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SUPPLEMENT

Safety impact—the risk/benefits of functional foods

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Abstract It is amazing to see how much the approach of the food risk analysis evolved in the recent years. For half a century and the birth of the risk assessment methodology in the food domain, only no appreciable health risk was considered acceptable by the manager. This is the vocabulary used in the case of a voluntary, deliberated human action, as the use of food additives (definition of ADI). In the case of risks not resulting from such an action, as that of the presence of contaminants, the risk assessor allocates provisional tolerable daily, weekly or monthly intake that are the basis for regulation. This vocabulary is in agreement with the objective which consists in approaching closer possible of the zero risk which is the wish of a majority of the consumers. Some years ago, the risk managers insisted to obtain from the assessors as often as possible a quantitative risk evaluation. More recently even, the managers would like to decide on the basis of a balance of risk and benefit acceptable for management purposes. Finally, they hope that general principles and tools will be available for conducting a quantitative risk-benefit analysis for foods and food ingredients. What is possible in the case of functional foods (FF)? Based on the definition of FF proposed in the programme FUFOSE, one has to distinguish between different situations in order to assess the risk: that of a micro-, that of a macro-component or that of a whole food. These situations have been clearly described in the document resulting from FOSIE. The standardized methodology relevant to assess micro-components is not well adapted to the assessment of whole food. Concepts of substantial equivalence and of history of safe use could be useful tools in this case. However, quantitative risk assessment remains a very difficult exercise. If a process for the assessment of health benefit of FF has been proposed as an outcome of the PASSCLAIM action, the quantification of this benefit needs adequate tools. An EFSA scientific colloquium on "Risk-Benefit Analysis of Foods" organized in July 2006 concluded that the risk-benefit analysis should mirror the current risk analysis paradigm and that its assessment should be performed with common scales. Disability adjusted life years (DALYs) or quality adjusted life years (QUALYs) have been proposed as some of these common scales. However, the meeting "concluded that the data available to undertake a quantitative risk-benefit assessment may be too scarce". Because it was considered that it was premature to formulate guidelines on good risk-benefit analysis practice and it is now time to "learning by doing", a reference to the upcoming ILSI Europe project BRAFO was done. All these aspects are discussed, in particular in relation to the specific case of FF.

Keywords Functional foods · Safety · Risk · Benefits

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Introduction

In a special issue of the British Journal of Nutrition [15] untitled "Functional Foods: Scientific and Global Perspectives", M.B. Roberfroid wrote in 2002 "Being foods, functional foods need to be safe according to all criteria

defined in current food regulations. …But that regulation does not concern nutritional properties or physiological effects of these novel foods. It is strictly a safety regulation. The requirement for safety is a prerequisite to any functional food development. Indeed the risk versus benefit concept, that is familiar to pharmacologists developing new drugs, does not apply to functional foods, except, maybe, in very specific conditions for diseases risk reduction when the scientific evidence is particularly strong."

This position with respect to the evaluation of the risks/benefits ratio of functional foods (FF) evolved during the last years to become a more systematic waiting.

In the same way, and since approximately the same amount of time, the vocabulary used for the communication of the result of risk assessment evolved considerably.

We more closely will examine this evolution in a first part of this paper. We will be interested then in the risk assessment in the specific field of functional foods. Finally we will see what can be implemented to evaluate their benefit.

Risk assessment: an evolution in the vocabulary used

It was in September 1955 that a joint FAO/WHO conference was held in Geneva, the main conclusion of which was to recommend to the Directors General of the two agencies that regular meetings be called of a joint committee of FAO/WHO experts to study the toxicological problems raised by the use of additives in foods. The JECFA (Joint FAO/WHO expert committee on food additives) was born. During its second meeting in June 1957, a chapter in the final report was included on "Evaluation of concentrations probably harmless to man". One member of JECFA, present in all these crucial first meetings, the French Pr. R. Truhaut, who believed that one cannot prove absolute non-toxicity, but only a very high degree of innocuousness, talked in terms of an acceptable daily intake for human [16]. For this reason, R. Truhaut was considered as the "Nestor" of the acceptable daily intake (ADI) concept [18]. A definition of ADI was later published by WHO in 1987 [19]: "Acceptable daily intake: an estimate by JECFA of the amount of a food additive expressed on a body weight basis that can be ingested over a lifetime without appreciable health risk (standard man = 60 kg)". From this definition, one can conclude that they are experts of JECFA who decide what is an appreciable health risk and what is acceptable for the consumers.

R. Truhaut was also instrumental in the application of the ADI concept to the specific case of pesticides in the first meetings of the Joint FAO/WHO experts committee on pesticide residues (JMPR, inaugural meeting in 1963). This concept applies thus to substances (food additives, pesticides) deliberately used and authorized by regulation. It is the reason why in the JECFA glossary of terms (IPCS Risk Assessment Terminology, http://www.who.int/entity/ipcs/food/jecfa/glossary.pdf), the ADI definition became "An estimate of the amount of a substance in food or drinking water, expressed on a body-weight basis, that can ingested daily over a lifetime without appreciable risk (standard human = 60 kg). The ADI is listed in units of mg per kg of body weight."

A comparable toxicological approach was then adopted by JECFA in the case of contaminants present in food, but the vocabulary could not obviously be the same one as for authorized substances. Thus, JECFA proposed in the case of contaminants with no cumulative properties to fix "provisional maximum tolerable daily intake" (PMTDI). In 1972 at its 16th meeting JECFA proposed to fix, for cumulative heavy metals (Hg, Pb, Cd) "provisionally tolerable weekly intakes" (PTWI). For contaminants with very long half-life in the human body, a "provisional tolerable monthly intake" (PTMI) could be allocated.

Also in the case of contaminants, it is clear that for JECFA they are experts who decide of what is tolerable.

In 1978 and 1980, the US Food safety council published a draft then a final report untitled "Proposed system for safety assessment" [11, 17] in which it is very interesting to read: "the word safe is here interpreted to mean presenting socially acceptable risk under expected conditions of consumption" and "the word accept may or may not include some form of restricted use rather than unlimited consumption". One can find in the report a comment on the "Choice of Societal Risk Level":

- We have attempted to give procedures which separate statistical and biological judgement from societal judgement;
- A major element in this judgement will be the choice of an allowable level of risk, P_0. The choice of $P_0 = 10^{-6}$ for potential cancer risks (one extra cancer from a particular chemical per one million persons exposed over a 70-year lifetime) by the Commissioner of the FDA was made after much discussion;
- It nevertheless seems to us that its value should not be fixed in advance for all agents and that its choice must depend on the value to society of the agent involved;
- It is incumbent upon those using the decision tree to do the necessary risk-benefit analysis by setting upon a value of P_0 and…"

Thus, for the US Food Safety Council, it is the Commissioner of FDA (a risk manager) who decides of the societal allowable level of risk, taking into account in particular the result of a risk-benefit analysis. It is, however, difficult to quantify the level of risk for human

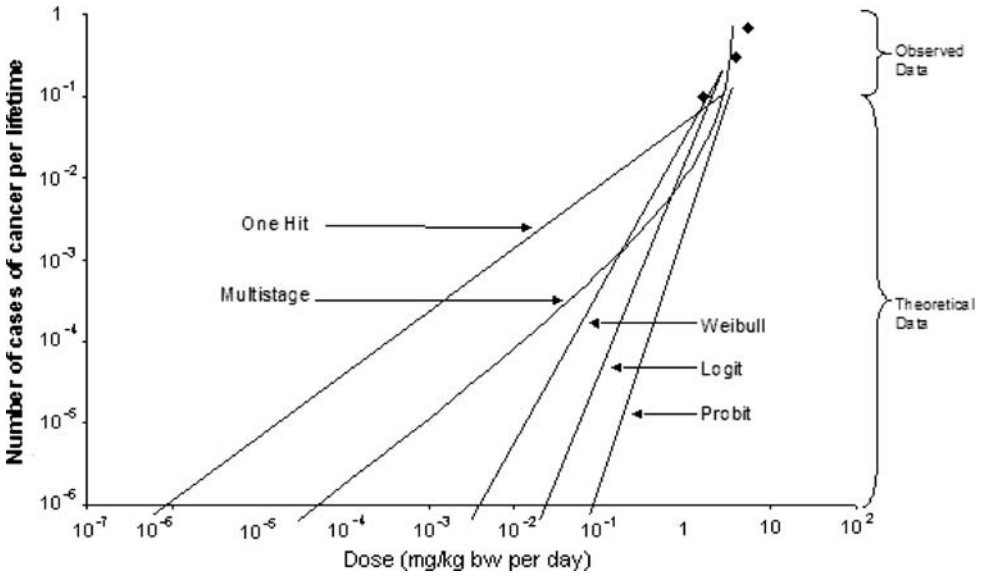

Fig. 1 Low dose extrapolation from animal carcinogenicity data using various models. Figure reproduced and modified from the Guidance on a strategy for the risk assessment of chemical carcinogens of the UK Committee on Carcinogenicity of chemicals in food, consumer products and the environment. Adapted from [3]

consumers by extrapolation from animal experiment taking into account the levels of exposure, the result depending on the model used for extrapolation. A good example (Fig. 1) was published by the UK-COC in 2004 [3].

Even if the question of carcinogenic effects of FF does not arise, the example of risk assessment and management of substances which are both genotoxic and carcinogenic is interesting because it shows how the scientific approach and the vocabulary used evolved during the last years. Because of the above mentioned difficulties, unlike the previous American quantitative approach, the approach was appreciably different in the majority of the European countries. In an opinion from the EFSA Scientific Committee [7] on "A harmonized approach for the risk assessment" the committee said "In many countries and especially in the EU, the advice given by the risk assessor has been to reduce the exposure to such substances to a level that is as low as reasonably achievable. However, it is recognized that such advice does not provide risk manager with a basis for setting priorities for action". Therefore, the Scientific Committee recommends using an approach known as the margin of exposure (MOE). It recommends the use of the benchmark dose (BMD) to obtain the MOE. The benchmark dose is a standardised reference point derived from the animal data by mathematical modelling within the observed range of experimental data. It uses all of the information obtained over the range of doses from the experiment. The Scientific Committee recommends the use of the BMDL10 (benchmark dose lower confidence limit 10%) which is an estimate of the lowest dose which is 95% certain to cause no more that a 10% cancer incidence in rodents (Fig. 2). The Scientific Committee notes that the benchmark dose approach can also be applied to human data when available.

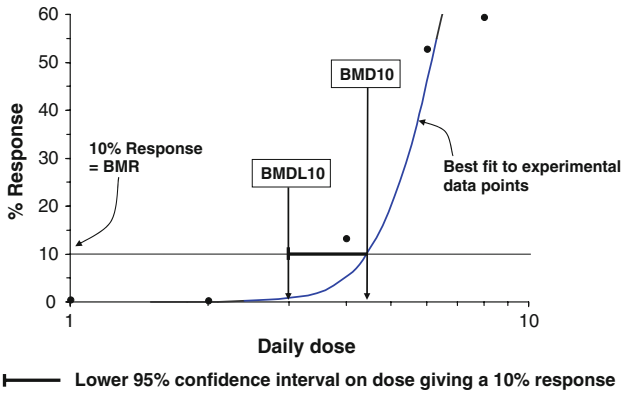

Fig. 2 Hypothetical dose response data illustrating the concepts of BMR, BMD and BMDL for a 10% incidence response above the control

Margins of exposure, calculated for different substances and intake scenarios can vary broadly. A small margin of exposure represents a higher risk than a larger margin of exposure. Consequently, the risk managers can use this information for priorities setting. This approach is now in process of harmonization at the international level.

This is one of the examples which show that experts' committees are more and more aware that their role consists in supplying to the risk managers scientific elements to help them to make management decisions, but that their mission does not consist in deciding on what is or not acceptable by the citizens. Thus, EU scientific steering committee (SSC) concluded in an opinion on "Harmonisation of risk assessment procedures" [10] that attention needs to be given to various approaches for the formal contextualisation of risk, e.g. by:

– comparison with possible replacements,
– risk ranking,
– risk/benefit assessment.

So the vocabulary used to estimate the risks evolved as well as the spirit in which is realized this evaluation. If until the end of the 80s, the experts who are the risk assessors or the civil servants who are the risk managers decided of what is acceptable in terms of health risks, without clear information of the citizens, for many hazards, particularly novel sources, a transparent risk-benefit analysis is now much needed. Assessment of the benefits needs to be carried out with the same rigour and expression of uncertainties as risk assessment [10].

This is a general survey of the evolution of risk assessment, but what is the situation in the case of FF?

The specific case of functional foods

To approach this question, I am going to adopt the working definitions of FF given in the Consensus Document of the concerted European action FUFOSE [5]: "a functional food can be:

– a natural food,
– a food to which a component has been added or has been removed by technological or biotechnological means,
– a food where the nature of one or more components has been modified,
– a food in which the bioavailability of one or more components has been modified,
– or any combination of these possibilities.

Functional foods must remain foods and they must demonstrate their effect in amounts that can normally be expected to be consumed in the diet: they are not pills or capsules, but part of a normal food pattern".

As a consequence of these elements of definition, the safety issues of FF could be summarized to the safety assessment (or the risk assessment) of foods or of food components, in other words:

– of low molecular weight micro-components which could be essential nutrients or not,
– or macro-components (nutrients or not) or whole food.

In the case of micro-components which are not essential nutrients, the classical methodology designed for food additives and contaminants should be applied for their safety assessment, with special attention to the safety factor. A complete survey of the hazard characterisation of chemicals in food was made on the occasion of the European concerted action FOSIE (Food safety in Europe), including a description of the context in which this methodology has to be applied [2].

In the case of micro-components which are essential nutrients (for example vitamins or trace elements) a novel approach has been proposed by an expert group of the ILSI Europe's Addition of Nutrients to Food Task Force, to compare beneficial and adverse effect across intake levels [14]. The model can provide advice for risk managers in a form that will allow the risk of deficiency or the risk of not experiencing the benefit to be weighted against the risk of toxicity. Using this approach, risk managers will be able to define ranges of intake based on a balance between the risk of deficiency (or lack of benefit) and toxicity. This case is representative of FF to which a component has been added.

The risk in the case of macro-components or whole food is more difficult to assess with the traditional approach and is different in many aspects from the one of food additives or contaminants. Dybing. [6] have clearly identified these differences from the report of a JECFA consultation [13]:

Additives/contaminants

- Simple, chemically defined substance
- Low proportion in the diet (usually less than 1%)
- No nutritional impact (with few exceptions)
- Specific route of metabolism, often simple to follow
- Acute effects obvious

Food

- Complex mixture
- High proportion in diet, high intake (often >10%)
- Nutritional impact possible depending on dose
- Complex metabolism with interactions
- Acute effects difficult to produce (usually absent)

The term "Wholesomeness" rather than safety better describes the evaluation of whole food; it encompasses several considerations, including toxicology, nutrition, microbiology and environmental effects. Macronutrients and whole foods present a special case because the quantities that may be ingested by consumers and because nutritional considerations are normally an essential part of safety evaluation. The current performance of the safety assessment of whole foods is mainly based on the protocols for low-molecular-weight chemicals such as pharmaceuticals, industrial chemicals, pesticides, food additives and contaminants. However, these protocols have limitations for testing of whole food. This primarily results from the fact that defined single substances can be dosed to laboratory animals at very large multiples of the expected human exposure, thus giving a large margin of safety. In contrast foodstuffs are bulky, lead to satiation and can only be included in the diet at much lower multiples of expected human intakes. When testing whole foods, the possible

highest concentration of the food in the laboratory animal diet may be limited because of nutritional imbalance of the diet, or by the presence of compounds with a known toxicological profile and the doses that can practically be applied cannot, in general, encompass the required uncertainty factor of 100.

The design of the study should be adapted from the OECD 90-day rodent toxicity study. The precise study design has to take into account the nature of the food and the characteristics of the new trait(s) and their intended role in the food.

Due to the limitation of the current risk assessment approach in the design of animal feeding studies and higher possibility of nutritional impact on overall diet, new strategy and concepts have been proposed in order to overcome these difficulties:

- the core of the present process of safety assessment of whole foods and macro-nutrients is based on a comparative principle, whereby the food being assessed is compared with one that has an accepted level of safety often based on "history of safe use" [4]. This is the concept of "substantial equivalence" [13]. In order to applied the concept of substantial equivalence, chemical and physical data for both the test material and the reference food or ingredient need to be available. However, there is often very limited information, e.g. on natural variation of plant components due to climatic influences or due to plant varieties [6]. Such chemical characterisation have advanced in recent years thanks to considerable progresses in analytical chemistry compared with the methods in use when early novel foods such as single-cell proteins were evaluated in the 1970s;
- in addition to the substantial equivalence concept application, nutritional testing and tolerance studies are necessary to ensure that the nutritional status of consumers is not jeopardised by substitution of existing foods of known nutritional value with new food with less known nutritional or anti-nutritional effects.

How to assess the risk-benefit ratio of functional foods?

Even if Dybing et al. [6] wrote on the occasion of the program FOSIE "But functional foods are notable in that an effect on "function(s)" in human is desired; this implies a degree of specificity (benefits without hazards) not sought for traditional food products", we saw that M. B. Roberfroid anticipated that it would be recommended to take into account the ratio risks/benefits in the case of FF leading to a disease risk reduction.

In line with the SSCs recommendation to take into account this ratio, EFSA organised a colloquium on "Risk-benefit analysis of foods: methods and approaches" in July 2006 [8]. The background was (announcement of this meeting) described as follow "The assessment of risk to human health of food substances or nutrients is usually conducted independently of possible health benefits. Furthermore, different scientific approaches are used to estimate health risks and health benefits of foods, food ingredients and nutrients. When a food or a food substance is associated with both potential health risks and benefits, and particularly when the levels of intake associated with risk and benefit are close, there is a need to define an intake range within the balance of risk and benefit is acceptable for risk management purposes. However, there is currently no agreement on the general principles or approaches for conducting a quantitative risk-benefit analysis for food and food ingredients. One of the main challenges of such an exercise is to define a common scale of measurement for comparing the risks and the benefits".

A "process for the assessment of scientific support for claims on foods" has been proposed as an outcome of the PASSCLAIM European concerted action [1]. This project builds on the principles defined within the previous EU project FUFOSE and delivers criteria to assess the scientific support for claims on foods. PASSCLAIM project focussed on beneficial effects of foods and foods components on health. Safety was not a consideration in the data supporting the scientific validity of claims but was as mentioned, the subject of the programme FOSIE. The discussion of both projects underlined the need to look at risks and benefits associated with a given food product or product modification. However, the quantification of the risks and benefits needs adequate tools.

Amongst conclusions of the EFSA Colloquium, the following possible common scale measures were mentioned:

- Incidences;
- Disability adjusted life years (DALYs);
- Quality adjusted life years (QUALYs). Like DALYs these are quantitative, but are still based on a number of assumptions and are more difficult to quantify than DALYs;
- Days of work lost;
- Cost in money. Requires equal cost structures across countries/world and is difficult to communicate. In practice it requires assumptions about costs of human life loss or about cost of changes in quality of life which are highly controversial.

The concept of QUALYs has been used extensively in medical technology assessment and in health economics to optimise decision making. It has been adopted as a basis for public health policy in a few countries, such as the Netherlands [12].

As a result of the EFSA Colloquium, a project for a Specific Support Action to investigate the Risk-Benefit Analysis for Foods (BRAFO) was elaborated and proposed to the FP6. It was accepted in 2007; one of its objectives is to test the developed methodologies including QUALY and DAILY-like methodologies, on selected case studies (folic acid, oily fish, fat replacement agents and heat processing of foods).

Conclusions

We limited ourselves in this review to the case of FF which meet the working definition proposed in the consensus document resulting from the project FUFOSE: FF are foods.

The case of food supplements and plant and herbal extracts is more controversial. The toxicological risk is indeed bigger with products for which there is no physical limitation in the exposure. With a food, there is a maximal quantity of its constituent, which a consumer can ingest because of the physical bulking effect of the food matrix. Such a limitation does not exist with supplements or herbals and the risk of an excessive exposure is then bigger. In addition, the bioavailability of the components of these products is higher than that of the same components inside a food matrix, leading to higher toxico-kinetics parameters.

Furthermore, if the concepts of substantial equivalence and of history of safe use can often apply to FF, in reference to food consumed in countries having an epidemiological surveillance system capable of discovering the deleterious effects of certain food, the concept of history of safe use can apply much more with difficulty for products coming from countries in which the epidemiological data are non-existent or non-credible. An ancestral consumption is not a sufficient assurance of safety!

On the basis of our definition of FF, the evaluation of their safety is relatively easy and can be decomposed into various situations:

- FF differs from a current food because it contains a substance added in relatively limited quantity. It is "substantially equivalent" to the normal food with the exception of this substance:
- If this substance is present in other current foods or present in bigger quantity than in the same current food, it is advisable to make sure that on the basis of the toxicological knowledge, a sufficient safety factor exists;
- If this substance does not exist naturally in current foods, it must be evaluated as any substance intentionally added to food or resulting from authorized treatments (vitamins, minerals, trace elements, food additives, pesticide residues…). FF becomes then a Novel Food and recommendations were proposed for its evaluation [9][1];
- FF is not "substantially equivalent" to a normal food because its composition is different from any food usually consumed with a new or intentionally modified primary molecular structure; it is a Novel Food and we are returned to the previous case.

They are the most delicate cases, because as it was underlined, there is no totally satisfying protocol to evaluate the safety of a food.

In every case, it is recommended when possible, to realize a quantitative risk evaluation or at least to place the risk on a scale which allows the risk manager to compare it to the others food.

In the case of FF, this recommendation is going to be difficult to implement because of the already evoked difficulties of the risk evaluation. A post marketing monitoring (PMM), which cannot be considered as an element of risk evaluation a priori, can, however, consolidate the premarketing risk assessment.

The research for a common scale of measurement of risks and benefits allowing estimating a ratio risks/benefits, can then appear as illusive. It is advisable to wait for the results of the program BRAFO, to know if the wishes of the risk managers can be satisfied. Science cannot always satisfy the managers (and the consumers) wishes!

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[1] Part I: Recommendations concerning the scientific aspects of information necessary to support applications for placing on the market of novel foods and novel food ingredients (Opinion expressed on 7 June 1996).

Part II: Recommendations concerning the scientific aspects of the presentation of information necessary to support applications for placing on the market of novel foods and novel food ingredients (Opinion expressed on 13 December 1996).

Part III: Recommendations concerning the scientific aspects of the preparation of the initial assessment reports on applications for placing on the market of novel foods and novel food ingredients (Opinion expressed on 13 December 1996).

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