

SCIENTIFIC REPORT OF EFSA

Report of the public consultation on the EFSA draft guidance on human health risk-benefit assessment of foods¹

European Food Safety Authority^{2, 3}

European Food Safety Authority (EFSA), Parma, Italy

BACKGROUND

On 3 February 2010, the EFSA Scientific Committee endorsed draft guidance on “human health risk-benefit assessment of foods”. The draft guidance had been prepared by an EFSA Scientific Committee working group composed of members of the Scientific Panels and Committee.

In line with EFSA’s policy on openness and transparency and in order for EFSA to receive comments from the scientific community and stakeholders on its work, EFSA engages in public consultations on key issues. The draft opinion was published for public consultation from 26 February until the 15 April 2010. EFSA has committed itself to publish the comments received as well as this technical report on the outcome of the consultation.

COMMENTS RECEIVED

At the deadline, EFSA had received 280 submissions (among which were 83 repetitive comments that were removed), from 19 interested parties (non-governmental organisations, industry organisations and national assessment bodies). All comments received were scrutinized and subsequently tabulated with reference to the contributor and the section of the draft opinion to which the comment referred. There was one set of comments received outside the electronic form which thus did not fulfil the EFSA submission criteria⁴. However, those comments were still considered and have been inserted in the table of comments when not duplicating already existing comments. Duplicate comments appear only once in the table. Comments submitted formally on behalf of an organization appear with the name of the organization. The table of all comments is published as an appendix of this document.

1 On request of EFSA, Question No EFSA-Q-2007-043b.

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3 Acknowledgement: EFSA wishes to thank the members of the Working Group on Risk-benefit Assessment for peer-reviewing this EFSA scientific report: Ada Knaap (Chair), Diane Benford, Alan Boobis, Helmut Hesseker, Rolaf van Leeuwen, Hildegard Przyrembel, Ivonne Rietjens, Josef Schlatter and Ivar Vågsholm, and EFSA’s staff member Bernard Bottex for the support provided to this EFSA scientific report.

⁴ See <http://www.efsa.europa.eu/en/consultationsclosed/call/sc100226.htm>

Suggested citation: European Food Safety Authority; Report of the public consultation on the EFSA draft guidance on human health risk-benefit assessment of foods. EFSA Journal 2010; 8(7):4. [48 pp.]. doi:10.2903/j.efsa.2010.1674. Available online: www.efsa.europa.eu

Organisations that submitted comments to the consultation (in alphabetical order)

Alliance for Natural Health International	UK
Association de la Transformation Laitière Française (ATLA)	FR
Confederation of the food and drink industries of the EU (CIAA)	BE
Council for Responsible Nutrition – International	USA
Coughlin & Associates	USA
Danone	FR
Istituto Superiore di Sanità	IT
European Botanical Forum (EBF)	BE
European Federation of Associations of Health Product Manufacturers (EHPM)	BE
European Responsible Nutrition Alliance (ERNA)	BE
Federal Institute for Risk Assessment	DE
Institute of Food Technologists (IFT)	USA
International Alliance of Dietary / Food Supplements Associations (IADSA)	BE
International Life Sciences Institute – Europe (ILSI Europe)	BE
International Nutrition Company BV	NL
National Institute for Public Health and the Environment (RIVM)	NL
Nuscana Biotechnika Laboratoryjna	PL
Polish Council for Supplements and Nutritional Foods	PL
Swedish National Food Administration	SE

SCREENING AND EVALUATION OF THE COMMENTS RECEIVED
GENERAL COMMENTS

The majority of the comments supported the stepwise and case-by-case basis approach for risk-benefit assessment proposed in the guidance document; by assessing not only risks, but also the benefits for human health, this approach is considered as a first step towards a more integrated assessment of foods.

Some of the comments received underlined a couple of general misunderstandings that have been further clarified in the guidance document by the working group of the Scientific Committee:

- The document provides methodological guidance on how to perform a risk-benefit assessment of foods; it is intended to cover the full range of EFSA activities. It is not a “guidelines”

document and therefore it is not intended to substitute for any risk assessment guidelines that already exist for some food/feed areas.

- Some of the comments highlighted the risk of overlap between the risk-benefit assessor and the risk-benefit manager's responsibilities, and questioned the independency of the risk-benefit assessment. The respective roles of the assessor and the manager have been clarified in the document: once both parties have agreed on the question to answer (problem formulation), the assessor is responsible for stating the level of evidence available from the data for both risks and benefits, and for communicating this information to the risk-benefit manager. It is the risk-benefit manager who then decides whether the level of information is adequate to come to a decision, by integrating this information with other considerations (economical, social, ethical, cultural) that are out of the scope of this guidance document, or whether further refinement of the risk-benefit assessment is needed.
- Some readers misunderstood the guidance document as asking for different levels of evidence, depending on whether risks or benefits are being assessed. Reference was made to the level of evidence required by EFSA to consider a health claim as scientifically substantiated. In line with the above-paragraph, it was clarified that the role of the risk-benefit assessor is limited to describing and, if possible, quantifying the identified risks and benefits, while stating the level of evidence. The decision on whether the information and the level of evidence are sufficient to make decision is the responsibility of the risk-benefit manager. In order to avoid confusion, all references to claims were removed from the guidance document. It is moreover underlined that it is not the purpose of this document to provide guidelines on how to perform a benefit assessment.

SPECIFIC COMMENTS

Definitions:

Some comments underlined the absence of a definition for "health". The working group considered the WHO definition ("*state of complete physical, mental and social well-being and not merely the absence of disease or infirmity*") but concluded that this is too broad for the scope of the guidance document. In the context of this work, health is understood to be an absence of disease or nutritional deficiency.

By "risk-benefit manager", is understood any decision-maker who will take action based on the outcome of the risk-benefit assessment, but also other factors such as economical considerations. At European Institution's level, the risk-benefit manager can be the European Commission, the Parliament or the Council. At Member States' level, it will be any relevant competent authority. Such a risk-benefit manager may be difficult to identify at an academic level, but will also exist in industry, often called "decision-maker". One key message of this guidance document is that the terms of reference for the risk-benefit assessment, i.e. the need for a risk-benefit assessment and the question to answer, have to be agreed between the assessor and the one using the outcome of the assessment for taking decisions.

A proposal was made to split the definition of "benefit" into "the probability of a positive effect on health", and "the probability of a reduction of an adverse health effect", so that a risk-benefit assessment applies only when there is really a benefit in the sense of a positive effect on health, to be compared with a risk. The working group underlined the fact that there would then be very few instances of benefit to consider and did not see any need to split the definition.

The suggestion was made to discard the "hazard" and "risk" terminology and speak of "(potential) beneficial / adverse effects". The working group had a lengthy discussion on terminology aspects and decided not to create new terms, to avoid lack of understanding by other parties working in the same and related areas.

Situations for which a risk-benefit assessment is appropriate

It is underlined that the various cases where a risk-benefit assessment is appropriate, listed under section 2.1 of the guidance document, are only examples and that this list is not intended to be definitive. The decision on whether to embark on a risk-benefit assessment is taken on a case-by-case basis during the problem formulation step, involving dialogue between the risk-benefit assessor and the risk-benefit manager.

Problem formulation:

Some comments stressed that the risk-benefit question is generally a choice between different policies or courses of action, described in the form of “scenarios”. The working group of the Scientific Committee disagree with the idea that a risk-benefit assessment always implies a comparison or “what if” question. Some risk-benefit assessment questions will imply comparison of different scenarios, e.g. in the case of a public health intervention, others not, e.g. what is the balance of risks and benefits caused in a population by consumption of a particular dietary component? This concept of scenarios has been clarified in section 2.2 of the guidance document.

About the proposed approach:

Some comments received underlined the fact that current legislation in place requires food placed on the European market to be safe; as such there is no need for a risk-benefit assessment but for a benefit assessment only. It is observed that a number of undesirable compounds such as acrylamide and methylmercury are present in food despite existing legislation. As risks (and benefits) are a function of consumption, they can be controlled (maximised) with specific management strategies, which avoids some foods simply being banned. Hence, there is a need for an approach to compare risks and benefits.

Some parties criticized the approach as being too “pharmacological” (one substance = one effect) and not looking at the food as a whole. The proposed stepwise approach implies that the assessment is focussed on ingredients during the initial steps; it then addresses the whole food when integrating risks and benefits by mean of the composite metric. In order to facilitate the risk-benefit comparison, it is logical that the approach for benefit assessment mirrors the well-established and internationally recognised risk assessment paradigm. The proposed approach is consistent with other risk-benefit assessment strategies (WHO, Danish, UK, German authorities). Finally, the working group wishes to underline that nowhere in the document reference is made to any kind of “pharmaceutical approach”.

Some parties argued that dose-response assessment is not appropriate for food and food components. Such a position can be challenged, as it implies that benefits or risks show no relationship to dose, and contradicts the observed growing obesity problem in Europe, which is obviously related to the quantity of food consumed.

The document provides guidance for risk-benefit assessments at the population level rather than for individual consumers. It is primarily intended for the EFSA Scientific Panels who, on occasion, undertake assessments to protect the European Union’s populations. The approach is however applicable to risk-benefit assessments for individual consumers if individual data are available.

Figure 1 may have been misleading, as some interpreted it as suggesting that the exposure assessment is common to the risk and the benefit characterisation. A footnote has been added to clarify that, depending on the nature of the risk-benefit assessment, the exposure assessment could be done in common or separately.

- *Step 1 of the assessment*

A remark was made that already at the initial step of the assessment, an absence of data can be identified and reported back to the risk-benefit manager. The related figure has been corrected accordingly. A second remark underlined that, since a common metric is not yet defined in step 1 of the assessment, step 1 will yield only crude indications of whether a potential risk or benefit may occur, based on assumed low and high levels of consumption. The working group of the Scientific Committee concurs with this remark but underlines that in some cases, this conservative assessment may already answer the needs of the risk-benefit manager.

- *Step 2 of the assessment*

Parties from industry underlined that it is not possible, based on the knowledge available before the launch of a product, to have sufficient data to derive estimates of disease incidence or mortality as a result of exposure to a new product. The working group of the Scientific Committee acknowledged that sometimes data may be lacking and underlined that in such cases, assumptions can be made to perform the risk-benefit assessment. The assumptions made should then be described when reporting the uncertainties associated with the assessment.

Another remark questioned the appropriateness of linking estimates of disease or mortality to the consumption of a particular food. The working group of the Scientific Committee agrees that it is not always possible but some examples show that this is sometimes feasible, e.g. consumption of Noni and risk of hepatotoxicity.

One comment underlined that asking for new data at the end of this step (step 2) will not solve the problem that sometimes no composite metric can be calculated, e.g. when measurements of the benefits are lacking. The working group of the Scientific Committee agrees with this remark but stresses that gathering new data may allow step 2 to be run again and hence enable further refinement of the risk-benefit assessment.

Metrics used in risk-benefit assessment:

Some comments called for “persistence” of effect to be mentioned in the guidance document. The working group of the Scientific Committee clarified that persistence is part of “severity”, which is already mentioned.

One comment questioned the adequacy of expressing the benefit of consuming a food in terms of severity of disease, morbidity and mortality. The working group of the Scientific Committee agrees that this cannot be done when the benefit is a positive health effect but confirmed that these metrics are adequate when dealing with a benefit that is a reduction of the risk for an adverse effect.

Importance of the selected endpoints and the (sub)populations considered:

The incorrect statement that “the obvious benefit endpoint will be the absence of risk for nutrition deficiency” has been corrected, as a benefit cannot simply be an absence of risk.

One remark stated that risk is to be considered for the whole population while benefit is linked to an individual choosing a functional food. The working group of the Scientific Committee disagrees with this statement as a benefit can also be for a whole (sub) population, e.g. food fortification programmes at national level, and a risk at an individual level.

Exposure:

Some comments called for explicit guidance on the extent to which alternative sources and pathways of exposure should be considered. The issue of exposure assessment is a common problem to any assessment and is therefore not specific to risk-benefit assessment. No change was made to the guidance document as a consequence of this remark.

Effects:

One comment addressed the limitation of randomised controlled trials (RCT) that are used to show causality in humans. The working group of the Scientific Committee agrees that RCTs are not primarily designed to look for risks but they can help in identifying them. The limitations of RCTs are highlighted in the guidance document.

Several comments called for a classification of the strength of evidence for risks or benefits. It is however not the purpose of this guidance document to provide guidelines on how to assess strength of evidence.

Extrapolation of animal and other data to the human situation:

Some comments questioned the applicability of the 100-fold safety factor used for risk assessment as a default when extrapolating animal data to the human situation, to benefit assessments. The working group of the Scientific Committee agrees that in the case of benefit assessment, where human data are used, there is no need for the 10-fold safety factor for interspecies uncertainty. The working group acknowledges also that there is currently no agreement on the use of an uncertainty factor for human variability in benefit assessment.

One comment stated that the majority of animal experiments are conducted for benefit assessment purposes. The working group of the Scientific Committee disagreed, as mostly human data are used for benefit assessment. Animal data can be used only if proof is provided that the mechanism of action in the animal is also valid in humans. Animal data for benefit assessment are therefore to be considered on a case-by-case basis.

A set of comments criticised the reference in this section of the guidance document to genotoxic and carcinogenic compounds and the recommendation to use the Margin of Exposure (MOE) approach, since this would not be relevant to products in development. The working group of the Scientific Committee cited the example of certain botanical food supplements containing some genotoxic and carcinogenic compounds, and also certain contaminants in food, which therefore justifies this insertion. Concerning the use of the MOE approach, it was clarified that it is applicable to step 1, but also to step 2 of the proposed approach; different scenarios will lead to different MOE values that can then be compared.

Uncertainties:

A number of points reflecting some of the uncertainties, e.g. not all substances of interest may have been identified, difficulty of assessing foods (as opposed to individual substances) because of matrix effects, were submitted. The guidance document goes to some length to emphasize the need to identify and evaluate the uncertainties in an assessment, in a transparent manner, and to bring these uncertainties, which are actually not specific to risk-benefit assessment, to the knowledge of the risk-benefit manager.

Examples of risk-benefit assessment:

Despite the disclaimers made in the opinion, some comments were received that the examples provided do not address all endpoints that can be identified from the literature. It was further clarified that the selenium intake and fish consumption examples are intended to illustrate how to apply the approach; they are not intended to be a full risk-benefit assessment of these scenarios.

Conclusions and recommendations:

One statement received concluded that the risk-benefit assessment methodology proposed is intended only for official evaluation bodies and should not be expected to be used by industry. As mentioned earlier in this document, the proposed approach for risk-benefit assessment can be used by any party, including industry. The type and quantity of data available will determine how far the evaluator can go in the assessment. Step 1 and step 2 can be easily applied, sometimes with some assumptions. Concerning step 3, a web-based tool has been developed by the EU-funded research project Qalibra⁵ for comparing risks and benefits using a composite metric.

One comment called for further development in risk characterisation in order to address what happens when safe levels are exceeded. The working group of the Scientific Committee took note of this remark but underlined that this issue is not specific to risk-benefit assessment, and is therefore outside of the scope of the guidance document.

Several parties called for further involvement of stakeholders. As for the risk-benefit assessment process, consultation processes are foreseen by EFSA when considered necessary. Different formats, such as public consultations, or physical meetings with stakeholders are used. As for the possibility for stakeholders of providing input into risk-benefit management decisions, such decisions are not the responsibility of EFSA.

⁵ <http://www.qalibra.eu/>

APPENDIX A: COMMENTS RECEIVED (ORGANISED BY SECTIONS OF THE GUIDANCE DOCUMENT)

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
CIAA	Summary	We stress the fact that regarding the risk assessment, there is nothing really new in this document. In addition, we support EFSA in its effort to go further in the benefit assessment, specifically for developing specific metric for health benefit assessment, symmetric to risk assessment metrics. Indeed, metrics as proposed (DALY's, QALY's) are not designed to investigate beneficial impact on health <i>per se</i> , but merely to measure the risk and risk reduction.
CIAA	Summary	We find it important that both the role of the risk assessor (EFSA) and the risk manager (Commission) in relation to risk/benefit assessment is better clarified in the document,
Alliance for Natural Health International	Background as provided by EFSA.	<p>Line 162: The term "risk-benefit assessment" should be expressed either as "risk/benefit assessment" or as "risk-benefit assessment". This change should be made throughout the document.</p> <p>Line 169: Instead of "Consideration of methods and approaches needed to assess the risks and benefits...", we suggest instead: "Evaluation and validation of methods and approaches appropriate to the assessment of the risks and benefits...". This helps to focus the work more, and allows for comparing and contrasting methods when utilised with real data, rather than simply their "consideration".</p>

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
<p>Association de la Transformation Laitière Française (ATLA)</p>	<p>Background as provided by EFSA.</p>	<p>On one hand, we highly appreciate that EFSA addresses in this document the health benefit assessment of foods and not only, as in the past, a single risk assessment. Benefits assessment tools are indeed less advanced than in the case of risk assessment and we agree that they need to be developed further. In this sense, we would be in favour of a document that enables an improvement of the knowledge on this topic. However, unlike stated in the document, we think that cultural considerations should also be taken into account in the benefit assessment as food has an important social dimension, in France but also in a lot of European countries. Reducing food to its sole functional dimension would be very questionable.</p> <p>On the other hand the risk assessment approach proposed in the document seems to be a duplicate of what is already done at international and European levels. For example, all the definitions regarding risk assessment already exist in the Codex Alimentarius (see for example principles and guidelines for the conduct of microbiological risk - CAC/GL 30-1999). Besides, the risk assessment is already done through the numerous European regulatory tools that ensure the food safety (regulation about additives, novel food, flavourings, microbiological criteria for foodstuffs, biocides...)</p> <p>Therefore in our opinion the draft guidance proposed by EFSA conveyed ideas that are likely to increase anxiety among consumers towards foods whereas food is basically safe and food safety is already covered in Europe. In our opinion, the risk of foodstuffs does not need to be addressed in another way than the one already done in the European regulation. In other terms, such a guide should develop the benefit assessment of food but for the risk part it should refer to current existing guidelines or procedures.</p> <p>As a conclusion we would like to remind that a pharmacological approach (one substance = one effect) that isolates nutrients and does not address food as a whole is not relevant for food (e.g. omega 3 is used as an example of benefit in fish but what about the other nutrients of the fish? And the way it is consumed? The food eaten is fish and not fatty acids). The food has to be considered as a whole, and inside a diet, because :</p> <ul style="list-style-type: none"> • Foods are complex combinations of nutrients and it is not always possible to predict the effect of foods on health based on their content of one or two nutrients. • Food patterns, food groups and individual foods, the food matrix, and individual nutrient requirements, and the physiological status of the consumer, all have an impact on health responses. <p>Our concern is that the EFSA approach will isolate nutrients and not give due consideration to the synergistic aspects of foods and nutrients or the aspect of total diet.</p>
<p>CIAA</p>	<p>Background as provided by EFSA.</p>	<p>Line 141: We think it is a reasonable approach to state that risk-benefit analysis "should only be undertaken when clearly needed". However, we wonder under which modalities this evaluation will be done. Who will decide the risk-benefit analysis is clearly needed, when and based on what criteria? Line 143: We would appreciate more clarity is given about who will be the risk manager: will it be political / administrative authorities? Same question for the risk assessor, will it be only official assessment authorities?</p>

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
Council for Responsible Nutrition	Background as provided by EFSA.	<p>Lines 120-155: EFSA is to be applauded for trying to systematize a process that to date has not been attempted by any other government health body. CRN-I generally agrees with the assessment that RCTs have had limited success in identifying benefits for nutrients and that EFSA and the world nutrition community would be able to better conduct benefit risk evaluations if more emphasis were placed on models that can be better used to measure nutrient based health benefits.</p> <p>Lines 121-6: This paragraph should acknowledge that most regulatory authorities, including the European Commission, separately regulate benefits and risks for foods. Policies and regulations for benefits are specified through Population Reference Intakes (PPI) or similar concepts and Health Claims (including disease risk reduction, and functions).</p>
DANONE	Background as provided by EFSA.	L143: We would appreciate more clarity is given about who will be the risk manager: will it be political / administrative authorities? Same question for the risk assessor, will it be only official assessment authorities?
DANONE	Background as provided by EFSA.	L 141: We think it is a reasonable approach to state that risk-benefit analysis "should only be undertaken when clearly needed". However, we wonder under which modalities this evaluation will be done. Who will decide the risk-benefit analysis is clearly needed, when and based on what criteria?
EHPM	Background as provided by EFSA.	<p>One question that arises is the need for such guidance. Under EU food legislation, there is no need for such guidance as all Foods have by definition to be safe if used according to the legal requirements today. To insure food safety within the EU food ingredients are either vitamins and minerals (risk assessment already done by EFSA) or foods by definition or food components with proven safety (e.g. additives, other nutrients, Carnitin, fatty acids, amino acids, CoQ10, lots of botanicals etc) or Novel Foods (with the respective safety assessment conducted also by EFSA). Therefore all food components used legally within the EU are safe by definition and due to the already existing assessment.</p> <p>Therefore, as there is zero risk, there is no analysis needed. So even if there would be only a small benefit by the use of food components in foods, the benefit to risk ratio can only be positive (as there is zero risk).</p>
EHPM	Background as provided by EFSA.	<p>EHPM Welcomes the implementation of the recommendation of the EFSA Colloquium No 6, 2006 to give guidance on the implementation of the conclusions of the Colloquium, noting that it was premature to develop such guidance into a recommendation for good risk-benefit analysis.</p> <p>In this context the EHPM welcomes the recommendation for communication between risk assessors and risk managers at all relevant stages of assessment in place of the current "Chinese wall" approach.</p>

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
Federal Institute for Risk Assessment	Background as provided by EFSA.	<p>1. Portrayal, consideration and comparison of risks and benefits of nutrition within the approach proposed by EFSA are generally appropriate. For example, the risks and benefits of a diet in early childhood with – even if to some degree contaminated – breast milk can be compared with the risks and benefits of a diet in early childhood without breast milk.</p> <p>2. There are concerns in regard to the application of the EFSA approach also for the assessment of the safety of food in terms of Article 2, 14 of Regulation (EC) No. 178/2002. The exceedance of health based limit values (e.g. ADI values, ARfD values, etc) or precautionary levels that are necessary as a result of scientific uncertainty cannot be justified with the argument that the foodstuffs in question constitute a special health benefit. In this respect foodstuffs differ from medicinal products.</p> <p>3. For the safety of foodstuffs a risk assessment is required, recitals 17 and 34 of Regulation (EC) 178/2002. A risk-benefit assessment, as EFSA seems to propose, would thus be a fundamentally unsuitable approach for assessing the safety of foodstuffs. According to the relevant legal regulations, foodstuffs are required to be “safe”. The marketing of medicinal products, in contrast, merely require their benefit to be greater than their risks, Article 1, Nr. 28 a, Art. 26 Directive 2001/83/EC.</p> <p>4. It is therefore not appropriate to compare the risks of fish containing methylmercury – or other contaminants such as dioxins or PCBs – with the benefits of fish containing methylmercury. This is the case at least so long as there is fish that does not exceed an acceptable amount of relevant contaminants. Assessments, as the EFSA draft also seems to propose for foodstuffs, which go beyond a risk assessment are in these cases unacceptable.</p> <p>5. The EFSA draft document addresses the prevention of microbial contamination, e.g. through the use of biocides, and the multiplying, surviving and dying off of microorganisms during the process of food production along the food chain. It also addresses the fact that young, old and immuno-compromised individuals are assumed to be more susceptible to microbial risks than healthy adults. If pathogenic microorganisms are present in foodstuffs, an estimation of the degree of severity of a risk as a result of an assessment with regard to (preventive) consumer health protection is relevant for those groups that are most vulnerable as opposed to a comparison between positive effects versus microbial risks. Yet the assessment may also lead to recommendations concerning the handling or avoidance of certain foodstuffs, especially for specific groups of individuals. Such recommendations are based on the potential hazard that exists due to exposure to a pathogen and not on the potential positive effects of a foodstuff. Usually, recommendations or warnings on the basis of microbial risk assessments are not aimed at specific foodstuffs (e.g. fish, meat or milk), but rather at certain dietary habits or food preparations (e.g. raw or cold-smoked).</p>
Federal Institute for Risk Assessment	Background as provided by EFSA.	Page 5, line 122: The term "risk-benefit manager" should be explained when it is first introduced.

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
Istituto Superiore di Sanità	Background as provided by EFSA.	<p>Line 126: The application framework of the risk-benefit approach should be defined with more detail. Whereas risk assessment represents the general framework, the risk-benefit approach should be clearly targeted to specific issues</p> <p>1) to cases where risks and benefits may be of comparable size (Fig 2 page 13);</p> <p>2) where specific issues arise concerning subpopulations with given characteristics related to</p> <ul style="list-style-type: none"> • age, nutrition or health conditions: e.g., folic acid fortification that may benefit especially folate-deficient women in childbearing age, but it might represent a risk for aged people with vitamin B12 deficiency or benign intestinal nodules and/or • environmental conditions: high exposure to bioaccumulating contaminants might lead to reconsider the health benefits of fish intake or breastfeeding
Istituto Superiore di Sanità	Background as provided by EFSA.	<p>Line 121-122: Where a food is recognized to have health risks that are unlikely to avoid together with its intrinsic nutritional value or where a food substance is recognised to have the potential to exert both health benefits and health risks (Explanation: The issues related to whole foods or food substances are somewhat distinct and should be presented separately)</p>
President, Institute of Food Technologists	Background as provided by EFSA.	<p>The Institute of Food Technologists (IFT) appreciates this opportunity to comment on the risk – benefit assessment guidance developed by the European Food Safety Authority’s (EFSA) Scientific Committee. IFT expresses gratitude to the EFSA for taking on this important project and expresses support for a careful risk – benefit approach to food safety assessment. IFT does not have specific edits or suggestions for the guidance. IFT has been following the progress of the EFSA effort and will continue to be involved in this topic. Our Expert Report, “Making Decisions about the Risks of Chemicals in Food with Limited Scientific Information,” published in 2009, noted the progress made to date by EFSA and within the 6th Framework Programme (BRAFO). IFT’s Expert Report (accessible at http://members.ift.org/NR/rdonlyres/8A675787-A0E9-4727-8C3D-47920379E684/0/IFTExpertReport_chemicalsinfoods0809.pdf) specifically addresses the risks and benefits of the Maillard browning reaction in products, with a case study on coffee, and comparison of methyl mercury risks of seafood with nutritional benefits. The Expert Report recognizes the importance of evaluating the beneficial health effects of foods and beverages. With respect to toxicological risks of heat-induced chemicals in foods, the Expert Report states that “such an evaluation must carefully consider how best to interpret animal toxicology results for individual chemicals as well as any information indicating that a food or beverage may actually be cancer protective when evaluated as a whole.”</p>

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
<p>The Polish Council for Supplements and Nutritional Foods (KRSiO)</p>	<p>Background as provided by EFSA.</p>	<p>The document prepared by the Scientific Committee of EFSA constitutes an interesting approach to performing risk-benefit assessments of food, in relation to human health risks and health benefits. It is based on previously-elaborated methodologies and metrics (such as DALYs or QALYs, PASSCLAIMS, a risk assessment model for vitamins and minerals). However, in its present form, the approach is quite theoretical and far from practical applications.</p> <p>For example, considering the trace mineral selenium might be promising. Individual substances can often be well characterised and studied in isolation, but this is almost impossible in the case of foodstuffs. Food -- like a carrot -- has few hundreds of chemical compounds and cannot only be considered a source of beta-carotene. While the process of risk assessment for isolated substances may be described, it is far more difficult to characterise the risk of foods, which are complex mixtures that normally undergo various processing steps. So, the concept needs to be addressed from the perspective of risk assessment for foodstuffs, rather than risk assessment of individual substances.</p> <p>It must also be noted that consumer behaviour (including the dietary habits of different groups of a society or of a particular country, the quality of food questionnaires, etc.) is an important factor to consider when addressing risk assessment. The genuine risks to a particular society should be distinguished from the theoretical risks.</p> <p>Clearly, food has physiological effects in addition to others, as evidenced through thousands of years of human history. Some foodstuffs may act therapeutically, and some are more beneficial to health than others. However, this scientific document reflects a “pharmaceutical” approach to food, mainly in the numerous references made to dose-effect response, which is typical of medicine but hardly applicable to food components and foods. Thus, supporting a general tendency towards “medicalization” of food (defining and treating food as a medicine), it would not benefit dietary practice.</p> <p>The general trend, present in the scientific opinion by EFSA on human health risk-benefit assessment of foods to focus the main attention on the “cause and effect” relation of food to human health risk-benefit assessment, rather than taking into account the other factors such as social or economic may result in over-classification and overrepresentation of a “medical model” rather than paying closer attention to the “social model” and “well established traditional evidences” of risk-benefit relation of foods to the human population in general or a particular populations in detail.</p> <p>In conclusion: The Polish Council for Supplements and Nutritional Foods (KRSiO) recognizes that the EFSA document on human health risk-benefit assessment of foods may be useful as a basis for further fundamental discussions (and not yet as EU accepted guidance).</p>
<p>European Responsible Nutrition Alliance</p>	<p>1. Introduction</p>	<p>General comments:</p> <ul style="list-style-type: none"> - Risk-benefit assessment is a competence of the risk manager. This should be clearly indicated in the document. - The weighing of the risk against the benefit needs to consider more than only the outcome of the risk and benefits assessments. It also needs to consider risk management measures already in place and fluctuations in exposure from consumer behaviour. - Risk-benefit assessment cannot be carried out for individual foods or food components. It is only relevant for public health measures. - There needs to be undertaken a fundamental discussion on benefit assessment, including notably what is considered a benefit in the framework of food. The mirroring of the steps of risk assessment is not appropriate as it induces a medicinal/pharmaceutical approach that is not appropriate for foods. Risks and benefits of foods are attenuated as compared to medicinal products by the regulatory framework that needs to be considered. - The level of evidence of both risk and benefit cannot be different and needs to be graded for the risk manager to be able to weigh the outcomes of both processes.

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CIAA	1. Introduction	L. 197-205: While this is interesting information it is not obvious how this is related to the role of EFSA.
CIAA	1. Introduction	L. 208-210: In fact the same message is given in lines 16-19 and lines 191-196, we therefore propose to remove the reference to EMEA and simply state that the reference for benefit risk assessment should be available scientific rules or approaches.
IADSA	1. Introduction	<p>Section 1. Line 210 p.7 & Section Conclusions and recommendations. Lines 641-645 p.32 IADSA highlights the need for detailed cost-benefit econometric studies to translate the evidence on specific nutritional interventions into economic and healthcare benefits.</p> <p>Key questions relate to:</p> <ul style="list-style-type: none"> • Does the nutritional intervention produce a nutritional or physiological effect as shown by a change in biological markers? • Does the nutritional or physiological effect create a change in health status/health benefit? • Can cost benefits be demonstrated (e.g. reduced costs of healthcare provisions, increased quality of life for individual(s) and/or population(s) at risk?
RIVM	1. Introduction	<ul style="list-style-type: none"> • We would like to make a plea to change risk-benefit into benefit-risk, if we talk about foods. This may sound trivial, but we eat on the first place for the beneficial effects of food (we simply need food), and indeed, at the same time, we have to realise that there may also be risks at eating foods. We believe that a first focus on risk may detract from the potential benefits. So a first focus on benefits with the notion that there may also be risks might be more appropriate from a public health perspective. • In the document additional terminology might be mentioned and explained that is relevant for benefit-risk assessment and public health, such as: Health Impact Assessment, Cost-Effectiveness Assessment. <p>Page7, Line189: Please add the latest benefit-risk project in Europe: BEPRARIBEAN (http://en.opasnet.org/w/Beparibbean).</p> <p>Page 7, Line 198: “cost benefit “ analysis is the common term</p> <p>Page 7, Line 209: EMEA has changed its name into EMA (http://www.ema.europa.eu/)</p>
Swedish National Food Administration	1. Introduction	The Swedish National Food Administration would like to thank for the opportunity to comment on the draft Opinion. The draft provides a comprehensive and useful framework for human health risk-benefit assessment in the area of foods and diets, and identifies a number of concepts and principles.
CIAA	1. Introduction	TITLE - Line 2: We propose to speak about "benefit risk assessment" instead of "risk-benefit assessment, because by definition foods should be free of risks for human health.
Council for Responsible Nutrition	1.1. Risk assessment - Definition.	Lines 232-238: Insert a sentence (or two) to acknowledge that Risk Analysis Principles by the Codex Committee on Nutrition and Foods for Special Dietary Uses describes the possibility that benefit could be described as a reduction in the risk of an adverse effect resulting from an inadequate intake of a nutrient. At minimum, this reference should be included with the current text.

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International Nutrition Company BV	1.1. Risk assessment - Definition.	<p>In the definition of risk, no mention is being made regarding the duration of the exposure and the length of time between first exposure and first signs of effect.</p> <p>This is relevant especially in the case of essential nutrients, where risk arises when dosages are deficient and when dosages are excessive. Especially on the deficiency side of the U-Shape Curve, the effects occur over time and cannot be immediately observed.</p> <p>In this regard, we refer EFSA to the following article: "New RDAs and Intended Normal Use (Part II) - Efficient Tools in the Universal Management of Risks and Benefits of Micronutrients," by Jaap Hanekamp and Bert Schwitters; published in Ensuring Global Food Safety; Elsevier; 2010; ISBN: 978-0-120374845-4.</p>
RIVM	1.1. Risk assessment - Definition.	<p>Page 8, section 1.1: First define "hazard" and "adverse [health] effect" in order to keep the logic order.</p> <p>Page 8, section 1.1: The definition can be expanded to include deficiency conditions. One might use 'exposure to agent' or 'nutritional status', these terms also include deficient intakes</p>
Council for Responsible Nutrition	1.2. Benefit assessment - Definition.	<p>Lines 252-258: In 2006, CRN commented to the Risk Analysis Working Group of the CCNFSDU that a Lower Level (LL) for benefits, and thus for the lowest recommended nutrient intake, could be defined and identified in a manner exactly analogous to the UL procedure for identifying the highest intake to be considered safe. Also, CRN concluded that acceptance and implementation of such a concept was unlikely because the PRI/RDA concept is so well entrenched.</p>
DANONE	1.2. Benefit assessment - Definition.	<p>L247-251 : We agree with the definition of benefit given in line 247-248: " the probability of a positive effect on health" and we agree on the fact that reduction of a risk be considered as beneficial for human health. However, we think it would better serve the purpose of the benefit risk assessment to keep these 2 notions distinct, so that the principles of benefit risk assessment only apply when there is really a benefit to be compared with a risk. In the case where there is a need to compare a risk with a reduction of a risk, classical risk assessment methodology can be used and this case should not fall under a "benefit risk assessment". Therefore, we would appreciate that the boxed definition of benefit at lines 250-251 only defines the benefit as expressed in lines 247-248. We propose the following boxed definition: "Benefit: The probability of a positive health effect in an organism, system or (sub)population, in reaction to exposure to an agent". We can also add a definition for "reduction of a risk", which could be "the probability of a reduction of an adverse health effect in an organism, system or (sub)population, in reaction to exposure to an agent", and which would be placed in the risk assessment definition paragraph.</p>
European Botanical Forum	1.2. Benefit assessment - Definition.	<p>Line 257: The approach towards benefit assessment as expressed in this paper is fundamentally pharmaceutical and it is very doubtful whether this approach is appropriate or even possible for food components. Before this approach is agreed, there would need to be a fundamental discussion on how to assess benefit of food components. Otherwise expectations may be too high as to what can be achieved by the intake of food components, or beneficial effects may be considered pharmaceutical from a regulatory perspective. Both would clearly be inappropriate.</p> <p>We note that EFSA is currently in the middle of the process of claims assessments. The methodology used has not been discussed or carefully considered and now results in subtle health contributions realistic for foods that are not recognized while pharmaceutical style dose-effect response are expected that would lead food components to be considered to fall under pharmaceutical law.</p>

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European Botanical Forum	1.2. Benefit assessment - Definition.	Line 240: The process of risk-benefit assessment contains a number of aspects that are more broad than only the individual outcomes of the risk assessment and the benefit assessment. Both are theoretical approaches the outcome of which in reality is influenced or modulated by a number of additional parameters. Theoretical risk of a substance may be reduced or even eliminated by cultivation, processing or handling activities that reduce or eliminate the danger. Exposure may be limited or modulated by conditions of use, limitations of use, predictable or unpredictable consumer behaviour, etc The same holds true for theoretical benefit assessment. The process of risk-benefit assessment cannot therefore be reduced to a mathematical equation weighing the one against the other. It must be performed by the risk manager considering all relevant aspects, be projected into reality and can therefore only be relevant for public health interventions, not for individual foods or food components.
European Responsible Nutrition Alliance	1.2. Benefit assessment - Definition.	Line 257: This approach very much reflects a pharmaceutical approach to food that is not appropriate and needs a fundamental discussion before this is agreed.
European Responsible Nutrition Alliance	1.2. Benefit assessment - Definition.	<p>Line 240: This definition is very broad and rather theoretic. Both risk and benefit can be addressed for a substance (food component) as well as for behaviour (including consumer behaviour and interventions). We believe both are fundamentally distinct and should be addressed by different methodologies. We do not believe the proposed principles can be used for all fields where risk-benefit assessment can be used.</p> <p>We believe that although the document claims that a lot of experience has been gathered with the classical process of risk assessment, even this concept needs to be addressed from the perspective of risk assessment of foodstuffs, rather than risk assessment of individual substances.</p> <p>While the process of risk assessment for isolated substances is well described and has gained a lot of experience, it becomes more difficult to characterise the risk of foods, which are complex mixtures of various components, that normally undergo various processing steps and is subject to sometimes unpredictable consumer behaviour. These elements need to be considered when addressing risk assessment.</p> <p>Whereas individual substances can often be well characterised and studied in isolation, this is almost impossible for foods, given the (often natural) inherent variability. Furthermore, not all substances of interest (i.e. pertinent to the risk) may always be present and some may not even have been identified.</p> <p>Substances are present in a complex matrix that may or may not influence their bioavailability or actions in the body. They may be present in combination with other compounds that may reduce or eliminate the risk associated to the individual substance or that may increase the risk by interactions. Although risk assessors tend to reduce the scope of the risk assessment to substances contained in the food, approaches have been proposed to address specific foods in a specific way (e.g. probiotics, botanicals, etc). It should be noted that no general consensus exists in relation to such specific risk assessment.</p> <p>Unlike individual substances, foods and food ingredients are processed in ways to reduce risks to a minimum. Appropriate selection and cultivation may lead to varieties of plants that are devoid of the substances of concern (cfr. Low erucic acid rape seed), appropriate raw material selection and control is effective to detect and avoid adulteration (cfr. Star anise), appropriate processing is applied to remove risks from many plants (e.g. drying (manioc), cooking (pulses), etc. Hygienic practices and quality control is applied to supply safe foods to the consumer. These elements need to be considered to distinguish true and real risks from theoretical risks.</p> <p>It must also be noted that consumer behaviour is an important factor to be considered in the ultimate risk assessment. Practices that are</p>

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		to be applied to reduce the risk but are not used by consumers increase the risk. Risky behaviour, such as smoking or barbecuing, that is unavoidable may increase the risk.
Federal Institute for Risk Assessment	1.2. Benefit assessment - Definition.	Page 9, line 254: The difference between food and medicinal products should be noted. Health claims do not justify the toleration of food risks. Also risks in regard to food supplements must not be weighed against an assumed or real benefit, and risks must not be tolerated. In respect to medicinal products, the situation is different and risk-benefit assessments are accepted even if they contain the same active substance as a food supplement: The quality, effectiveness and harmlessness of medicinal products must be substantiated in an authorisation procedure and examined by the competent authorities with a positive result.
IADSA	1.2. Benefit assessment - Definition.	Section 1.2. line 252 p.9 & Section 2.3. lines 373-375 p.12 IADSA highlights the fact that the World Health Organisation (WHO, 2004) the World Cancer Research Fund (WCRF, 1997, 2007) have long used scientific evidence as the basis of dietary goals and guidelines. The conclusions and recommendations of these international organisations have taken into account the strength of the evidence and balance of probabilities that an association exists between a food or food component and a health benefit. WHO, WCRF and other national and international scientific committees have used four grades of evidence: convincing, probable, possible and insufficient, to assess the totality of the available data and to weigh the evidence. IADSA observes that the concepts developed by PASSCLAIM and WHO/WCRF have been used to underpin the regulatory approaches to the scientific substantiation of nutrition and health claims in the European Union. Foods or food components can have specific beneficial effects on life expectancy, healthy life years, as well as on metabolic, psychological and cognitive functions, wellbeing, satiety and hunger. Likewise, ingredients and a whole range of substances with beneficial effects could be included under the new legislation as long as the strength of the evidence supports the health relationship.
IADSA	1.2. Benefit assessment - Definition.	Section 1.2. lines: 252-258, p.9 & Section 2.3. lines: 373-375, p.12 IADSA notes that EFSA may require conclusive evidence of cause and effect for a diet/food health relationship for a health claim, whereas EFSA's definition of benefit for risk-benefit assessment refers to the probability of a benefit. It is likely that benefit assessments will be proportionately more difficult to define and weigh if the approach is the same as that used for the substantiation of a health claim.
ILSI Europe	1.2. Benefit assessment - Definition.	Line 249: the risk assessment is a well-established process consolidated through years. On the contrary benefit assessment is often expressed as reduction of risk. A correspondent health metric does not still exist. A comment should be inserted in the guidelines to further define the term benefit and how to quantify it.
International Nutrition Company BV	1.2. Benefit assessment - Definition.	In the definition of benefit, no mention is being made regarding the duration of the exposure and the length of time between first exposure and first signs of beneficial effect. This is relevant especially in the case of essential nutrients, where benefits arise over time. In addition, the classic RDA's seem to be inappropriate tools to measure long term effects. When effects are measured over time, e.g. on a lifespan basis, RDA's seem to be deficient. In this regard, we refer EFSA to the following article: "New RDAs and Intended Normal Use (Part II) - Efficient Tools in the Universal Management of Risks and Benefits of Micronutrients," by Jaap Hanekamp and Bert Schwitters; published in Ensuring Global Food Safety; Elsevier; 2010; ISBN: 978-0-120374845-4.

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RIVM	1.2. Benefit assessment - Definition.	<p>P8 Section 1.2 and p 9 Figure: positive health/reduced health effect as counterpart of hazard and benefit as counterpart of risk is understandable if one insists on holding on to ‘hazard’ and ‘risk’ for tradition sake, but nevertheless is artificial. Why not discard the ‘hazard’ and ‘risk’ terminology and speak of ‘(potential) beneficial effects’ and ‘(potential) adverse effects’ and a ‘benefit-harm’ assessment? Or ‘risk of loss’, ‘risk of gain’ and gain-loss risk analysis? N.B. ‘Positive’ and ‘negative’ are in general terms to be avoided, because they have different meanings within disciplines.</p> <p>P9 L250-251 Delete “and/or the probability of a reduction of an adverse health effect”. This is an ugly academic construct typically from a committee. “The probability of a positive health effect” defines it all and is crisp clear. Then also delete in other places in the doc.</p>
Swedish National Food Administration	1.2. Benefit assessment - Definition.	<p>The approach taken that risk-benefit analysis should mirror steps in risk analysis is good. The inclusion of “probability of a reduction of an adverse health effect” in the definition of “benefit”, in addition to “positive health effect” is useful, since most of the data on “health benefits” of foods and diets refer to risk reductions, e.g. of chronic diseases and associated risk factors. This is important and should be more pronounced and explicit in the document. There are several international reports dealing with this issue and which could be referenced, e.g. on page 9, after the definition of Benefit (WHO Global Health Risks 2009; van Kreijl et al. Our food our health 2006; Cohen et al. 2005 (see section 2.2).</p> <p>p. 8-9. The definition and description of “benefit” would be clearer if some examples are given, this would clarify the distinction between “positive health effect” and “probability of a reduction of an adverse health effect”. Examples of the former include quality of life indicators, e.g. improved well-being, vigilance, functional capacity, cognition, etc. (mentioned on p. 20, line 171-172), while the latter mainly refers to reduced risks of, e.g. of chronic diseases and lowering of metabolic risk factors, maintaining healthy body weight, metabolic risk markers. Inclusion of “satiety” and “hunger” as positive health effects is dubious, and needs to be qualified, since an effect may be both positive and negative depending on the setting.</p>
Alliance for Natural Health International	1.3. Risk-benefit assessment - Definition.	<p>Line 262: the word “generalised” should be inserted before the word “approach, as it is only the general approach of using the 3-step approach that is similar. Other aspects of the approach cannot therefore be mirrored as the Codex or FAO/WHO nutrient risk assessment project do not take benefits into account.</p>
Council for Responsible Nutrition	1.3. Risk-benefit assessment - Definition.	<p>Line 267: Here and in several other sections the document needs to clearly state that persistence of the adverse effect is either added or included in the concept of severity.</p>

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DANONE	1.3. Risk-benefit assessment - Definition.	L284: The figure 1 might be misunderstanding, suggesting that the exposure assessment is common for both the risk characterisation and the benefit characterisation. The box entitled "exposure assessment" should be split in at least two boxes: one for the risk and one for the benefit, as different data are collected. For example, the exposure to n3-LCPUFAs and the exposure to methylmercury will be assessed separately for the risk-benefit assessment of fish consumption. It is also highlighted in the section 2.3.1 (Step 1 - initial assessment) that the exposure must be considered at both high and low dietary exposure for risk and benefit (scenarii 1 and 2).
DANONE	1.3. Risk-benefit assessment - Definition.	L 281-282: Two types of comparison will then possibly occur: "risk / benefit" comparison or "risk / reduced risk" comparison. This distinction is important to make from the beginning because the benefit risk assessment methodology will only be needed for a "risk / benefit" comparison. It is quite easy today to compare a risk with a reduced risk, using common tools for comparison, when it is much less easy to really compare a risk and a benefit, as adequate tools are not available today. That's why development of a benefit risk assessment methodology is needed today.
DANONE	1.3. Risk-benefit assessment - Definition.	L 273-274 : According to previous comment on the definition of benefit, we believe the "benefit" arm of the procedure should be clearly split into 2: one arm for identifying and characterising a real "positive health effect", and one arm for identifying and characterising a "reduced adverse health effect" which must be measured as a risk.
EHPM	1.3. Risk-benefit assessment - Definition.	The aim of a risk-benefit assessment is to weigh risks and benefits in case of foods/substances that clearly can exert both effects. It is not clear however if there would be many of such foods (see our comment on Background). That risk-benefit assessment is useful to assess intake and interventions from a public health perspective is logic. The main question is if this kind of approach is also appropriate for foods/substances as such. The approach is clearly medicinal, as in many places, clear reference is made to dose-effect response, which is hardly feasible for food components. The EFSA approach ignores that food components can have a contribution to health even if no minimum dose can be identified that shows an effect.
EHPM	1.3. Risk-benefit assessment - Definition.	The proposed stages for the benefit assessment process needs far better characterisation. It is not appropriate to apply a parallel with risk assessment as benefit is fundamentally different from risk. Furthermore dose-response assessment is appropriate for pharmaceutical preparations. Extending such approach to foods or food ingredients is not appropriate and will ignore the contribution many food components can have for the maintenance of health. This is a fundamental discussion EFSA still needs to carry out.
EHPM	1.3. Risk-benefit assessment - Definition.	The first fundamental question that should be considered in the framework of this discussion is whether risk-benefit assessment Falls under the remit of the risk assessor or the risk manager. It is not a discipline that exists in parallel to risk assessment and benefit assessment but is in fact part of the risk management process applied by the risk manager. It is a process that combines the outcome of the risk assessment process with the outcome of a benefit assessment process. The expressions of common currency that are referred to in the EFSA document can be applied in both assessments but the weighing of policy alternatives based on the results of the risk assessment and other factors is to fall onto the risk manager.

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EHPM	1.3. Risk-benefit assessment - Definition.	Consultation provides no adequate procedure for taking account of this key function of nutritional supplements (by desirable addition of nutrients to the diet to develop health from "being alive" to "being in full vigour") in societies where the issue is not the removal of starvation but of malnutrition in the presence of plenty.
European Botanical Forum	1.3. Risk-benefit assessment - Definition.	Line 282: The approach is clearly medicinal. Throughout the document, clear reference is made to dose-effect response, which is hardly possible for food components, whose primary function is in relation to homeostasis, not in relation to disease or abnormalities. The EFSA approach to claims already today ignores that food components can have a contribution to health if no minimum dose can be identified that shows an effect.
European Botanical Forum	1.3. Risk-benefit assessment - Definition.	Line 273: In the context of food law, this approach would make it very unlikely that there would be situations where the benefit would outweigh the risk.
European Botanical Forum	1.3. Risk-benefit assessment - Definition.	Line 271: We do not think it is appropriate for foods and food components to mirror stages for the benefit assessment to the risk assessment process. These stages needs far better consideration, especially in relation of that is defined as benefit (e.g. is a health effect that affects normality considered as beneficial or not?). As already stated, dose-response assessment is appropriate for pharmaceutical preparations, not for food. Extending such approach to foods or food ingredients is not appropriate and will ignore the contribution many food components can have for the maintenance of health.
European Botanical Forum	1.3. Risk-benefit assessment - Definition.	Line 266: While risk-benefit assessment may be feasible for public health interventions, it is not for the consideration of individual foods or food components given the regulatory environment. As food should be safe and health effects should be restricted to physiological functions or effects on risk factors for human disease, both the risks and benefits will be very much attenuated as compared with medicinal products. And any risk of overexposure will be considered by conditions of use. Risk-benefit assessments of individual foods and food components may therefore in reality be superfluous.
European Botanical Forum	1.3. Risk-benefit assessment - Definition.	Line 260: It should be clearly stated in this document that risk-benefit assessment is a competence of the risk manager, as it consists of the weighing of the outcomes of the process of risk assessment and risk management, taking into consideration all relevant factors. It is not just a scientific equation.
European Responsible Nutrition Alliance	1.3. Risk-benefit assessment - Definition.	Line 282: The aim of a risk-benefit assessment is to weigh risks and benefits in case of foods/substances that clearly can exert both effects. It is not clear however if there would be many of such foods. Furthermore, how likely is it that foods/substances would be found to show more benefit than risk, especially if the current level of scientific justification is expected. That risk-benefit assessment is useful to assess intake and interventions from a public health perspective is logic. We doubt that this kind of approach is also appropriate for foods/substances as such.

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European Responsible Nutrition Alliance	1.3. Risk-benefit assessment - Definition.	Line 273: This approach would make it very unlikely that there would be situations where the benefit would outweigh the risk, also given the regulatory perspective. This again calls for an application of risk-benefit assessment only in the framework of public health interventions and performed by the risk manager.
European Responsible Nutrition Alliance	1.3. Risk-benefit assessment - Definition.	Line 271: The proposed stages for the benefit assessment process needs far better characterisation. It is not appropriate to apply a parallel with risk assessment, as benefit is fundamentally different from risk. Furthermore dose-response assessment is appropriate for pharmaceutical preparations. Extending such approach to foods or food ingredients is not appropriate and will ignore the contribution many food components can have for the maintenance of health. <u>This is a fundamental discussion EFSA still needs to carry out, but has consistently avoided in the framework of the claims assessment.</u>
European Responsible Nutrition Alliance	1.3. Risk-benefit assessment - Definition.	Line 266: It is quite doubtful if this is appropriate and feasible for food, as one has to consider the regulatory environment. On the one hand it is a prerequisite of foods to be safe for consumption and although no food can be absolutely risk-free, the level of safety has to be assured under the normal conditions of use. On the other hands, foods cannot be presented for the prevention, treatment of cure of a disease. Benefit assessment therefore cannot relate to disease prevention, which would be a major benefit. We believe that risk-benefit assessment can only be of value in the framework of public health interventions. <u>Aspects of single foods and food ingredients should be covered by separate risk and benefit assessments.</u>
European Responsible Nutrition Alliance	1.3. Risk-benefit assessment - Definition.	Line 260: Neither the document, nor the approach makes a distinction to the scope of the risk-benefit assessment. It should be clearly stated in this document that risk-benefit assessment is a competence of the risk manager. While risk assessment and benefit assessment fall under the competence of the risk assessor, the weighing of both clearly falls under the responsibility of the risk manager. Risk-benefit assessment is not a discipline that exists in parallel to risk assessment and benefit assessment but is in fact part of the risk management process applied by the risk manager. It is a process that combines the outcome of the risk assessment process with the outcome of a benefit assessment process. The expressions of common currency that are referred to in the EFSA document can be applied in both assessments but the weighing of policy alternatives based on the results of the risk assessment and other factors is to fall onto the risk manager.
RIVM	1.3. Risk-benefit assessment - Definition.	P10, L284: Delete reduced adverse health effect from the positive health box or add to the hazard box reduced beneficial effect P10, L301-302: we are interested in a level where benefits are greater than risks P10, L306: “enriched” should be “fortified” (“enriched” would entail that there is already folic acid in the diet, which is not true [only folate]).
Swedish National Food Administration	1.3. Risk-benefit assessment - Definition.	p. 9, table: Replace Positive health effect identification with “Identification of positive health effect /reduced adverse effect”

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ILSI Europe	2. Proposed approach for risk-benefit assessment	Lines 371-372: in accordance to what written in lines 371-372, in Figure 2 an arrow from ‘Initial Assessment’ to ‘Problem formulation’ should be inserted.
Nuscana Biotechnika Laboratoryjna	2. Proposed approach for risk-benefit assessment	Generally I am lacking in the document the food allergen approach. These naturally appearing food components mean an increasing threat for the European population and at the same time are present at foods with high health value, like nuts or vegetables.
Alliance for Natural Health International	2.1. Examples of situations for which a risk-benefit assessment might be appropriate.	Line 304-327: Given that these examples allude to policy decisions such as folic acid fortification and fluoridation, there should also be reference to policies which would restrict amounts of nutrients that are based on risk. Therefore we propose the addition of an additional example, as follows: <ul style="list-style-type: none"> • Where statutory limitation of nutrients based on risk (and not benefit) has occurred or is contemplated.
Coughlin & Associates	2.1. Examples of situations for which a risk-benefit assessment might be appropriate.	<p>Lines 309-316: Comment on Page 11, Bullet 1:</p> <p>This bullet summarizes the risk-benefit evaluation of nitrate in vegetables, comparing the beneficial effects such as supplying micronutrients and preventing certain types of cancer vs. the potential hazards such as methaemoglobinaemia in infants and nitrosamine formation. I have carefully reviewed the report, “Nitrate in Vegetables. Scientific Opinion of the Panel on Contaminants in the Food Chain” (adopted on 10 April 2008) which forms the basis of what is stated here for nitrate. While the report did discuss some aspects of the beneficial effects of nitric oxide, I would recommend a much more rigorous evaluation, taking into account the entire knowledge base of nitric oxide biology. I would suggest your thorough review of a paper I recently co-authored: “Review: Nutritional epidemiology in the context of nitric oxide biology: A risk-benefit evaluation for dietary nitrite and nitrate.” A. Milkowski, HK Garg, JR Coughlin and NS Bryan, Nitric Oxide 22: 110-119 (2010).</p> <p>For a much more expansive treatment of the role of nitric oxide in food and nutrition, I would also recommend the following 2010 monograph, with a Foreword written by Dr. Louis J. Ignarro, one of the three 1998 Nobel Laureates in Physiology and Medicine for his seminal work on nitric oxide. Editor Nathan Bryan authored several of the monograph’s chapters, including the introductory chapter co-authored with his colleague at the University of Texas/Houston, Dr. Ferid Murad, one of the other 1998 Nobel Laureates: Food, Nutrition and the Nitric Oxide Pathway: Biochemistry and Bioactivity. Ed. Nathan S. Bryan, DEStech Publications, Inc., Lancaster, Pennsylvania, 2010.</p>

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
Council for Responsible Nutrition	2.1. Examples of situations for which a risk-benefit assessment might be appropriate.	Line 316: Specify that the concern with nitrosamine formation is the carcinogenicity of most members of this chemical class.
EHPM	2.1. Examples of situations for which a risk-benefit assessment might be appropriate.	The impact of the Consultation on the assessment of risk-benefit of nutritional supplements is severely limited by the focus of the Colloquium on foods and the assessment of the impact on them of adventitious and unwelcome additions – pathogens, toxins, heavy metals.
European Botanical Forum	2.1. Examples of situations for which a risk-benefit assessment might be appropriate.	Line 324: This is not a risk-benefit assessment but a risk assessment
European Responsible Nutrition Alliance	2.1. Examples of situations for which a risk-benefit assessment might be appropriate.	Line 321: Food should be safe in the first place.
CIAA	2.1. Examples of situations for which a risk-benefit assessment might be appropriate.	L. 321: It might be not easy to find examples. There is a thin line between human health risks and human health benefits derived from food, maybe it is therefore very or even too ambitious to have the two approaches, the opinion refers to ingredients of food, it is suggested to reflect also on examples such as natural or process contaminants.
European Responsible Nutrition Alliance	2.1. Examples of situations for which a risk-benefit assessment might be appropriate.	Line 317: In this case the risk-benefit assessment needs to be done by the risk manager.

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
Federal Institute for Risk Assessment	2.1. Examples of situations for which a risk-benefit assessment might be appropriate.	Page 11, line 321: Deletion of this example. It is not appropriate to compare the risks associated with possible residues in foodstuffs resulting from chemical decontamination during food production with the benefit of chemical decontamination (surface pathogen elimination). A risk-benefit assessment concerning expected possible residues in foodstuffs therefore remains unacceptable at least as long as there are production methods that manage without comparable risks. The rules of good hygiene practice should be noted.
Federal Institute for Risk Assessment	2.1. Examples of situations for which a risk-benefit assessment might be appropriate.	Page 10, line 297: It may be useful to explain in this section that the availability of objective measures of benefit is a requirement for considering risk-benefit analyses (see line 327).
Istituto Superiore di Sanità	2.1. Examples of situations for which a risk-benefit assessment might be appropriate.	Examples are excellent and could be translated in a general framework of application. We suggest to add, however, Line 328: in general, where there is evidence that health risks and benefits are significantly different according to gender, age and/or lifestage. Examples relevant to foetuses and small children are iodine fortification of table salt which might lead to special benefits, and methylmercury in fish which is related to specific risks.
RIVM	2.1. Examples of situations for which a risk-benefit assessment might be appropriate.	P10 Section 2.1: the list of examples is somewhat confusing, as it is a mix of management situations (start of intervention, change in consumption, improved processing procedure) and status quo, more food/nutrient oriented cases (single compound having adverse and beneficial effects, single food having adverse and beneficial effects, biocides example could be a subexample of a food having adverse and beneficial effects depending on the question).
CIAA	2.2. Problem formulation.	L. 334: The section would benefit from rewording. It is suggested to change the Title, into for instance "Negative effect identification" to make the title consistent with the terminology used in figure 1. Problem formulation in benefit assessment would qualify as an "oxymoron"
Council for Responsible Nutrition	2.2. Problem formulation.	Lines 342-343: Add a sentence to acknowledge that use of risk-benefit analysis to control entry of new products into the marketplace would require new legislation or regulation because most jurisdictions now regulate citation of benefit and safety under separate reviews and decisions. 349-354: If EFSA believes there is a legitimate reason to keep stakeholders out of the assessment, it should be stated here. Otherwise this paragraph should indicate that procedures will be established to permit the participation.

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
DANONE	2.2. Problem formulation.	L 355: We find the Terms of Reference should also identify from the beginning potential pitfalls of the assessment, for example if there is very little data either on the risk or the benefit side, or on both. The guidance should then specify what happens in cases where there is not enough data to perform the assessment.
European Botanical Forum	2.2. Problem formulation.	Line 350: This is not part of the methodology but of the process. Stakeholders should always be involved to provide input into risk management decisions.
Federal Institute for Risk Assessment	2.2. Problem formulation.	Page 11, line 345: In our opinion, it is important (not only "helpful") to specify the target population for the assessment. The authors of the report should also provide their advice whether the separate assessment of risks and benefits, possibly conducted in different subpopulations, addresses also the risk-benefit balance for the individual consumer. If this is not the case, what additional considerations are necessary for answering a question about risk-benefit balance for individual consumers?
Federal Institute for Risk Assessment	2.2. Problem formulation.	Page 10, line 330: It should be emphasised that the subject of the assessment must be determined very carefully and documented in a risk-benefit assessment.
ILSI Europe	2.2. Problem formulation.	Line 347: in the terms of reference it should be explained that a risk-benefit question can be integrated into three terms: reference scenario (current situation, business as usual), alternative scenario and target population(s). The risk-benefit question is generally a choice between alternative policies or courses of action, described in the form of scenarios. A scenario is a narrative that describes a hypothetical or real situation, in this context referring to some intake of food or food constituent and its consequences. Risk-benefit assessment supports decision-making by characterising the expected difference in health outcome for alternative scenarios. A risk-benefit question is thus in essence a what-if question. The scenarios and their associated change in dietary intakes represent the if-part of the question. The what-part is characterised by the net health effects that result from the difference between the scenarios. Writing the risk-benefit question in words can help the parties involved to define it more clearly and identify the relevant scenarios.
RIVM	2.2. Problem formulation.	<p>P11, L339-343: Generally there is only one main type. Comparing the net health effect of a change in intake. Even though, this can be used to find an intake scenario that improves or optimizes health, see the selenium example. So one could make a distinction between two types of questions. In one type two scenarios are compared, in the other type there is a search for a better scenario compared with the current.</p> <p>The first bullet point shows a problem that is not clearly formulated. Are we comparing the current diet with a recommended diet? And are we comparing eating fish (how much, which species...) with not eating fish (replacing meat, bread...)</p> <p>This illustrates our general remark about comparing (at least) two scenarios.</p>

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
Swedish National Food Administration	2.2. Problem formulation.	<p>p. 11, Section 2.2, 1st para: replace “very little” to “less”, the following references could be added.</p> <p>Van Kreijl CF, Knaap AGAC, van Raaij JMA (eds). Our food, our health. Healthy diet and safe food in the Netherlands. National Institute for Public health and the Environment, RIVM, Bilthoven, 2006.</p> <p>Cohen JT, Bellinger DC, Connor WE, Kris-Etherton PM, Lawrence RS, Savitz DA, Shaywitz BA, Teutsch SM, Gray GM. A quantitative risk-benefit analysis of changes in population fish consumption. <i>Am J Prev Med</i> 2005a;29:325-34.</p> <p>Ponce RA, Bartell SM, Wong EY, LaFlamme D, Carrington C, Lee RC, Patrick DL, Faustman EM, Bolger M. Use of quality-adjusted life year weights with dose-response models for public health decisions: a case study of the risks and benefits of fish consumption. <i>Risk Anal</i> 2000;20:529-42.</p> <p>Becker W, Darnerud PO, Petersson-Grawé K. Risks and benefits of fish consumption. Risk-benefit analysis based on the occurrence of dioxin/PCB, methyl mercury, n-3 fatty acids and vitamin D in fish. Report 12 - 2007. National Food Administration, Uppsala, Sweden. http://www.slv.se/upload/dokument/rapporter/mat_naring/2007_12_risks_and_benefits_of_fish_consumption.pdf.</p> <p>Sand S, Becker W, Darnerud PO. Aspects of risk-benefit assessment of food consumption. Directions for the future. <i>TemaNord</i> 2008:586. Nordic Council of Ministers, Copenhagen, Denmark. http://www.norden.org/da/publikationer/publikationer/2008-568.</p>
Council for Responsible Nutrition	2.3. Proposed approach for risk-benefit assessment	<p>Lines 362-364: This is a false comparison. Stepwise procedure and quantitative analysis are not mutually exclusive.</p> <p>Lines 367: It is not clear how Step 1 can be validated without Step 2. This also applies to other locations in the document.</p> <p>Lines 373-375: This double standard is not justified. It allows for, or facilitates, pernicious neglect of benefits.</p>
CIAA	2.3. Proposed approach for risk-benefit assessment	<p>L. 370-372: What will be the means anticipated by EFSA to preserve the full independency of the risk-benefit assessment through the definition of the Terms of Reference by both the risk-benefit assessor and the risk-benefit manager?</p>
CIAA	2.3. Proposed approach for risk-benefit assessment	<p>L. 373-375: This is not the case from industry perspective, the risks should be based also on data as convincing as the benefit (this is a Regulatory requirement at least for FSMP products). In most cases if a conservative approach is chosen for the risk assessment, no new product can be formulated. The preliminary risk assessment might be conservative, but this is often solved by filling in the data GAP analysis.</p>

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
EHPM	2.3. Proposed approach for risk-benefit assessment	Line 373-374 - Why would this be commonly required? The reverse proportionary principle should apply. This is to be considered on a case-by-case basis based on the degree of health benefit. Although risk weighs over benefit, the approach should be the same. The difference should lie in the balance.
European Botanical Forum	2.3. Proposed approach for risk-benefit assessment	Line 373: We would strongly disagree with the statement that that a different level of evidence is commonly required for benefit and risk; for benefit the evidence frequently needs to be convincing whereas for risk it may be more appropriate to take a conservative approach on the basis of a lower weight of evidence. We believe that also for benefit the evidence may be of a lower weight. The acceptance of claims that are probable, or even possible, as compared to convincing would stimulate research in these fields. Furthermore, strong benefits should be given the benefit of the doubt when further evidence is gathered. The example of intervention with folic acid to prevent neural tube defects is a clear example of a benefit that merits to be acknowledged in a early phase, i.e. when indications point to a beneficial effect but the evidence is not yet convincing. We believe it is very important to be able to invoke the “inverse precautionary principle”. Since, should further evidence not support the beneficial effect, no harm would be done. But if further research would confirm the effect, then many more people would have benefited from the effect before it became convincing. We strongly believe therefore that the benefit assessment process should include a system of grading of the evidence to enable the risk manager to attribute the appropriate weights to both the outcome of the risk assessment process as well as of the benefit assessment process in the same way and in the full knowledge of the subtleties of the evidence present for both. We believe that the current way in which EFSA assesses claims benefits, with yes-no outcomes does not allow the risk manager to conduct this balance of weighing. To enable a balance weighing of the risks and benefits a system of grading is essential both for risk assessment and for benefit assessment.
European Responsible Nutrition Alliance	2.3. Proposed approach for risk-benefit assessment	Line 373: Why would it be commonly required to have a different level of evidence? We believe that both for risk assessment and for benefit assessment, the degree or level of evidence should be clearly noted and that beneficial effect that are probable or even possible should be indicated as such for the risk manager to take this into consideration. In the case of risk assessment he could invoke the precautionary principle to install a higher level of protection in view of the scientific uncertainties. But likewise, in the case of benefit assessment he could invoke the inverse precautionary principle to let the citizens benefit from a health effect that may be valid, but where the evidence is not yet convincing. It should be noted that the way in which EFSA currently assesses claims and delivers yes-no opinions denies this possibility to the risk manager We strongly believe that grading of the evidence is essential in case of a risk-benefit assessment. If not, it would not be possible for the risk manager to weigh in an appropriate way the delicate and nuanced outcome of the risk assessment process against the yes-no outcome of the benefit assessment.

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
IADSA	2.3. Proposed approach for risk-benefit assessment	<p>Section 1.2. line 252 p.9 & Section 2.3. lines 373-375 p.12</p> <p>IADSA highlights the fact that the World Health Organisation (WHO, 2004) the World Cancer Research Fund (WCRF, 1997, 2007) have long used scientific evidence as the basis of dietary goals and guidelines. The conclusions and recommendations of these international organisations have taken into account the strength of the evidence and balance of probabilities that an association exists between a food or food component and a health benefit. WHO, WCRF and other national and international scientific committees have used four grades of evidence: convincing, probable, possible and insufficient, to assess the totality of the available data and to weigh the evidence.</p> <p>IADSA observes that the concepts developed by PASSCLAIM and WHO/WCRF have been used to underpin the regulatory approaches to the scientific substantiation of nutrition and health claims in the European Union. Foods or food components can have specific beneficial effects on life expectancy, healthy life years, as well as on metabolic, psychological and cognitive functions, wellbeing, satiety and hunger. Likewise, ingredients and a whole range of substances with beneficial effects could be included under the new legislation as long as the strength of the evidence supports the health relationship.</p>
IADSA	2.3. Proposed approach for risk-benefit assessment	<p>Section 1.2. lines: 252-258, p.9 & Section 2.3. lines: 373-375, p.12</p> <p>IADSA notes that EFSA may require conclusive evidence of cause and effect for a diet/food health relationship for a health claim, whereas EFSA's definition of benefit for risk-benefit assessment refers to the probability of a benefit. It is likely that benefit assessments will be proportionately more difficult to define and weigh if the approach is the same as that used for the substantiation of a health claim.</p>
Alliance for Natural Health International	2.3.1. Step 1 – Initial assessment	<p>We have serious concerns about this approach. First, it presupposes that risks and benefits can be directly compared, implying that the comparisons are based on the same currencies. There are very great subjective elements in any such assessment. An example is nicotinic acid: how would the assessor compare a flushing reaction against that might occur at just 100 mg intake, with the benefits associated with blood cholesterol management at daily dosages 10 times this amount.</p> <p>See: Verkerk, R.H.J., The paradox of overlapping micronutrient risks and benefits obligates risk/benefit analysis. Toxicology (2010), doi:10.1016/j.tox.2010.02.011 for a much more in depth discussion of this example, along with three others.</p> <p>We propose that the most appropriate forward is to evaluate the full pattern of risks and benefits that are associated with different dosages of intake that reflect known use-patterns. This allows the data to be collated centrally and to be referenced at any later stage during the process. The notion of discarding the approach if there is “no appreciable health risk (based on scenario 1) or no appreciable health benefit 30 (based on scenario 2)” is also problematic, given there are many possible interpretations over what is “appreciable”.</p> <p>We support the continuation of the risk-benefit assessment and the use of modelling approaches for this. However, the modelling approaches are not defined and therefore of little value.</p>

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
Council for Responsible Nutrition	2.3.1. Step 1 – Initial assessment	<p>Lines 27-29: The intent of this sentence is not clear.</p> <p>Line 38: Probabilistic is very general. What exactly is meant?</p> <p>Lines 40-41: Dose response modelling has many forms. What exactly is meant?</p>
DANONE	2.3.1. Step 1 – Initial assessment	<p>L 15-17 : It is very confusing to include the term "hazardous compound" since food ingredients might also be concerned, which are in principle not considered as hazardous. Also in case of new ingredients no health based guidance exists. This needs to be derived based on the generated evidence (Industry)</p>
DANONE	2.3.1. Step 1 – Initial assessment	<p>L 2 - 6: We feel the key point that should be assessed in step 1 is whether there is enough data to perform the risk-benefit assessment or not. The assessor should gather all data available to consider the question asked, and identify whether the body of data is balanced between risk and benefit, or if there is clearly more data for one aspect or the other. The assessor should then decide if the assessment can be conducted based on available data, or if key data are missing from the beginning. In this case, it should be decided whether new data has to be generated before starting the risk-benefit assessment.</p>
European Botanical Forum	2.3.1. Step 1 – Initial assessment	<p>Line 5: It is not clear how such a scientific assessment can be made because risk cannot be considered in isolation. The impact of the risk also depends on the risk management factors that are put in place. A theoretical risk, e.g. alkaloids in <i>Borago officinalis</i>, is completely absent when appropriate quality assurance is applied. The risk posed by residues and contaminants is managed by maximum levels.</p>
European Responsible Nutrition Alliance	2.3.1. Step 1 – Initial assessment	<p>Table: For most foods, sufficiently detailed data on exposure will not be available in sufficient detail to perform this refinement of the assessment.</p>
European Responsible Nutrition Alliance	2.3.1. Step 1 – Initial assessment	<p>Line 30: Is this is not a theoretical approach by scientists that love to have symmetric systems, rather than what is feasible in reality? It does not reflect reality, as it does not take into consideration differences that may exist because of consumer behaviour.</p>

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
Federal Institute for Risk Assessment	2.3.1. Step 1 – Initial assessment	Page 14, line 9: It may be misleading to compare risks and benefits based on step 1 results because in this step a common metric for both is not yet defined. Step 1 can probably only yield crude and conservative indications of whether a potential risk or benefit may occur based on assumed low and high levels of consumption. The range between lower and upper reference points for benefit and risk, respectively, is informative and should be reported.
Swedish National Food Administration	2.3.1. Step 1 – Initial assessment	p. 14, refer to Fig 2 in 1st paragraph.
Council for Responsible Nutrition	2.3.2. Step 2 – Refinement of the assessment	Lines 15-16: The meaning is vague. When is quantification “full?” Lines 20-24: A major need for good data and detailed analysis is the need to support risk communication. This should be included in the paragraph.
DANONE	2.3.2. Step 2 – Refinement of the assessment	L 11-12: It is not possible for Industry based on the knowledge before launch of a product, to have this amount of data and to be able to derive estimates of disease incidence or mortality as a result of the exposure to a new product.
European Botanical Forum	2.3.2. Step 2 – Refinement of the assessment	Line 11: We do not think it is appropriate to link estimates of disease risk or mortality to the eating of a particular food. It shows that risk-benefit assessment only makes sense for public health interventions in the framework of the whole diet.
European Responsible Nutrition Alliance	2.3.2. Step 2 – Refinement of the assessment	Line 15: Quite doubtful whether this would be possible.
European Responsible Nutrition Alliance	2.3.2. Step 2 – Refinement of the assessment	Line 13: Probabilistic approaches carry may inherently overestimate the risk depending on the into-parameters and assumptions.
European Responsible Nutrition Alliance	2.3.2. Step 2 – Refinement of the assessment	Line 11: Isn’t it rather far fetched to link estimates of disease risk or mortality to the eating of a particular food. It shows that risk-benefit assessment only makes sense in the framework of the whole diet.

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
European Responsible Nutrition Alliance	2.3.2. Step 2 – Refinement of the assessment	Line 6: This is crucial. Although the document states that in many cases quantification may not be possible, the model depends on this, and provision for assessment without it is not adequately defined.
Federal Institute for Risk Assessment	2.3.2. Step 2 – Refinement of the assessment	Page 16, line 21: The distinction between "net risk" and "net benefit" does not seem logical. Do both terms relate to the "net health impact" mentioned earlier? These terms should be defined.
Federal Institute for Risk Assessment	2.3.2. Step 2 – Refinement of the assessment	Page 15, Fig 3: New data will not always solve the problem that no composite metric is available (bottom left box). For example, objective measurements of benefits may be lacking or the benefits may be unrelated to any metric that applies to risk.
RIVM	2.3.2. Step 2 – Refinement of the assessment	<ul style="list-style-type: none"> • In step 2 (page 16) the integration of benefits and risks is left for the benefit-risk manager. That means (s)he needs to know all relevant parameters for each benefit and risk. In our view these are: <ul style="list-style-type: none"> o number of people affected (incidence) o duration of the effect o severity of the effect o induced mortality, years of life lost <p>Furthermore, the benefit-risk manager must know if the risk and benefits appear in different subpopulations. So that winners and losers can be identified, this allows the manager to decide whether a potential policy is fair</p> <p>P16, L8-10: That is an outcome that does not allow a RB manager to take a decision, being above a minimum dose level may imply quite different health effects than being below a dietary reference value. See general remark about step 2</p> <p>P16, L13-14: To do this the variability in intake (the intake distribution) has to be taken into account but other approaches than a probabilistic (Monte Carlo) simulation can work also see e.g. Hoekstra et al. 2008, Danei et al. 2009</p>
EHPM	2.3.3. Step 3 – Comparison of risks and benefits using a composite metric.	In contrast, the micronutrients in Nutritional supplements are not only essential to maintain life but are, in many instances, desirable additions to the diet to develop health from “being alive” to being in” full healthy vigour”.

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
European Responsible Nutrition Alliance	2.3.3. Step 3 – Comparison of risks and benefits using a composite metric.	Line 44: The claims assessment process shows that there is very little chance for benefits to be sufficiently supported in the light of the current approach.
RIVM	2.3.3. Step 3 – Comparison of risks and benefits using a composite metric.	P17, L42: Why should a composite metric combine 2 or more of those elements? Disease burden and quality of life are unclear parameters. A DALY and QALY combine morbidity (numbers of years suffered), mortality (number of years lost) and severity (a quality of life weight) WTP combines every aspect (also how rich he is) implicitly by showing how much money a person would spend to prevent suffering from a specific disease during a certain time period
Swedish National Food Administration	2.3.3. Step 3 – Comparison of risks and benefits using a composite metric.	p. 17: refer to Fig 4 in 1st para.
Swedish National Food Administration	2.3.3. Step 3 – Comparison of risks and benefits using a composite metric.	p. 16, 2.3.3: refer to Fig 3 in 1st para.

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
Alliance for Natural Health International	2.4. Metrics used in Risk-benefit assessment	<p>When developing any metric for a food or food ingredient, it is essential that the food or food ingredient is accurately characterised. For example, the risks and benefits of canned versus fresh tomatoes or fish are quite different, as those for raw vs. deep fried fish. This same situation applies for food ingredients, where the ingredient and its specific molecular form are critically important to the evaluation of both risks and benefits. For example, the risks and benefits of synthetic folic acid commonly used in supplements and fortified foods, as compared with polyglutamate folates as found in green-leaved vegetables or in botanical extracts in food supplements, are quite different. The same can be said for the majority of other nutrients. Accordingly, we propose that this guidance should be much more specific in terms of the characterisation of the food or food ingredient and it should at least make reference to the molecular form of the latter.</p> <p>The significance of this issue is explained further by our group in the following two papers: Verkerk, R.H.J., Hickey, S., A critique of prevailing approaches to nutrient risk analysis pertaining to food supplements with specific reference to the European Union. <i>Toxicology</i> (2010), doi:10.1016/j.tox.2009.12.017 Verkerk, R.H.J., The paradox of overlapping micronutrient risks and benefits obligates risk/benefit analysis. <i>Toxicology</i> (2010), doi:10.1016/j.tox.2010.02.011</p> <p>The issue of the problems over finding suitable metrics is reasonably handled in this section — and the statement that further work is recommended (lines 93-94) is of utmost importance. It should be realized that for many nutrients (food ingredients) it will generally not be possible to utilize QALYs and DALYs. In fact, most metrics of interest will not in any way involve mortality (e.g. risks will not include mortality rates, and benefits will not include lifespan). These data will simply not be able to be generated in any reasonable time for the vast majority of nutrients. However, where the data are available, such as from national poisons databases, these should be used (e.g. National Poison Data System in the USA, and/or equivalents elsewhere).</p> <p>However, there are ways in which semi-quantitative weightings of risks and benefits could be fairly simply developed and agreed for comparative purposes. It is recognized that such weighting involves considerable subjective decision-making, but assuming adequate expertise in such decision-making, using not only peer reviewed literature but also clinical experience (particular from the field of nutrition) this is not necessarily a major problem. It is critical that such evaluations are undertaken taking into account dose responses.</p> <p>Adverse effects for particular levels of exposure/intake can be classified and negatively weighted according to specific sub-populations:</p> <ul style="list-style-type: none"> • Onset: acute, chronic or delayed (including mutagenicity, carcinogenicity, teratogenicity) • Severity: mild, moderate or severe • Reversibility: reversible in short-term, medium-term, long-term, or not reversible • Nature of effect: organ or body part affected, symptomatology, etc. <p>Benefits can be similarly classified, and positively weighted, using a numeric weighting scale. For example:</p> <ul style="list-style-type: none"> • Locality of benefit: local, general • Nature of benefit: minor, moderate or major health benefit (including disease risk reduction potential) <p>The sum of the weightings for specific levels of exposure/intake provides some general guidance over the interplay of various risks and benefits.</p>

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
Council for Responsible Nutrition	2.4. Metrics used in Risk-benefit assessment	<p>Line 61 and 65: Persistence should be mentioned here, or severity defined to include it.</p> <p>Line 89: “for discussion” would be more accurately replaced by “to dispute.”</p> <p>Lines 83-94: The degree to which DALY and QALY values are arbitrary is not adequately described.</p> <p>Lines 105-109: This is a good example of an unjustified double standard. ADI or TDI values do not require the data to demonstrate causality, but the RDI and related values require demonstration of causality through RCTs. This structure guards against false claims but does nothing to prevent pernicious neglect to provide benefits. Oppositely, the structure provides excessive caution against adverse effects—even non-existent ones.</p> <p>Lines 121-123: Another approach is that in the recent R-B analysis for vitamin D (Bischoff-Ferrari et al., Osteoporosis International). That analysis does not try to equate the health or societal value of the risk and the benefit, but instead examines the intake and serum 25OH vitamin D levels at which the risk and the benefit occur. Thus it can identify a safe and beneficial range of intakes without assigning somewhat arbitrary HALY or DALY values.</p>
DANONE	2.4. Metrics used in risk-benefit assessment	<p>L 90-94: DANONE stresses the fact that regarding the risk assessment, there is nothing really new. In addition, DANONE supports EFSA in its effort to go further in the benefit assessment, specifically for developing specific metric for health benefit assessment, symmetric to risk assessment metrics. Indeed, metrics as proposed (DALY’s, QALY’s) are not designed to investigate beneficial impact on health per se, but merely to measure the risk and risk reduction.</p>
European Botanical Forum	2.4. Metrics used in risk-benefit assessment	<p>Line 65: We do not think it is realistic to express the benefit of consumption of a food or food components in terms of severity of disease, morbidity and mortality. Benefit and risks of individual foods can simply not be compared using such common currency.</p>
European Responsible Nutrition Alliance	2.4. Metrics used in risk-benefit assessment	<p>Line 114: It is clear this cannot be applied to individual foods, but only for dietary patterns.</p>
European Responsible Nutrition Alliance	2.4. Metrics used in risk-benefit assessment	<p>Line 72: It is questionable if this approach that may work for pharmaceuticals is feasible for food. This would be an important further step towards the medicalisation of food, which we feel would not benefit dietary practice.</p>
European Responsible Nutrition Alliance	2.4. Metrics used in risk-benefit assessment	<p>Line 65: Is it feasible to think that the benefit of consumption of a food or food components can actually be expressed in terms of severity of disease, morbidity and mortality? Benefit and risks of foods can simply not be compared using such common currency.</p>

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
Federal Institute for Risk Assessment	2.4. Metrics used in risk-benefit assessment	Page 19, line 105: Do the authors suggest evaluating the percentiles of consumption (low and high level) with regard to the cited reference values (for example percentage exceeding the reference values)?
Federal Institute for Risk Assessment	2.4. Metrics used in risk-benefit assessment	Page 18, line 65: Definitions of "common metric" and "composite metric" should be provided. According to this sentence, composite metric also has the connotation of being a multivariate construct ("number of dimensions of health") applying to the definition of risk.
Istituto Superiore di Sanità	2.4. Metrics used in risk-benefit assessment	Line 85: the conceptus (unborn child) should be cited further to children and adults
IADSA	2.4. Metrics used in risk-benefit assessment	Section 2.4, lines 60-61 p.18 IADSA believes that, from a pragmatic point of view, the EFSA proposals may be too restrictive to define a common scale of measurement, and it is likely that both quantitative and qualitative information will be needed to answer the two questions—a benefit answer and a risk answer from which the risk manager will still have to weigh one against the other. Certainly, more than one metric will be needed to capture all dimensions of health for a risk-benefit assessment, because not all relevant dimensions of health are captured in Disability Adjusted Life Years (DALYs) and Quality Adjusted Life Years (QALYs).
ILSI Europe	2.4. Metrics used in risk-benefit assessment	Line61: morbidity rate should be added before mortality rate.
Swedish National Food Administration	2.4. Metrics used in risk-benefit assessment	p. 18, 1st para: "... in the case of positive health effects also quality of life."

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
Alliance for Natural Health International	3.1. Importance of the selected endpoint(s) and the subpopulation(s) considered in the assessment	<p>Lines 137-138: The statement: “the obvious benefit endpoint will be the absence of risk for nutrient deficiency” is incorrect. A benefit cannot be simply an absence of risk. An absence of risk simply nullifies risk and does not establish benefit. However, at a particular level of exposure, risk of inadequacy might be nullified and in addition, further benefits may be encountered. For example, taking 18 mg of niacin daily is likely to eliminate any risk of inadequacy (pellagra). However, benefits may occur in a diverse range of body systems (e.g. eye health, blood cholesterol management) with intakes in excess of 100 mg. However, at this exposure/intake level, some individuals might experience skin flushing, which is generally seen as a minor, reversible complaint which disappears or declines with habitual use of higher dosages of niacin.</p> <p>This is considered in further details in: Verkerk, R.H.J., The paradox of overlapping micronutrient risks and benefits obligates risk/benefit analysis. <i>Toxicology</i> (2010), doi:10.1016/j.tox.2010.02.011</p>
Council for Responsible Nutrition	3.1. Importance of the selected endpoint(s) and the subpopulation(s) considered in the assessment	<p>Lines 128-136: This discussion does not adequately convey the concept that specificity and causality are issues for health benefit and risk effects.</p> <p>Lines 137-141: See comment for lines 121-123, above.</p> <p>Line 142: Risk-benefit likelihood values may be estimated, but the assessment cannot be determined directly for the individual—except after an occurrence.</p>
European Botanical Forum	3.1. Importance of the selected endpoint(s) and the subpopulation(s) considered in the assessment	<p>Line 130: The example given is an example of a positive consequence for health. It is however very unlikely that foods or food components will be able to show that their use will indeed increase resistances to infection. One can of course then argue that there is no benefit until an effect has been shown by intervention trials. Nevertheless, given the practical almost impossibility to show such pronounced effects in normal subjects, it then remains problematic to show that such intervention is also effective for the whole population, under the various dietary patterns that exist in reality.</p>
European Responsible Nutrition Alliance	3.1. Importance of the selected endpoint(s) and the subpopulation(s) considered in the assessment	<p>Line 142: It is questionable if the proposed methodology for a risk-benefit assessment is suitable on the level of the individual.</p>
European Responsible Nutrition Alliance	3.1. Importance of the selected endpoint(s) and the subpopulation(s) considered in the assessment	<p>Line 136: This is definitely important as the risk-benefit assessment will unavoidably be subject to assumptions and uncertainties.</p>

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
European Responsible Nutrition Alliance	3.1. Importance of the selected endpoint(s) and the subpopulation(s) considered in the assessment	Line 130: It is not clear if this reflects the health status on individual or population level. While dietary changes are likely to change the health status of a population (e.g. to obtain less cardiovascular disease or even to lower cholesterol levels) this is very unlikely of individual foods, leave alone food components. In order to identify a desirable change in health status, it is important to define what a health status is. In contrast to risk assessment, where adverse effects can be defined as effects that originate in disease or abnormal situation, a health benefit cannot be defined as the inverse, namely an effect that would cure or treat a disease or abnormal situation.
Istituto Superiore di Sanità	3.1. Importance of the selected endpoint(s) and the subpopulation(s) considered in the assessment	Line 147: it might be better to specify "the greatest impact on health outcomes or where..."
Istituto Superiore di Sanità	3.1. Importance of the selected endpoint(s) and the subpopulation(s) considered in the assessment	Line 144: "sensitivity" it is taken as general term fitting to both risks and benefits? I.E., equivalent to vulnerability/susceptibility when only risks are considered?
RIVM	3.1. Importance of the selected endpoint(s) and the subpopulation(s) considered in the assessment	<ul style="list-style-type: none"> Regarding 3.1, it should be noted that traditionally (and with good reason) the selection of endpoints is very different in risk assessment compared with benefit assessment. Risks are considered (TDI) if there is evidence for a possible effect. Benefits are considered (claims) when the evidence for an effect is convincing. Selection of endpoints in a benefit-risk assessment should bear this in mind and note that the assessment is biased if selection of endpoints is based on accepted procedures from toxicology and nutrition science (epidemiology) It should be realized that all benefit-risk assessments are performed as ordered by a manager. For example, academia may perform such an assessment without interaction with management or link to communication. This is not mentioned as such in the document. <p>P20, L137-141: Please refer here to the scientific substantiation of health claims under Regulation 1924/2006.</p>
Council for Responsible Nutrition	3.1.1. Types of data.	Lines 174-176: Many cardiac drugs have biomarkers that have been only loosely validated to indicate morbidity or mortality risk. Lines 180-181: Progress toward this goal should be indicated here.

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
DANONE	3.1.1. Types of data.	L150: his paragraph only deals with cases when there is data available to perform the assessment. However, this part should also deals with the case where no or insufficient data are available.
DANONE	3.1.1. Types of data.	L 180: We fully agree with the need of a clear strategy for biomarker qualification, as this is key for designing relevant studies about the benefits of foods. As Danone, we would be happy to contribute / support further work on that topic in the frame of relevant scientific institutions.
European Botanical Forum	3.1.1. Types of data.	Line 180: We would very much welcome a fundamental discussion on the aspect of benefits assessment as the experience with the current approach of EFSA to assess claims effects is unsatisfactory. It reduces foods and food components to medicinal products by expecting dose-effect relationships and ignores subtle contributions intake of food components can have. A clear strategy is needed indeed and it still needs to be fundamentally discussed.
European Responsible Nutrition Alliance	3.1.1. Types of data.	Line 183: It is not clear what is meant by supportive. Can any evidence be supportive only when more conclusive evidence is already available? Is there then a need? Is it as with animal and experimental data that are only considered supportive if the human trials already provide sufficient proof? We believe that the concept of supportive evidence should be considered in the framework of the totality of the evidence and play an important role to the grading of the evidence.
European Responsible Nutrition Alliance	3.1.1. Types of data.	Line 180: This is quite strange as EFSA is doing full speed claims assessments today. If such considerable advances are expected and a clear strategy is needed, upon what is the current EFSA approach based then? We would certainly welcome a fundamental discussion on this aspect.
European Responsible Nutrition Alliance	3.1.1. Types of data.	Line 172: If improvements of a normal body function can be demonstrated, the benefit is likely to be judged low, as the functions are already normal. This in itself may make risk-benefit assessments superfluous.
European Responsible Nutrition Alliance	3.1.1. Types of data.	Line 161: Despite the fact that EFSA acknowledges the supportive role of certain types of evidence (in vitro studies, animal studies, observational studies) it is very unlikely that beneficial effects would be identified without the availability of strong human data. Without this, a risk-benefit assessment has little chance to reach steps 2 and 3 of the assessment.

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
Federal Institute for Risk Assessment	3.1.1. Types of data.	Page 20, line 175: An assessment of validity of the biomarker should be included (maybe that was meant by "limitations").
IADSA	3.1.1. Types of data.	<p>Section 3.1.1. Lines 174-184 p.20</p> <p>IADSA notes that, in theory, the PASSCLAIM scientific criteria and the EU legislative provisions for assessment of the strength of the evidence could provide a benefit framework to determine the extent to which a food or food component provides the probability of a benefit. IADSA also notes that the use of biomarkers of exposure to a food component, target function/biological response, enhanced target function, markers of intermediate endpoint may or may not be the markers of risk of excessive intake. However, the benefit framework, in principle, could help to identify biomarkers as long as they relate to appropriate endpoints (both short- and long-term outcomes) in health and well-being. The EFSA report emphasises benefit data from human intervention studies and the use of 'hard' biomarkers (see Section 4 below).</p> <p>The EFSA opinion, however, recognised that there is a need for the establishment of a clear strategy for biomarker qualification and the use of surrogate biomarkers in place of frank endpoints in benefit and risk assessment.</p>
IADSA	3.1.1. Types of data.	<p>Section 3.1.1. Line 153 p.20</p> <p>IADSA believes that the approaches for demonstrating the probability of a benefit should take into account the totality of the available scientific data (i.e. sources of evidence include human intervention studies, epidemiological studies, animal and in vitro studies as well as history of use) and by weighing of the evidence (i.e. a clear scientific framework for assessing the strength, consistency and plausibility of the evidence, such as convincing, probable, possible, insufficient or strong, moderate, weak) to demonstrate the extent to which:</p> <ul style="list-style-type: none"> • The science supports that a food or food component is beneficial for human health • A cause-and-effect relationship is established between consumption of the food or food component in humans (such as strength, consistency, specificity, dose-response and biological plausibility of the beneficial relationship). • The quantity of the food or food component and the pattern of consumption required to obtain the beneficial effect • The specific population or population subgroup for which the benefit is intended
RIVM	3.1.1. Types of data.	<p>P20, L168: add confounding</p> <p>P20, L174-184: Copy the thinking of the Passclaim project and the EFSA-NDA health claim guidance on the use of biomarkers. Biomarkers should be:</p> <ol style="list-style-type: none"> 1a. Biologically valid 1b. technologically valid <p>A change in biomarker should be:</p> <ol style="list-style-type: none"> 2a. statistically significant 2b. biologically relevant

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
Council for Responsible Nutrition	3.1.2. Subpopulation selection.	Lines 187-192: Folic acid could be mentioned as an example.
European Responsible Nutrition Alliance	3.2.1. Exposure.	Line 196: Risk is something to consider for the whole population, whereas benefit is mostly linked to an individual choosing for a functional food. This is an additional difficulty and argument why risk-benefit assessment does not make sense for individual foods or food components.
European Responsible Nutrition Alliance	3.2.1. Exposure.	Line 195: This section is only a small part of the document but presents the major difficulty as the estimation of intake of substances, especially in low quantities and under the form of supplements is currently hardly possible given the intake data that exist.
Federal Institute for Risk Assessment	3.2.1. Exposure.	Page 21, line 195: Some more explicit guidance should be provided on the extent to which alternative sources and pathways of exposure should be considered. Does this standard approach for risk assessment apply equally to benefit assessment?
Council for Responsible Nutrition	3.2.2. Effects.	Lines 222-239: A major limitation of RCTs is not mentioned here but should be. Although RCTs are necessary to show causality in humans, a failure to identify a specific beneficial effect in a specific RCT should not be overly generalized. The failure to find benefit may reflect a choice of an inappropriate endpoint, or it may reflect the status of the test cohort but not a majority of the population or a significant subpopulation.
Federal Institute for Risk Assessment	3.2.2. Effects.	Page 22, line 245: The strength of evidence for risk should be classified using some grading scheme such as, for example, the U.S. Preventive Services Task Force system.

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
IADSA	3.2.2. Effects.	<p>Section 3.2.2. Lines 222-248 p.22</p> <p>IADSA notes that, although this section of the EFSA opinion includes discussion on the limitations of RCTs, the text illustrates again the dominance of the pharmaceutical approaches to scientific substantiation of the beneficial relationships between diet and health and the EFSA focus on conclusive evidence of cause and effect for a claimed health benefit. The emphasis should be on the totality of the available data, the weighing of the evidence to determine its strength, consistency and plausibility, and a framework for the evaluation of the probability of a benefit to health.</p>
RIVM	3.2.2. Effects.	<p>P22, L234: Randomised double-blind placebo-controlled....</p> <p>P22, L246: I do not agree that “risk” is mentioned here, so delete “risk”. Typically RCT’s are NOT done to determine health risks.</p>
Council for Responsible Nutrition	3.3. Considerations on how animal and other data can be extrapolated to the human situation in order to facilitate human risk-benefit comparison.	<p>Line 268: Give at least one example of such nutrients.</p> <p>270-277: The usual example of the 100x factor for extrapolation from animal data to humans, and the separation of the 100 into 10 x 10 has much more history than justification. The assignment of 10x for inter-individual variation may be appropriate in this context but often leads to unworkable answer when applied to human data. For example, a 10x factor for calcium, iron or zinc would lead to UL values well below the PRI values.</p>
European Responsible Nutrition Alliance	3.3. Considerations on how animal and other data can be extrapolated to the human situation in order to facilitate human risk-benefit comparison.	<p>Line 266: This is illustrative of the pharmaceutical toxicological approach.</p>

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
CIAA	3.3. Considerations on how animal and other data can be extrapolated to the human situation in order to facilitate human risk-benefit comparison.	<p>L. 266-267: For nutrients the basis for benefit assessment starts with preclinical investigations. Only in case a new food ingredient is concerned this is also the case for the risk assessment.</p> <p>L.270-277: As stated in my general comments for nutrients this proposed extrapolation is not suitable (using these uncertainty factors is only applicable for unwanted substances within the food, not for desired nutritional substances; for micronutrient you will end up in a deficiency state and for functional foods, you will not reach the dose that is efficacious). Therefore human data are of utmost importance to support animal data in risk assessment. It is recommended to put some more emphasis on the nutrient risk assessments and the difficulties often encountered (recent discussion on NOVEL Food guidance document held by EFSA).</p> <p>L. 281-282: It is not applicable at all from industry perspective to refer to both genotoxic and carcinogenic compounds, since these will not be applied in products in development. This will only apply to contaminants, which we will control and use the ALARA principle. This is again a Governmental perspective. Furthermore it is stated that in the field of nutrition, extrapolation from animal data to assess the positive health effect in humans is unusual</p> <p>L. 296-297: It should be noted that the majority of our animal experiments are conducted for benefit purposes! just a very minor part for risk assessment purposes .</p>
RIVM	3.3. Considerations on how animal and other data can be extrapolated to the human situation in order to facilitate human risk-benefit comparison.	<p>P23, L289: I think MOE can be useful in only in step 1 as a screening mechanism just as TDI and ADI. They are not useful in step 2 because the do not in any way quantify a probability of effect. A MOE of 10 for some effect is cannot be judged better or worst than a MOE of 1000 for another effect even if you weigh the severity of the effect subjectively because the dose-response functions can have very different shapes.</p>
Council for Responsible Nutrition	4. Uncertainties in the risk-benefit assessment approach.	<p>Line 317: See line 304 in Section 4, above.</p> <p>Lines 328-338: See comment above for Section 3.3 lines 270-277.</p>
Council for Responsible Nutrition	4. Uncertainties in the risk-benefit assessment approach.	<p>Line 304: Imperfect knowledge is not a useful term—do we ever have “perfect knowledge?”</p>

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
European Botanical Forum	4.1. Uncertainty in the hazard and the positive health effect characterisation.	Line 321: This is a further argument that for the purpose of risk-benefit assessment the evidence underlying benefit needs to be graded to allow the risk manager to invoke the inverse precautionary principle. When there are indications of a health-benefit, but the evidence is not yet convincing, the risk manager may still choose to attribute an appropriate weight to the potential health benefit, given its importance for public health (e.g. the case of folic acid and neural tube defects).
European Responsible Nutrition Alliance	4.1. Uncertainty in the hazard and the positive health effect characterisation.	Line 341: There is a full area of food components with potential beneficial effects that are not considered nutrients.
European Responsible Nutrition Alliance	4.1. Uncertainty in the hazard and the positive health effect characterisation.	Line 321: This is why risk-benefit assessment can only work if the evidence underlying benefit is graded. The expectation of 100% convincing evidence may be needed to offset risk, but will in practice not work because under the regulatory requirements, risk should be minimal anyway. We would call for the inclusion in this document of the inverse precautionary principle in the field of benefit assessment. This means that when there are indications of a health-benefit, but the evidence is not yet convincing, the benefit of the doubt is given to the health benefit. In that way consumers could already choose to benefit from advances in science before they are convincingly demonstrated. The case of folic acid and neural tube defects shows the importance of such an approach. But this approach requires the risk manager to weigh the evidence and indicate the strength of it in a way that the risk manager can apply the inverse precautionary principle.
Istituto Superiore di Sanità	4.1. Uncertainty in the hazard and the positive health effect characterisation.	line 328: it might be better to detail: "...may differ for different subgroups. Under this respect special attention should be given to sensitivity related to gender, age, lifestage (e.g., pregnancy, puberty, post-menopausal), metabolic status (e.g., overweight), nutritional status (subclinical deficiency or increased requirement for a certain nutrient) and/or other factors (e.g., lifestyles entraining exposure to additional health risks: one example is the adverse interaction between beta-carotene intake and smoking)."
Council for Responsible Nutrition	4.2. Uncertainty in the exposure assessment	Lines 344-347: The limitations of RCTs mentioned in the comment for lines 222-239 should be acknowledged here.
DANONE	4.3. Uncertainty in risk-benefit comparison.	L378: How will uncertainty in risk-benefit comparison impact risk-benefit management decisions? Uncertainty in risk assessment may lead to adoption of risk management measures in the frame of the precautionary principle (art 7 of Regulation 178/2002). Can we expect a similar approach to be defined for dealing with uncertainty in risk-benefit assessment?

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
Council for Responsible Nutrition	5. Examples of risk-benefit assessment	Line 381: Again the double standard: Benefits must be “likely” but risks need to be only “potential.” This standard can produce pernicious neglect of providing benefits, while overreacting to possible risks.
Alliance for Natural Health International	5.1. Risk-benefit assessment of an indispensable nutrient: Selenium.	<p>The example mentions different forms of selenium present in natural foods (e.g. selenocysteine), but fails to discuss the implications of different molecular forms on risk or benefit.</p> <p>Other benefits such as the effects of selenium on immuno-competence and male fertility have been ignored. They should be factored in to the example.</p> <p>It would be useful to have a further example included, perhaps the example of folate being of particular relevance.</p> <p>For further information see: Verkerk, R.H.J., The paradox of overlapping micronutrient risks and benefits obligates risk/benefit analysis. Toxicology (2010), doi:10.1016/j.tox.2010.02.011</p>
Swedish National Food Administration	5.1. Risk-benefit assessment of an indispensable nutrient: Selenium.	p. 25, Selenium example: The role and impact of intake in the form of foods, fortification and especially supplements, as well as chemical forms, could be highlighted more.
RIVM	5.1.1. Problem formulation.	<p>P26, L417: The problem is not clearly formulated. Do we want to compare risks and benefits (net health impact) of the current intake with no intake?</p> <p>If you follow the assessment steps, it shows that the problem formulation actually is: Is there an alternative selenium intake scenario that improves health (the balance between risks an benefits) compared to current intake</p>
Council for Responsible Nutrition	5.1.3.1. Step 1 – Initial assessment	<p>Line 432: For Scenario 1, the heading is misleading. “Maximising the risks” reads as though this is an objective. Would it be better to say “Conditions of maximum risk?”</p> <p>Line 449: For Scenario 2, the heading would better read “Conditions of minimum risk.”</p>

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
European Responsible Nutrition Alliance	5.1.3.2. Step 2 – Refinement of the assessment	Line 482: This paper addresses metrics to apply in risk assessment and benefit assessment separately or to compare both. These metrics all relate to severe end points, i.e. mortality and morbidity linked to diseases. Whereas this focus on disease and mortality may certainly be appropriate in the case of acute toxic substances (from the risk perspective) and pharmacological treatment of diseases (from the benefit perspective), it is quite questionable if these metrics are useful in the field of food where adverse and beneficial effects are often less outspoken and linked to the complex interactions between all food components, i.e. very difficult to identify effects of individual food components in isolation.
Council for Responsible Nutrition	5.1.3.3. Step 3 – Comparison of risks and benefits using a composite metric.	Lines 486-489: This is easy to say and difficult to achieve. What composite matrix could be used?
Swedish National Food Administration	5.2. Risk-benefit assessment of fish consumption and exposure to methylmercury.	p. 28, Fish example. The example is complex, given that intake of MeHg and n-3 fatty acids generally come from different fish species. One could also refer to examples where risk-benefit assessments are based on constituents from the same fish species, e.g. Cohen et al.
CIAA	5.2.1. Problem formulation.	L. 517-519: The possible risk attached to n-3 PUFA's (over consumption) is missing in the example used,
RIVM	5.2.1. Problem formulation.	P29, L519: compared to not eating fish? Again referring to our general remark that RB assessment is about comparing different intake scenarios
Coughlin & Associates	Conclusions and recommendations.	<p>I appreciate this opportunity to comment on your risk-benefit assessment guidance document and wish to express my support and congratulations on a very well thought-out document. Your report is a major contribution to a field which badly needed attention. While I have specific guidance on only one section (page 11, bullet 1), I do wish to present a few general comments.</p> <p>With an apparently conflicting animal vs. human database, we in the coffee/health world ask that coffee's impact on human health be evaluated by looking at the whole beverage, taking into account risks and benefits, just as you are addressing in your report. Our IFT Expert Report recognized the importance of evaluating the beneficial health effects of foods and beverages and undertaking a thorough risk-benefit evaluation of whole foods or beverages. Consequently, I would urge you in your continuing evaluation of risk-benefit assessment to consider conducting a case study of coffee and cancer as a potentially informative example of your assessment methodology.</p>

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
DANONE	Conclusions and recommendations.	L653-654: We notice that today, metrics are starting to be developed for assessing reduction of a risk, but we still totally lack metrics for assessing a real benefit of food consumption. Therefore, a strong recommendation of the Scientific Committee to develop specific metrics for characterization of risk reduction and start research work on benefit characterization would be welcome
CIAA	Conclusions and recommendations.	L. 657-660: We fully agree with the need to design surveys in a way the data will be useful for both risk and benefit assessment, and with the need to develop hard biomarkers of both risk and benefit.
DANONE	Conclusions and recommendations.	L641-645 : We support the need for communication between the risk-benefit assessor and the risk-benefit manager at various steps of the process. In addition, we think other relevant stakeholders should be included in a dialogue with the risk-benefit manager after the benefit risk assessment, because in the benefit risk management decision other considerations will have to be taken into account, such as the consumer perception of this question, because in the end the decision will affect the consumer food choices. We believe that food companies shall be relevant partners to provide information about consumer perception of such food linked issues.
DANONE	Conclusions and recommendations.	We agree with the approach taken and consider it would be helpful to have clear guidelines on how is performed a risk-benefit assessment. Nevertheless, we feel more clarity should be given about when and by whom this approach would be used and what would be the interactions between all players. Is it a tool to prepare the development of new regulations? Will it be used only by authorities and official institutions, or will industry have to follow these principles? These key questions have to be clearly addressed when publishing the final document. We want to mention that most of the metrics listed at the end of the document cannot be accessible for industry players. Therefore, it seems appropriate to specify in the guidance that this benefit risk assessment methodology is intended for official evaluation bodies only, and should not be expected to be used by industry.
Istituto Superiore di Sanità	Conclusions and recommendations.	L652 We suggest the following additional sentences "...already when entering the first steps of the assessment. Moreover, in some cases, risk-benefit assessment might be required in the absence of established guidance values (e.g., TDI, as for non-dioxin-like PCBs, or UL, as for manganese): the potential for such cases to occur should be also considered when developing a science-based framework for risk-benefit assessment"
Istituto Superiore di Sanità	Conclusions and recommendations.	Line 653-4 "...are further developed, with special attention concerning relevant special sensitivities to health risks or benefits in population subgroups".

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
IADSA	Conclusions and recommendations.	<p>Section 1. Line 210 p.7 & Section Conclusions and recommendations. Lines 641-645 p.32</p> <p>IADSA highlights the need for detailed cost-benefit econometric studies to translate the evidence on specific nutritional interventions into economic and healthcare benefits. Key questions relate to:</p> <ul style="list-style-type: none"> • Does the nutritional intervention produce a nutritional or physiological effect as shown by a change in biological markers? • Does the nutritional or physiological effect create a change in health status/health benefit? • Can cost benefits be demonstrated (e.g. reduced costs of healthcare provisions, increased quality of life for individual(s) and/or population(s) at risk?
ILSI Europe	Conclusions and recommendations.	<p>Line 630: it should be noted that Risk-benefit assessment is not easy:</p> <ul style="list-style-type: none"> • It requires a high level of expertise in several fields including nutrition, exposure assessment, toxicology, epidemiology, modelling and statistics. • It requires substantial data or assumptions. • It is affected by many uncertainties. • It requires careful interpretation and communication.
RIVM	Conclusions and recommendations.	<p>P33, L653: risk characterization also needs to be further developed; it should not stop at defining a safe level but should describe what happens if that level is exceeded.</p>
DANONE	Appendix - Metrics for use in risk-benefit assessment	<p>L750-751: We feel there is a big discrepancy between metrics available for assessing risks and benefits. The majority of available tools enable to assess risks, in link with disease, when very few metrics can measure benefits in itself. Further research need to be done to develop tools that can measure the outcome of a positive health effect.</p>
European Responsible Nutrition Alliance	Appendix 1. Common metrics for assessing separately risks and benefits.	<p>Line 756: If it is accepted that generally agreed metrics for some positive health effects and well being are currently lacking, how is EFSA then assessing whether a health effect is beneficial?</p>
European Responsible Nutrition Alliance	Appendix 1. Common metrics for assessing separately risks and benefits.	<p>Line 755: This approach would lead to think that the outcome of any risk and any benefit is an increase or decrease of disease-related parameters. This is at the far end of adverse effects and will be very hard to measure in a human population. It may be a nice statistical approach, but the practical value is questionable.</p>

ORGANISATION	CHAPTER_TEXT	COMMENT_TEXT
ILSI Europe	Appendix 1. Common metrics for assessing separately risks and benefits.	Line 750: it should be stated that few metrics are available to direct measure a benefit health effect, therefore more emphasis should be given to the development of tools to measure the outcome of positive health effects.
DANONE	Appendix 2. Composite metrics for comparing risks and benefits.	L763-764: We consider these metrics are relevant to compare a risk with a reduced risk. However, they do not enable today to compare a risk with a real benefit. Further research should be performed to identify ways to measure the outcome of a benefit, to express it and define on which grounds this could be compare with the measurement of the risk.
European Responsible Nutrition Alliance	Appendix 2. Composite metrics for comparing risks and benefits.	Table: All these measures are population based. Individual intake is very difficult to assess and therefore risk-benefit assessment can only be considered at population level.
RIVM	Appendix 2. Composite metrics for comparing risks and benefits.	P36, DALY: Please also refer to Gold et al 2002 Ref. HALYS and QALYS and DALYS, Oh My: similarities and differences in summary measures of population Health. Gold MR, Stevenson D, Fryback DG. Annu Rev Public Health. 2002;23:115-34.
Swedish National Food Administration	Appendix 2. Composite metrics for comparing risks and benefits.	p. 37, line 791: “ The QALY ... years of life with perfect health that would ... “.