Risk Benefit Analysis of Foods

BRAFO

This Specific Support Action project is carried out with the financial support of the European Commission, DG Research under the Sixth Framework Programme (FP6), Priority 5, Food Quality and Safety, Contract Number: FOOD-CT-2007-031731

As the burden of health costs within society increases due to a longer lifespan, overall balanced nutrition can play an important role in disease prevention. There is considerable disparity in the way benefits and risks are compared for compounds found in food, relying almost always on subjective judgement. This prevents adequate comparison of alternatives and renders resource prioritisation difficult. In addition, it is extremely difficult to provide comprehensible advice to consumers. It is therefore vital that an effective strategy is developed to enable a holistic analysis of the net health impact of compounds in food, in a manner similar to the current assessment of risk.

ILSI Europe

Risk assessment

The risk assessment of compounds in food is a mature process that follows a well-developed scientific approach; the strategy followed is the result of a substantial amount of thought and experience. Such a risk assessment has served society well to the extent that it has protected consumers from the potentially harmful effects of chemicals to which they might otherwise have been exposed through food consumption. For chemicals used to secure the integrity of food that require prior approval, such as pesticides or packaging materials, this works reasonably well, although it is difficult to weigh the indirect benefit against residual risk. For compounds with direct health benefits such as vitamins or phyto oestrogens, the situation is more complex. It is necessary to evaluate risks, manifest as negative impacts on health, and benefits that produce a positive impact on health.

Project aim

The aim of the project was to develop a framework that allows quantitative comparison of human health risks and benefits of foods and food compounds based on a common scale of measurement. It was based on the evaluation of changes in the quality/duration of life using a system that allows weighting of data quality and severity of effect, with quantification by Quality Adjusted Life Year (QALY) or Disability Adjusted Life Year (DALY)-like methodology. The framework took into account how risks and benefits interrelate. It is intended that the methodology developed is sufficiently transparent to serve as a reference for the harmonisation of the evaluation methods used within the European Union and more widely in international evaluations.

A European network was set up in September 2007, which involved expertise in benefit/risk analysis and nutrition, with representatives from academia, regulatory agencies and the food industry. A methodology group reviewed and assembled the methodologies available. This group collaborated with three case study groups to integrate the methodological findings in their area and to develop a framework applicable to a wide range of foods and food compounds. The development of a benefit-risk framework was expedited by its use on a number of selected examples of foodstuffs and food components.

Three case studies were conducted: Natural Foods, Dietary Intervention and Heat Processing. In October 2008, the cae study groups commenced work on applying and adapting the methodological approach developed to undertake a risk assessment, a benefit assessment, and quantitative net health impact assessment on the selected cases. Publications after each of these steps on methodological review, three worked examples and the proposed framework are currently available in literature and on the ILSI Europe webpage.

For detailed information, visit the BRAFO website at www.brafo.org

Objectives of the project

The primary aim of this project was to develop a framework that allows for the quantitative comparison of human health risks and benefits in relation to foods and food compounds by expressing these on a common scale, which takes account of quality of data and severity of effect.

The objectives of this project were to:

- Establish a common scale of measurement for comparing benefits and risks of food and food components present in the diet;
- Provide a scientific framework to aid in the objective comparison of benefits and risks and in decision-making;
- Improve harmonisation of the principles and practices in the benefit-risk analysis process;
- Create a stronger scientific base for communication of benefits and risks to the consumer, including appropriate expression of uncertainty.

The principal outputs are:

- A literature review on the benefit-risk evaluation of food;
- A full description of beneficial and adverse effects of BRAFO's targeted food components in the population at large. These examples were organised in three categories: natural foods, foodstuffs used for dietary interventions, and heat processed compounds;
- A comprehensive framework that can be used to compare the quantitative and qualitative values of human health risks and benefits of compounds based on the same scale of measurement.

These outputs led to:

- Improved understanding of the qualitative and quantitative comparison of human health risks and benefits of compounds in foods;
- A framework describing benefit- risk methodology that could be extended to take into consideration indirect health effects, economic, societal and environmental impacts;
- The ability to directly compare the net health benefits and net risks of the selected examples;
- Improved interaction between European researchers working in the risk and benefit areas and less duplication of effort.

Structure of the project

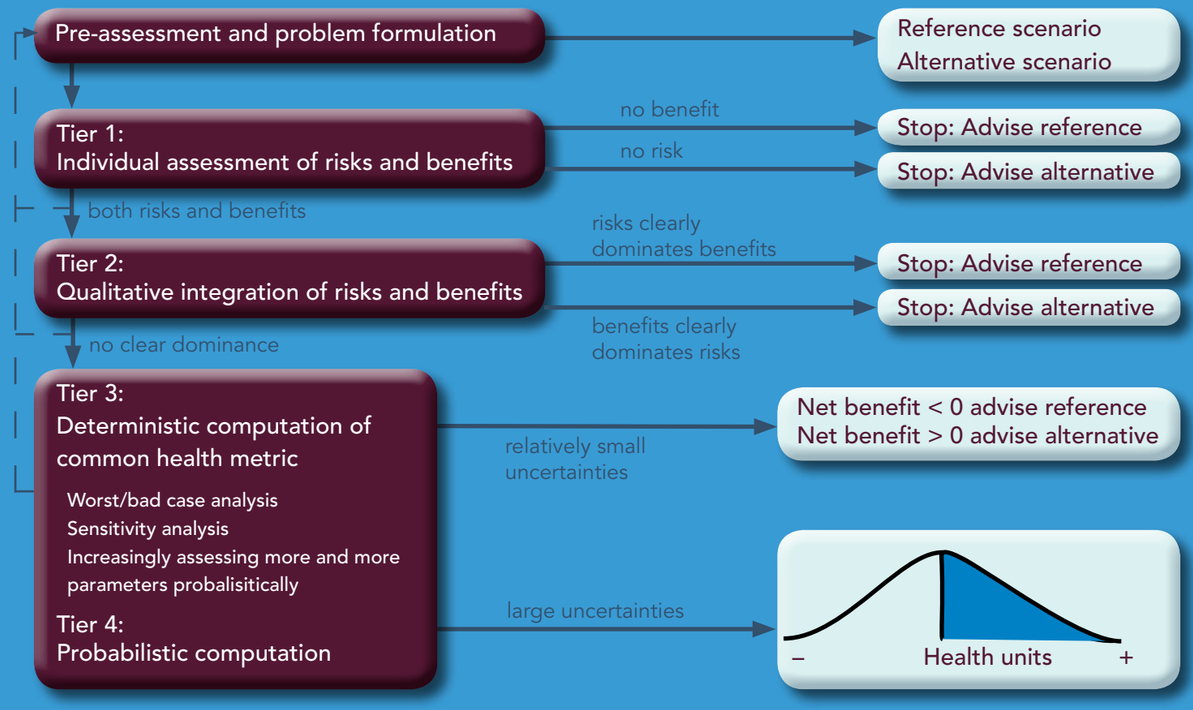

Figure 1. A flow chart of the BRAFO tiered approach for health benefit-risk assessment of different dietary scenarios (reference and alternative). The formulation of the benefit-risk question may be iteratively refined in consultation with the risk manager/policymaker as the assessment progresses, as indicated by the dashed arrows at the left side of the figure.

During the first year of the project, a methodology group brought together methodologies from several disciplines relevant to the evaluation of benefits and risks in food. Much of the primary data required for this evaluation existed in a form that may be only partially useful and would therefore require remodelling for better estimates of benefits and risks.

The reprocessing of available data to achieve a standard representation of inputs and outputs (costs and consequences) was required, which in turn necessitates the formulation of agreed guidelines that were common to all constituent elements of the project. This group reviewed and assembled the methodologies available. A guidance document describing a tiered ('stepwise') approach for performing benefit and risk assessments of foods was produced. It was then presented at the BRAFO Methodology Workshop held on 25-26 September 2008, in Rome. The process starts with a pre-assessment and problem formulation step to set the scope of the assessment. This includes defining two scenarios for comparison in the assessment: the reference scenario (e.g. current diet, or a zero intake scenario), and an alternative scenario (e.g. introducing a new food or food policy).

The approach consists of 4 tiers (see Figure 1). In many cases, a lower tier assessment using simple methods may be sufficient to show a clear difference between the health impacts of the two scenarios. In other cases, increasingly sophisticated methods are used at higher tiers until there is sufficient certainty for decision-making.

Tiered approach

The tiered approach is capable of assessing the benefits and risks of changing from the reference scenario to an alternative, resulting in a statement about which scenario is preferred in terms of net health effects. The focus of the macronutrient replacement example is on the quantification of any residual risks associated with the toxicity of these substances at intakes above the Accepted Daily Intake (ADI) or similar accepted levels, the potential for nutritional interferences, and the nutritional benefits associated with typical ranges of intake.

In Tier 1, each benefit and risk is assessed independently. These assessments will often use standard screening methods, but it may be worth using more refined methods if this avoids the need to proceed to Tier 2. Tier 1 comprises a separate but as comprehensive as needed benefit assessment, and a separate risk assessment.

In Tier 2, benefits and risks are compared in a qualitative way; no common metric is used yet, although the assessment of each individual benefit or risk can be quantitative or even probabilistic.

In Tier 3, benefits and risks are integrated quantitatively in a common metric, by a deterministic approach.

In Tier 4, benefits and risks are integrated quantitatively in a common metric by a probabilistic approach.

As indicated in Figure 1, there is in practice a continuum between Tiers 3 and 4. Initially, all parts of the assessment are treated deterministically (i.e. as fixed values) after which, progressively, more parameters are treated probabilistically (i.e. using probability distributions) until the net health impact is sufficiently well characterised for decision-making. The steps needed to reach a

conclusion in each tier follow largely the same steps as in the risk assessment paradigm. But after the first tier, comparison (Tier 2) and integration (Tier 3 and 4) of the risks and benefits follow. This is shown in Figure 2.

Benefit-risk framework

The development of the benefit-risk framework was expedited by its use on a number of selected examples of foodstuffs and food components. During the second year of the project, the three case study groups have worked on applying and adapting the methodological approach developed to undertake a benefit assessment, a risk assessment, and quantitative net health impact assessment on the selected cases.

Case study "natural foods"

There is evidence that consumption of fish, particularly oily fish, has substantial beneficial effects on health. As a result the public is advised to increase its fish consumption as in many countries people consume considerably less than optimal. On the other hand it should be noted that some fish contain hazardous substances like dioxins, PCBs or methyl-mercury. The negative effects of these substances include the possible development of cancer or effects on the developing foetus.

As a consequence oily fish is an exceptionally good example of consumer confusion and therefore has been selected as a case study. Both qualitative and quantitative reviews of benefits and risks within BRAFO are linked to the work developed in the EU funded project QALIBRA, in which fish in general is one of the case studies. QALIBRA developed a web-based tool for quantitative assessment that integrates the benefits and the risks of dietary change into a single measure of net health impact, allowing quantification of associated uncertainties.

Therefore, based on the present benefit calculations, it was concluded that the consumption of 200g/week of oily fish (farmed salmon) was more beneficial than no consumption at all, as it resulted in a significant reduction of incidence of cardiovascular disease. Although this scenario increased the intake of contaminants, for methyl-mercury as well as for dioxins the intake did not exceed the provisional total weekly intake level.

Soy was selected as a second example of a natural food because it is recognised as a healthy food delivering various essential nutrients. In addition, soy intake is associated with a reduced risk for cardiovascular disease. However, phytochemicals occurring naturally in soy, such as isoflavones, can have both beneficial and adverse effects, as demonstrated in a number of animal studies. For this case study, it was not necessary to go to Tier 3. It could be concluded at Tier 2 that soy protein consumption would result in an overall benefit for the general adult population.

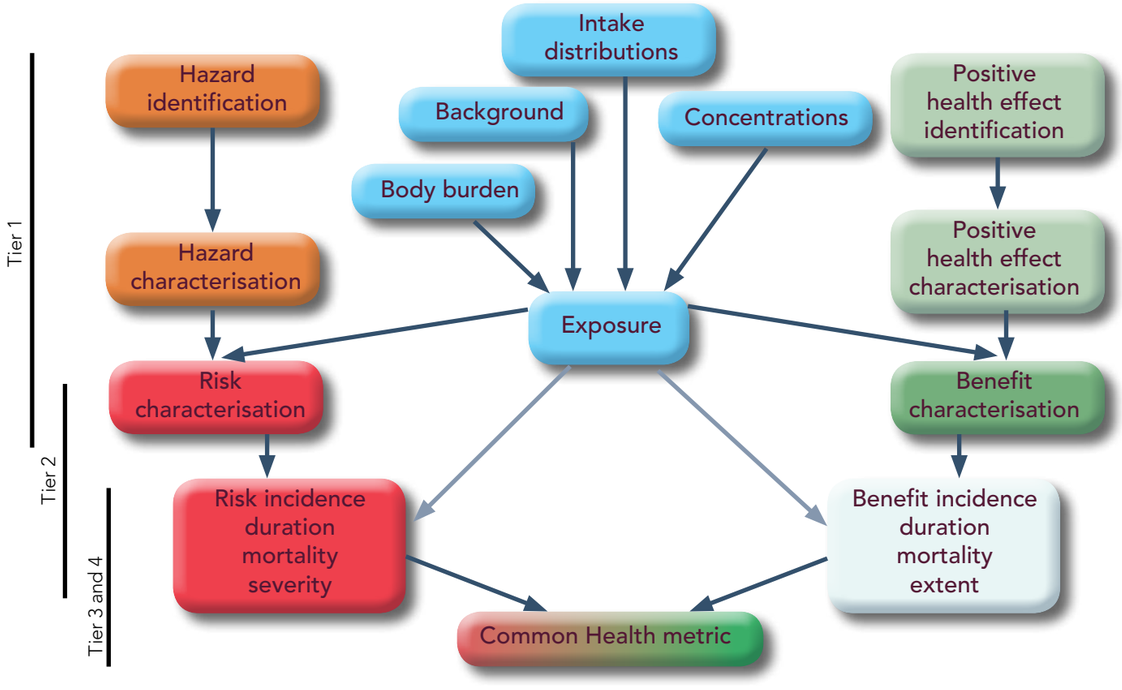

Figure 2. A schematic description of the steps within each tier.

Case study "dietary interventions"

This topic consisted of an assessment of benefits and risks associated with dietary interventions.

The work comprised as an example folic acid fortification of flour. The folic acid case described in details the beneficial effects of intake of folic acid across dose levels in qualitative and quantitative aspects up to Tier 3, taking into account sub-groups who would experience the greatest benefits or risks, i.e. pregnant women and the elderly. Although it would be necessary to accept both health risks and health benefits, it was possible to identify a scenario in which the benefits substantially outweighed the risks.

The work of this group also comprised examples of macronutrient replacement/food substitution: the isocaloric replacement of saturated fatty acids with carbohydrates, the replacement of saturated fatty acids with monounsaturated fatty acids, and the replacement of sugar-sweetened beverages containing mono- and disaccharides with low calorie sweeteners. The isocaloric replacement of saturated fatty acids would result in an overall health benefit in relation to cardiovascular disease, in the absence of health risks but did not constitute a genuine benefit-risk question.

The focus of the exchange of mono- and disaccharides for low calorie sweeteners was on the quantification of any residual risks associated with the toxicity of these substances at intakes above the Acceptable Daily Intake (ADI) or similar accepted levels, the potential for nutritional interferences, and the nutritional benefits associated with typical ranges of intake. This case study stopped after Tier 2 when it was apparent that there was essentially no risk associated with low calorie sweeteners.

Finally, an example of addition of specific ingredients to food, chlorination of drinking water, was addressed. In this case there were clear benefits and risks. However, the quantitative comparison of these falls short because of a lack of suitable scenarios and underlying data.

The respective examples illustrated how the BRAFO-tiered approach provided various results, ranging from a quick stop as the result of an early, clear conclusion that benefit outweighs risk or non-genuine benefit-risk questions to continuation through the tiers into deterministic/probabilistic calculations.

Case study "heat processing"

There is evidence that the traditional ways of cooking or heat-processing of foods besides the desired effects (like preservation, increased digestibility and flavour formation) lead also to the formation of heat-formed contaminants that could be damaging to our health.

Due to the individual reactivity of food components (e.g. amino acids, sugars and fatty acids) substantial interactions and changes occur during heat processing. Benefit-risk assessment can be used to give a clearer picture of quality profiles of food systems and their optimisation via positive balancing of the benefit-risk ratio for suitable nutrition.

Building on existing information related to the benefits and risks associated with changes known to occur during such heat treatment processes, this work package focused on three different examples of heat treatment of foods. Two examples involved individual undesired process contaminants (acrylamide and benzo(a)pyrene) as well as health benefits or risks associated with alternative processing methods minimizing these compounds.
The work package also addressed changes occurring during the heat treatment of milk and milk products which is commonly seen as beneficial, but also leads to changes in availability of relevant components/ nutrients in this natural foodstuff.

Results

The results on the applicability of the BRAFO methodology on three series of case studies were presented and discussed at a second workshop held in October 2009, in order to adapt the methodology according to the findings of the case studies.

Consensus of the final framework

Following this workshop, the BRAFO Consensus work package started its work. The aim of this group was to knit together the work performed by the different expert groups. It established the extent to which the BRAFO methodology applied to the three case studies is broadly applicable across various benefit/risk categories, based on the experience obtained from the case studies. Priority is given to the harmonisation of the approaches identified by applying the framework to the specific case studies.

This group finalised a paper addressing a number of outstanding issues related to benefit risk assessment of foods, such as exposure assessment, level of evidence, which biomarkers to use and when, how to deal with animal data or uncertainty factors, particularly when using QALY or DALY methodology, and finally how to extrapolate data to different populations.

The final manuscript reported on the implications of the experience gained during the development of the BRAFO project for the further improvement of benefit-risk assessment methodology.
It was concluded that the BRAFO methodology proposed is applicable to a range of situations and that it does help in optimising resource utilisation through early identification of those benefit-risk questions where benefit clearly outweighs risk or vice versa.

BRAFO partners: pictures taken during the kick-off meeting on February 2008: from left to right Dr. Jeljer Hoekstra, Dr. Alessandro Chiodini, Dr. Detlef Müller, Dr. Stéphane Vidry, Dr. Katrin Schütte, Mr. Bernard Bottex, Prof. Gerhard Rechkemmer, Dr. Nico van Belzen, Prof. Alan Boobis. (Inserted picture: Prof. Hans Verhagen).

Publications

The results of the work of the experts which included the detailed BRAFO methodology and its application to a series of case studies were published in *Food and Chemical Toxicology*, which includes the following manuscripts:

- BRAFO tiered approach for benefit-risk assessment of foods. Hoekstra J, Hart A, Boobis A, Claupein E, Cockburn A, Hunt A, Knudsen I, Richardson D, Schilter B, Schütte K, Torgerson PR, Verhagen H, Watzl B, Chiodini A. *Food Chem Toxicol*. 2012 Nov; 50 Suppl 4:S684-98.
- Application of the BRAFO tiered approach for benefit-risk assessment to case studies on natural foods. Watzl B, Gelencsér E, Hoekstra J, Kulling S, Lydeking-Olsen E, Rowland I, Schilter B, van Klaveren J, Chiodini A. *Food Chem Toxicol*. 2012 Nov; 50 Suppl 4:S699-709.
- Application of the BRAFO tiered approach for benefit-risk assessment to case studies on dietary interventions. Verhagen H, Andersen R, Antoine JM, Finglas P, Hoekstra J, Kardinaal A, Nordmann H, Pekcan G, Pentieva K, Sanders TA, van den Berg H, van Kranen H, Chiodini A. *Food Chem Toxicol*. 2012 Nov; 50 Suppl 4:S710-23.
- Application of the BRAFO tiered approach for benefit-risk assessment to case studies on heat processing contaminants'. Schütte K, Boeing H, Hart A, Heeschen W, Reimerdes EH, Santare D, Skog K, Chiodini A. *Food Chem Toxicol*. 2012 Nov; 50 Suppl 4:S724-35.
- Critical appraisal of the assessment of benefits and risks for foods, 'BRAFO Consensus Working Group'. Boobis A, Chiodini A, Hoekstra J, Lagiou P, Przyrembel H, Schlatter J, Schütte K, Verhagen H, Watzl B. *Food Chem Toxicol*. 2012 Nov 2

To download the BRAFO publications click here or visit www.ilsi.org/Europe/Pages/BRAFO.aspx

Partners

The International Life Sciences Institute is a non-profit, worldwide foundation established in 1978 to advance the understanding of scientific issues relating to nutrition, food safety, toxicology, risk assessment, and the environment. By bringing together scientists from academia, government, industry, and the public sector, ILSI seeks a balanced approach to solving problems of common concern for the well-being of the general public. ILSI Europe, the European branch of ILSI was established in 1986 to identify and evaluate scientific issues related to the above topics through symposia, workshops, expert groups, and resulting publications. The aim is to advance the understanding and resolution of scientific issues in these areas. ILSI Europe focuses on the specific needs defined by the Institute's European partners.

Dr. Stéphane Vidry and
Dr. Alessandro Chiodini

europe.ilsi.org/

The Max Rubner-Institut is the Research Institute of Nutrition and Food of the German Federal Ministry of Food, Agriculture and Consumer Protection. Its research focus is health and consumer protection in the food sector. Important research fields are the determination and nutritional assessment of health relevant food constituents, the investigation of careful and resource-preserving procedures of processing, the quality assurance of plant and animal food as well as the investigation of the motivation of nutritional behaviour, and the improvement of nutrition information.

Prof. Bernhard Watzl.

www.mri.bund.de

The National Institute for Public Health and the Environment (RIVM) is a recognised leading centre of expertise in the fields of health, nutrition and environmental protection. RIVM works mainly for the Dutch government. RIVM also shares its knowledge with governments and supranational bodies around the world. The results of research, monitoring, modelling and risk assessment are used to underpin policy on public health, food, safety and the environment. RIVM employs over 1500 employees, many of whom work in multidisciplinary fields.

Prof. Hans Verhagen and
Dr. Jeljer Hoekstra

www.rivm.nl/en/aboutrivm/

Procter and Gamble is a worldwide operating consumer goods company. Products include a number of food brands (snacks, coffee, tea, hard candy, dietary supplements) as well as household detergents, cosmetic and personal care products, absorbent hygiene products, and pharmaceuticals.

Dr. Katrin Schütte

www.eu.pg.com/

Imperial College London is a world-renowned centre for research and teaching in medicine and science. The role of the Faculty of Medicine is to develop and advance new therapies for disease whilst helping in disease prevention. It draws upon the skills of basic scientists and clinicians with expertise in molecular biology, genetics, histopathology, toxicology, clinical investigation and risk assessment.

Prof. Alan Boobis

www3.imperial.ac.uk/

Other contributors

Work Package	*Name*	*Affiliation*	*Country*
WP2 Steering Committee	Dr. M. Knowles	Coca-Cola European Union Group	BE
	Dr. L. Fischer	UEAPME	BE
	Mr. B. Bottex – *Observer*	European Food Safety Authority	IT
	Prof. G. Rechkemmer	Max Rubner Institut	DE
	Prof. J. Schlundt	World Health Organisation	CH
WP3 Methodologies	Dr. E. Claupein	Max Rubner Institut	DE
	Dr. A. Cockburn	Visiting Professor University of Newcastle	UK
	Dr. A. Hart	Central Science Laboratory	UK
	Dr. B. Schilter	Nestlé	CH
	Dr. I. Knudsen	Ministry of Food Agriculture and Fisheries	DK
	Dr. D. Richardson	DPR Nutrition	UK
	Dr. A. Hunt	University of Bath	UK
	Dr. P. Torgenson	Ross University	KN
WP4 Natural Foods	Dr. E. Gelencsér	Central Food Research Institute	HU
	Prof. S. Külling	University of Potsdam	DE
	Mrs. E. Lydeking-Olsen	Institute for Optimum Nutrition	DK
	Prof. I. Rowland	University of Reading	UK
	Dr. B. Schilter	Nestlé	CH
	Mr. J. van Klaveren	RIKILT Institute of Food Safety	NL
WP5 Dietary Interventions	Dr. R. Andersen	Technical University of Denmark	DK
	Dr. J-M. Antoine	Danone	FR
	Mr. P. Finglas	Institute of Food Research	UK
	Dr. A. Kardinaal	Nutriton and Food Research Institute	NL
	Dr. H. Nordmann	Ajinomoto	CH
	Prof. G. Pekcan	Hacettepe University	TR
	Dr. K. Pentieva	University of Ulster	IE
	Prof. T Sanders	King's College London	UK
	Dr. H. van den Berg	Netherlands Nutrition Centre Foundation	NL
	Dr. H. van Kranen	RIVM	NL
WP6 Heat Processing	Prof. H. Boeing	German Institute of Human Nutrition	DE
	Prof. W. Heeschen	Federal Dairy Research Centre - *retired*	DE
	Dr. E. Reimerdes	German Institute of Food Technology	DE
	Dr. D. Santare	Food and Veterinary Service of Latvia	LV
	Dr. K. Skog	University of Lund	SE
WP7 Consensus	Prof. H. Przyrembel	Federal Institute for Risk Assessment – *retired*	DE
	Dr. J. Schlatter	Swiss Federal Office of Pubic Health	CH
	Dr. P. Lagiou	University of Athens Medical School	GR
WP8 Dissemination	Dr. L. Fischer	UEAPME	BE
	Ms. B. Kettlitz	CIAA	BE
	Prof. O. Renn	University of Stuttgart	DE
	Dr. A.Thiel	DSM	CH
	Mr. R. Fitzhenry	European Food Information Council	BE

Contact Information

Dr. Stéphane Vidry, Project Coordinator
Dr. Alessandro Chiodini, Scientific Project Manager

ILSI Europe
Avenue E. Mounier 83, box 6
B-1200 Brussels, Belgium
Tel: +32-2-775-9145
E-mail: Publication@ilsieurope.be

European Commission Scientific officer

Dr. Jürgen Lucas
European Commission, DG Research – Directorate E,
Food, Health & Well-being
Unit E3
E-mail: Jurgen.lucas@ec.europa.eu