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PUBLIC HEALTH COMMITTEE (PARTIAL AGREEMENT) (CD-P-SP)

**COMMITTEE OF EXPERTS ON NUTRITION, FOOD AND CONSUMER HEALTH
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(PARTIAL AGREEMENT) (P-SP-NU-FS)**

**Homeostasis,
a model to distinguish between foods
(including food supplements)
and medicinal products**

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NOTE TO THE READER

The document Homeostasis, a model to distinguish between foods (including food supplements) and medicinal products should be read in conjunction with the Guidelines on the quality, safety and marketing of plant-based food supplements (24.06.2005).

The documents are available on the Internet website of the Partial Agreement in the Social and Public Health Field:

www.coe.int/soc-sp

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Homeostasis, a model to distinguish between foods (including food supplements) and medicinal products

I. Introduction

Progress in education and knowledge has increased expectations of the public towards efficient natural based solutions for improving the quality of their health and daily life

In our society there is a clear tendency for people to try to reach a high quality of life, and this expectation extends until a high age. This is, without any doubt, the result of increased education and knowledge. Due to these reasons and in conjunction with a growing range of products one sees an increased desire to supplement the daily diet with efficient, natural and nutrition related solutions in order to increase the quality of one's daily life. People are willing to improve their health and decrease the risk to develop diseases. Maintaining the body's condition by regular sport activities, increasing awareness of the importance of the quality of food and the way people select their diet, the increasing use of functional food and food supplements are clear signs of this evolution. Whereas formerly food was only considered in the context of avoiding or preventing nutritional deficiencies, there is now an important increase in the research and development of various functional, health promoting, and health protecting food ingredients. This is also acknowledged by the European Union in the financial support it gives to projects to develop this science (e.g. FUFUSE, PASCLAIM) and the adoption of the regulation on nutrition and health claims made on foods¹, establishing a procedure for the scientific evaluation of claims and under which for the first time ever reduction of disease risk claims will be possible for foodstuffs, including food supplements. Furthermore, the Food Supplement Directive 2002/46/EC provides the framework for nutrients like vitamins and minerals and foresees the possibility to regulate other substances like herbals. The population grows older and the impact on the social security cost is therefore important. Improving health and decreasing disease risk is not only positive for the individual but benefits the whole population and society.

Consequences

With the health-aspect comes into discussion the practical as well as the legal delimitation between the food and medicinal legislation. Both legislations focus on health and use identical terms, as for example "physiology", without however defining the terms. Consumer demand for health promoting products and business opportunities have moved the industry forward towards product innovation to be able to offer more specific and specialised solutions. This evolution narrows the distance between food and medicines and leads into discussions on the status of specific products. Such discussions are in essence not necessary because medicinal law is made for medicinal products to control efficacy and safety of products intended to prevent, cure or treat diseases or have a therapeutic activity, while food supplements are intended to supplement the diet for health purposes on the basis of nutritional and/or physiological effects and where safety and validity of claimed effects are ascertained under the food law framework. But since the same substances can be used for both therapeutic purposes and health promoting purposes on the basis of nutritional and/or physiological effects a pragmatic solution is needed to delimit both legislations and create legal security for the industry as well as for

¹ Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods, OJ L 404, 30.12.2006, p. 9–25, Corrigendum: OJ L 12, 18.1.2007, p. 3–18

the authorities. In this paper, the two directives addressing the subjects of food supplements and medicines are briefly discussed. This discussion brings out and emphasizes the need for a pragmatic and feasible system to distinguish between foods, including food supplements and medicinal products. A practical model, the homeostasis model, is presented; it helps to define the conditions according to which a product is judged to be a food supplement or a medicinal product and hence if it falls in or out of the scope of the second paragraph (b) of the definition of a medicinal product (Directive 2001/83/EC).

Especially for botanical products this model can be of value as botanicals or some of the active principles thereof are used in food and food supplements as well as in medicines. This document explicitly only considers the application of the homeostasis model to **botanical products**. Moreover, as food supplements have to be in line with all requirements of food safety, the homeostasis model cannot be applied to toxic or harmful botanicals/botanical preparations. In addition, the model is also not applicable to botanicals/botanical preparations which are not acceptable as food ingredients due to other legitimate reasons (e.g. not authorised novel foods).

II. Food supplements and medicinal products, the European legislation

We will consider the two main directives, Directive 2002/46/EC on food supplements and the Directive 2001/83/EC as amended by Directive 2004/27/EC on medicinal products. Furthermore, it should be remembered, that the European Court of Justice has dealt with the classification of products as foods or as medicines in several court cases. The corresponding judgements contribute as integral part to EC-legislations.

• Definition of a food supplement: Directive 2002/46/EC on food supplements

'Food supplements' means foodstuffs the **purpose** of which is to **supplement the normal diet** and which are **concentrated sources** of nutrients or other substances with a **nutritional or physiological effect**, alone or in combination, marketed in dose form, namely forms such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquids, drop dispensing bottles, and other similar forms of liquids and powders designed to be taken in measured **small unit quantities**.

In the context of this definition, a physiological effect has to be understood as an optimisation of a physiological function and not the restoration, correction or modification of it. This can be deduced from the directive on medicinal products.

• Definition of a medicinal product: Directive 2001/83/EC on medicinal products

Art 1 (2)

(a) Any substance or combination of substances **presented** as having properties for **treating or preventing disease** in human beings; or

(b) Any substance or combination of substances which **may be used** in or administered to human beings either with a view to **restoring, correcting or modifying** physiological **functions** by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.'

A product will be considered a medicinal product either by virtue of its "presentation" or its "function". A product constitutes a medicinal product if it falls within either of these two categories.

Art. 2(2):

In cases of doubt, where, taking into account all its characteristics, a product may fall within the definition of a 'medicinal product' and within the definition of a product covered by other Community legislation the provisions of this directive shall apply.

In the context of this directive following terms are of importance:

a)

Treating disease: to bring physiological functions back to normality

Preventing disease: to avoid that physiological functions fall out of normality

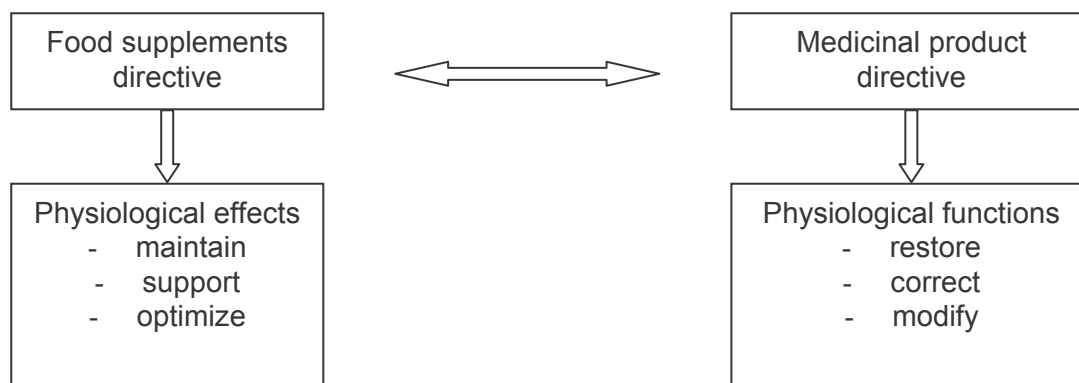
b)

Restore: supposes the absence or damage of a well defined physiological function (e.g. thyroid hormones in hypothyroidism)

Correction: supposes a deviation, an abnormality, a pathology in relation to a specific physiological function (e.g. medicine for hypertension)

Modify: supposes the intention to modify a specific physiological function in a way that is no longer physiological (e.g. contraceptives)

The following scheme clarifies the differences between the two directives:



Although this scheme seems logical, there is a lack of clear definitions and measurable parameters to judge whether a product falls under the food supplements directive or the medicinal one. Therefore, in addition to the juridical approach set out by the directives, a scientific and feasible model has to be developed in relation with paragraph (b) of the definition of a medicinal product, without prejudice of paragraph (a) of this definition.

This model has to provide descriptive and quantifiable parameters to be able to distinguish between the use of a substance, i.e. botanical/botanical preparation in food supplements and in medicinal products. The homeostasis model provides these tools. This model has to be seen as a tool providing guidance to finally obtain a clear view on the status of the product (food supplement or medicine) in regard to paragraph (b) of the definition of a medicinal product.

When necessary, efficacy studies can be performed to also quantify the nature and extent of the activity of a given product. However, the homeostasis model is not developed to make a distinction between **disease prevention**, which is to be ascribed to medicinal products and **reduction of disease risk** ascribed to food supplements.

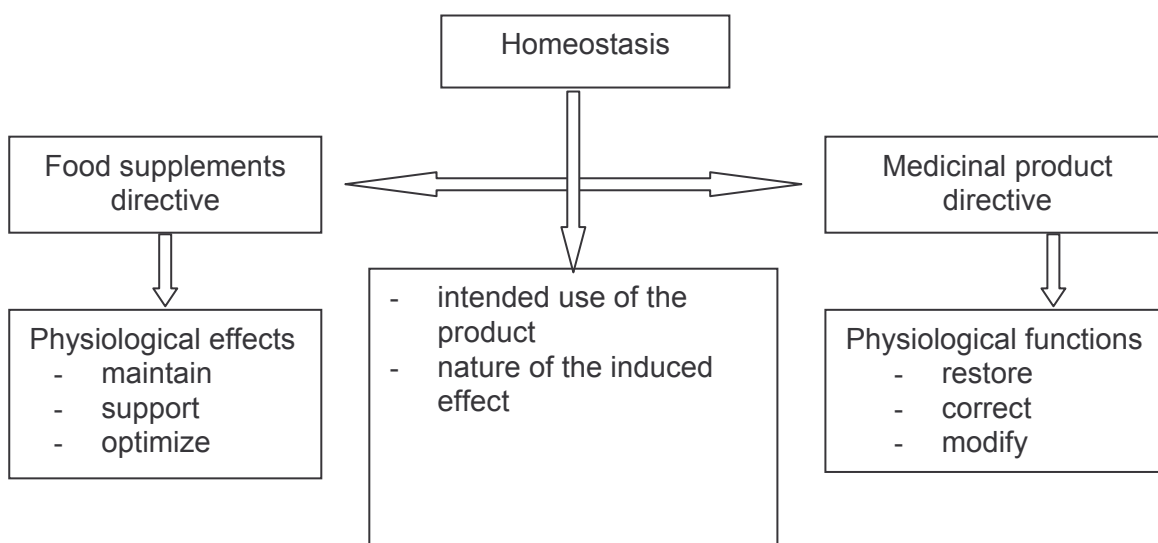
III. The homeostasis model

Referring to the Council of Europe Guidelines on the quality, safety and marketing of plant-based food supplements (2005), **homeostasis can be defined as the status of a person whose physiological parameters function within the limits considered as normal.** The EC legislation indicate that food supplements are taken with the aim to support, maintain or optimize the normal physiological processes and hence the homeostasis, without altering or blocking these functions. Medicines are intended to be taken when physiological functions fall out of normality and hence are pathological or also to prevent diseases. The aim of medicines is to bring them back into normality: in other words into homeostasis (“restore or correct”) or to prevent disease (safeguard the homeostasis). It is clear that products altering or changing physiological processes in order to bring them out of normality are also considered to be medicines (“modify”). Contraceptives are a clear example thereof.

In order to distinguish between both frameworks, in the homeostasis model a product needs to be evaluated against the following **fundamental criteria**:

- *The intended use of the product*
- *The nature of the induced effect on one or more physiological parameters*

We can therefore improve the scheme by adding the homeostasis as a tool to distinguish both categories:



Once the product has been examined in the light of these criteria, the category of the product is defined regarding paragraph (b) of the definition of a medicinal product. In order to quantify the extent of an effect for a specific physiological function, if necessary, specific parameters can be measured. In a number of cases relevant parameters to describe physiological functions and the limits considered as normal are known. (As an example the values of cholesterol: < 225 mg/dl and triglycerides: 50 -150 mg/dl). However, in other cases it may be difficult to identify or reach consensus on relevant parameters that accurately reflect specific physiological functions in question, as well as to define their normal ranges. Also it may be necessary to consider several different parameters.

- **The intended use**

The fundamental pillar to distinguish between food supplements and medicines is the precise description of the intended use of a product. This criterion helps to distinguish in a juridical way between food supplements and medicines. Indeed, it is linked with the first part of the medicines definition, the presentation criterion. Products which are presented to treat or to prevent a disease will fall under the medicinal law. However, the intended use has to be seen in a broader perspective than just the presentation of the product. A product can also be classified as a medicine when the properties of this product correspond to the second part of the definition of a medicine. As an example, a sportsman can by means of adapted food (supplements) and training improve his physical condition, increase his performance and optimize his system. In the same context food supplements can be taken with the intention to maintain, support or optimize immunological, metabolic and other specific physiological parameters. This is not the same as correcting, modifying or restoring physiological functions or parameters. Therefore, the homeostasis model delimits the application field of food supplements and hence the intended use to products to be taken with the intention to maintain, support or optimize physiological functions which are functioning in between the limits of normality and hence are in homeostasis. This requires a precise definition of all relevant physiological parameters and moreover of the limit-values in which a given parameter is considered as normal, parameters which exist and even with a broad consensus. For situations where a demarcation between physiological condition and diseasedness is difficult a decision should be made from case to case.

- **The nature of the induced effect**

The second pillar to help distinguish between food supplement and medicinal use of a substance is the **nature of the induced effect** on a specific physiological parameter. In most of the cases this will be linked to the **dosage of the active principles** used.

A pragmatic method to help to differentiate between the use of a substance as food supplement and medicinal product is best done via defining the **minimal therapeutic dosage**. This is the minimum amount of the substance, necessary to induce a therapeutic effect on a well-defined pathology at which proof of therapeutic activity still exists. If a product contains an amount of the substance which is lower than the minimal therapeutic dosage for a given pathology, the product can no longer fulfil the requirements of art. 1 point 2, b of Directive 2001/83/EC. But this does not preclude the use of the substance in food supplements, provided the product has shown to be safe by adequate risk assessment and is not presented as a medicine. If no clinical proof for a therapeutic effect exists appropriate scientific data on “well established use” (according to Art. 10 a of Directive 2001/83/EC) or adequate bibliographic data on the “traditional medicinal use” (according to Art. 16 a of Directive 2001/83/EC; “traditional herbal medicinal products”) should be taken into consideration. If a minimal effective therapeutic dosage (based on above mentioned data) can not be established, then there is no need to apply restrictions to the use of these ingredients (i.e. botanicals/botanical preparations), provided of course the safety of these ingredients has been proven by adequate risk assessment and provided the product fulfils all requirements of food law and is not presented for the treatment or cure of a disease in humans.

It can be concluded that the nature of the effect, and hence the dosage, is an important criterion to distinguish between the use of a substance in food supplements and medicinal products.

IV. Practical application of homeostasis model in relation to food supplements

From all the above, we can conclude that both criteria have to be considered: the intended use and the nature of the effect. But what also comes out from the above discussion is that there is a need for a model describing:

- which are the limits of what can be considered health/physiological effect, and more particularly,
- what are the values of the physiological parameters which are considered as normal and hence will define the borders within which substances with a health/physiological effect can and may be active. Figure 1 clarifies the principles of the homeostasis model.

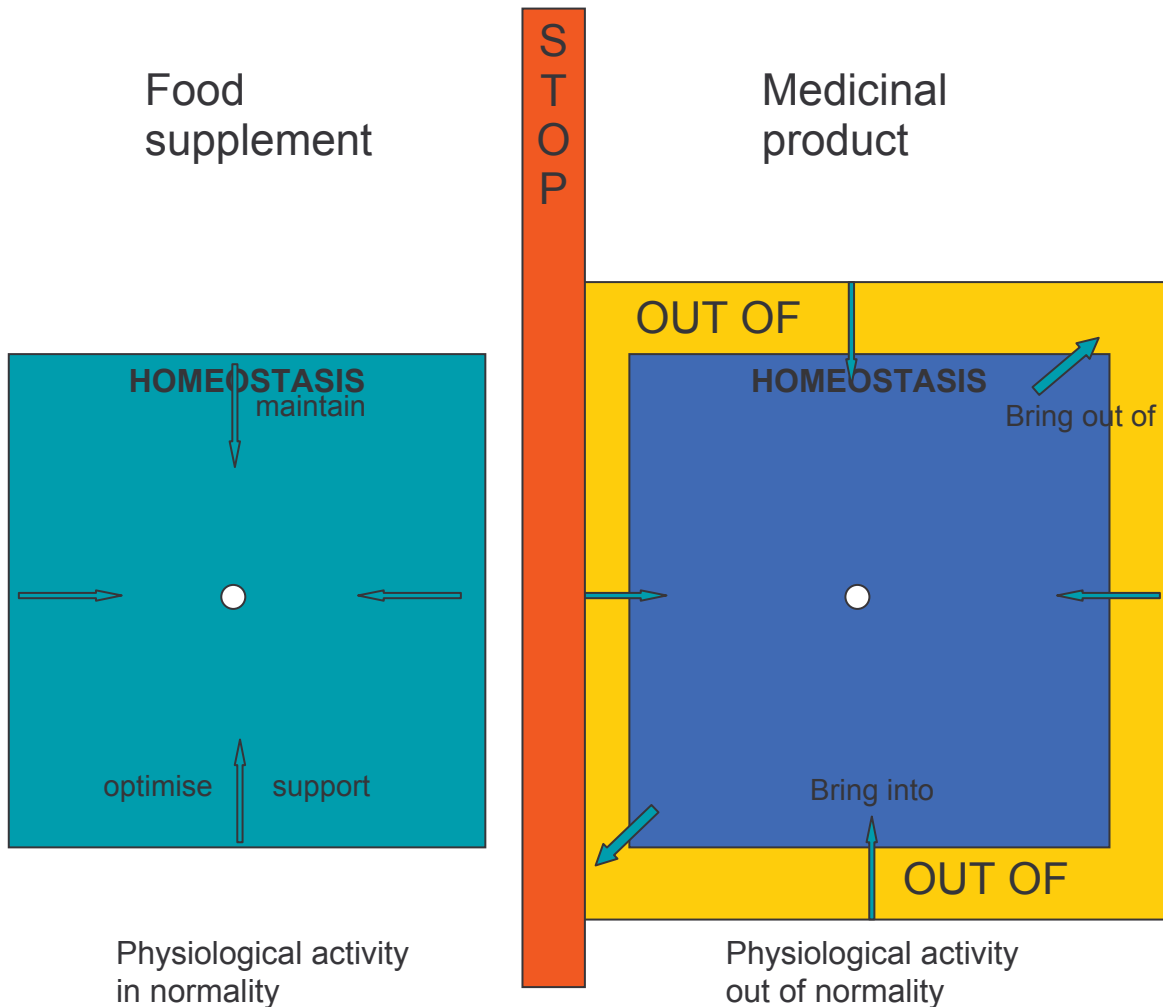


Fig 1. Graphical presentation of the homeostasis model

The borders of the inner frame represent the limits of normality of the different physiological processes in homeostasis. Inside the frame, the optimal status (the goal to achieve) is represented as a small circle. Health promotion acts within the limits of the normal physiological parameters in order to move them away from the border and bring them into the inner circle. Medicinal activity however acts on parameters which are out of the borders with the aim to bring them back into the normal limits.

The parameters considered to signify normality of some important physiological functions are known and generally accepted. Indeed, these are the parameters defining the trigger point from which on medication can become necessary. This means the range of normality of a physiological function is quantified. As a consequence the nature of the effect of a product can be measured or derived from existing data like clinical studies or adequate bibliographical data on “well established use” (according to Art. 10 a of Directive 2001/83/EC) or adequate data on the “traditional medicinal use” (according to Art. 16 a of Directive 2001/83/EC “traditional herbal medicinal products”). When clinical studies or other data subject to regulations of Directive 2001/83/EC exist, the fixation of a dosage for food supplements becomes easier. Indeed, based on these data, the minimal therapeutic dosage necessary to induce a therapeutic effect on a well defined physiological parameter can be defined. When the dosage is set lower than that minimum therapeutic one, the product can no longer fulfil the criteria of art. 1 point 2, b of Directive 2001/83/EC but can be regulated under the food supplement directive, provided the product is safe and the potential claim can be verified under the Health Claims Regulation 1924/2006. This safety requirement restricts the application field of the homeostasis model to products fulfilling all the legal requirements for food supplements.

Any potential claim for foods and food supplements containing a non-therapeutic and non-toxic dosage of a botanical/botanical preparation should be verified under Regulation 1924/2006 on nutrition and health claims made on foods. It has to be noted that it is possible that below the therapeutic dosage a physiological effect cannot be demonstrated according to the provisions in the above mentioned Regulation 1924/2006 which would exclude the concerned products from bearing any health claim in relation to the botanical/botanical preparation in question.

- The Belgian approach

A pragmatic method to fix the maximum dosage for active ingredients has been developed by the Commission for Advice of Plant Preparations of the Belgian Federal Public Service Public Health, Food Chain Security and Environment. It has to be noted that the Belgian approach has been put into place before Directive 2001/83/EC was amended by Directive 2002/24/EC on traditional herbal medicinal products.

Some statements are the basis of the methodology:

- *When for a given dosage of a substance or active principles a clinical proof of a therapeutic effect on a well-defined pathology exists, then a product containing this substance at a bioequivalent level is a medicinal product and will have to comply with the rules of the medicinal law.*
- *When for a specific active substance(s) two distinct dosages exists with two distinct therapeutic effects, then as a rule the lowest dosage will be taken into account for the determination of the maximum acceptable amount in food supplements.*
- *When from dose response studies it has been shown that for a small change in dose, the effect is changing strongly, the distance between the maximum acceptable dosage in food supplements and the minimal therapeutic dosage has to increase.*

Based on the available high quality clinical studies the minimum dosage to induce a well defined therapeutic effect on a well defined pathology is then derived. This is called the minimum therapeutic dosage. In case of new clinical evidence, it is possible that this dosage has to be reviewed. To fix the maximum amount for food supplements, from the minimal therapeutic dosage one goes down 10% due to analytical uncertainties plus an extra 10% (minimum) to make the distance. Whenever the observed effect change is strong with small dosage changes, an extra % is brought in to increase the distance with the minimal therapeutic dosage. However, this has to be done carefully as to avoid the product has no longer any physiological effect which then should come in conflict with the requirements of the Food Supplement directive.

V. Conclusion

The delimitation of the application field for food supplements to the domain of a physiological function in a state of homeostasis delivers a model which can help to distinguish food use from medicinal use of a herb or herbal preparation. Because the parameters considered as normal for some given function are known, in these cases we do have measurable factors in order to prove an effect in relation to maintaining, supporting or optimizing physiological functions. This is also important to substantiate a possible claim. The homeostasis model delivers a guide to help to substantiate the classification of a given food supplement, based on the use of measurable parameters, coupled to two criteria: (1) intended use and (2) nature of the effect. It is up to the manufacturer of a product to prove with all available tools (literature, studies ...) that his product fulfils the homeostasis model in these criteria, and acts within the physiological borders considered as normal.