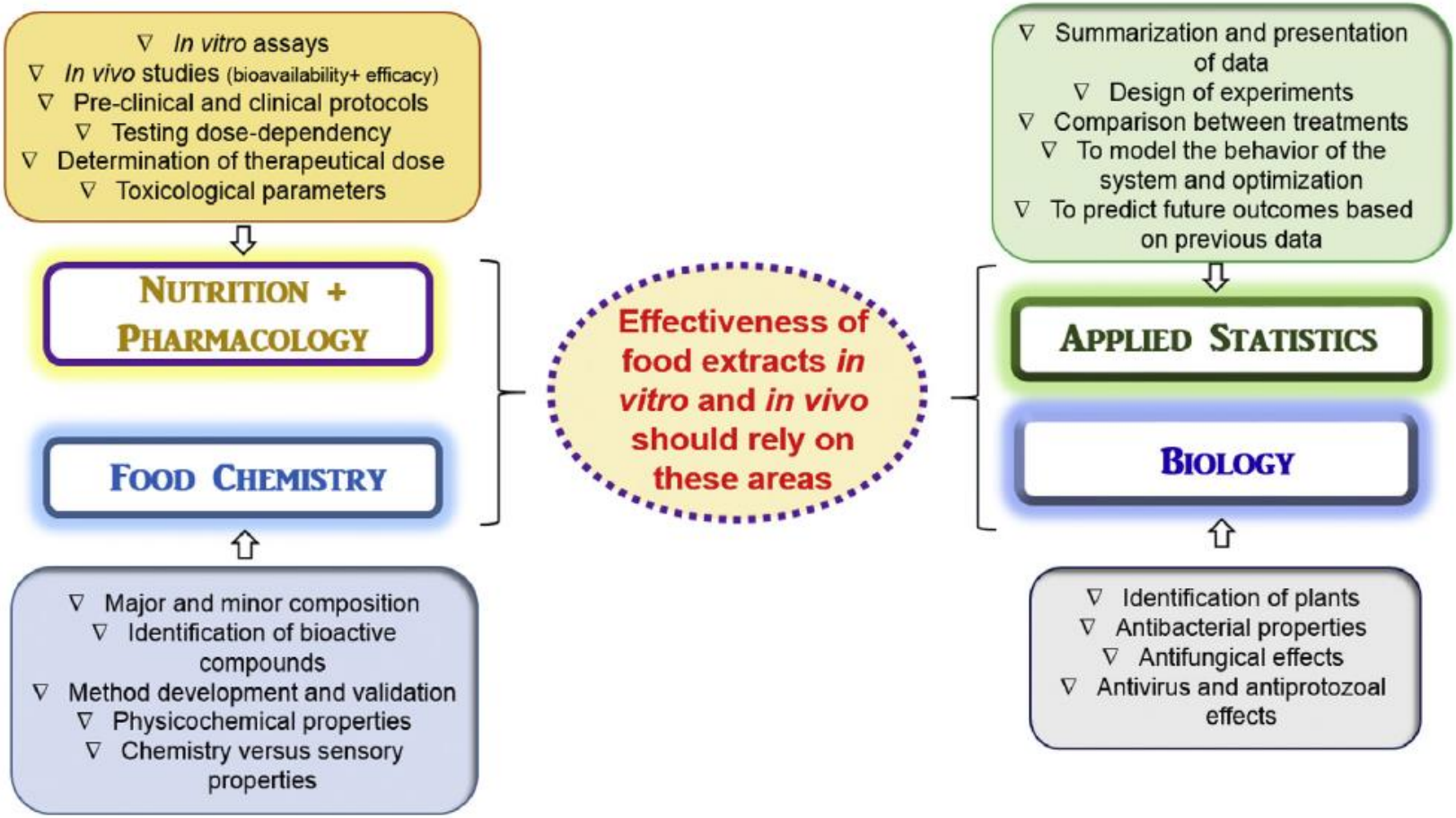


Fig. 2. Representation of the major aims of each area related to the assessment of functional properties of herbal and food extracts.

Trends in Food Science & Technology 62 (2017) 13–22

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Review

An integrated strategy between food chemistry, biology, nutrition, pharmacology, and statistics in the development of functional foods: A proposal

Daniel Granato [a, *], Domingos Sávio Nunes [b], Francisco J. Barba [c]

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[b] Department of Chemistry, State University of Ponta Grossa, Ponta Grossa, Brazil
[c] Nutrition and Food Science Area, Faculty of Pharmacy, Universitat de València, Avda. Vicent Andrés Estellés, s/n, 46100 Burjassot, Spain

In developing a functional food based on botanicals

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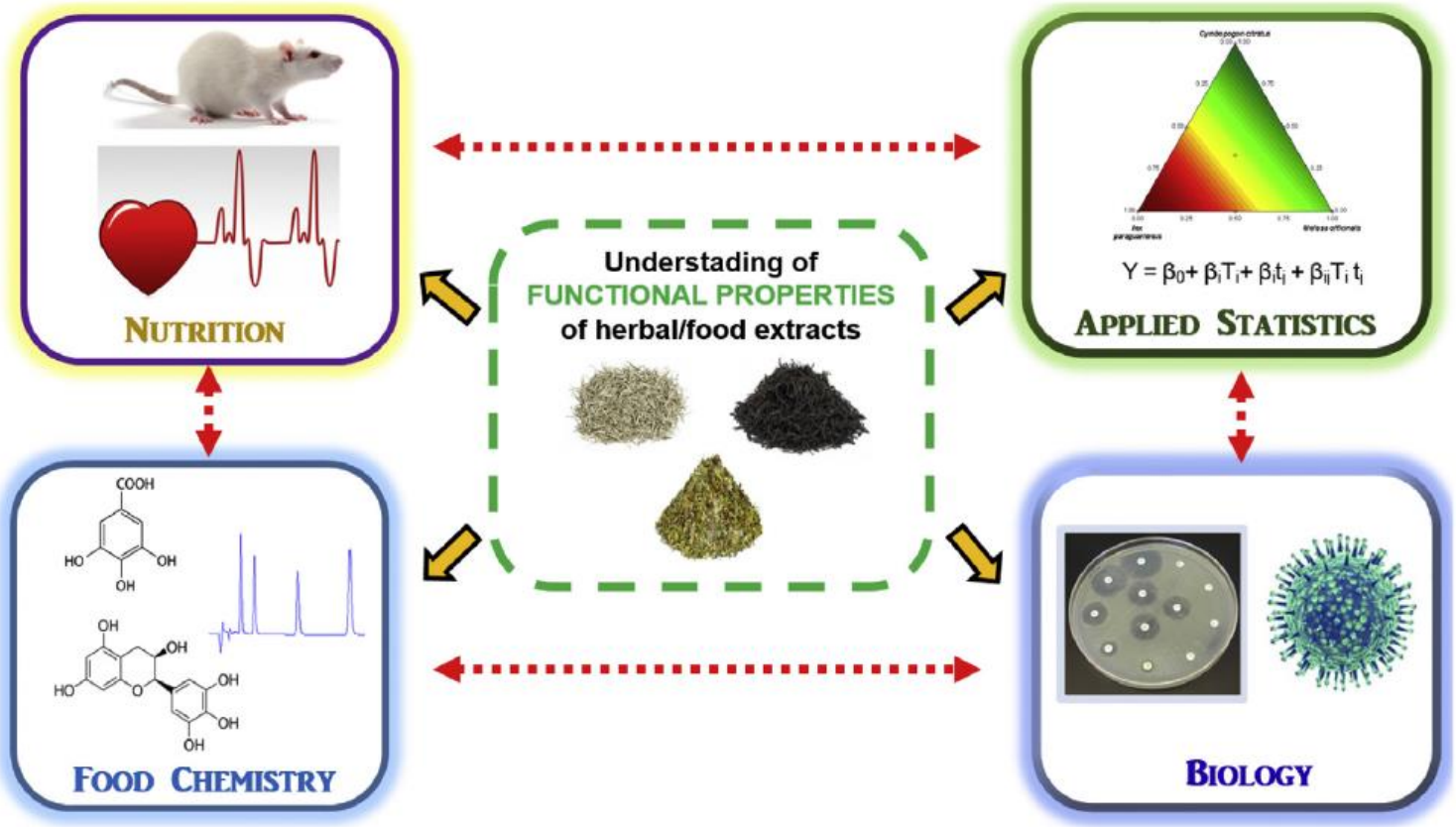

Fig. 3. Summary on how the integration between science fields should be interlinked aiming to assess the functional properties of plant-based and herbal extracts and preparations.

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In developing a functional food

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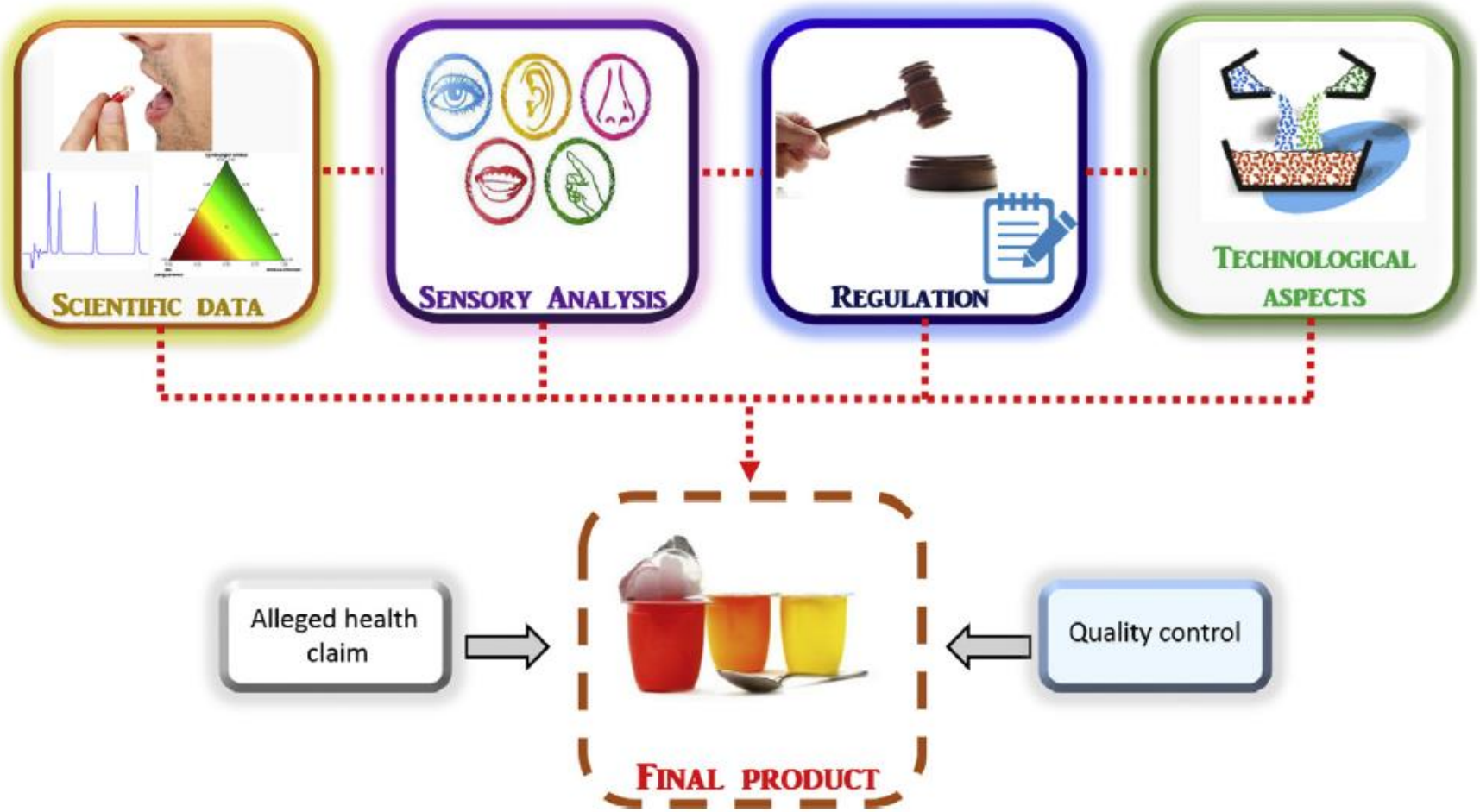

Fig. 4. Practical and systematic approach that can be used to develop a functional food product according to various factors.

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In developing a functional food

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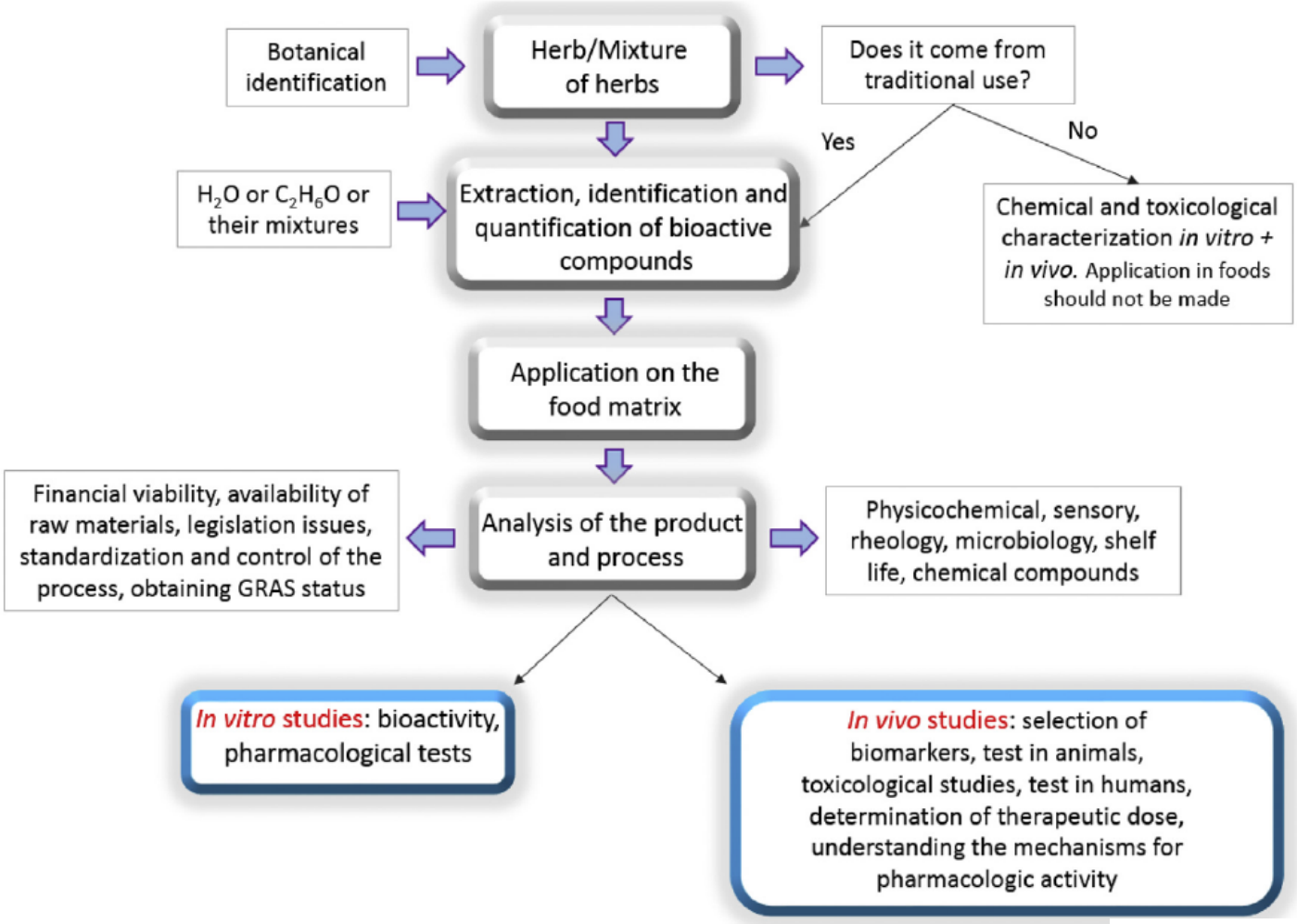

Fig. 5. Practical workflow to develop and test new potentially functional foods by food companies.


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Industrial developing of a “functional food”

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	Idea	Formulation development	Industrialization	Industrial production and management of the finished product
Activities	• Analyze market and trends • Studying the literature and the innovations in raw materials • Implement the innovation meeting • Develop the business model • Create the theoretical formulation • Estimate the cost • Perform risk analysis	Pre-evaluate teor. formulation · Choose the raw materials and check its quality · Develop the formulation · Set up analyzes on raw materials and the finished product · Definition of primary packaging · Make mock-up tests · Preliminary stability	-Realize the pilot lot and validate the process productive · Validate the analysis method · Check stability of the pilot lot · Confirm the material of packaging · Make the labels for MdS	· Check raw materials · Archive counter samples of finished product · Perform stability analysis and release on the finished product · Manage complaints
Actors	· R & D · MARKETING · REGULATORY	· R & D · REGULATORY · QUALITY ASSURANCE · QUALITY CHECK · PACKAGING DIVISION	· R & D · PRODUCTION · QUALITY CHECK · PACKAGING DIVISION · REGULATORY	· PRODUCTION · QUALITY CHECK · QUALITY ASSURANCE

Enriched or fortified foods?

U5

▶B REGULATION (EC) No 1925/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 20 December 2006

on the addition of vitamins and minerals and of certain other substances to foods

(OJ L 404, 30.12.2006, p. 26)

Consolidated version of Regulation (EC) No 1925/2006 (as at 1 April 2015)

Both enriched and fortified terms mean that nutrients have been added to make the food more nutritious. Enriched means nutrients that were lost during food processing have been added back. An example is adding calcium/Vitamin D in milk or dairy products, probiotics in yogurth or vitamin B9 in breakfast cereals. Fortified means vitamins or minerals have been added to a food that weren't originally in the food. An example is adding iodine to salt or adding fluoride to water.

Enriched or fortified foods? Requirements

U5

ADDITION OF VITAMINS AND MINERALS

Article 3 Requirements for the addition of vitamins and minerals

1. Only vitamins and/or minerals listed in Annex I, in the forms listed in Annex II, may be added to foods, subject to the rules laid down in this Regulation.

2. Vitamins and minerals in a form that is bio-available to the human body may be added to foods, whether or not they are usually contained therein, in order to take into account, in particular:
(a) a deficiency of one or more vitamins and/or minerals in the population or specific population groups that can be demonstrated by clinical or sub-clinical evidence of deficiency or indicated by estimated low levels of intake of nutrients; or
(b) the potential to improve the nutritional status of the population or specific population groups and/or correct possible deficiencies in dietary intakes of vitamins or minerals due to changes in dietary habits; or
(c) evolving generally acceptable scientific knowledge on the role of vitamins and minerals in nutrition and consequent effects on health.

REGULATION (EC) No 1925/2006 OF THE EUROPEAN PARLIAMENT

Enriched or fortified foods? Restrictions

U5

Article 4 Restrictions on the addition of vitamins and minerals

Vitamins and minerals may not be added to:
(a) unprocessed foodstuffs, including, but not limited to, fruit, vegetables, meat, poultry and fish;
(b) beverages containing more than 1,2 % by volume of alcohol, except in wine marketed prior to the adoption of this Regulation; and provided that no nutrition or health claim is made.

Art 6 Conditions for the addition of vitamins and minerals

When a vitamin or a mineral is added to foods, the total amount of the vitamin or mineral present, for whatever purpose, in the food as sold shall not exceed maximum amounts
The maximum amounts is referred to:

(a) upper safe levels of vitamins and minerals established by scientific risk assessment based on generally acceptable scientific data, taking into account, as appropriate, the varying degrees of sensitivity of different groups of consumers; and
(b) intakes of vitamins and minerals from other dietary sources

When the limit is near the USL also take in account:
the contribution of individual products to the overall diet of the population in general or of sub-groups of the population;

Enriched or fortified foods? Labelling

U5

Article 7 Labelling, presentation and advertising

1. The labelling, presentation and advertising of foods to which vitamins and minerals have been added shall not include any mention stating or implying that a balanced and varied diet cannot provide appropriate quantities of nutrients.
2. The labelling, presentation and advertising of foods to which vitamins and minerals have been added shall not mislead or deceive the consumer as to the nutritional merit of a food that may result from the addition of these nutrients.
3. Nutrition labelling of products to which vitamins and minerals have been added and which are covered by this Regulation shall be compulsory.

CONSUMI DI RIFERIMENTO

PARTE A — CONSUMI DI RIFERIMENTO GIORNALIERI PER VITAMINE E SALI MINERALI (ADULTI)

1. Vitamine e sali minerali che possono essere dichiarati e relativi valori nutritivi di riferimento

Vitamina A (µg)	800	Cloruro (mg)	800
Vitamina D (µg)	5	Calcio (mg)	800
Vitamina E (mg)	12	Fosforo (mg)	700
Vitamina K (µg)	75	Magnesio (mg)	375
Vitamina C (mg)	80	Ferro (mg)	14
Tiammina (mg)	1,1	Zinco (mg)	10
Riboflavina (mg)	1,4	Rame (mg)	1
Niacina (mg)	16	Manganese (mg)	2
Vitamina B6 (mg)	1,4	Fluoro (mg)	3,5
Acido folico (µg)	200	Selenio (µg)	55
Vitamina B12 (µg)	2,5	Cromo (µg)	40
Biotina (µg)	50	Molibdeno (µg)	50
Acido pantotenico (mg)	6	Iodio (µg)	150
Potassio (mg)	2 000		

Significant amounts of Vitamins & Minerals

15% RNI o RDA par 100g

REGULATION (EC) No 1925/2006 OF THE EUROPEAN PARLIAMENT

Enriched or fortified foods? Marketing

- folic acid added to cereal for breakfast to help reduce the risk of babies born with spina bifida
- Vitamin D - The enrichment would be particularly useful in the elderly to preserve their mental health as low levels in the blood correspond to memory impairment, decreased cognitive ability and memory, mood disorders with depression, because the skin's exposure to sunlight lose effectiveness
- Enrichment with fiber, probiotics and prebiotics, flavonoids, carotenoids and antioxidants in functional drinks
- Enrichment with magnesium due to effects on muscle and bone function, hypertension, inflammation, asthma, migraines and diabetes
- Enriching of table salt with iodine (iodine prophylaxis)

Novel Food? Reg EU 258/1997

U5

Novel Food is defined as food that has not been consumed to a significant degree by humans in the EU prior to 1997, when the first Regulation on novel food came into force.

'Novel Food' can be newly developed, innovative food or food produced using new technologies and production processes as well as food traditionally eaten outside of the EU.

Novel Food **must be**:
Safe for consumers
Properly **labelled** to not mislead consumers

REGULATION (EU) 2015/2283 OF THE EUROPEAN PARLIAMENT AND OF THE
of 25 November 2015
on novel foods, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001

2018

(i) food with a new or intentionally modified molecular structure, where that structure was not used as, or in, a food within the Union before 15 May 1997;
(ii) food consisting of, isolated from or produced from microorganisms, fungi or algae;
(iii) isolated from or produced from material of mineral origin;
(iv) isolated from or produced from plants or their parts
(v) isolated from or produced from animals (insects) or their parts,
(vi) food consisting of, isolated from or produced from cell culture or tissue culture derived from animals, plants, micro-organisms, fungi or algae;
(vii) food resulting from a production process not used for food production within the Union before 15 May 1997, which gives rise to significant changes in the composition or structure of a food, affecting its nutritional value, metabolism or level of undesirable substances;
(viii) food consisting of engineered nanomaterials as defined in point (f) of this paragraph;
(ix) vitamins, minerals and other substances, where: — a production process not used for food production within the Union or — they contain or consist of engineered nanomaterials as;
(x) food used exclusively in food supplements within the Union before 15 May 1997, where it is intended to be used in foods other than food supplements

Novel Food? Authorization for market

U5

Art 10 Procedure for authorizing the placing on the market within the Union of a novel food and updating the Union list

(i) The application for an authorisation shall include:
(a) the name and address of the applicant;
(b) the name and description of the novel food;
(c) the description of the production process(es);
(d) the detailed composition of the novel food;
(e) scientific evidence demonstrating that the novel food does not pose a safety risk to human health;
(f) where appropriate, the analysis method(s);
(g) a proposal for the conditions of intended use and for specific labelling requirements which do not mislead the consumer or a verifiable justification why those elements are not necessary

For a traditional food from a third country
(h) the country or countries of origin of the traditional food;
(i) documented data demonstrating the history of safe food use in a third country;

FULL AUTHORIZATION

SEMPLIFIED:
SUBSTANTIAL EQUIVALENCE

Monitoring post-market
There will be some additional obligations to ensure the protection of health:

For example, the Commission, for food safety reasons and taking into account the opinion of EFSA, may predict subsequent monitoring obligations to the placing on the market of new food

Novel Food? On-line catalogue

U5

1. Public consultation on the draft guidance on the preparation and presentation of an application **for authorisation of a Novel Food**
2. Public consultation on the draft guidance on the preparation and presentation of a notification **for authorisation of Traditional Foods from third countries**

efsa European Food Safety Authority

http://ec.europa.eu/food/safety/novel_food/catalogue/search/public/index.cfm

Novel Food?

U5

Nano-Insights

Nanotechnology and the agrifood sector: applications and their safety assessment

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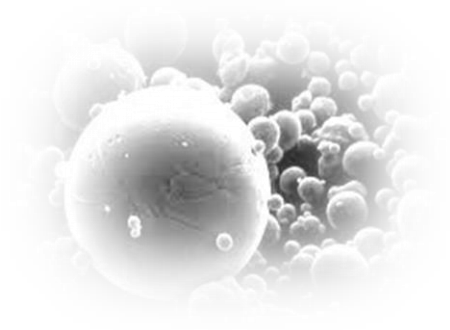


National Scientific Expert in the EFSA Network for Risk Assessment of Nanotechnologies in Food and Feed

Expert in the EFSA Cross Cutting Working Group on nanoscience and nanotechnology in food/feed

Environmental and anthropogenic nanoparticles

U5

Natural nanoparticles

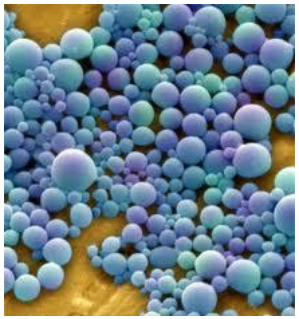
Silicates, oxides, carbonates, metal sulfides

Accidentally manufactured nanoparticles

Micronized materials (e.g. food additives)

Anthropogenic nanoparticles
(e.g. combustion generated)

Intentionally manufactured nanoparticles



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Exposure routes

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Natural nanoparticles

Silicates, oxides, carbonates, metal sulfides

Accidentally manufactured nanoparticles

Micronized materials (e.g. food additives)

Production, use

Food, drugs

Cosmetics

Inhalation

Oral

Dermic

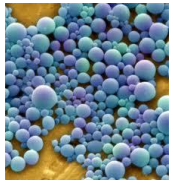
Production, use

Food, drugs

Cosmetics

Anthropogenic nanoparticles
(e.g. combustion generated)

Intentionally manufactured nanoparticles



* General population

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Nanotechnology applications in the food sector: regulatory issues

U5

Agricultural production

e.g. nanopesticides, other nanosized agrochemicals

Food processing

e.g. nanosized additives, nanoencapsulates, nutritional supplments

Packaging & storage

e.g. nanocomposites, nano-coatings and other food contact materials

Situation today in the EU

- Authorisation required for whatever application in the food sector: EFSA evaluates possible health risks
- The new Novel food Regulation gives the rules for the use nano-ingredients in food (since 2018)
- Some nanosized additives authorised for use in plastic food contact materials
- No nanosized additives authorised for use in food, but some «older» additives have been found to be partially in nanoform e.g. TiO_2 (E171) and especially SiO_2 (E551) (recently re-evaluated by the EFSA)

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Size ranges: what is the nanorange?

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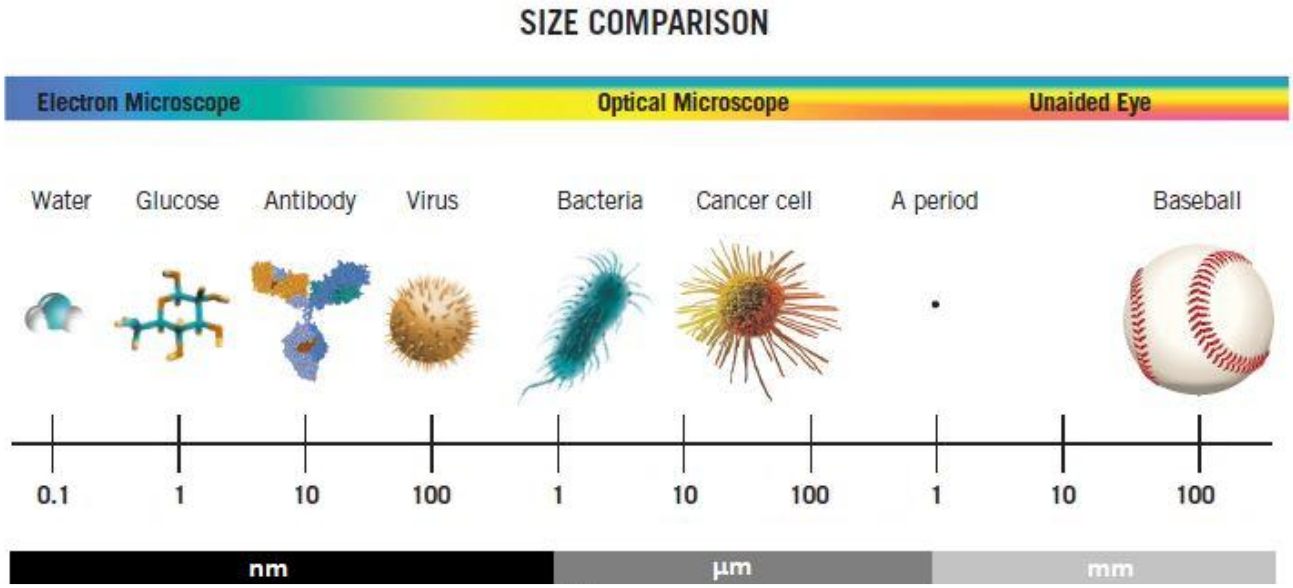

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Examples of matter on the nanoscale

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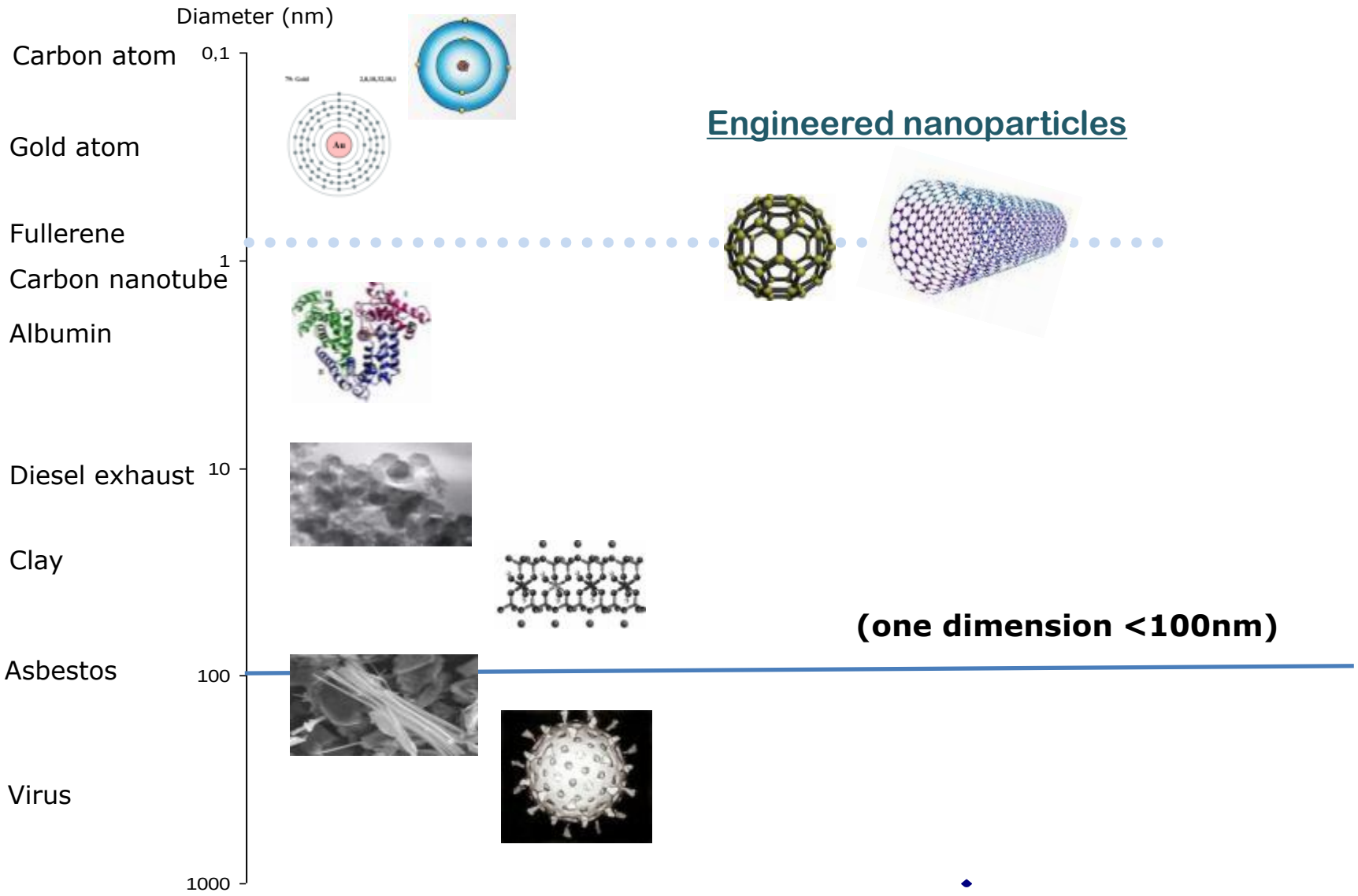

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Nanosized natural components of food products

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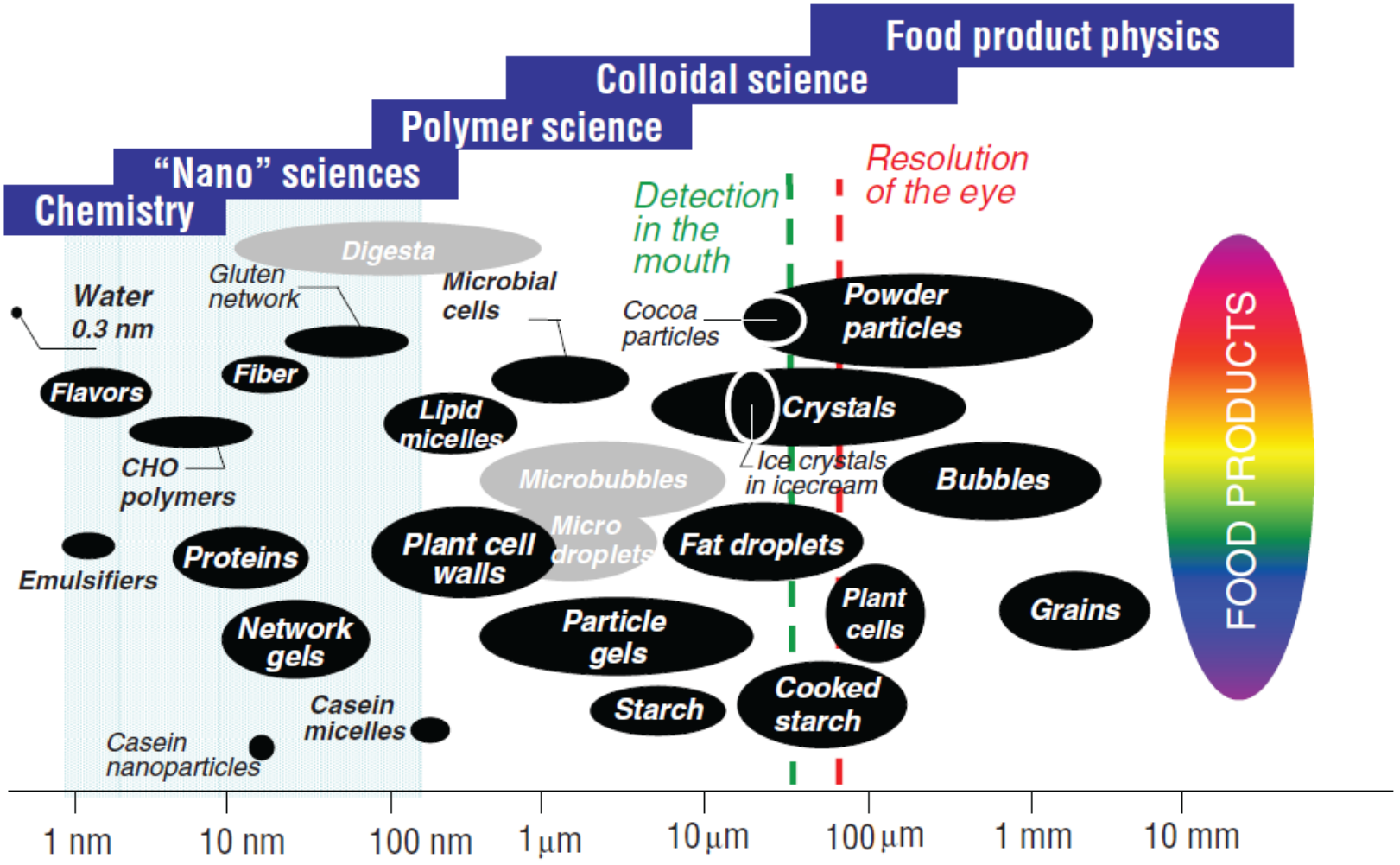

Risk Analysis framework in the EU

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How Risk analysis is performed in the EU?

Who are the players?

- In the **EU food safety system**, **Risk Assessment is carried out *by an independent body* with respect to Risk management**

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European legislation on NMs: FCMs

U5

Food packaging (Regulations 10/2011 and 450/2009)

- Nanomaterials in plastic food contact materials (FCMs) and active and intelligent FCMs: **authorisation required**

Whereas:

(23) New technologies engineer substances in particle size that exhibit chemical and physical properties that significantly differ from those at a larger scale, for example, **nanoparticles**. These different properties may lead to different toxicological properties and therefore these substances should be **assessed on a case-by-case** basis by the Authority as regards their risk until more information is known about such new technology. Therefore it should be made clear that authorisations which are based on the risk assessment of the conventional particle size of a substance do not cover engineered nanoparticles.

Article 9. Specific requirements on substances….2) **Substances in nanoform shall only be used if explicitly authorised** and mentioned in the specifications in Annex I

Article 13. 4. The substances not listed in the Union list or provisional list referred to in paragraph 2(b) shall not belong to either of the following categories: … *(b)* substances in nanoform.

'Hard' NM already approved in the EU as **additives in food contact materials: carbon black**, **silicon dioxide**, **titanium nitride**, **kaolin**, and **copolymers**, e.g. "methacrylic acid, ethyl acrylate, n-butyl acrylate, methyl methacrylate and butadiene".

Risk assessments were based on zero exposure scenarios as there was no appreciable migration into the food

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European legislation on NMs: Food Additives

U5

Food additives (Regulation 1333/2008)

- New risk assessment is needed for new additives or already authorised additives **when there is a change in particles size due to new production processes**

Food additives, enzymes and flavourings must undergo a common (EU-wide) assessment and authorisation prior marketing, for which Regulation (EC) 1331/2008 (European Parliament and Council) lays down the common procedure

All **food additives that were permitted before 2009** are currently under **re-evaluation**. This includes also some of the **common particulate food/feed additives***, which have been in use for years, such as anti-caking/free-flow powders, pigments and others (*e.g.* **E171, E551**)

* Pre-market approval - authorisation procedure based on a scientific risk assessment - is also required for **feed additives**

Feed marketing is regulated by Regulation 767/2009. Substances added to feed (feed additives) for technological, nutritional, organoleptic or zootechnical purposes (e.g. animal performance) or as coccidiostats/histomonostats are regulated by Regulation (EC) No 1831/2003 on additives for use in animal nutrition. Regulation (EC) No 429/2008 describes the detailed rules for the implementation of this regulation

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European legislation on NMs: Labelling regulation ('FIC')

U5

Food information to consumer (Regulation 1169/2011)

- All **ingredients** present in the form of engineered NMs shall be clearly indicated in the list of ingredients.
- The names of such ingredients shall be followed by the word 'nano' in brackets

«Ingredients» in this context include:

- ❑ Food additives
- ❑ New foods and food ingredients (e.g. minerals or vitamins) specifically designed to be nano-sized = by definition ***'NOVEL FOODS'***

Definition of **'NOVEL FOODS'**: foods that have not been consumed to a significant degree in the EU before May 1997

- ❑ They have to undergo a **pre-marketing authorization procedure** to assess the safety for human consumption
- ❑ **NMs for food use** (different from additives, flavourings or enzymes) were implicitly covered by the 'old' novel food Regulation 258/97/EC*

* *"foods and food ingredients to which has been applied a production process not currently used, where that process gives rise to significant changes in the composition or structure of the foods or food ingredients which affect their nutritional value, metabolism or level of undesirable substances"*

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The new Novel Food Regulation: EU 2015/2283 (1)

U5

NMs for food use are explicitly covered*:

*"To ensure a high level of protection of human health and consumers' interests, **food consisting of engineered nanomaterials** should be considered a **novel food** under this Regulation"*

*"**Vitamins, minerals or other substances that contain or consist of engineered nanomaterials** should also be considered **novel foods** under this Regulation and should be re-assessed first in accordance with this Regulation and subsequently in accordance with the relevant specific legislation"*

Novel Food WG at the EFSA NDA Panel

* Apart from those falling in the categories of additives, flavourings, enzymes, extraction solvents (which are regulated elsewhere)

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The new Novel Food Regulation: EU 2015/2283 (2)

U5

The NM definition *is incorporated in this regulation and deleted from the FIC regulation*:

"The term 'engineered nanomaterial' is currently defined in Regulation (EU) No 1169/2011 of the European Parliament and of the Council.

For consistency and coherence purposes, it is important to ensure a single definition of engineered nanomaterial in the area of food law.

The appropriate legislative framework for including such a definition is this Regulation.

Accordingly, the definition of engineered nanomaterial, along with the related conferral of delegated powers to the Commission, should be deleted from Regulation (EU) No 1169/2011 and replaced by a reference to the definition set out in this Regulation.

Furthermore, this Regulation should provide that the Commission should, by means of delegated acts, adjust and adapt the definition of engineered nanomaterial set out in this Regulation to technical and scientific progress or to definitions agreed at international level"

The new regulation shall apply from 1 January 2018

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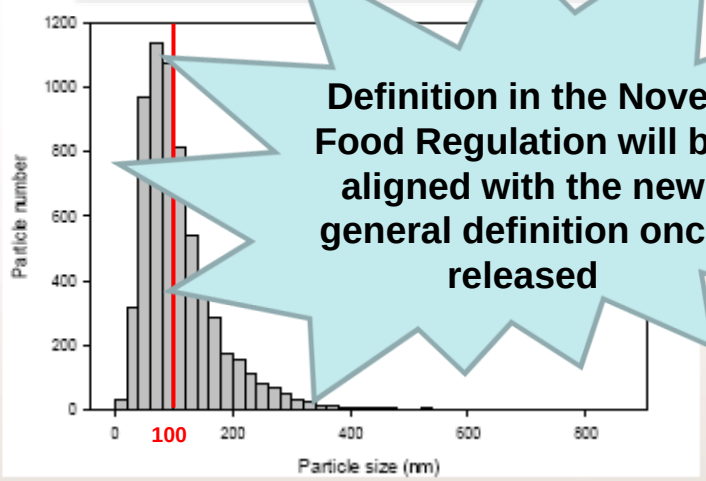
The new Novel Food Regulation: EU 2015/2283 (3)

U5

The NM definition as it currently appears (***pending update***):

> *" 'engineered nanomaterial' means any intentionally produced material that has one or more dimensions of the order of 100 nm or less or that is composed of discrete functional parts, either internally or at the surface, many of which have one or more dimensions of the order of 100 nm or less, including structures, agglomerates or aggregates, which may have a size above the order of 100 nm but retain properties that are characteristic of the nanoscale.*
>
> *Properties that are characteristic of the nanoscale include: (i) those related to the large specific surface area of the materials considered; and/or (ii) specific physico-chemical properties that are different from those of the non-nanoform of the same material "*

Particle size distribution



Definition in the Novel Food Regulation will be aligned with the new general definition once released

European Commission's definition of nanomaterial for legislative and policy purposes **(under revision)**

…rcentage of particles with one or more external dimensions in the size range 1-100 nm

> 50 % (number size distribution)

(>1% in specific cases)

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The new Novel Food Regulation: EU 2015/2283 (5)

U5

How to assess potential risks for human health?

Assessment of the safety risks arising from novel foods:

" ***Criteria for the assessment of the safety risks arising from novel foods*** *should also be clearly defined and laid down.*

In order to ensure the harmonised scientific assessment of novel foods, such assessments should be carried out by the ***European Food Safety Authority ('the Authority')****.*

Under the procedure for authorising a novel food and updating the Union list, the Authority should be requested to give its opinion if the update is liable to have an effect on human health. In its opinion, the Authority should ***assess, inter alia, all the characteristics of the novel food that may pose a safety risk to human health and consider possible effects on vulnerable groups of the population****.*

In particular, the Authority should verify that, where a novel food consists of engineered nanomaterials, the most up-to-date test methods are used to assess their safety "

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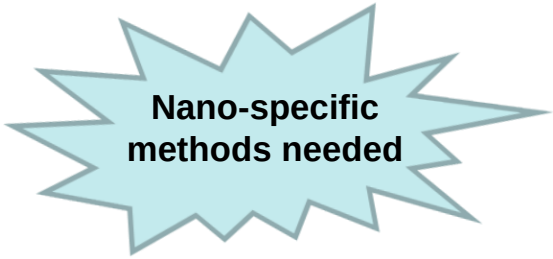
The new Novel Food Regulation: EU 2015/2283 (6)

U5

Methods for NM characterisation and toxicological testing:



" *As regards the possible use of nanomaterials for food use, the Authority considered in its opinion of 6 April 2011 on* ***Guidance on the risk assessment*** *of the application of nanoscience and nanotechnologies in the food and feed chain that* ***limited information is available in relation to aspects of nanotoxicokinetics and toxicology of engineered nanomaterials and that existing toxicity testing methods may need methodological modifications****.*

The ***Organisation for Economic Cooperation and Development Council Recommendation*** *of 19 September* ***2013*** *on the Safety Testing and Assessment of Manufactured Nanomaterials concluded that the* ***approaches for the testing and assessment of traditional chemicals are, in general, appropriate for assessing the safety of nanomaterials, but may have to be adapted to the specificities of nanomaterials****.*

In order to better assess the safety of nanomaterials for food use and in order to address the current gaps in toxicological knowledge and measurement methodologies, test methods, including non-animal tests, which take into account specific characteristics of engineered nanomaterials may be needed "

Nutraceutical

U5

Nutraceutical = "nutrition“ and “pharmaceutical"
in 1989 by Stephen DeFelice.

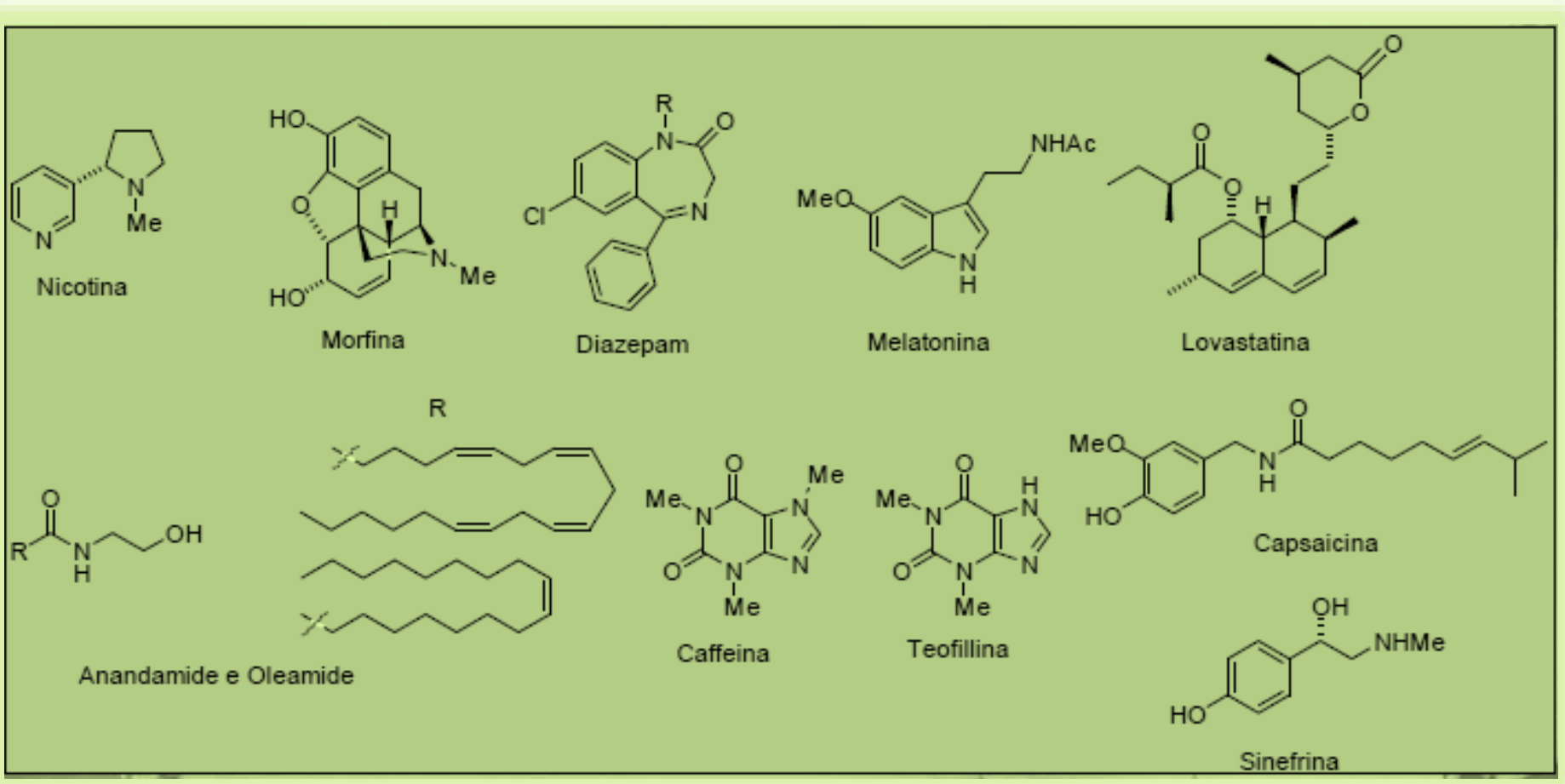
“…discipline that studies the food components with nutritional or physiological effect that play an important role in the maintenance of a healthy life and in the prevention of chronic diseases..”

Food constituents can be isolated and presented in medicinal forms and take in higher concentrations than those obtainable with the diet and with function also beyond that nutritive (Science).

However, the term nutraceutical as commonly used in marketing has no regulatory definition

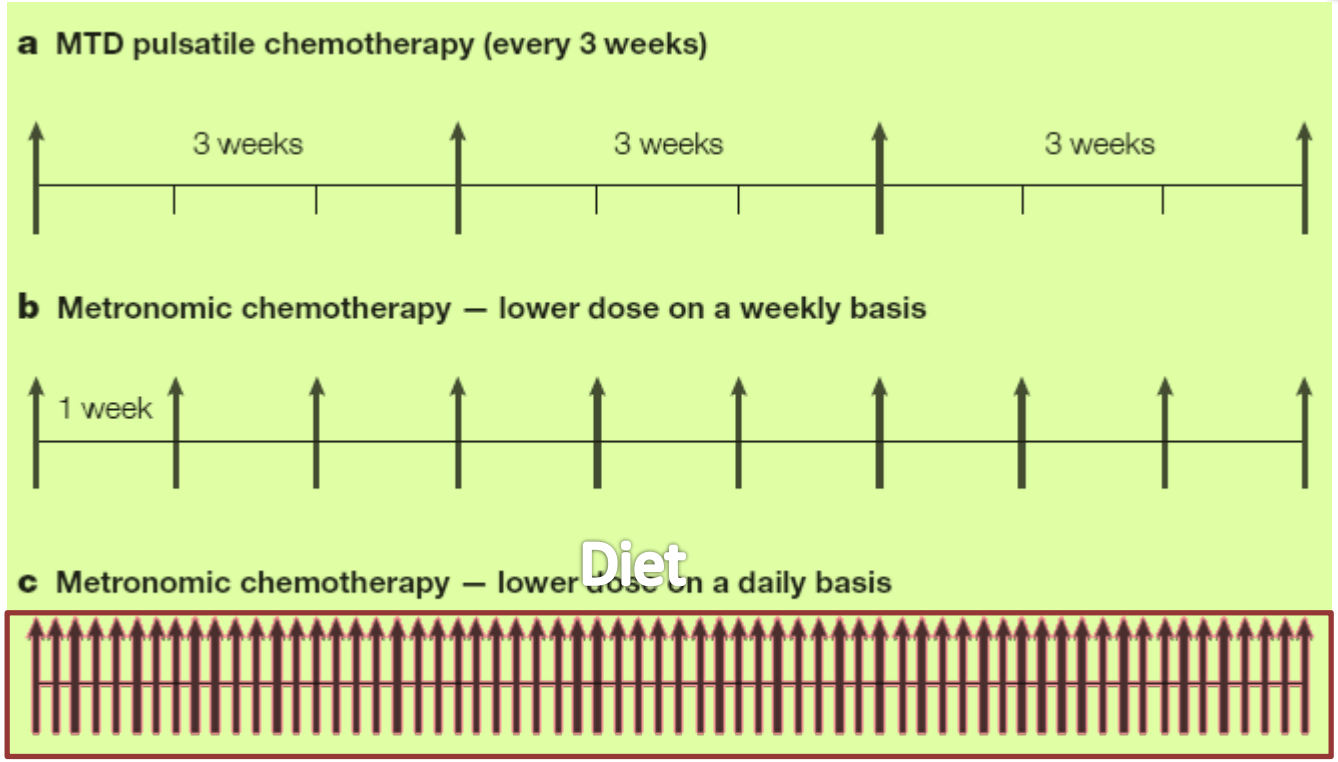
Nutraceutical

U5



Metronomic approachs from diet: nutriterapy?

U5



R.S. Kerbel et al. *The anti-angiogenic basis of metronomic chemotherapy*. Nature Reviews (2004) , 4, 423-436

The metronomic pharmacological approach is the continuing administration to small doses of drugs, because they try to reduce the toxicity of biological and metabolic chemotherapy, reducing the side effects, but also in dealing with the fight against cancer.

The food metronomic approach employs not individual compounds with metabolomic impact, but the set of all those present in selected foods consumed each day that can prevent the development of chronic-degenerative diseases such as cardiovascular disease and cancer.

Food supplements

U5

"Supplements or dietary supplements are products that are **a concentrated source of** Nutrients, such as vitamins and minerals, or other physiological substances, but not exclusively, amino acids, essential fatty acids, vegetable fibers and extracts, whether mono-or multi-purpose, intended to supplement the diet. "

Form

These products are **sold packaged in pre-formulated form such as capsules, tablets, pills, chewing gums**, **powders, vial-containing liquids, dropper bottles** and other similar forms of liquids and powders intended for use in small Unitary quantities.

Functions

Their purpose is to optimize nutritional contributions, provide substances of nutritional interest to protective or trophic effect, and improve metabolism and physiological functions of the body.