ISSN 1830-4737

6

EFSA SCIENTIFIC COLLOQUIUM
SUMMARY REPORT

RISK-BENEFIT ANALYSIS OF FOODS

METHODS AND APPROACHES

13-14 July 2006 - Parma, Italy


efsa
European Food Safety Authority

EFSA SCIENTIFIC COLLOQUIUM
SUMMARY REPORT

6

RISK-BENEFIT ANALYSIS OF FOODS

METHODS AND APPROACHES

About EFSA

The European Food Safety Authority (EFSA) was established and funded by the European Community as an independent agency in 2002 following a series of food scares that caused the European public to voice concerns about food safety and the ability of regulatory authorities to fully protect consumers.

In close collaboration with national authorities and in open consultation with its stakeholders, EFSA provides objective scientific advice on all matters with a direct or indirect impact on food and feed safety, including animal health and welfare and plant protection. EFSA is also consulted on nutrition in relation to Community legislation.

EFSA's work falls into two areas: risk assessment and risk communication. In particular, EFSA's risk assessments provide risk managers (EU institutions with political accountability, *i.e.* the European Commission, European Parliament and Council) with a sound scientific basis for defining policy-driven legislative or regulatory measures required to ensure a high level of consumer protection with regards to food and feed safety.

EFSA communicates to the public in an open and transparent way on all matters within its remit.

Collection and analysis of scientific data, identification of emerging risks and scientific support to the Commission, particularly in case of a food crisis, are also part of EFSA's mandate, as laid down in the founding Regulation (EC) No 178/2002 of 28 January 2002.

For more information about EFSA, please contact:

European Food Safety Authority
Largo N. Palli 5/A
I-43100 Parma
Italy

Tel: +39 0521 036 111
Fax: +39 0521 036 110
info@efsa.europa.eu
www.efsa.europa.eu

CONTENTS

PREFACE

EFSA Science Colloquia aim to achieve a better understanding of the fundamental scientific issues related to risk assessment of food and feed and are therefore organised in a way to provide ample opportunity for an interactive exchange of expert views. To that end the Science Colloquia are sufficiently informal to allow for substantial debates if needed, however, at the same time, they are adequately structured and managed to enable participants to reach conclusions and make recommendations, as appropriate. The meeting on **"Risk-benefit analysis: methods and approaches"** was the sixth in the series of Science Colloquia.

The assessment of risk to human health of food substances or nutrients is usually conducted independently of possible health benefits. Furthermore, different scientific approaches are used to estimate health risks and health benefits of foods, food ingredients and nutrients. When a food or food substance is associated with both potential health risks and benefits, and particularly when the levels of intake associated with risk and benefit are close, there is a need to define an intake range within which the balance of risk and benefit is acceptable for risk management purposes. However there is currently no agreement on the general principles or approaches for conducting a quantitative risk-benefit analysis for food and food ingredients. One of the main challenges of such an exercise is to define a common scale of measurement for comparing the risks and the benefits.

The objectives of the colloquium were:

(i) to have an open debate on scientific approaches and methods available and tools and data needed for conducting a risk-benefit analysis of foods and food components,

(ii) to explore opportunities and limitations for defining a common scale of measurement (common currency) to quantitatively compare risks and benefits, and

(iii) to define further research needs.

We are very pleased with the lively discussions and very constructive contributions by all participants and the outcome of the meeting. Special appreciation is expressed to the Chair and Co-Chair of the Colloquium, the Chairs and Rapporteurs of the various discussion groups and to Iona Pratt and John Christian Larsen who have been so kind as to draft the summary report of the meeting.

Herman B.W.M. Koëter
Deputy Executive Director
and Director of Science

Juliane Kleiner
Senior Scientist of
Scientific Expert Services

I. INTRODUCTION

Where a food or food substance is recognized to have the potential to exert both health risks and health benefits, it is important for risk managers to be able to weigh the risk against the benefit by performing a qualitative or quantitative risk-benefit analysis. However, there is currently no broad scientific consensus on the general principles or approaches for conducting risk-benefit analysis for food and food ingredients, and the assessment of risk to human health of food substances or nutrients is usually conducted independently of possible health benefits.

The human health risk assessment of food constituents is an internationally agreed and well-established process, being an integral part of the risk analysis process, which also includes risk management and risk communication. These three elements are separate tasks, performed by different players, but are part of an interactive and iterative process.

The **risk assessment** of chemicals in food is a purely scientific process that requires expertise in toxicology, nutrition and exposure assessment. It contains the following steps:

- The *hazard identification* describes the adverse effects of the substance. Human data are seldom available (e.g. from human observational studies or occupational studies) and the risk assessor has to rely on results from toxicological studies in experimental animals and *in vitro* studies.

- The *hazard characterization* describes and evaluates dose-response relationships for the most sensitive adverse health effects reported in the available studies. In cases where the compound exerts toxicity by a mechanism that has a threshold, the hazard characterization often results in the establishment of an acceptable daily intake (ADI) or tolerable daily intake (TDI).

- The third step is the *exposure assessment*. Here, the intake of the compound from food is estimated. The estimates should embrace both average, medium, and maximum intake figures from regular food, special foods, and all foods (regular and special foods) and should concern the whole population, segments of the population, and individuals.

- Finally, the *risk characterization* combines the hazard characterization and the exposure assessment and evaluates the qualitative and quantitative probability for a health risk in a given population as well as the seriousness of any health risk.

The **risk management** includes an identification of the food safety problem, consideration of its magnitude and seriousness, and consequently how to handle it. In this process, the risk manager may include cost-benefit considerations before deciding how to manage the case (ban the compound, introduce limitations, provide specific dietary advice or accept the status quo). Finally, the risk analysis should include a clear and interactive **risk communication** with consumers, industry, and other stakeholders.

No such internationally agreed scientific approach is available for health benefit assessments of foods, food ingredients and nutrients. Attempts to derive criteria for the scientific substantiation of health claims on foods and food constituents have been undertaken, for instance in the European Commission Concerted Action Project "Passclaim". These criteria emphasize the need for direct evidence of benefit to humans (based on human data, primarily from intervention studies) in circumstances consistent with the likely use of the food, and recognize the usefulness of markers (of proven validity) of intermediate effects when ideal endpoints are not accessible to measurement. Thus, different scientific methods and approaches may be used to estimate health risks and health benefits.

In order to have an open scientific debate on the methods and approaches for risk-benefit analysis of foods, EFSA organized its sixth Scientific Colloquium on 13-14 July 2006 in Tabiano, Italy (the programme is given in Annex 1). About 100 participants (listed in Annex 2) representing the scientific community, risk-benefit managers, risk-benefit assessors, the food industry and EFSA staff participated in an active debate. After a number of introductory presentations (Annex 3) to introduce current approaches for comparing human health risks and human health benefits of foods and food ingredients, the participants were split up into discussion groups, each addressing different specific issues related to methods and approaches for the risk-benefit analysis.

The discussion groups focused on methods and data needed for risk assessment and benefit assessment, in order to allow a quantitative comparison of the risks and benefits and to explore whether it is possible to develop a common scale of measurement for risk and benefit. Further points of discussion included factors that need to be considered in a risk-benefit analysis, and the borderline between risk (-benefit) assessment and risk management. Subsequently, the outcome of the debate from each group (Annex 4) was presented and discussed in plenary.

There were four discussion groups (DGs). They were asked to answer a number of (interlinked) questions in relation to three different risk-benefit analysis scenarios. DG 1 and 2 both discussed methods and approaches in relation to *nutrient content of food versus toxic contaminants/constituents*, DG 3 discussed *risk and benefit analysis of food fortification and "functional foods",* and DG 4 discussed *food preservation versus microbial hazards.*

The specific questions asked were:

1. What human health risks and human health benefits should be considered?

2. What human health risks and human health benefits can be quantified?

3. What tools/data do we currently have to quantify the human health risks and human health benefits?

4. What tools/data would be needed to quantify the human health risks and human health benefits?

5. What type of risk-benefit analysis is needed? (systematic qualitative assessment, semi-quantitative assessment, fully quantitative assessment)

6. Do we need risk-benefit analysis for different population groups?

7. When is it useful to carry out a risk-benefit analysis?

8. What could be a common scale of measurement to compare human health risks and benefits?

9. Where is the borderline between risk-benefit assessment and risk management?

Dr. Sue Barlow *(Great Britain)* was the overall chairman and Professor Vittorio Silano *(Ministry of Health, Italy)* acted as co-chair. Dr. Iona Pratt *(Food and Safety Authority of Ireland)* and Dr. John Christian Larsen *(Danish Institute of Food and Veterinary Research)* volunteered to be the overall rapporteurs. Dr. Ada Knaap *(RIVM, the Netherlands)*, Dr. Josef Schlatter *(Swiss Federal office of Public Health)*, Dr. Pagona Lagiou *(University of Athens Medical School, Greece)*, Professor Albert Flynn *(University College of Cork, Ireland)* and Professor Bevan Moseley *(Great Britain)* offered to be discussion group chairs. Professor Hildegard Przyrembel *(Federal*

Institute for Risk Assessment, Germany), Dr. Hans Verhagen *(RIVM, the Netherlands)*, Professor Alan Boobis *(Imperial College London, Great Britain)* and Dr. Angelika Tritscher *(WHO, Geneva, Switzerland)* were the corresponding discussion group rapporteurs.

II. SUMMARY OF THE DISCUSSIONS

The introductory presentations, the Discussion Groups and the Plenary addressed several generic issues related to risk-benefit analysis. In particular there was a general consensus that a risk-benefit analysis should mirror the paradigm already well established for risk analysis, consisting of a risk-benefit assessment part, a risk-benefit management part, and a risk-benefit communication part. Consequently, the benefit assessment part of the risk-benefit assessment should include *benefit identification, benefit characterisation* (dose-response assessment), *exposure assessment*, and *(probability for) benefit characterisation*. In addition, the risk-benefit analysis should contain a means, quantitative if possible, to compare/weigh the potential risk against the potential benefit *(a risk-benefit comparison).*

The decision to initiate a risk-benefit analysis should be made on a case-by-case basis and, given the resources required to carry out such an analysis, should only be undertaken when clearly justified. The meeting stressed that problem formulation ("why is the risk-benefit analysis being done, why do we need it?") is pivotal, and that the question asked by the risk-benefit manager to the risk-benefit assessor should be clearly understandable. For example, it should be made clear whether the health risk-benefit assessment is related to acute, short-term or long-term exposure, and whether only certain population groups, e.g. vulnerable groups, should be considered. For these reasons each risk-benefit analysis needs a narrative up-front to describe precisely both the risk(s) and the benefit(s) to be assessed and to formulate clearly the task, its scope and its intention, in order to ensure transparency.

It was also emphasized that in order to provide confidence in the outcome of a risk-benefit analysis, the assumptions made for the assessment and analysis as well as the uncertainties in the outcome should be made very clear. The meeting considered that, provided the above issues were taken into account, risk-benefit analysis could improve communication of risk to the consumer. There was however some debate about whether the term "risk-benefit analysis" was the appropriate terminology, because the process involves the weighing of the likelihood and **severity** of a hazard against the likelihood and **magnitude** of a benefit, and unless "benefit" includes considerations of probability as does "risk", terminology such as hazard-benefit analysis or risk-chance [for benefit] analysis for benefit may be more appropriate.

A summary of the conclusions of the discussion groups on the specific questions presented for discussion follows. Participants considered that the questions were interlinked, in particular Question 1 and 2, and the discussions in the groups broadly addressed both of these questions together.

1. What human health risks and human health benefits should be considered?

2. What human health risks and human health benefits can be quantified?

As already mentioned above, all groups agreed that problem formulation is pivotal in deciding which human health risks and human health benefits should be considered. A definition of risk can be found in Regulation (EC) No 178/2002:

"Risk assessment means a scientifically based process consisting of four steps: hazard identification, hazard characterisation, exposure assessment and risk characterisation".

Risk also includes nutritional risk, resulting from both deficient and excessive intake. As regards a definition of benefit, it was proposed to either convert the definition of risk into positive wording or to include any identifiable potential positive effect in connection with food. This would also include reduction of risk.

One reason to initiate a risk-benefit assessment is to help policy makers in their decisions. As an example, regulatory measures taken solely from a risk point of view could restrict the availability of a given food, whereas the health consequences of not eating that food might be more serious than the risk. Another reason would be to inform consumer choices. Consumers need a certain level of nutrients to reach the recommended daily intake (RDI) but in so doing, by choosing a particular food, they should not exceed the tolerable daily/weekly intake (TDI/TWI) of a contaminant in that food. Therefore, consumers need indications to select appropriate foods within a category (e.g. fruit, fish, meat, eggs) without being confused by conflicting messages about nutritious food versus hazards or risk from consuming the same food.

Ideally both acute, short-term, and long-term human health risks and benefits should be addressed, but it was realised that effects having long latencies, either adverse or beneficial, might be difficult to pick up. It was also emphasised that there would only be a few cases where the quality of the existing databases were sufficiently adequate to permit a quantitative risk-benefit assessment. Therefore in most cases a narrative, qualitative, risk-benefit assessment is likely to be the starting point for the risk-benefit assessor (and manager).

Health benefit assessments can be undertaken at different compositional levels of the diet and dietary constituents: the diet as a whole (assessed in a holistic way as in the Dutch report "Our food, our health; healthy food in the Netherlands"; see Annex 3), or more specifically a single food (e.g. fish (xenobiotics versus nutrients), as assessed in the Norwegian study on fish and seafood consumption in Norway (see Annex 3) or the UK SACN report on "Advice on fish consumption: benefits & risks"), or a single component, functional food, micronutrient, or supplement.

The two groups discussing *risk-benefit assessment of nutrient content of food versus toxic contaminants/ constituents* concluded that the human health risks and benefits that should be considered for qualitative risk-benefit assessment and which could eventually be quantified were:

- Those that can be clearly identified.
- Those amenable to observational studies in humans, intervention studies in humans, and animal experiments. In particular the human studies need validated markers of exposure and effect.
- Those for which data of good quality are available. Such data should preferably be obtained from human interventional and observational studies; when animal data are used their relevance for humans needs to be considered.
- Those for which causality with food or food components exist.
- Those for which reliable exposure assessment is possible.
- Those with a magnitude of effect that permit a dose-response assessment.
- Those which are manifest in the same population group (e.g. fish contaminated with methylmercury and negative versus positive developmental effects in infants/children) as well as those manifest in different population groups (e.g. folic acid to prevent neural tube defects in neonates versus masking of pernicious anaemia in the elderly)

The assessment needs participation of both toxicologists (risk) and nutritionists (health benefits), but the discussion groups realised that especially the health benefit assessment can be difficult because of the uncertainties in the relationships. Here it was suggested to use results from substantiation data for health claims.

The discussion group considering *risk and benefit analysis of food fortification and "functional foods"* used folate as a case study to exemplify the considerations (other useful cases could have been phytosterols, long-chain omega-3-fatty acids, iodine, iron, vitamin D, zinc, or calcium). The human health benefits of sufficient and adequate folate/folic acid intake by pregnant women are prevention of neural tube defects (NTD) in their newborns and prevention of megaloblastic anaemia in subjects with low folate status. There might also be possible cardiovascular benefits, albeit that recent studies do not support this, and a possible reduction of cancer risk in some groups. The potential risks from high intake of folic acid are masking of pernicious anaemia in elderly subjects with vitamin B12 deficiency, interactions with anti-folate drugs, and possible increase in risk for some cancers. This example illustrates that risks and benefits can be specific to particular groups in the population and that the benefits may not apply to some of the groups potentially at risk; therefore separate analyses are needed for different sub-groups. Which effects should be considered will depend on the existence and quality of data, i.e. the strength of evidence of risk and/or benefit.

This group considered that the human health risk and benefits that should be assessed were those effects for which there is evidence for causality, obtained from human observational studies, randomised controlled trials (RCT), or toxicological studies. The weight/strength of evidence for the effects reported in these studies should be carefully evaluated. In this respect mechanistic studies could add to the confidence in the results. As regards potential risks from food fortification and functional foods, the available human database will usually be poor and the assessment may have to rely on toxicological data from experimental animals. Here dose-response data and the shape of the dose-response curve are invaluable for the quantitative assessment of both risk and benefit, providing information on the optimum intake range that would minimise risk and maximise benefit, as demonstrated in Figure 1 below (presented by Professor Renwick in an introductory presentation, see also Annex 3).

The traditional approaches

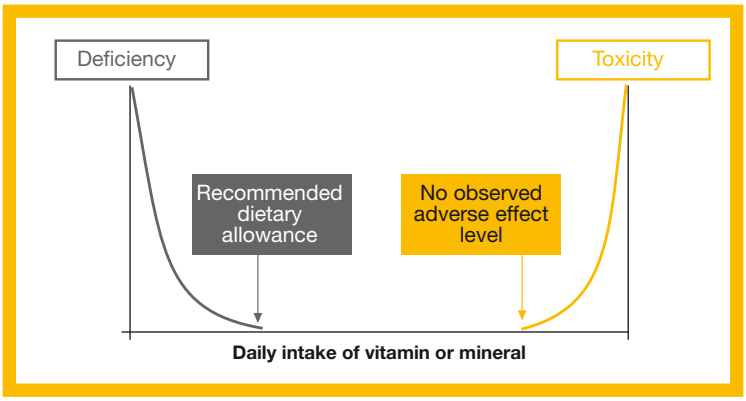


Fig: 1: Traditional approaches to determine the recommended dietary allowances for micronutrients, above which there is a low risk of deficiency, and safe upper levels below which there is a negligible risk of toxicity.

The group noted that even for the well-recognised benefit of folate supplementation (prevention of NTD) the dose-response data are not ideal. Therefore, most benefits and risks can only be estimated, and this will require a number of assumptions, resulting in considerable uncertainty. One particular problem is the low sensitivity of human studies for the estimation of many risks and benefits (because of differences in background, latency, and at risk populations). Therefore, validated biomarkers for earlier/more sensitive detection of relevant endpoints are clearly needed.

The group that discussed *food preservation versus microbial hazards* considered that the main issue was to evaluate the benefits of food preservation in reducing the risk of food-borne microbiological illness, or, expressed in another way, the benefit of a reduced risk of food-borne illness versus a much higher risk. Although assessment of acute illness (outbreaks) was most often in focus there was a need to also consider potential long-term health effects. An example of this was Campylobacter infection that starts with acute infection followed in a small percentage of cases by chronic illness (Guillain Barré syndrome, an acute neuromuscular paralytic syndrome). Food preservation also offers other, indirect health-related benefits, such as longer shelf life and wider distribution (although this may also potentially mean a risk of wider spread of disease). Another benefit is that food preservation ensures that regulators

and consumers have confidence in the safety of the food and can make choices based on nutrition without having to worry about micro-organisms. However, certain preservation methods can also have negative effects on nutrition, and there may be a risk of formation of chemical residues with potentially adverse effects from use of certain preservatives (e.g. the possible formation of benzene in soft drinks from reaction between benzoates and ascorbic acid).

Examples of risk-benefit assessments that warrant consideration were:

- Minimally processed foods, such as fresh fruits and vegetables (responsible for 20-25% of food-borne outbreaks).
- Nitrite in meat products (nitrosamine formation versus preservation).
- Probiotics, which may be beneficial for parts of the population but can be a risk for other parts.
- Active chlorine used in food processing.
- Reduction of pathogenic bacteria by salt versus increase of other health risks, such as risk of cardiovascular disease, from ingestion of too much salt.
- Preservation technologies, inclusive of packaging, are generally regarded as having beneficial effects, but it is important to assess also potential risks from the process of preservation.

3. What tools/data do we currently have to quantify human health risks and human health benefits?

The groups discussing *risk-benefit assessment of nutrient content of food versus toxic contaminants/constituents* considered that the tools and types of data available to assess risk from chemicals are well established as integral parts of the risk assessment process. The groups suggested that the parallel benefit assessment steps should mirror the classical risk assessment steps. Traditionally, the hazard characterisation step can be used to establish an ADI/TDI. This in turn can be used as a tool for risk characterisation, in which the ADI/TDI is compared with an estimated exposure.

The ADI/TDI is established by using uncertainty factors and does not provide a quantitative risk assessment but rather a safety assessment: if the estimated intake does not exceed the ADI/TDI, then it can be concluded that there will be no appreciable risk to health. The equivalent tool for beneficial nutritional intake is the Recommended Daily Amount (RDA). The ADI/TDI and RDA are not appropriate for quantitative risk-benefit assessment, but may be useful for identifying whether or not an assessment is needed. An example could be the situation where a recommendation to increase the consumption of a given food (for example fish) in order to achieve a beneficial nutritional effect would lead to the TDI of a contaminant in the same food being exceeded (for example dioxins in oily fish). The groups nevertheless considered that tools might be (or currently are being) developed for better expressing quantitative health risks from exposure to xenobiotics based on animal dose-response data that can be transferred to human data. One such tool, already established, is the benchmark dose (BMD) concept, and future tools may be based on probabilistic modelling.

For the benefit assessment, human dose-response curves or data for benchmark dose fitting are mostly not available for foods and scarce for single nutrients. Exposure is a crucial tool, but detailed, reliable data on food intakes are often not available. As an example it was stressed that "fish" is not just "fish", but must be broken down to e.g. oily versus non-oily, data on intake of specific species such as salmon must be available, etc. Therefore quantitative assessments of health benefit will be resource-intensive and are still few in number. However, the available (national) data from human studies (observational monitoring or intervention data) can be used in qualitative assessments with a transparent narrative description of data gaps, uncertainties, assumptions and interpolations.

In discussing current data and tools for assessment of *risk and benefit analysis of food fortification and "functional foods"* using folate/folic acid as an example, the importance of speciation of the nutrient form was stressed: folic acid has 1 glutamic acid moiety, whereas natural folate has two or more glutamic acid moieties. Other important data necessary for a risk-benefit assessment of folate include:

- information on dose-response relationship (from observational studies, randomised controlled trials (RCT), medical records, toxicological studies),

- good data on dose (intake) and response,

- quantification of the benefit at a range of fortification levels of folate for:

  - prevention of neural tube defects (foetus/pregnant woman), and
  - elimination of folate deficiency (in the elderly), and
  - estimation of risks of masking of Vitamin B12 deficiency in the elderly.

In arriving at a quantitative risk-benefit assessment, deterministic approaches using "points of departure" (POD) such as a no-observed-adverse-effect level (NOAEL), lowest-observed adverse-effect level (LOAEL), or benchmark dose for a particular incidence of effect (BMDx), and application of uncertainty or safety factors could initially be used. The possibility of using compound-specific adjustment factors as a replacement for default uncertainty factors should also be explored.

It is of crucial importance to identify the population at risk or likely to benefit (numbers or proportion), and the discussion group noted that direct comparison of the risks with the benefits was very difficult, particularly in cases where the risks and benefits apply to different sub-populations. Although benefit in certain individuals can be defined and risk in other individuals can be defined, they are not necessarily the same individuals, and the identified risks and benefits cannot be compared directly. In this case an additional narrative is needed to compare risk and benefit in the different sub-populations, and the outcome may present the risk manager with difficult decisions. Therefore, risk-benefit assessments should be done for each population group, rather than weighing one population group against another.

In the case of *food preservation versus microbial hazards* the data and tools identified were:

- Number of outbreaks in a population can be used as a measure of increased or decreased, acute risk. However, an outbreak can have other reasons than those related to food preservation. The epidemiological link between a food and outbreak in people may be related to home-prepared foods, to retailers, or to food service.

- Background incidence of disease. This may require laboratory tests in individuals.

- Sentinel studies are very informative if done properly, but also very expensive.

- Population studies are very informative if done properly, but also very expensive.
- Incidence of outbreaks and quantification of the impact of the disease in the population (burden of disease).
- Mandatory reporting of outbreaks (International Health Regulations). When enforced this can contribute to quantification of disease incidence.
- Nutritional status (in certain population) can be quantified.
- Beneficial effects of food preservation. Determination of decrease of outbreaks by comparison with historical data (difficult).
- Days of work lost.
- Disability Adjusted Life Years (DALYs).
- Reduction in cost for drugs. Determination of a decrease in the use of medicines to treat infections will only work if its relationship to the food borne outbreak is known or confirmed.
- Cost of food-borne diseases (e.g. total health burden of salmonellosis, expressed as cost factor)

4. What tools/data would be needed to quantify the human health risks and human health benefits?

The use of Disability Adjusted Life Years (DALYs) and Quality Adjusted Life Years (QUALYs) were discussed to some extent in relation to this question, but were dealt with mainly under the heading of question 8.

The discussion groups considering *risk-benefit assessment of nutrient content of food versus toxic contaminants/constituents* considered that the data needed for quantification of the human health risks and human health benefits include reliable exposure data with known distributions, suitable for eventual modelling. This in turn requires comprehensive intake data and actual (measured) food composition data.

Derivation of reliable exposure data requires consideration of food variability, matrix effects on bioavailability, and interaction between components. Proof of causality between food, food components and adverse or positive effects need to be established. The discussion groups considered that tools for classification of hazards and of benefits would need to be developed, together with tools for comparison and prioritisation of hazards and benefits, and that both tools and data should simultaneously be available, together with a common scale of measurement for risk and benefit.

The groups noted that qualitative tools are available, but quantitative assessment is confronted with many uncertainties; therefore, the more data that become available the more quantitative the risk-benefit assessment that can be performed.

The discussion group working on *risk and benefit analysis of food fortification and "functional foods"* also emphasised the importance of good quality exposure assessment, again requiring better intake data and validated, robust biomarkers of exposure. Other tools/data needed were:

- Data in relevant sub-populations for risks and for benefits.
- Dose-response data of good quality.
- Effect measures in humans on risks and benefits, including validated, robust biomarkers of effect. In this context, the importance of animal studies in biomarker development was noted, especially for long term effect outcomes.
- Probabilistic approaches to risk-benefit assessment, both on exposure and effect measures.
- Relevant animal data; in particular mechanistic studies, studies enabling comparison of pharmacokinetics and pharmacodynamics across species (animal/man), and studies to characterise dose-response relationships.

This group, like the groups dealing with *risk-benefit assessment of nutrient content of food versus toxic contaminants/constituents* considered it would be essential to have some means (a common scale) to directly compare risks and benefits.

In relation to *food preservation versus microbial hazards* new tools/data mentioned were epidemiological studies on food preservation and on microorganisms. There are almost no epidemiological studies on the effects of chemical residues (preservatives),

and such studies are only available for very few micro-organisms. The group stressed that tools/data were needed to move from qualitative to quantitative microbiological risk assessment, and there are currently many data gaps.

5. What type of risk-benefit analysis is needed? (Systematic qualitative assessment, semi-quantitative assessment, fully quantitative assessment)

It was emphasised that risk-benefit analysis should not be performed as a routine procedure but only applied in those cases where an impact on public health outcomes can be expected. It was generally agreed by all four discussion groups that all of the types of risk-benefit analysis mentioned (systematic qualitative assessment, semi-quantitative assessment, fully quantitative assessment) should be considered. What was needed or feasible would depend on the available data and the requirements of the risk-benefit manager. This could be to give dietary advice to the population as a whole or to sub-populations and/or to regulate particular foods, food ingredients, and contaminants.

The problem formulation should be clear and the risk-benefit manager should consider the potential impact of the possible outcomes. Risk-benefit analysis of breast-feeding was seen as a good example to objectively weigh risks against benefits, however, it entails consideration not only of risks and benefits but also other aspects such as socioeconomic considerations in the context of conditions in specific countries/regions. Only when these questions and the management considerations are in place can a decision be reached on the type of risk-benefit assessment needed, e.g. a full quantitative assessment versus a more rapidly available answer from a qualitative assessment.

However, the decision on which type of risk-benefit analysis should be performed may largely be determined by the availability of data. Although quantitative assessments are to be preferred, the available data are in most cases scarce. It was generally advised to use a tiered approach, and start with categorisation. For qualitative and semi-quantitative analysis the detailed description of the process and of all uncertainties, assumptions and deductions is crucial. If a qualitative analysis indicates that the risk clearly outweighs the benefit or vice versa, this may be sufficient for the risk manager to make decisions without recourse to quantitative analysis.

6. Do we need risk-benefit analysis for different population groups?

There was widespread agreement that risk-benefit analyses were needed for different population groups. Even if the final output is on a total population basis (e.g. when considering mandatory fortification) it will be necessary to evaluate risks and benefits in the appropriate population groups. Such information may be of value to the risk manager both for policy making and for communication, and such information will be needed for a combined risk-benefit assessment. In addition to the young, old, pregnant, and immunocompromised (YOPI), relevant genetic polymorphisms in a population could also be considered, as this can determine the need for data and the influence the assessment. In addition, the potential different life stages for the manifestation of risks and benefits should be considered. Thus, a benefit for one age group can be a risk in another age group, e.g. prevention of neural tube defects by folic acid versus masking vitamin B12 deficiency.

7. When is it useful to carry out a risk-benefit analysis?

The meeting considered that a risk-benefit analysis would be useful:

- When there is, or likely to be, a narrow margin of safety.
- When the result of the risk-benefit analysis is likely to have a desirable impact on public health.
- When nutritional and dietary advice to the population is revised, in order to assess prospectively the possible positive or negative consequences on dietary behaviour, nutritional status and public health.
- When the risk manager needs such analysis to help in making decisions.
- Before implementing new measures.
- When the risk or the benefit is thought to be very large (to check this assumption and to determine residual benefit or risk).

- When dietary consumption changes significantly (qualitatively or quantitatively) as a consequence of fortification, introduction of functional foods, etc.

- Prior to launch or post-launch, with different objectives.

- If new knowledge emerges that would trigger the need for risk-benefit analysis.

Although no groups of compounds or foods were excluded *a-priori*, there was agreement that a risk-benefit analysis would be a waste of resources if the qualitative assessment of the benefit by far outweighs the risk (e.g. pasteurization). Risk-benefit assessments were generally not needed for health reasons for regulated substances (e.g. authorised food additives) although it could be worthwhile in certain situations. One such example could be addition of nitrite/nitrate to certain cured foods in order to protect against growth of *Clostridium botulinum*. However, this may on the other hand lead to the formation N-nitroso compounds, which are potent carcinogenic agents. In addition, it was acknowledged that the communication of risk-benefit analysis was a demanding task because of the need to avoid confusing messages and to maintain the trust of consumers in the safety of food in general.

Finally it was noted that risk-benefit analyses for economic and technology reasons (i.e. in the food production chain) is outside the scope of EFSA.

8. What could be a common scale of measurement to compare human health risks and benefits?

It was generally agreed that a common scale ("common currency") for risk and benefit would facilitate the communication of the results of risk-benefit analysis. However, because this scale is likely to differ for different analyses, no generally applicable measurement scale is likely to be developed. One discussion group questioned the need for a common metric as the results from the risk-benefit analysis would depend on the questions being asked. Therefore a narrative is needed for both qualitative and quantitative assessments.

The aim of the risk-benefit analysis process is not a judgement on acceptability or safety. But the assessments of both risk and benefit ideally should be performed under the same criteria for weighing the evidence and identifying the uncertainties. The presentation of the results of the risk-benefit assessment must fit the

predefined purpose of the request and make clear where the certainties and uncertainties are in order to compare the relative confidence on the benefits with the risks. This comparison of the results can be performed by the assessor, the manager, or even the consumer.

The meeting considered that when society-wide considerations are needed the risk-benefit assessment should be performed with a common scale. Where possible, these scales should be population based (aggregate measures) health-related quality of life (QoL) indices, and experience will be needed in order to guide the choice of which scale to use.

The following possible common scale measures were mentioned:

- Incidences.
- Disability Adjusted Life Years (DALYs).
- Quality Adjusted Life Years (QUALYs). Like DALYs these are quantitative, but are still based on a number of assumptions, and are more difficult to quantify than DALYs.
- Days of work lost.
- Costs in money. Requires equal cost structures across countries/world and is difficult to communicate.

DALYs are applied at the societal, rather than the individual, level. It is possible to apply DALYs in risk-benefit assessment, but appropriate data may seldom be available. The advantages of using DALYs are that they represent an established procedure to compare risks of different nature (e.g. acute microbiological versus chronic chemical risk), and have a time-scale (includes whole life-span) and may provide guidance to the risk manager on how to prioritize the direction of targeted intervention measures. In this context a narrative is needed on which sub-populations are affected by the risks and benefits, especially if different. The difficulties in using DALYs are that clear messages are needed so that the numbers generated are not taken out of context. For instance, when the long-term perspective is evaluated one should not just consider individual "numbers" and forget the whole picture. It also seems difficult to include preventive aspects (such as effects of preservation) or absence of risk rather than benefit. Finally, the

difficulty in expressing results from toxicological studies in experimental animals as DALYs needs to be overcome.

Options others than to combine risk and benefit in a common scale were suggested, e.g. (1) to give a detailed risk-benefit description and leave any decisions to the risk-benefit manager, or (2) to express the assessment results as changes in risk or benefit (increments) and calculate the risk + benefit difference.

It was agreed that more research and experience with different approaches are needed.

9. Where is the borderline between risk-benefit analysis and risk management ?

The meeting considered that the borderline is the delivery by the group of assessors to the risk manager of the output of the risk-benefit assessment, which should include a clear narrative. The borderline is not fixed and can shift with the nature of the output. Currently, in most foreseeable assessments the risk-benefit manager gets two answers, a risk answer and a benefit answer, and it is the responsibility of the manager to weigh one against the other. However, science tools are becoming available (such as DALYs and others) to allow the assessor to quantify risks and benefits and combine them in one assessment, moving the task of risk-benefit comparison from the risk-benefit managers to the risk-benefit assessors.

It was stressed many times that continuous iterative interaction between the assessors and managers, with possible inputs from stakeholders, is essential throughout the whole process, but the independence of the risk-benefit assessor from the risk management process needs to be ensured. There should be a clear problem formulation and the risk-benefit assessment should address the needs of the risk manager. Formulation of the task determines the form of the output; communication between assessors and managers will help in a specific risk-benefit assessment, for instance in choosing a common measurement scale, if needed.

If QUALYs and DALYs are to be used in future risk-benefit assessments, consideration needs to be given as to whether they are applicable and acceptable

across the EU. This requires, initially, harmonisation of the derivation of the DALYs and QUALYs, and quality assurance of their use. This may require the involvement of other expertise than just that of health science assessors, in the interface between assessment and management.

In every risk-benefit assessment there is a need for an accompanying narrative, which also includes evaluations of uncertainties. Risk-benefit assessments can be extended to include presentation of alternative outputs based on sensitivity analysis. It should identify data deficiencies and their consequences for the risk-benefit analysis. It should avoid conclusions that encroach into risk management.

III. FINAL DISCUSSION

The final discussion showed that there was a broad agreement across the participants on the general methods and approaches to be applied for risk-benefit assessment and analysis, in particular that the risk-benefit analysis should mirror the current risk analysis paradigm and consist of a risk-benefit assessment, a risk-benefit management, and a risk-benefit communication parts.

There was also consensus that the decision to initiate a risk-benefit analysis should be made on a case-by-case basis and that problem formulation ("why is the risk-benefit analysis being done, why do we need it?") is pivotal. The question asked by the risk-benefit manager to the risk-benefit assessor should be clearly understandable, for example it should be made clear whether the health risk-benefit assessment is related to acute, short-term or long-term exposure, and whether only certain population groups, e.g. vulnerable groups, should be considered.

The meeting concluded that although quantitative risk-benefit assessments are preferable, the data available to undertake a quantitative risk-benefit assessment may be too scarce. A tiered approach should then be used, starting with a qualitative analysis. If this indicates that the risk clearly outweighs the benefit or vice versa, this may be sufficient for the risk manager to make decisions. For these reasons each risk-benefit analysis needs a narrative up-front to describe precisely both the risk and the benefit to be assessed and to formulate clearly the task, its scope and its intention, in order to ensure transparency.

The meeting considered that when society-wide considerations are needed the risk-benefit assessment should be performed with common scales. These scales should ideally be population based (aggregate measures) health-related quality of life (QoL) indices such as Disability Adjusted Life Years (DALYs) or Quality Adjusted Life Years (QUALYs), although more research was needed in the "common scale" area, including exploration of how to best make use of animal data for this purpose.

Some specific points were addressed during the final discussion:

1) How to deal with genetic variability?

In principle, risk-benefit assessment should be done for each different population group; in particular all known risk groups should be assessed. However, it was stressed that weighing of one population group against another should be avoided,

although in some cases risk managers have to do precisely that. Genetic variability could be managed, for instance, by assuming that all are as sensitive as the most sensitive group. However, the most extreme variations in the human population should not normally be considered, because what would be a nutritional benefit in such a group could constitute an appreciable risk for other, "normal", people. For example, iron intakes low enough to protect heterozygotes for haemochromatosis would impose severe anaemia on a large majority of the population, while phenylalanine intakes low enough to protect those with phenylketonuria could impose deficiency on those members of the population whose minimum phenylalanine requirement is higher.

2) Can animal data be used for e.g. DALYs?

It was agreed that animal data could not be directly used, as DALYs are based on human data. However, hazard characterisation is normally based on animal data, and the animal dose-response data can be converted into a human equivalent by scaling, using for instance physiologically based pharmacokinetic (PBPK) modelling or allometric scaling (i.e. body weight raised to the 0.75 power).

The procedure would be to select an adverse effect in animals that was considered relevant for humans, then to use an intake (dose) associated with that effect in the animals, such as a BMD. The BMD can be scaled by using PBPK modelling as a starting point to estimate the equivalent human dose to the BMD at which the adverse effect was observed in animals. DALYs can then be applied following correction for animal/human variations in toxicodynamics. A range of different effects will need to be modelled because the dose-response curve will be different in each case.

Guidance/framework document on risk-benefit assessment?

It was agreed that the "state-of-the-art" of risk-benefit assessment had advanced beyond the brainstorming stage, and it was now time to advance to "learning by doing". The meeting noted that several research projects on risk-benefit assessment have recently been funded by DG Research (the upcoming ILSI Europe project BRAFO, and the EU projects Beneris and Qalibra that will study risk-benefit of fish consumption). Several attendees suggested that a guidance/guideline document

should be developed by e.g. EFSA with respect to methodology, approaches, tools and potential pitfalls in the risk-benefit assessment. The meeting considered that it was premature to formulate guidelines on good risk-benefit analysis practice, but there was agreement that some preliminary guidance could be derived in line with the conclusions from this meeting, including a glossary of common risk-benefit language. This could be helpful for people who want to perform risk-benefit assessments.

ANNEXES

ANNEXES

Annex 1: Programme of the Colloquium

Annex 2: Participants at the Colloquium

Annex 3: Presentations made at the Colloquium

Annex 4: Slides of Discussion Groups

Annex 1: Programme of the EFSA Colloquium

EFSA Scientific Colloquium on Risk-Benefit Analysis of Foods:
Methods and Approaches
13-14 July 2006, Tabiano (Parma), Italy

Programme

Chair: Sue Barlow
Co-chair: Vittorio Silano
Rapporteurs: John Christian Larsen, Iona Pratt

Thursday 13 July 2006

12.00-13.00	COLD BUFFET LUNCH	
13.00-13.30	Briefing meeting with overall chairs and discussion group chairs and rapporteurs	
13.30-16.30	**Session 1: INTRODUCTORY PLENARY SESSION**	
13.30-13.45	Welcome and Introduction to EFSA	Herman Koëter, Sue Barlow
13.45-14.10	Opportunities and limitations of current approaches used in benefit assessment	Albert Flynn
14.10-14.20	Discussion	
14.20-14.40	Opportunities and limitations of current approaches used in risk assessment	Diane Benford
14.40-14.50	Discussion	
14.50-15.10	Risk-benefit analysis of micronutrients	Andrew Renwick
15.10-15.20	Discussion	
15.20-15.40	Analysis of health and safety aspects of diet and food in the Netherlands	Rolaf Van Leeuwen
15.40-15.50	Discussion	
15.50-16.10	Risks and benefits of fish consumption in Norway	Jan Alexander
16.10-16.20	Discussion	
16.20-16.30	Introduction to discussion groups	Juliane Kleiner
16.30-17.00	COFFEE/TEA BREAK	

17.00-19.00 **Session 2:**
DISCUSSION GROUPS (DG)

DG 1	Nutrient content of food Vs toxic contaminants/ constituents	Chair: Rapporteur:	Ada Knaap Hildegard Przyrembel
DG 2	Nutrient content of food Vs toxic contaminants/ constituents	Chair: Rapporteur:	Josef Schlatter Hans Verhagen
DG 3	Risk and benefit analysis of food fortification and "functional foods"	Chair: Rapporteur:	Pagona Lagiou/ Albert Flynn Alan Boobis
DG 4	Food preservation Vs microbial hazards	Chair: Rapporteur:	Bevan Moseley Angelika Tritscher

20.00 DINNER

Friday 14 July 2006

08.30-10.00	**Session 3:** **REPORT BACK OF DISCUSSION GROUPS OUTCOME**	
08.30-08.45	Report back from DG 1	Hildegard Przyrembel
08.45-09.00	Discussion	
09.00-09.15	Report back from DG 2	Hans Verhagen
09.15-09.30	Discussion	
09.30-09.45	Report back from DG 3	Alan Boobis
09.45-10.00	Discussion	
10.00-10.15	Report back from DG 4	Angelika Tritscher
10.15-10.30	Discussion	
10.30-11.00	COFFEEE/TEA BREAK	
11.00-13.00	**Session 4:** **CONTINUATION OF DISCUSSION GROUPS**	
11.00-12.00	Discussion on opportunities and limitations to derive a common scale of measurement	
12.00-13.00	Discussion groups to prepare their conclusions and recommendations	

13.00-14.00 LUNCH

14.00-16.45	**Session 5:** **FINAL PLENARY SESSION - DISCUSSION AND CONCLUSION**	
14.00-15.45	Report back to Plenary	Hildegard Przyrembel Hans Verhagen Alan Boobis Angelika Tritscher
15.20-15.45	COFFEE/TEA BREAK	
15.45-16.45	General discussion and conclusion	
16.45	Colloquium adjourns	

Annex 2: Participants at the Colloquium

Name	Affiliation	Country	Discussion Group (DG)
Prof. Peter Aggett	University of Central Lancashire	UK	3
Mrs. Kostantia Akkelidou	Office of the Commissioner Kiprianou	CY	2
Dr. Jan Alexander	Norwegian Institute of Public Health	NO	1
Dr. Ebba Barany	European Commission	BE	1
Dr. Susan Barlow		UK	2
Mr. Manuel Barreto Dias	National Food and Economy Safety Authority (ASAE)	PT	4
Dr. Diane Benford	Food Standards Agency	UK	1
Mrs. Urska Blaznik	Institute of Public Health	SLO	1
Prof. Alan Boobis	Imperial College of London	UK	3
Dr. Antonio Brunacci	IEE SA	LUX	4
Dr. Clark Carrington	Food and Drug Administration	US	2
Ms. Ute Ruth Charrondiere	Food and Agriculture Organization (FAO)	IT	2
Prof. John Daniel Collins	University College of Dublin	IE	4
Mr. Patrick Coppens	European Responsible Nutrition Alliance (ERNA)	BE	3
Mr. Stephen Crossley	Food Standards Australia and New Zealand	AU	1
Dr. Dario De Medici	National Health Institute (ISS)	IT	4
Dr. Koenraad Duhem	French National Interprofessional Centre of the Dairy Economy (CNIEL)	FR	1
Ms. Kirstin Færden	Scientific Committee for Food Safety	NO	2
Dr. Maurizio Ferri	Ministry of Health	IT	4
Prof. Albert Flynn	University College of Cork	IE	3
Mrs. Barbara Gallani	European Consumers' Organisation (BEUC)	BE	2

Name	Affiliation	Country	Discussion Group (DG)
Prof. Eva Gelencser	Central Food Research Institute	HU	1
Dr. Sandra Goldbohm	TNO Quality of Life	NL	3
Dr. Matthias Greiner	Federal Institute for Risk Assessment (BfR)	DE	4
Dr. Roland Grossgut	Agency for Health and Food Safety	AT	1
Dr. Anja Hallikainen	Food Safety Authority Evira	FI	1
Dr. Hanne Boskov Hansen	Veterinary and Food Administration	DA	3
Dr. John Hathcock	Council for Responsible Nutrition	US	3
Dr. Hans Peter Jensen	Institute for Food and Veterinary Research	DA	4
Dr. Ada Knaap	National Institute for Public Health and the Environment (RIVM)	NL	1
Dr. Ed Komorowski	Dairy UK	UK	4
Dr. Mariella Kuilman	DSM Nutritional Products	NL	2
Dr. Pagona Lagiou	University of Athens	GR	3
Dr. John Christian Larsen	Institute of Food and Veterinary Research	DA	2
Dr. Jean-Charles Leblanc	French Food Safety Agency (AFSSA)	FR	2
Dr. Alberto Mantovani	National Health Institute (ISS)	IT	2
Mr. Laszlo Meszaros	Food Safety Office	HU	4
Dr. Clara Montesissa	University of Padua	IT	2
Dr. Angelo Moretto	University of Milan and ICPS	IT	1
Prof. Bevan Moseley		UK	4
Prof. Jean-François Narbonne	University of Bordeaux 1	FR	2
Dr. Elsa Nielsen	Institute for Food and Veterinary Research	DA	1
Dr. Hervé Nordmann	Ajinomoto Switzerland AG	CH	3
Prof. Servé Notermans	Food Doctors	NL	4

Name	Affiliation	Country	Discussion Group (DG)
Mr. Gatis Ozolins	Food Centre of Food and Veterinary Service	LV	3
Prof. Antonello Paparella	University of Teramo	IT	4
Dr. Kierstin Petersson-Grawé	National Food Administration	SE	1
Dr. Marino Petracco	Illycaffè	IT	1
Dr. Iona Pratt	Food Safety Authority	IE	1
Prof. Hildegard Przyrembel	Federal Institute for Risk Assessment	DE	1
Prof. Andrew Renwick	University of Southampton	UK	2
Dr. Dace Santare	Food Centre of Food and Veterinary Service	LV	2
Dr. Sirpa Sarlio-Lähteenkorva	Food Safety Authority Evira	FI	3
Dr. Josef Schlatter	Federal Office of Public Health	CH	2
Dr. Derek Schrimpton	European Federation of Associations of Health Product Manufacturers	UK	3
Mrs. Isabelle Sioen	Ghent University	BE	2
Prof. Vittorio Silano	Ministry of Health	IT	1
Dr. Anca Violeta Stoicescu	Hygiene Veterinary Public Health Institute	RO	4
Dr. Teodor Stoichev	National Center of Public Health Protection	BU	1
Dr. Hans Peter Stueger	Institute of Biostatistics (AGES)	AT	4
Dr. Jan Stulc	State Veterinary and Food Administration	SL	4
Dr. Lourdes Suarez	Food Safety Agency	ES	1
Mr. Andras Szoradi	International Life Sciences Institute (ILSI)	BE	1
Dr. Angelika Tritscher	World Health Organization (WHO)	CH	4

Name	Affiliation	Country	Discussion Group (DG)
Prof. Jouko Tuomisto	National Public Health Institute (KTL)	FI	1
Dr. Jouni Tuomisto	National Public Health Institute (KTL)	FI	2
Prof. Ivar Vågsholm	National Veterinary Institute	SE	4
Mr. Antonius van Dongen	PURAC Biochem	NL	4
Dr. Jacob Van Klaveren	Institute for Food Safety (RIKILT)	NL	1
Dr. Rolaf Van Leeuwen	National Institute for Public Health and the Environment	NL	2
Ms. Elizabeth Vavasour	Health Canada	CA	3
Dr. Hans Verhagen	National Institute for Public Health and the Environment (RIVM)	NL	2
Dr. Robert Verkerk	Alliance for Natural Health	UK	3
Mr. Frans Verstraete	European Commission	BE	2
Dr. Milena Vicenova	Ministry of Agriculture	CZ	4
Ms. Sara Visentin	International Centre for Pesticides and Health Risk Prevention (ICPS)	IT	2
Dr. Christiane Vlemickx	Scientific Institute of Public Health	BE	3
Dr. Marion Wooldridge	Veterinary Laboratories Agency	UK	1
Dr. Elizabeth Yetley	National Institutes of Health	US	3
Mrs. Eva Yngvadottir	Icelandic Fisheries Laboratories	IS	2
Mr. Peter Zweipfenning	Food and Consumer Product Safety Authority (VWA)	NL	3

EFSA Staff

Mrs. Ulla Bertelsen	Panel on Contaminants in the Food Chain
Mr. Jan Bloemendal	International and Institutional Affairs
Mrs. Lucia De Luca	Team Communication
Dr. Hubert Deluyker	Scientific Experts Service
Ms. Vanessa Descy	Administrative Support
Mrs. Anne-Laure Gassin	Team Communication
Mr. Daniel Glanville	Team Communication
Dr. Leng Heng	Panel on dietetic products, nutrition and allergies
Mr. Alun Jones	Team Communication
Dr. Juliane Kleiner	Scientific Experts Service
Dr. Herman Koëter	Deputy Executive Director and Director of Science
Dr. Djien Liem	Scientific Committee
Ms. Cecilia Lloyd	Administrative Support
Mr. Neil Martinson	Team Communication
Ms. Marina Paluzzi	Administrative Support
Mrs. Valérie Rolland	Scientific Committee
Ms. Julia Rüter	Team Communication
Ms. Francesca Salvi	Administrative Support
Mrs. Irene Van Geest	Team Communication
Mrs. Katty Verhelst	Administrative Support
Dr. Didier Verloo	Scientific Experts Service

Annex 3: Presentations made at the Colloquium

COMPARING RISKS AND BENEFITS OF FOOD: COMPARING APPLES AND ORANGES OR IS THERE A COMMON DENOMINATOR?

HERMAN B.W.M. KOËTER
Deputy Executive Director and
Director of Science
EFSA

EFSA's Mission and Tasks [Reg 178/2002]

- ... provide **scientific advice** and **scientific and technical support** ... [Art. 22. 2];
- ... shall provide **scientific opinions** ... [Art. 22.6];
- ... **collect and analyse data** to allow the characterization and monitoring of risks ... [Art. 22.4];
- promote and co-ordinate the **development of uniform risk assessment methodologies** [Art. 23(b)];
- ... commission **scientific studies** ... [Art. 23(d)];
- ... undertake action to **identify emerging risks**... [Art. 23(f)].

Scientific activities (work themes)

- Providing scientific opinions, guidance and advice in response to questions;
- Assessing the risk of regulated substances and development of proposals for risk-related factors;
- Monitoring of specific animal health risk factors and diseases;
- **Development, promotion and application of new and harmonized scientific approaches and methodologies for hazard and risk assessment of food and feed.**

Investing in food science

- Harmonization of detection methodology for chemical and microbiological contaminants in food/feed;
- Improvement of current and development of new and harmonised RA methodologies and approaches (e.g., environment, animal health and welfare, quantitative/qualitative);
- Openness and transparency in process and science (with other RA bodies, national food agencies, stakeholders).

Science Colloquia (2-3 per year):

- Setting threshold levels for Dioxins and PCBs (2004);
- Qualified Presumption of Safety of micro-organisms in food and feed (2004);
- European Food Consumption Database: medium and long term strategy (2005);
- Principles of risk assessment of animal health and welfare (2005);
- Food based dietary guidelines (2006);
- Risk/benefit analysis (June 2006).
- Active participation in and monitoring of scientific projects, conferences and other scientific meetings in Member States;
- Organization of open scientific EFSA meetings, to discuss in-depth topical and sensitive issues related to EFSA's mission : EFSA Science Colloquia;
- Adequate follow-up on EFSA Scientific Colloquia (e.g. development of Guidance Documents).

EFSA SCIENTIFIC COLLOQUIUM 6

Risk-Benefit Analysis of Foods: Methods and Approaches

13-14 July 2006 - Tabiano, PR, Italy

The Colloquium is:

- an interactive event rather than only a passive listening to lectures;
- a platform for scientists to have in-depth discussions on scientific approaches and methods available and tools and data needed for conducting a risk-benefit analysis of foods and food components
- an event to explore opportunities and limitations for defining a common scale of measurement (common currency) to quantitatively compare risks and benefits, and
- an opportunity to define further research needs.

The Colloquium is not:

- an attempt to agree on the details of a preferred strategy or approach, if any
- an attempt to finalise a blue print for the work ahead of us;
- a "who is right and who is wrong" discussion.

Thank you for sharing your views with EFSA.

Thank you for being frank, open and constructive.

BENEFIT ASSESSMENT - OPPORTUNITIES AND LIMITATIONS OF CURRENT APPROACHES

Prof. Albert Flynn
University College, Cork, Ireland

Outline

Assessment of human health benefits of :

- Fortification (voluntary) of foods for ensuring nutritional adequacy
- Folic acid fortification (mandatory) of staple foods for prevention of neural tube defects (NTD)
- Phytosterol containing foods on reduction of LDL-cholesterol (and risk of CVD)
- Other health outcomes
- Conclusions

Assessing health benefits of diet

- Define health outcome
  - ▷ Nutrient balance, nutrient status indicator, disease risk marker, biochemical/clinical change
- Establish causality and dose response
- Estimate benefit for a given intake
  - ▷ Prevalence, magnitude/severity of effect

FORTIFICATION (VOLUNTARY) OF FOODS FOR ENSURING NUTRITIONAL ADEQUACY

Recommended nutrient intakes

Requirement - lowest level of continuing intake that will maintain a defined level of nutriture in an individual [for a specified criterion of adequacy]

Average requirement (AR) - daily intake that meets the requirements of 50% of a population group

RDA - the level of intake of a nutrient that is adequate to meet the requirements of practically all healthy persons

RDA = AR + 2 SD
RDA covers needs of 97-98% of population
Assume normal distribution of requirement
Assume CV of requirement =10-15%

Estimating prevalence of inadequate intake

Prevalence of inadequacy = % with intakes < AR

- Distribution of habitual intakes
  - *No. of days, under-reporting of intakes, uncertainty of food values*

Assumptions:

- Intakes independent of requirements
- Requirements symmetrically distributed
- SD intake > SD requirement

(Beaton, 1994; IOM, 2000; Carriquiry, 2001)

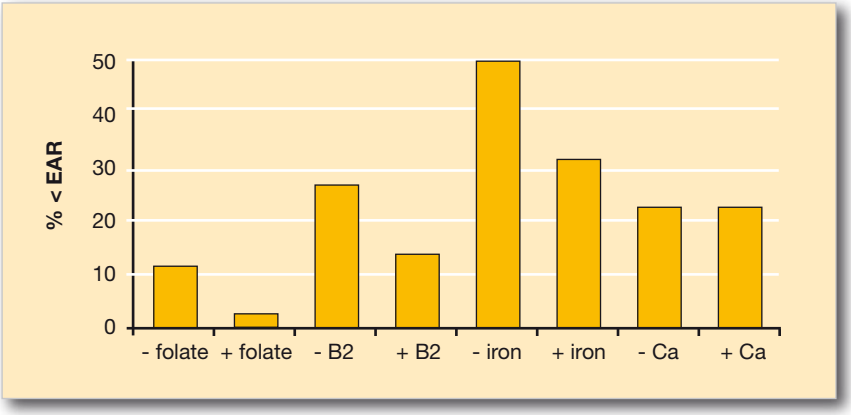
Assessing prevalence of nutrient inadequacy in Irish women (18-64 yr)

- National Food Consumption Database
  - ▷ 7 day record of food intake
- Nutrient composition of foods
  (IUNA, 2001)
- AR/Criteria
  - ▷ Folate: 140µg; serum folate maintenance
  - ▷ Iron: 10/6mg; maintenance of balance
  - ▷ Calcium: 550mg; maintenance of balance
  - ▷ Riboflavin: 1.1 mg/d; tissue saturation

  SCF, 1993

Effect of (voluntary) fortification of foods on nutrient inadequacy in Irish women (18-64 yr)

Consumers of fortified foods



Hannon et al. (2001)

FOLIC ACID FORTIFICATION (MANDATORY) OF STAPLE FOODS FOR PREVENTION OF NEURAL TUBE DEFECTS (NTD)

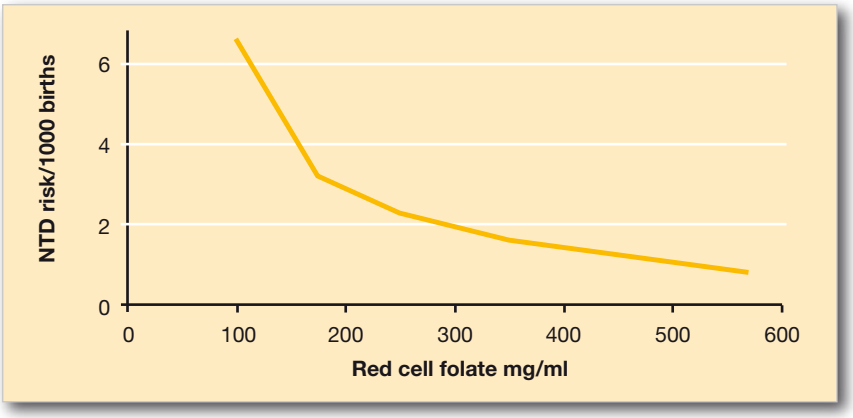
Folate and Neural Tube Defects (NTD)

- NTD - spina bifida, anencephaly
- most common birth defects
- prevalence IRL = about 1 - 1.5/1000 births
- periconceptual folic acid can prevent up to about 70% NTD

(MRC, 1991; Czeizel & Dudas, 1992)

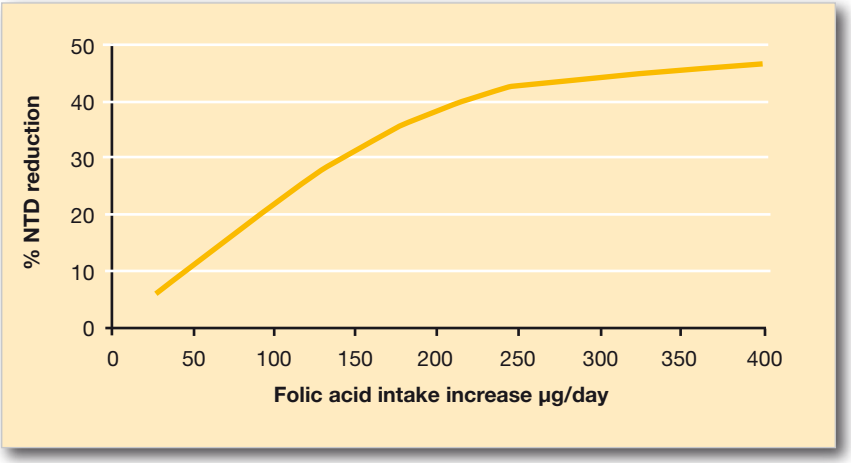
Relationship of folate status & NTD

Daly et al. 1995



Relationship of folate intake and NTD

Daly et al. 1995, 1997



Modelling of folic acid fortification of foods

Modelling (probabilistic/other) of folic acid addition to flour/bread

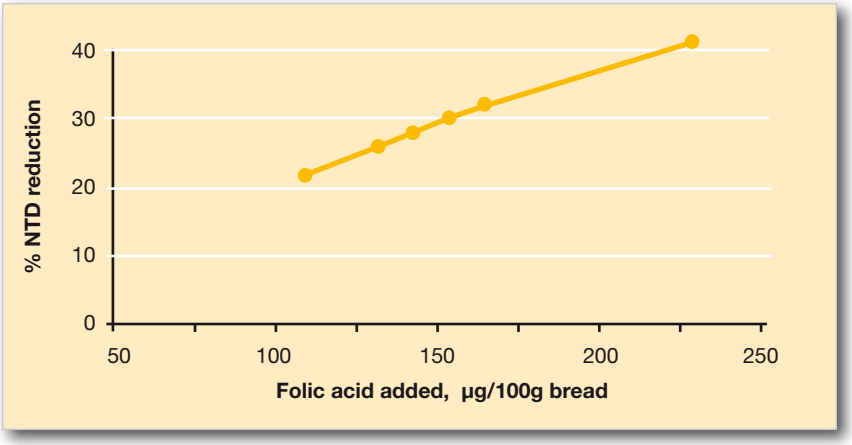
- National Food Consumption Database (IUNA, 2001)
- 7 day record of food intake

[Univ. College Cork & Food Safety Authority of Ireland]

Estimate of benefit

- Incremental intake of folic acid in women of reproductive years
- % reduction of NTD
- Other benefits
  - Reduced prevalence of megaloblastic anaemia (older adults)
  - Reduced plasma homocysteine (CVD disease risk?)

Effect of folic acid fortification of bread on NTD in Ireland - modelling



Folic acid fortification in USA/Canada (1998-)

Plan

- Added folic acid = 140 µg/100g grain
- Additional 100 µg/d folic acid intake in women of reproductive years (= 20% NTD reduction)

Outcome

- Higher folic acid intakes than planned (up to ~200µg?)
- 20-80% reduction of NTD
  - ▷ Depends on NTD rate pre-fortification
- Other benefits - reduced megaloblastic anaemia, reduced plasma homocysteine

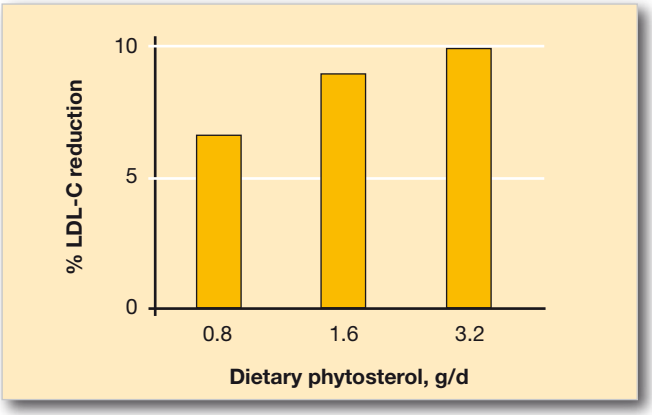
EFFECTS OF PHYTOSTEROL CONTAINING FOODS ON REDUCTION OF LDL-CHOLESTEROL (AND RISK OF CVD)

LDL cholesterol - marker of CVD risk

- Strong and consistent evidence of causal relationship with CVD risk
- Well-validated, easy applicable, and generally accepted biomarker of CVD risk
- Clear evidence that diet-induced changes in LDL-C alter the risk of CVD

Effect of phytosterols on serum LDL-cholesterol

Adults: 3.5 wk RCT



Hendriks et al. (1999)

Other health outcomes

Disability Adjusted Life Years (DALYs) :

- Integrated measure of health gain/loss in populations
- Combines death and illness, using a disability weighting factor for the seriousness of the disease
- Causality and dose-response
- Comparative benefits/risks of diet
- Priority setting for public health

Conclusions

Quantitative benefit assessment needs:

- Defined health outcomes
- Causality
- Dose response relationships for relevant outcomes
  - ▷ validated markers of effects
- Good estimates of intake distributions
  - ▷ high quality data on food consumption for population groups, food/supplement composition
- Consider frequency & severity of effects, variability between individuals

OPPORTUNITIES AND LIMITATIONS OF CURRENT APPROACHES USED IN RISK ASSESSMENT

Dr Diane Benford
Food Standards Agency
London, UK

COMPREHENSIVE RISK-BENEFIT ANALYSIS FOR FOOD

WHY DO RISK-BENEFIT ASSESSMENT?

- Inform prioritisation of action to improve public health
- Underpin acceptance of products or processes
  - Micronutrients
  - Unavoidable contaminants in otherwise nutritious foods
  - Chemicals with benefit in food production?

MICRONUTRIENTS

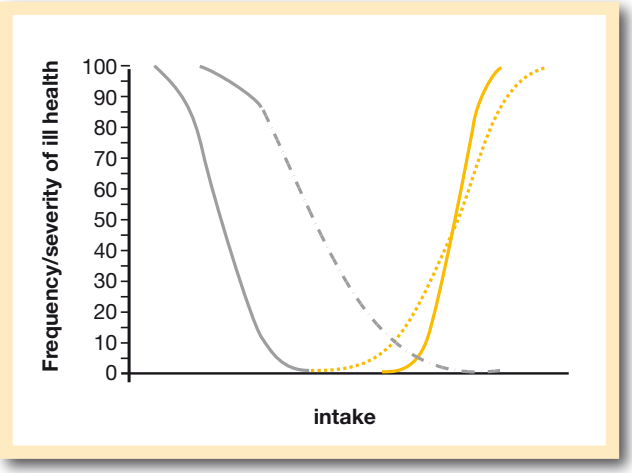
- Aim to increase population exposure
  - Mandatory fortification of staple foods as public health measure
- May increase exposure for consumers of selected products
  - Voluntary fortification of individual foods with vitamins, minerals, anti-oxidants, etc for market advantage
  - Dietary supplements
- Are different nutrient sources comparable from nutritional and toxicological view?

- Who benefits and who is at risk?
  - ▷ Low level consumers could benefit from increased exposure
  - ▷ High level consumers could be at risk from increased exposure

CHEMICALS USED IN FOOD PRODUCTION

- To increase production
  - ▷ pesticides, veterinary drug residues
- To preserve food
  - ▷ antimicrobial products and processes
  - ▷ anti-oxidants
- Is there any health benefit?

DOSE RESPONSE RELATIONSHIPS



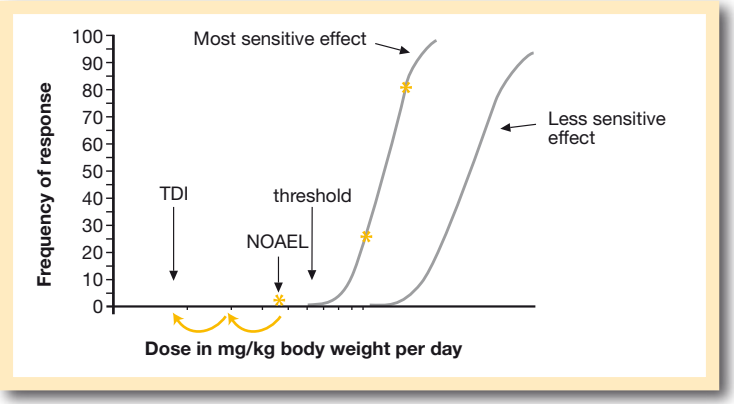
WHAT DO WE COMPARE?

- Human data vs animal data?
- Are health endpoints comparable?
- Beneficial intake for some individuals could be harmful for others
  - ▷ Variability with life stage, genetics, environmental factors, physiology, etc
- Need to consider risks and benefits to vulnerable subgroups

CURRENT APPROACHES TO RISK ASSESSMENT FOR FOOD CHEMICALS

- Threshold/non-genotoxic chemicals
  - ▷ Safety assessment
  - ▷ Establishment of acceptable or tolerable daily intake (ADI/TDI) - an amount that can be consumed daily over a lifetime without appreciable risk to health
- Genotoxic carcinogens
  - ▷ No level without risk
  - ▷ Margin of Exposure

SETTING TOLERABLE INTAKE LEVELS

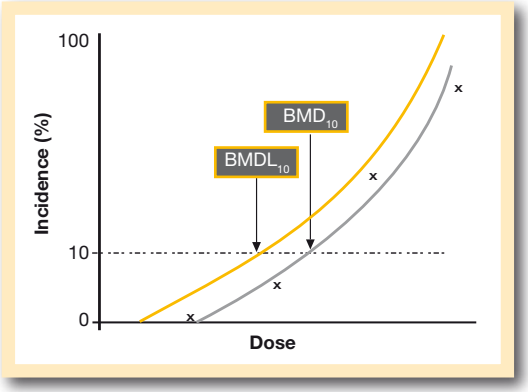


LIMITATIONS IN THE TDI APPROACH

- Not a threshold for risk
- Data gaps can lead to application of large uncertainty factors
- Many people could have intakes much higher than the TDI without appreciable risk
  - ▷ especially if the critical effect only occurs in a specific subgroup
- Risk above the TDI cannot be quantified

DOSE-RESPONSE ASSESSMENT

Benchmark dose approach preferred (IPCS, 2004)



- **Uses all of the data**
- **BMDL reflects quality of data**

REFINING THE TDI APPROACH

- Modelling the dose-response relationship(s) offers potential for quantitative approach to risk-benefit analysis
  - ▷ likely to still require uncertainty factors
- Use of chemical-specific adjustment factors rather than default uncertainty factors
- Do we have adequate data?

APPROACHES FOR GENOTOXIC CONTAMINANTS

- Cancer risk estimates
  - ▷ Low-dose extrapolation
  - ▷ Linear extrapolation from a point of departure (PoD) on the observed dose range

- Calculation of Margin of Exposure (MoE) between PoD and estimated dietary exposure

LIMITATIONS IN APPROACHES FOR GENOTOXIC CONTAMINANTS

- Need carcinogenicity data

- EFSA does not use cancer risk estimates in its risk assessments

- MoE does not provide an estimate of risk because of uncertainties in the dose response relationship

EXPOSURE ASSESSMENT

- Do toxicologists and nutritionists use comparable methodology?
  - ▷ e.g. fish consumers vs population mean

- Micronutrients
  - ▷ Risks and benefits total exposure
  - ▷ Do we have data on fortification and potential future trends?
  - ▷ Consumers with high level dietary exposure may also choose supplements and fortified foods

FSA REVIEW OF RISKS AND BENEFITS OF FISH CONSUMPTION

- Long-standing UK advice on fish consumption:
  - ▷ Eat at least two portions of fish a week, of which one should be oily
  - ▷ Well-established benefits (reduced risk of cardiovascular disease) exceed possible risks (of chemical contaminants in fish)

- Advice criticised for not advising on risks of eating more than the recommended amount

NUTRITIONAL CONCLUSIONS

- Confirmed that people should eat at least two portions of fish a week of which one should be oily.
  - ▷ Significant public health benefit in terms of reducing risk of cardiovascular disease
  - ▷ May also be beneficial effects on fetal development

- May be beneficial for some subgroups to consume more then the guideline recommendation

- Not possible to identify a level

GUIDELINES FOR METHYLMERCURY IN FISH - COT 2004

- 2003 JECFA PTWI of 1.6 µg/kg bw/week for women who are pregnant, or may become pregnant within the next year
- no new information to indicate 3.3 µg/kg bw/week not sufficiently protective of the general population
- 3.3 µg/kg bw/week can be used as a guideline level for other groups

GUIDELINES FOR DIOXIN INTAKE FROM FISH

- Analogous to methylmercury
- Apply TDI of 2 pg TEQ/kg bw/day for those at risk of reproductive effects
  - ▷ women of reproductive age, girls
- Guideline level derived from carcinogenicity data for those not at risk of reproductive effects

CHALLENGES

- Dealing with uncertainty and data gaps
- Should we use methodology that we do not consider justifiable in safety assessment?
- Incorporation of societal judgements into the scientific process
  - ▷ Weigh different types of health effect?
  - ▷ Comparison of proven benefit to few with possible risk to many?

CONCLUSIONS

- Purpose of risk-benefit analysis needs to be clearly defined in advance
- Quantitative dose-response data are needed for risk-benefit assessment but are rarely available
- It might be possible to refine the risk assessment process to allow a more quantitative approach, and to avoid over-precautionary use of uncertainty factors
- Need clear communication to distinguish risk assessment from risk management issues

RISK-BENEFIT ANALYSIS OF MICRONUTRIENTS

AG Renwick
School of Medicine
University of Southampton
Bassett Crescent East
Southampton SO16 7 PX — UK
Email- A.G.Renwick@soton.ac.uk

Reprinted from

Food and Chemichal Toxicology

Volume 42, Number 12, Pages 1903-1922, 2004

Risk Benefit Analysis of Micronutrients

Authors*

A.G. Renwick[1], A. Flynn[2], R.J Fletcher[3], D.J.G Müller[4], S. Tuijtelaars[5], H. Verhagen[6]

1. University of Southtampton, Clinical Pharmacology Group, Biomedical Sciences Building, Basset Crescent East, Southtampton SO16 7PX, UK
2. University College Cork - Departement of Food & Nutritional Sciences, Cork, Ireland
3. Kellogg's Company of Great Britain Ltd., Talbot Road, Manchester, M16 OPU, UK
4. Procter & Gamble European Service GmbH, Zentrale Rechnungsprüfung, Sulzbacher str. 40, Schwalbach am Taunus, 65824, Germany
5. ILSI Europe, Av E. Mounier 83, box 6, 1200 Brussels, Belgium
6. Unilever Health Institute, P.O. Box 114, 3130 AC Vlaardingen, The Netherlands

ILSI

International Life Sciences INSTITUTE

Report prepared under the responsibility of the

ILSI Europe Addition of Nutritients to Food Task Force

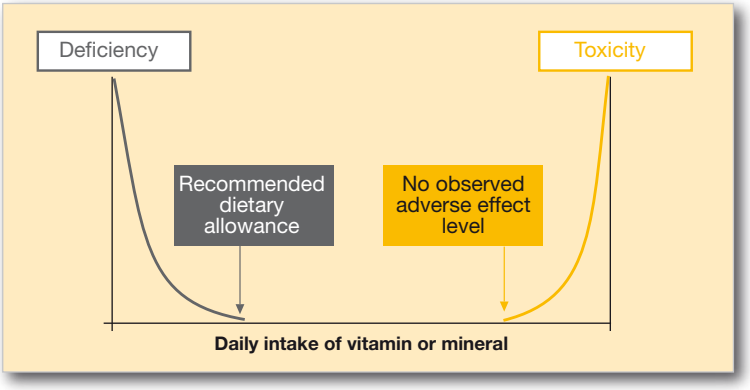
* Correspondence: ILSI Europe, 83 Avenue E. Mounier, Box 6, B-1200 Brussels, Belgium

RISK-BENEFIT REQUIRES

- 1. A common method of dose-response assessment to describe the relationships between the intake and the beneficial and adverse responses.

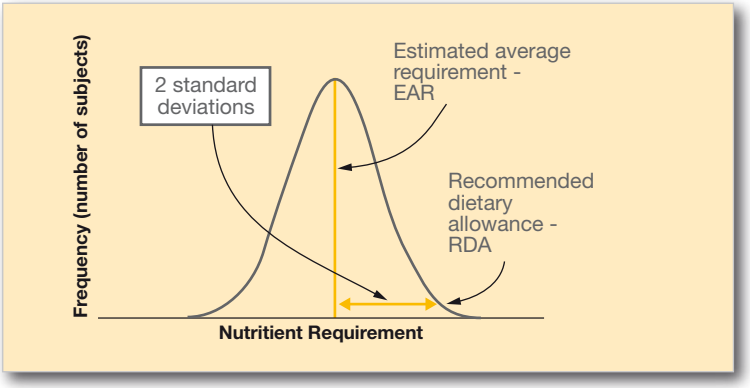
- 2. A common currency to describe the health impacts of the beneficial and adverse responses – i.e. to allow one effect to be weighed against the other (e.g. quality of life years).

The traditional approaches

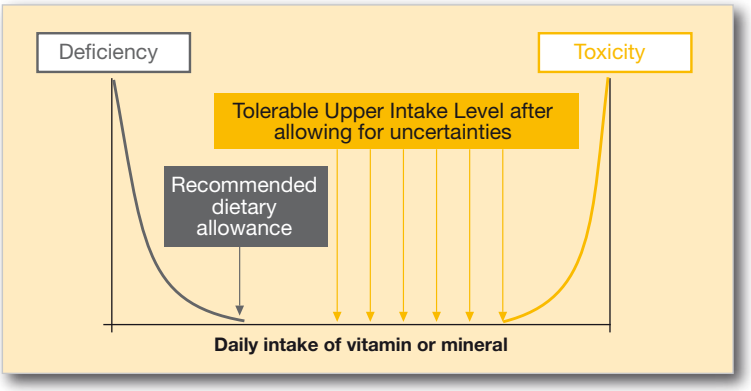


How is the Recommended Dietary Allowance (RDA) determined?

Population distribution of requirements for a nutrient



The traditional approach to setting an upper level



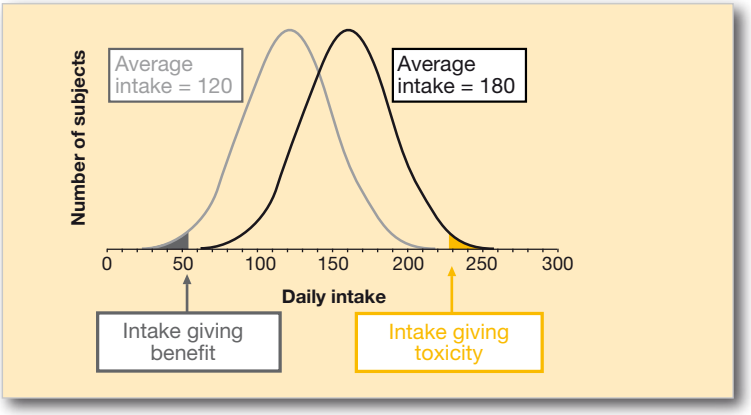
Need to ensure that setting the upper intake level does not produce deficiency.

For some micronutrients point estimates for **"absolute sufficiency for all"** or **"absolute safety"** are not realistic possibilities.

A "common method" of dose response assessment is essential for comparisons of "adequacy" and "safety".

A simple "common method" of dose response assessment would be to model **population distributions of defined magnitude of responses** of benefit and adversity.

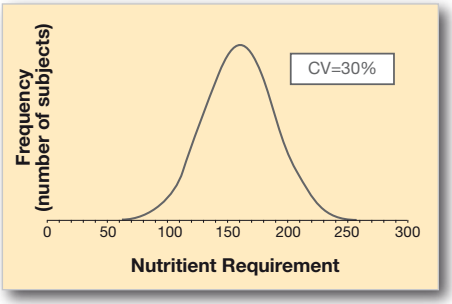
- A population distribution can be used to describe the consequences of an increase in intake.
- Increasing the average intake means that fewer individuals are at risk of not getting the benefit but more individuals are at risk of toxicity.

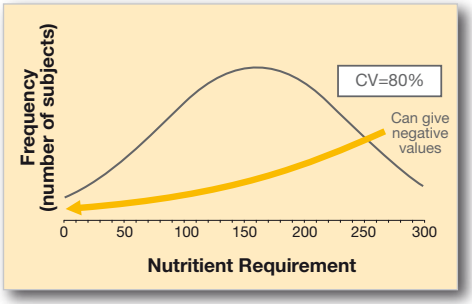


CHOICE OF POPULATION DISTRIBUTION MODEL

Unimodal does not allow for variation due to polymorphisms

Normal (Guassian) distribution

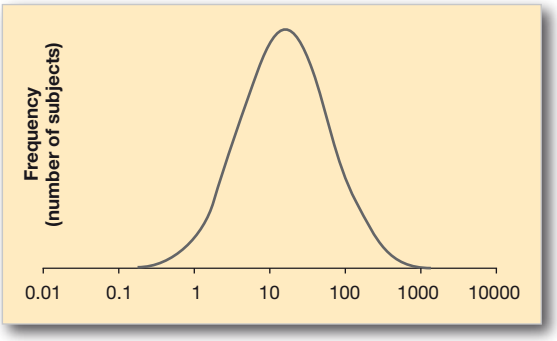




- Can give meaningless values e.g negative requirement
- The differences above and below the mean are different
  - e.g. if mean is 100 and SD is 40 then
  - +2SD = 180 (1.8-fold) and -2SD = 20 (5-fold)

Unimodal does not allow for variation due to polymorphisms

Lognormal distribution



- Better reflects human variability in biochemical and physiological differences.
- The fold-differences above and below the mean are the same.
- Cannot give negative values.

Polymodal Can allow for variation due to polymorphisms

A polymodal model could be useful if

- The incidence of the polymorphism is defined.
- The magnitude of the difference in sensitivity is defined.
- The subgroup cannot be given specific advice because they cannot "self-recognise".

In application of the risk-benefit model - data on sub-groups are best analysed separately and given as specific advice to the risk manager.

A simple lognormal distribution is proposed as the default model but more appropriate models could be applied if suitable data were available.

Application of a lognormal distribution model to data on either benefit or toxicity requires only limited data.

The model is used to fit the change in the **incidence of a predetermined level of response with change in intake** and NOT the change in the magnitude of the effect with change in intake.

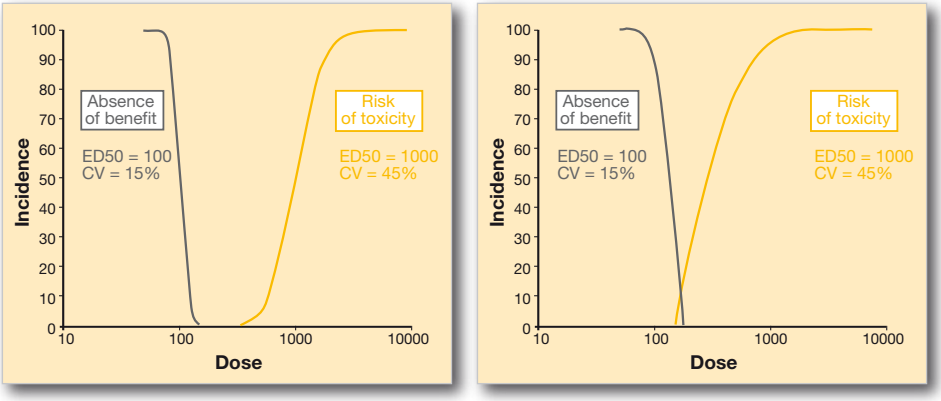
In consequence the model can be extrapolated over a wide range without producing biologically implausible effects (e.g. a liver size that would be incompatible with life).

Define the dose-response data as **dose-incidence** data i.e. as the incidence of a pre-determined level of response at different doses.

The incidence at higher or lower intakes will depend on the coefficient of variation (CV) within the exposed group of interest - humans.

The minimum information necessary to model the data are:

- the incidence of the pre-determined response at one dose level and
- the selection of a suitable CV to represent human variability



Most human variability is represented by a **log-normal population distribution model.**

The selection of the appropriate CV (coefficient of variation) is the only assumption that is required.

Species differences can be taken into account if animal data have to be used for toxicity.

CHOICE OF CV TO REPRESENT HUMAN VARIABILITY

Benefit

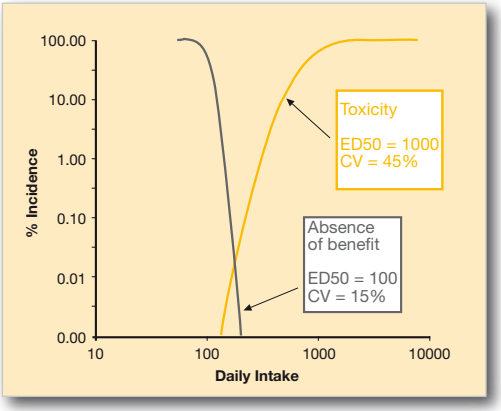
There is a history of use of a CV of **15%** by the SCF and of 10% by the IOM to convert the EAR into an RDA.

This is based on nutritional considerations such as variations in energy requirements and metabolic rates.

Toxicity

Occurs at high intakes which may saturate homeostasis and normal physiological and nutritional processes and the nutrient may be metabolised and excreted like a foreign compound.

Data on human variability in drug kinetics and dynamics indicate a suitable default would be a CV of about **45%.**



The model compares the health "risk" due to the absence of a benefit with the risk due to the presence of toxicity.

- The model can define the **optimum intake** if the 2 effects are of similar severity - BUT
- The nature of the benefit and toxicity may be very different.

The acceptability of any particular balance of the risks of lack of benefit and presence of toxicity is a risk management decision.

Defining only the optimum is not practical advice.

Advice to risk managers should describe the calculated risks at different intakes.

Advice to risk managers should describe the **nature** of the "risks".

Advice to risk managers can be based on a generic tabulation if the generic default CVs are used for benefit and toxicity.

Specific modelling and a specific tabulation would be needed is nutrient-specific CVs are used.

Simplified Table of Incidence of Deficiency and Toxicity

		Incidence of toxicity				
		1:10	1:100	$1:10^3$	$1:10^5$	$1:10^6$
Incidence of deficiency or absence of benefit	1:10	1.21A - 0.58B	1.21A - 0.37B	1.21A - 0.27B	1.21A - 0.16B	1.21A - 0.13B
	1:100	1.41A - 0.58B	1.41A - 0.37B	1.41A - 0.27B	1.41A - 0.16B	1.41A - 0.13B
	$1:10^3$	1.59A - 0.58B	1.59A - 0.37B	1.59A - 0.27B	1.59A - 0.16B	1.59A - 0.13B
	$1:10^5$	1.89A - 0.58B	1.89A - 0.37B	1.89A - 0.27B	1.89A - 0.16B	1.89A - 0.13B
	$1:10^6$	2.03A - 0.58B	2.03A - 0.37B	2.03A - 0.27B	2.03A - 0.16B	2.03A - 0.13B

Notes
A – is the ED50 for the benefit
B – is the ED50 for the toxicity
CVs of 15% and 45% are used to defines the slopes for benefit and toxicity

APPLICATION OF THE APPROACH

The approach does NOT solve issues of database inadequacies but rather adds to the problem by requiring **incidence data** from which to derive the ED50 in order to apply the model.

The approach does NOT compare benefits and risks using a **common currency.**

CONCLUSIONS

There is no *a priori* reason to expect that high intakes of micronutrients will be any more safe than high intakes of other food chemicals.

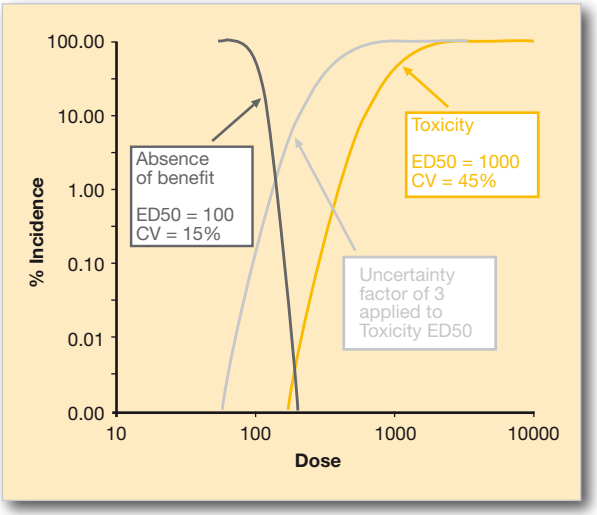
The database available on micronutrients often contains extensive data from human studies but these rarely address the potential for toxicity; the animal and human studies usually do not meet the quality standards for risk assessment.

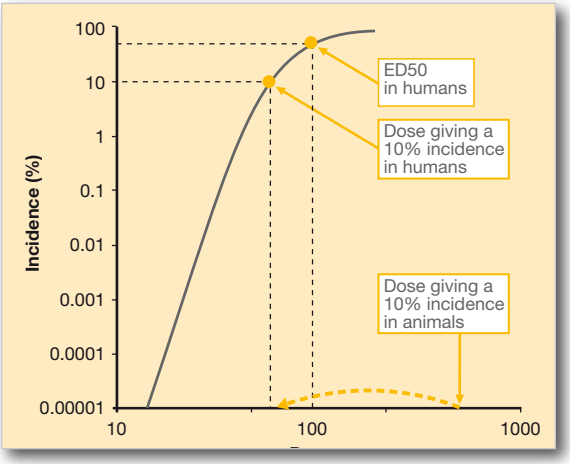
The human database may identify adverse effects but rarely defines the incidence at a given intake.

The risk benefit model does not take into account the severity of the adverse health effects due to a lack of benefit or toxicity.

The risk benefit model is a practical method but does **not** resolve risk assessment issues that require expert judgement.

Uncertainties, such as species differences, can be allowed for by adjusting the ED50 – equivalent to an uncertainty factor





Extrapolation

1. Select GSD
2. Determine NORMSINV for %ile
3. Multiply log GSD*NORMSINV
4. Antilog product for dose ratio to ED50

In example - 61mg gives 10% incidence

1. CV = 40% : GSD = 1.47
2. NORMSINV for 10% = -1.286
3. Log GSD*-1.286 = -0.2144
4. Antilog = 0.610
5. ED50 = 61mg/0.61 = 100mg

OUR HEALTH, OUR FOOD

HEALTHY DIET AND SAFE FOOD IN THE NETHERLANDS

F.X. Rolaf van Leeuwen
National Institute for Public Health and the Environment
Bllthoven, The Netherlands

HISTORY OF PRESENT REPORT

In 2001 RIVM was commissioned by the Ministry of Health, Welfare and Sports to study the healthiness of the Dutch dietary habits and the safety of the Dutch food.

The results of this study, including an executive summary in English, were published in September 2004

QUESTIONS ADDRESSED

- How healthy is the Dutch diet?
- How safe is Dutch food?
- What health gains can be achieved through better diet, better eating habits and by reducing overweight?
- What is the appropriate balance between the desire for a healthy diet and the need to ensure safe food?
- How will this affect the various parties involved in food production, distribution and consumption?

HISTORY OF PRESENT REPORT

EFSA considered the report to be a significant contribution to the international discussion on the risks and benefits of food, and therefore decided to provide financial support for the translation of the report into English.

In May 2006 the English version was presented to EFSA

CURRENT PRESENTATION

- What is the health impact of the most important nutritional determinants?
- What is the health impact of foodborne infections?
- What is the health impact of harmful chemicals in food?

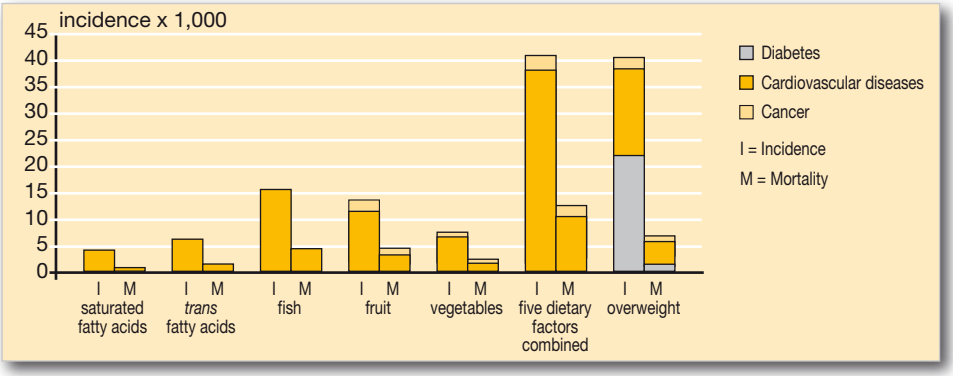
HEALTHY DIET

Actual consumption of the five most important dietary health determinants compared to the recommended intake in the Netherlands

Dietary factor	Recommanded intake	Average consumption 1998	Trend
Saturated fatty acids	< 10 energy per cent	14.5 energy per cent	Favourable
Trans fatty acids	< 1 energy per cent	1.8 energy per cent	Favourable
Fish	1 or two times per week	2 to 3 times per month	Favourable
Fruit	2 pieces per day (200 grams)	102 grams	Unfavourable
Vegetables	150-200 grams	120 grams	Unfavourable

Our food, our health; Table 1

Estimated health loss because consumption of various food items, as well as bodyweight fails to meet the recommendations

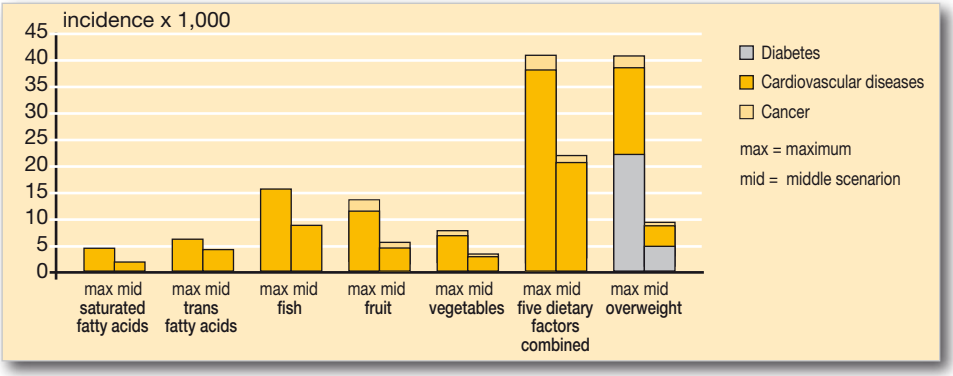


Our food, our health; Fig 2

MIDDLE (REALISTIC) SCENARIO

- consumption of saturated fatty acids reduced by 2.5 energy per cent
- consumption of trans fatty acids reduced by 0.5 energy per cent
- consumption of fish increased by one or two portions per month
- consumption of vegetables increased by 50 grams per day
- consumption of fruit increased by 50 grams per day.

Reduction in annual incidence of disease in the Netherlands: maximum and middle scenarios.



Our food, our health; Fig3

Estimated health gain through healthy diet and appropriate body weight

Factor	DALYs		Life expectancy Total		Life expactancy free of disease	
Scenario	Maximum	Middle	Maximum	Middle	Maximum	Middle
Saturated fat	25.000	10.000	0.1	<0.1	0.2	0.1
Trans fatty acids	32.000	22.000	0.1	0.1	0.3	0.2
Fish	82.000	46.000	0.3	0.2	0.5	0.3
Fruit	95.000	38.000	0.5	0.2	0.7	0.3
Vegetables	47.000	21.000	0.3	0.1	0.4	0.2
Five dietary factors combined	246.000	128.000	1.2	0.6	2.0	1.0
BMI	215.600	56.000	0.8	0.3	2.3	1.0

Our food, our health; Table 2.7

▷ DALY's for persons of >20 year and life expectancy for persons >40 year
▷ Maximum scenario: everyone meets the recommendations
▷ Middle scenario: realistic, feasible interventions

To compare the potential health threats caused by an unhealthy diet and by microbiological and chemical contamination of food the DALY was chosen as integrated measure of health impact.

DALY (Disability Adjusted Life Years) = YLL + YLD

YLL = number of life years lost (deaths)

YLD = number of years with illness or disability, corrected for the seriousness of the effect with a weighing factor varying between 0 (totally healthy) and 1 (as serious as death)

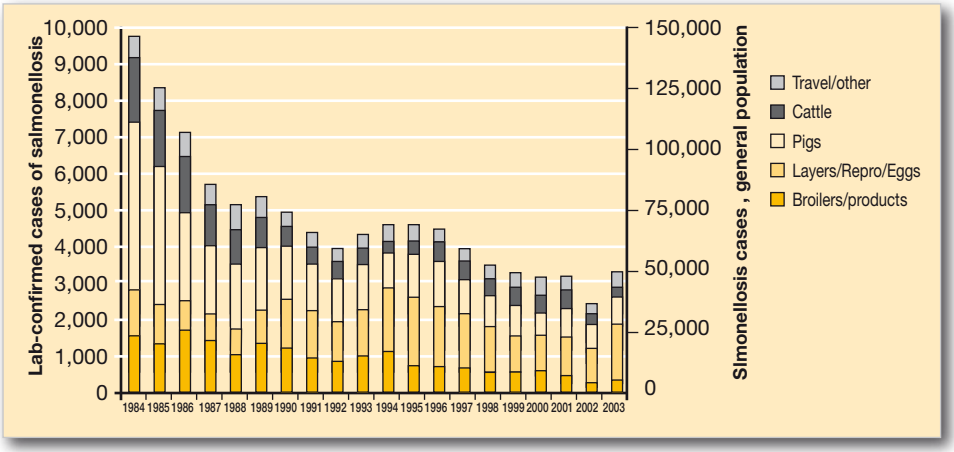
(Murray & Lopez, 1996; WHO, 2002)

EXAMPLES OF WEIGHING FACTORS IN THE DALY APPROACH

Disease	Weighing factor
Parkinson	0.68
Stroke	0.61
AIDS	0.57
Multiple sclerosis	0.53
Lung cancer	0.44
COPD	0.31
Coronary heart disease	0.29
Tuberculosis	0.23
Breast cancer	0.21
Arthrosis	0.19
Astma (severe)	0.08
Gastroenteritis	0.03
Influenza	0.01

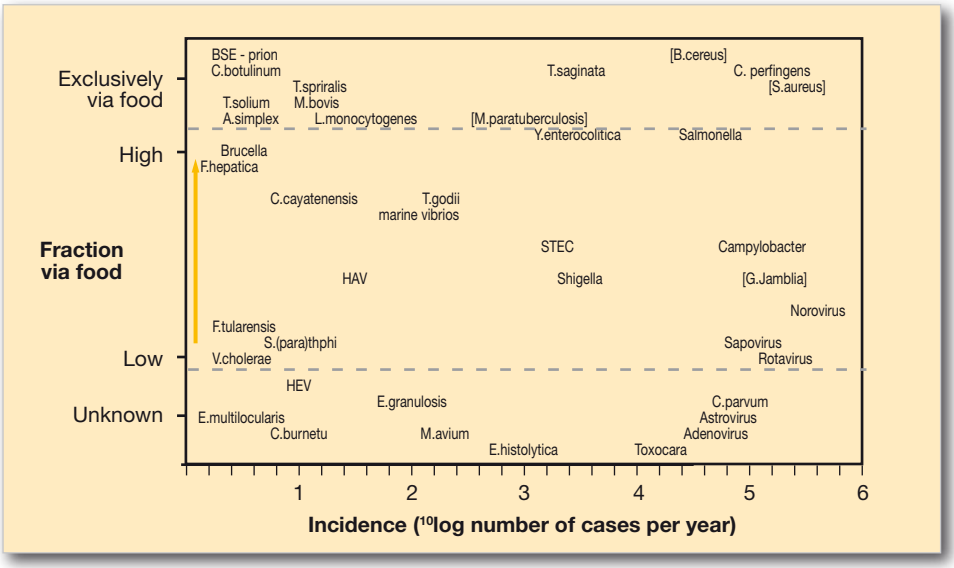
(Hoeymans & Poos, 2002)

Trends in salmonellosis in the Netherlands



Our food, our health; Fig 4

Estimated incidence of foodborne infections in the Netherlands



Our food, our health; Fig 4.2

Incidence of food-related gastroenteritis caused by known pathogens in the Netherlands

Organism	Incidence gastroenteritis (per year, all causes)	Food attributable fraction	Incidence food-related gastroenteritis (per year)
Campylobacter spp.	107,000	0.3 - 0.8	32,100 - 85,600
Salmonella spp.	53,500	> 0.9	48,200 - 53,500
Shigella spp.	1,000 - 10,000	0.1 - 0.5	100 - 5,000
Escherichia coli 0157	1,250	0.5 - 0.9	625 - 1,125
Yersinia enterocolotica	1,000 - 10,000	> 0.9	900 - 1,000
Total infectious bacteria			**82,000 - 146,000**
Clostridium perfringens toxins	147,000	1	147,000
Staphylococcus aureus toxins	0 - 236,000	1	0 - 236,000
Bacillus cereus toxines	0 - 35,700	1	0 - 35,700
Total toxinogenic bacteria			**147,000 - 419,000**
Norovirus	499,500	0.1 - 0.2	50,000 - 100,000
Sapovirus	107,000	0 - 0.1	0 - 10,700
Rotavirus group A	191,800	0 - 0.1	0 - 19,200
Total virusses			**50,000 - 130,000**
Giardia lamblia	0 - 165,000	< 0.3	0 - 50,000
Total protozoa			0 - 50,000
Total known microorganisms			**279,000 - 745,000**

Our food, our health; Table 4.2

Burden of disease due to various infectious diseases

Disease	Incidence (per year)	Mortality (per year)	DALYs
Pneumonia and acute bronchitis/bronchiolitis	640,000	7,000	74,000
Influenza	1,000,000	370	14,000
Acute urinary tract infections	720,000	12	11,000
Sepsis	No reports	820	11,000
Upper respiratory tract infections	400,000	24	8,400
AIDS	1,700	130	5,400
Foodborne infections and intoxications*	300,000 - 750,000	20 - 200	1,000 - 4,000
Meningitis (bacterial form)	930	91	2,600
Bacterial STD	27,000	23	2,400
Tuberculosis	830	91	1,300

* by known pathogens.

Our food, our health; Table 4.5

Chemical food constituents which are potentially harmful

Naturally occurring chemical compounds

- allergens
- mycotoxinen, fycotoxinen, fytotoxinen
- nitrate

Non-naturally occuring chemical compounds

- deliberately added (e.g. additives, flavourings)
- result of deliberate handling (e.g. veterinary drugs, pesticides, food contact materials)
- unintentionally present (environmental or process contaminants)

ALLERGENIC SUBSTANCES

- Of the (adult) Dutch population 2% suffer from some form of food allergy.
- Assume that 10% are unaware of the cause, and therefore cannot avoid it and have more or less permanent symptoms of illness.
- This gives the total of 32,000 disability years (0.2% of 16 million).
- The weighing factor is 0.03 (comparable with light-to-moderate asthma).

The health loss is therefore 0.03 x 32,000 = approx. 1,000 DALYs.

NITRATE/NITRITE

- Consumption of vegetables which are rich in nitrates combined with fish can result in the formation of nitrosamines.
- Based on conservative estimates this can result in approximately 20-100 additional cancer cases per year.
- It's assumed that premature death represents an average loss of 5 life-years.

The resultant health loss is approximately 100 to 500 DALYs.

PHYCOTOXINS

- The ASP incident in Canada has been taken as the reference.
- There were three deaths representing, an average loss of twenty life years = 60 DALYs.
- There were 105 acute intoxications giving serious but temporary effects (comparable to a transitory disease such as pneumonia).
- A weighing factor of 0.1 was applied resulting in 10.5 DALYs.

The resultant health loss is approximately 70 DALYs.

ACRYLAMIDE

- Based on extrapolations from animal carcinogenicity studies the current exposure level in the Netherlands may lead to an additional 75-130 cancer cases each year.
- It is assumed that each case will result in premature death and an average loss of five life-years,

The resultant health loss can be calculated as 375-650 DALYs.

Chemical substances in food in the Netherlands, with health risks and the possible health gains if exposure is avoided

Group of substances	Type of effect				DALYs to be gained
	Acute	Carcinogenic	Chronic other	Allergenic	Designated as order of magnitude due to the uncertainty
Various proteins in food				Shellfish, fish, milk, nuts, wheat.	Ca. 1,000
Mycotoxins		Aflatoxins			Aflatoxin B1 < 1
Phycotoxins	DSP, ASP				Ca. 10 - 70
Phytotoxins	Anisatin				< 1
Nitrate/nitrite		Nitrosamines			Nitrosamines Ca. 100 - 500
Growth promoters	Clenbuterol				Ca. 1
Process contaminants		PAHs, Acrylamide			PAHs 5 - 10; Acrylamide 300 - 700

Our food, our health; Table 4.8

Estimated health loss or potential health gain following improved diet and avoidance of exposure

Unfavourable diet	128,000 - 245,000	DALYs
Foodborne infections	1000 - 4000	DALYs
Chemical contamination	1500 - 2000	DALYs

Annual health loss due to dietary factors, against other lifestyle factors, environmental factors and disease categories in the Netherlands.

DALYs lost	Diet			Other		Disease
	Dietary factors	Microbiological contamination	Chemical contamination	Other lifestyle factors	Environmental factors	Selection from Public Health Status Forecast 2002
> 300,000	Unhealthy diet total[1]			Three lifestyle factors combined[2], Smoking		Cardiovascular diseases, all cancers
100,000 - 300,000	5 dietary factors toghether, energy-balance[3]			Lack of physical activity		Coronary heart diseases, depression, lung cancer, diabetes, alcohol-dependency
30,000 - 100,000	Excess of *trans* fatty acids, too little fruit, vegetables and fish			Alcohol consumtion[4]		Road traffic accidents, breast cancer
10,000 - 30,000	Excess of saturated fatty acids			Particulate matter in atmosphere	Schizophrenia, prostate cancer, influenza	
3,000 - 10,000		Gastroenteritis caused by micro-organisms in food		Passive smoking	Upper respiratory tract infections, HIV/AIDS[5], stomach and intestinal ulcers	
1,000 - 3,000				Radon (interior)	Bacterial meningitis, bacterial STDs[5], tuberculosis	
300 - 1,000		Campylobacter in food	Allergens, acrylamide			
< 300		STEC 0157[5]	PAHs[5], other substances	Various substances		

KEY MESSAGES

Dutch people are less healthy than they could be due to an unhealthy diet.

Dietary interventions can reverse a substantial proportion of the health loss.

Much greater health gains are to be made through encouraging a healthy diet than through improving food safety.

ACKNOWLEDGEMENT

Editors in chief:

C.F. van Kreijl, A.G.A.C. Knaap and J.M.A. van Raaij

Editors:

M.C.M. Busch, A.H. Havelaar, P.G.N. Kramers, D. Kromhout, F.X.R. van Leeuwen, H.M.J.A. van Leent-Loenen, M.C. Ocké, and H. Verkleij

Contributors;

Drs. E. Anten-Kools, Dr. A.J. Baars, Dr. M.I. Bakker, Dr. ir. R.A. Bausch-Goldbohm, Ir. W. Bosman, Drs. M.C.M. Busch, E.J.M. Buurma-Rethans, Dr. Y.T.H.P. van Duijnhoven, Dr. E. Duizer, Ir. H.P. van Egmond, Dr. ir. E.J.M. Feskens, Dr.ir. A.W. van de Giessen, Dr. J.W.B. van der Giessen, Dr. L..A. van Ginkel, Dr.ir. C.P.G.M. de Groot, Dr.ir. A.H. Havelaar, Ir. R.T. Hoogenveen, Dr. K.F.A.M. Hulshof, Dr.ir. E.H.J.M. Jansen, Dr.ir. M.C.J.F. Jansen, Dr..ir. N. de Jong, Drs. A.G.A.C. Knaap, Prof.dr. F. van Knapen, Dr. M.A. Koelen, Dr. M.P.G. Koopmans, Drs. L.M. Kortbeek, Dr. P.G.N. Kramers, Dr. C.F. van Kreijl, Prof.dr.ir. D. Kromhout, Ir. H.M.J.A. van Leent-Loenen, Dr. F.X.R. van Leeuwen, Mr.F.M. van Leusden, Prof.dr. H. van Loveren, Dr. S. Lijklema, Dr.ir. M.C. Ocké, Dr. W. van Pelt, Dr.ir. M.N. Pieters, Dr. W.H.M. van der Poel, Dr.ir. J.M.A. van Raaij, Ing. J.H.J. Reimerink, Prof.dr. S. A. Reijneveld, Dr. C.J.M. Rompelberg, Dr.ir. C.T.M. van Rossum, Prof.dr.ir. J. Seidell, Prof.dr. W.A. van Staveren, Dr. C. Thijs, Dr.ir. W.M.M. Verschuren, Dr. H. Verkleij, Dr. T.L.S. Visscher.

BENEFITS AND RISKS OF FISH CONSUMPTION IN NORWAY

Jan Alexander
Norwegian Scientific Committee for Food Safety
and
Norwegian Institute of Public Health

This presentation is based on the report:

"Fish and seafood consumption in Norway – benefits and risks"

Authors: J Alexander, L Frøyland, G-I Hemre, BK Jacobsen, E Lund, HM Meltzer, JU Skåre (Chair)

Norwegian Scientific Committee for Food Safety, 28 March, 2006

Prepared at the request of the Norwegian Food Safety Authority

Background: UK report, Danish report and EFSA report in 2005

Apparently contradictory advise on fish consumption:

It is beneficial for health to eat more fish

Adverse health effects may occur from environmental contaminants in fish

BENEFIT ANALYSIS

Role of fish in nutrient supply

- Reference points: Recommended intakes

(Nordic Nutrition Recommendations 2004)

- Dietary sources other than fish of the nutrient

Role of fish intake for health outcome

- Epidemiological studies: meta analyses

RISK ANALYSIS

Role of fish in contaminant exposure

- Reference points: Tolerable intakes (EFSA, WHO, SCF)
- Dietary sources other than fish of the contaminant

Role of fish intake for adverse health effects

- Epidemiological studies: specific contaminants, meta analyses

RISK – BENEFIT ANALYSIS

Major problem:

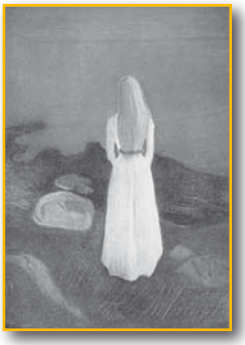
- No quantitative comparison of benefits and risks possible
  - ▷ No tool developed
  - ▷ References of comparison are recommended intakes and tolerable intakes, point estimates and not dose-responses
- Challenges:
  - ▷ Describe the situation as accurately as possible: intake of nutrients and exposure to contaminants
  - ▷ Assess the health consequences of intake of the food in question as such
  - ▷ Identified conflicts between risks and benefits

What characterises consumption of fish and other seafood in Norway?

Fish consumption in Norway is different from other countries:

- Consumption is high: Median intake 65 g/day
  - ▷ (10th perc.: 27g and 90 perc.: 119 g/day)
  - ▷ NB! Largest uncertainty at the distribution tails Fraction of lean fish is high (2/3 versus 1/3)
- More fish is consumed on bread due to several bread meals per day

Young women...



- ...eat less fish than the mean consumption of the adult population
- Median ~ 46 g/day (equiv. 1.5 dinner serving pr week)
- About 2/3 is lean fish
- Consumption of oily fish:
  - ▷ median 9.4 g/day
  - ▷ 95th percentile 44 g/day (equiv. 1.5 dinner serving/week)

Nutrients and beneficial compounds in fish and other seafood

- Protein
- Marine n-3 PUFA (oily fish)
- Vitamins A + D (oily fish)
- Vitamin B-12
- Iodine
- Selenium

Assessment of nutritional aspects

- No realistic intake can result in adverse effects of nutrients. This also includes children
- Focus of interest:
  - ▷ Consequences of a low intake
  - ▷ Consequences of not eating fish
  - ▷ Consequences of a low intake of oily fish

Nutrient scenarios at different fish intakes

Ulike inntaksscenarier		Lavkonsument 10-persentil 27 g/dag		Mediant inntak 50-persentil 65 g/dag		Hoykonsument 90-persentil 119 g/dag	
		per dag	%RI NNR	per dag	%RI NNR	per dag	%RI NNR
Retinol (µg/dag)	Mager fisk	1	0.1	1	0.1	2	0.3
	2/3 mager og 1/3 fet fisk	3	0.3	7	0.8	13	1
	Fet fisk	8	0.9	19	2	34	4
Vitamin D (µg/dag)	Mager fisk	0	4	1	10	1	18
	2/3 mager og 1/3 fet fisk	1	14	2	27	4	53
	Fet fisk	2	27	6	83	10	133
Vitamin B12 (µg/dag)	Mager fisk	1	28	1	66	2	122
	2/3 mager og 1/3 fet fisk	1	58	3	140	5	256
	Fet fisk	2	120	6	290	10	500
Selen (µg/dag)	Mager fisk	8	16	20	39	36	71
	2/3 mager og 1/3 fet fisk	9	18	22	44	41	82
	Fet fisk	9	19	23	45	42	84
Jod (µg/dag)	Mager fisk	120	80	290	193	530	353
	2/3 mager og 1/3 fet fisk	76	51	180	120	340	227
	Fet fisk	14	9	34	23	63	42
Total n-3 PUFA (µg/dag)	Lean fisk	0.0	1	0.1	2	0.1	4
	2/3 mager og 1/3 fet fisk	0.3	12	0.7	29	1.4	53
	Oily fisk	0.9	34	2.2	85	4.0	154
Sum n-6-fettsyrer (µg/dag)	Mager fisk	0.0	-	0.0	-	0.0	-
	2/3 mager og 1/3 fet fisk	0.2	-	0.4	-	0.7	-
	Fet fisk	0.4	-	1.0	-	1.9	-

Together with ALA from plant food n-3 recommended intake met

Below UL 5E%

From a nutritional point of view – intake of nutrients

- Increased consumption of oily fish recommended, particularly for those eating low amounts of oily fish and the half of the population eating the least amount of fish
  - ▷ otherwise difficult to meet recommended total intake of n-3 PUFA including αlinoleic acid (ALA) from plants and recommended intake of marine n-3 per se.
  - ▷ recommended vit D intake can only be partially met.

- There are no problems related to an intake equivalent to 4 dinner servings per week.

- It is advisable to eat different kinds of fish.

Health effects associated with fish consumption

- Differentiate between studies investigating the effect of a diet containing fish

  ... and studies on effects following intake food supplements containing high levels of marine n-3 PUFA (cod liver oil, fish oil capsules etc.).

- Difficulties related to the use of "fish" as exposure parameter in epidemiological studies.

FISH CONSUMPTION AND CANCER

- meta analyses of epidemiological studies

- Fish consumption does not show any significant association with cancer risk – neither protective nor increasing the risk of any common form of cancer

Beneficial health effects for the foetus and the child

- n-3 PUFA – health effects

- Intake of cod liver oil/fish oil associated with increased birth weight (Olsen, 1986, 2002, Olafsdottir, 2005).

- Positive effect on visual ability of premature infants (Lauritzen, 2004).

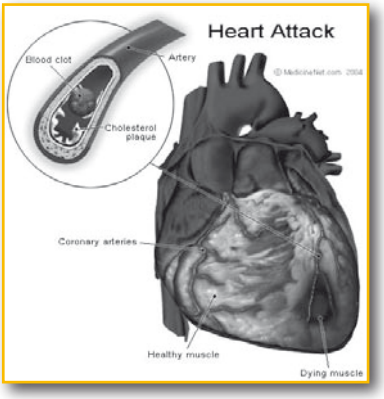
- Norwegian study: positive neuropsychological development at 4- years when the mother received cod liver oil throughout pregnancy and the infant was given cod liver oil the first 3 months (Helland et al, 2003).

However:

- High intake of marine n-3-PUFA early in pregnancy associated with increased risk of hypertension and pre-eclampsia (Olafsdottir, 2006).

Conclusion: some is good, more is not necessarily better

FISH AND CARDIO-VASCULAR DISEASE



- Many epidemiological studies since 1985
- Some studies show protective effects associated with fish consumption
- … and others do not

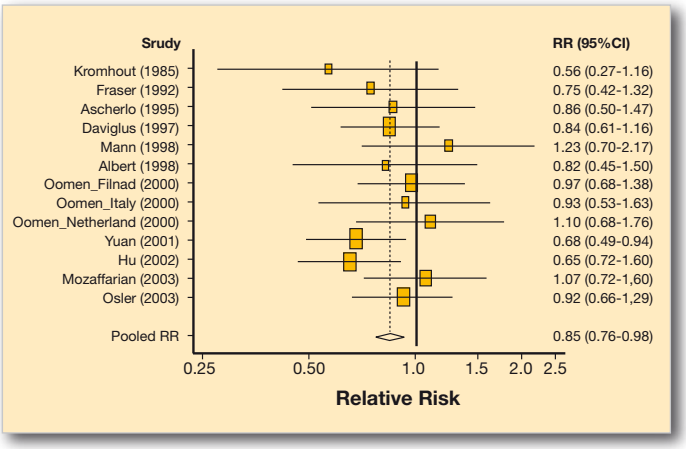
Kromhout 1985 (Zutphen-study)

- 852 men followed for 20 years
- Endpoint: coronary death

Fish consumption	Risk ratio
0 g fish/day	1
1 - 14 g/day	0.64
15-29 g/day	0.56
30 - 44 g/day	0.36
> 45	0.39

New Engl J Med 1985;303:1205-9.

Meta-analysis, fish and cardio-vascular diseases (He et al 2004)



Pooled estimate of RR and 95% CI of CHD mortality rates for fish consumption 1/week vs <1/month. Squares indicate adjusted RR in each study. Size of the square is proportional to the percent weight of each study in the meta-analysys; horizontal line represents 95% CI. Studies are ordered by year of publication. Pooled RR and 95% CI are indicated by unshaded diamond.

CONCLUSIONS: These results indicate that fish consumption is inversely associated with fatal CHD. Mortality from CHD may be reduced by eating fish once per week or more.

Studies showing beneficial effect:

- Populations of low consumers
- Beneficial effect only related to n-3 PUFA in one study
- Largest difference between consumers and non-consumers
- Also low intake of lean fish may be beneficial

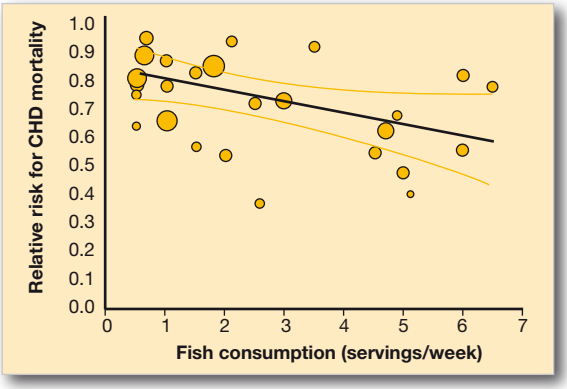
Studies not showing a beneficial effect:

- Populations with high intake of fish - 'More is not necessarily better'
- Mercury might modify the beneficial effect of n-3 PUFA (Virtanen 2005)
- Other modifiers?

The whole meal, not only the fish is important:

- Norway: Fish, particularly lean, is eaten together with melted butter and potatoes
- Spain: Fish is eaten together with onion, garlic, tomato and potatoes (baccalao)

Is there a dose-response-relationship?



Regression of CHD mortality risk versus fish consumption in the general population. Note: The area of each data point is proportional to its statistical weight. The upper and lower bands denote the 95% confidence interval on mean of the predicted value. CHD, coronary heart disease.

(König et al 2005)

Fish and cardio-vascular disease conclusions

- Fish consumption has a beneficial effect on cardio-vascular disease and mortality
- Amount? Increasing fish consumption is probably more efficient for those with no or low intakes
- Based on König 2005: Increasing fish intake by one serving per week might reduce coronary mortality by 4 % or 300 cases per year in Norway

CONTAMINANTS

Most important in fish:

- PCB and dioxins
  (the focus of this presentation)
- Organic mercury
- Mercury exposure well below the PTWI
- Consumption of predatory fish species (pike, trout, tuna, halibut) might lead to excursion of the PTWI - dietary advice for pregnant women

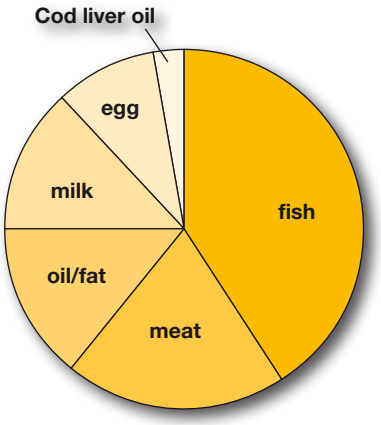
Methyl mercury

- Estimates show that even for those who eat large amounts of fish, the mercury exposure falls well below the PTWI
- For some fish species (e.g. predatory fish species, pike, trout, tuna, halibut) the mercury content is higher and consumption might lead to excursion of the PTWI. Hence, dietary advice for pregnant women is well founded.

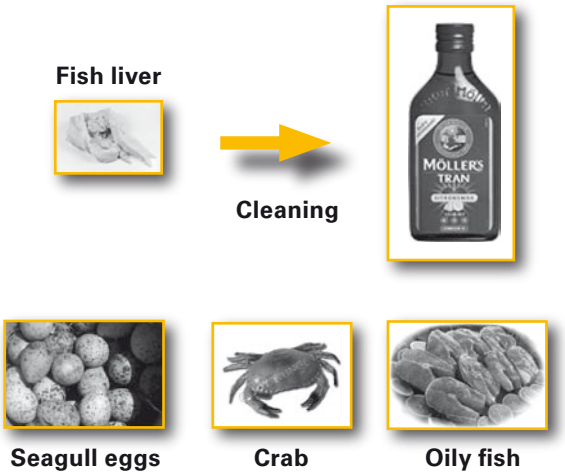
PCB-exposure during foetal life

- Epidemiological evidence for neurodevelopmental effects associated with PCB exposure:
  - BMD **(1 ug/g lipid)** and BMDL about **0.6 ug/g lipid** of the Michigan study (EFSA 2005).
- Exposure level in Norwegian women (fertile age) is below 0.181 ug/g lipid **(PCB7)** in blood and breast milk. Corresponds to about 0.3 ug total PCB /g lipid.
- Exposure level well below BMD

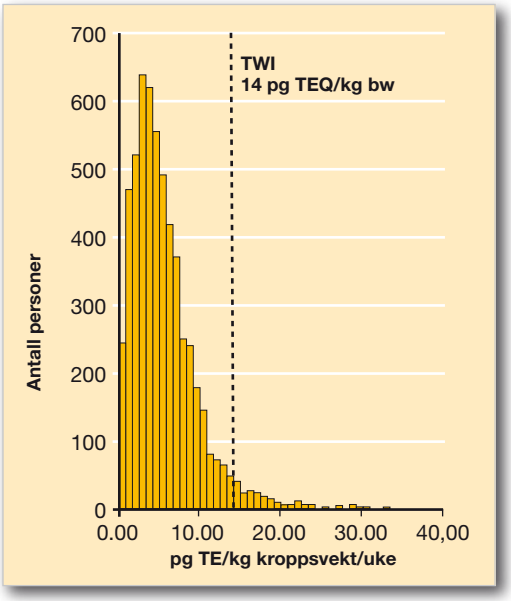
Intake of dioxins and PCB from different foods in Norway



Seafood "naturally high" in PCB/dioxin



Total intake, pg TEQ/kg bw/week from fish and seafood



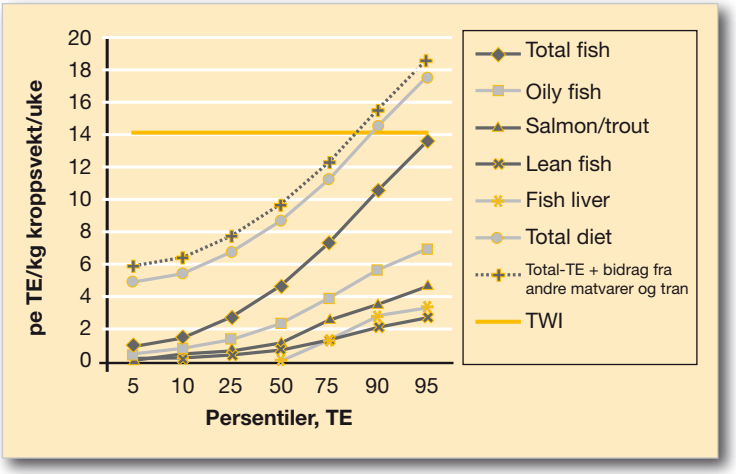
Based on "Fish and game study"

Nation wide study

n = 5663 (18 – 79 years)

95 percentile 13.7 pg TEQ/kg bw.

Exposure to dioxins and dl-PCB - contribution from different fishes



Toxicological aspects

- At least 85% of the adult Norwegian population has an estimated total intake of dioxins and dl-PCB below the TWI.

Scenarios – contaminant exposure from fish

Intake scenarios		Lavkonsument 10-persentil 1 måltid/uke (27g/dag)	Median intake 50-persentil 2 måltider/uke (65g/dag)	High consumer 90-persentil 4 måltider/uke (199g/dag)
		pg TEQ /kg b.w./week		
Kvikksølv (µg)	Mager fisk	0,1	0,2	0,4
	2/3 mager og 1/3 fet fisk	0,1	0,2	0,4
	Fet fisk	0,1	0,2	0,4
dl-PCB (pgTE)	Mager fisk	0,1	0,5	0,6
	2/3 mager og 1/3 fet fisk	0,8	1,8	3,4
	Fet fisk	2,6	6,3	12
Dioksin (pgTE)	Mager fisk	0,1	0,3	0,6
	2/3 mager og 1/3 fet fisk	0,4	0,9	1,6
	Fet fisk	1,3	3,1	5,6
Dioksin +PCB (pgTE)	Lean fish	0,3	0,9	1,2
	2/3 Lean fish 1/3 fatty fish	1,1	2,7	5,0
	Fatty fish	3,9	9,3	17

Four dinner servings of fatty fish.

Summary - toxicological perspective

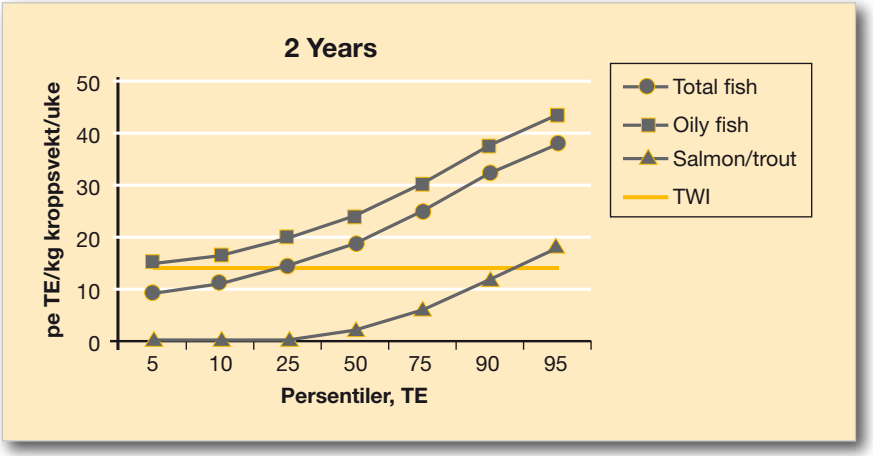
- There is no risk associated with eating fish and other seafood equivalent to 4 meals or more per week...
  - ▷ when consumption is varied (lean and oily)
  - ▷ and provided the oily fish, at the current level of dioxins and dl-PCB, does not constitute more than two meals per week
  - ▷ this is especially important in regard to fertile women.

Young women and increased intake of fatty fish

- Based on knowledge about young women's consumption of fatty fish (95th percentile, 1.5 dinner meal)

- There is little reason to believe that a general recommendation to increase fish consumption would result in fertile women consuming fatty fish > 2 dinner servings/week over a prolonged period...
  resulting in an intake of dioxins and dl-PCB exceeding the TWI and constitute a health risk for the foetus

Exposure in children to dioxins and dl-PCB from fish alone and from the total diet and also cod liver oil.



Reduction of human exposure to dioxins and PCB and fish farming

- Level of contamination similar in wild and farmed fish
- Level of contamination in wild fish can only be reduced by reducing emission of contaminants to the environment
- Exposure to dioxins and dl-PCB from farmed fish can be reduced within a reasonable time frame without reducing the consumption of oily fish

FISH FARMING

- Reduced contamination of farmed fish can be done by choosing feed ingredients naturally low in organic contaminants or by introducing cleaning processes (nutritional value should be secured)
- The total exposure to dioxins and dl-PCB from the whole diet can be reduced by about 25% by reducing the level in fish from 2 to 0,5 pg TEQ/ g fish.
- The implication of a reduction to a level of 0.5 pg TEQ/g in farmed fish:
  - ▷ the adult population would not exceed the TWI for dioxins and dl-PCB
  - ▷ consumption of oily fish does not need to be restricted

Integration of nutritional and toxicological aspects of fish as food

- Generally Norwegians can eat more fish, and both lean and fatty fish should be included
- The adult part of the population, particularly those at risk for cardio- vascular disease, will gain the greatest health-related benefit from increasing their consumption of fatty fish in particular
- The next group to benefit is pregnant women due to the potentially beneficial effects on pregnancy and foetal development
- Consumption of fish has not been shown to increase or reduce the risk of any common form of cancer
- The level of exposure to PCB in Norwegian women is presently well below the level were lasting neuro-developmental effects have been seen

BENEFITS AND RISKS

- Some children may exceed the TWI of dioxins and dl-PCB via the diet, but for most children (2-13 years) the contribution from foods other than fish is dominating

- Even if small children might overstep the TWI during the first years of life by eating fish and cod liver oil, the positive effects of eating a varied diet, outweighs any possible negative effects. For children growing fast the body burden of dioxins and PCB will be diluted.

Conclusion - benefits and risks

- VKM supports the general Norwegian recommendation to eat more fish, both on bread and for dinner

- The level of contaminants in cod liver oil and farmed fish should be monitored closely. The manufacturers should be encouraged to ensure that their products contain the lowest possible level of organic pollutants.

- The levels of nutrients in fish feed should also be monitored.

Thank you for listening!

INSTRUCTIONS FOR DISCUSSION GROUPS

ORGANISATIONAL DETAILS

- 4 parallel discussion groups
- 17:00-19:00 DG 1st round (day 1)
- 08:30-10:30 Touch base with Plenary (day 2)
- 11:00-13:00 DG 2nd round
- 14:00-16:45 Final Plenary session – conclusion and recommendations

Focus of the colloquium is only on methods and approaches for

HUMAN HEALTH RISKS

HUMAN HEALTH BENEFITS

DISCUSSION GROUP THEMES

DG 1 and DG 2:

Nutrient content of food vs. toxic contaminants/constituents

e.g. fish, cereals, vegetables, meat

DG 3

Risk and benefit analysis of food fortification and functional foods

e.g. calcium, phytosterol esters, iodine, folate

DG 4

Food preservation vs. microbial hazards

e.g. minimally processed food, poultry carcass treatment, nitrate,

ISSUES TO BE DISCUSSED

- What risks and benefits should be considered?
- What risks and benefit can be quantified?
- What tools/data do we currently have?
- What tools and data would be needed?
- What type of risk-benefit analysis do we need?
- Risk-benefit analysis for different population groups?
- When should we carry out a Risk-benefit analysis?
- Can we define a common currency?
- Where is borderline to risk management?

SUMMARY REPORT OF COLLOQUIUM

- Draft summary report of colloquium to be prepared by rapporteurs (Sept 2006)
- 1st review by DG chairs and rapporteurs (Oct. 06)
- Review of revised draft by all participants (Nov. 06)
- Publication of summary report and power point presentations on EFSA website (Dec. 06) and in EFSA Science Colloquium Report Series (Mar. 06)

Annex 4: Slides of Discussion Groups

DISCUSSION GROUP 1

NUTRIENT CONTENT OF FOOD VS

TOXIC CONTAMINANTS/CONSTITUENTS

Day 1 and 2

1. What human health risk and human health benefits effects should be considered ?

- **Definition risk: see 178/2000/EU**
  (concerns morbidity, mortality, development), includes Nutritional risk (see CCNFSDU discussion paper on risk analysis: both deficient and excessive intake)

- **Definition benefit:** it is proposed to convert the definition of risk into positive wording or any identifiable positive effect in connection with food, includes reduction of risk

  It is important to describe precisely both the risk and the benefit to be assessed and to formulate clearly the task, its scope and its intention.

2. What human health risks and human health benefits can be quantified ?

- Those that can be clearly identified
- Those for which data of good quality are available (such data should be preferably human, interventional and epidemiological; with animal data their relevance for humans needs to be considered)
- Those for which causality with food or food components exist
- Those for which reliable exposure assessment is possible
- Those for which valid markers of effect are available
- Those which permit a dose-response assessment
- Those which both manifest in the same population group (example methylHg in fish and negative versus positive developmental effects in infants/children, Cohen et al., 2005)
- The decision for a risk-benefit analysis must be made on a case-by-case basis and must be justified

3. What tools/data do we currently have to quantify the human health risks and human health benefits ?

- The benefit assessment steps should mirror the classical risk assessment steps (benefit identification, *benefit characterisation*, dose-response assessment, exposure assessment, *probability-for*-benefit characterisation).
- The description of data gaps, uncertainties, assumptions and interpolations needs to be transparent.
- Human dose response curves or data for benchmark dose fitting are mostly not available for foods and scarce for single nutrients.
- Further discussion in the group with respect to the availability of tools and the feasability of their application: *preferability of probabilistic modelling*.

4. What tools/data would be needed to quantify the human health risks and human health benefits ?

- Reliable exposure data (intake, food composition data *which are actual*) with known distribution for eventual modelling
- Consideration of food variability, matrix effects on bio-availability and interaction between components
- Proof of causality between food, food components and adverse or positive effects
- Simultaneous availability of both tools and data

5. What type of risk-benefit analysis is needed ? (systematic qualitative assessment, semi-quantitative assessment, fully quantitative assessment)

- Risk-benefit analysis of food should not be performed as a routine procedure, but in those cases only where an impact on public health outcomes can be expected.
- Quantitative assessment is to be preferred; for qualitative and semi-quantitative analysis the detailed description of the process and of all uncertainties and deductions is crucial.
- The decision which type of risk-benefit analysis is performed is largely determined by the availability of data.

6. Do we need risk-benefit analysis for different population groups ?

- Yes
- Agreement with other groups
- In addition to YOPI, identified genetic polymorphims in a population should be considered; this can determine the need for data and the assessment
- In addition, the potential different time frames for the manifestation of risks and benefits should be considered

7. When is it useful to carry out a risk-benefit analysis ?

- When the result of the risk-benefit analysis is likely to have a desirable impact on public health
- When nutritional and dietary advice to the population is revised, to assess prospectively the possible positive or negative consequences on dietary behaviour, nutritional status and public health

- When the risk manager needs such analysis to help him making decisions
- Risk-benefit analysis should not result in confusing messages and should not result in destroying the trust in the safety of food in general
- No *a-priori* exclusion of groups of compounds or foods.

8. What could be a common scale of measurement to compare human health risks and benefits ?

- A "common currency" will facilitate the communication of the result of the RB analysis. More research and experience with different approaches is needed.
- This "common currency" can differ for different RB analyses, therefore, no general applicable measurement scale is likely to be developed.
- Possible "currency" is incidence, DALY, QUALY etc. Experience is needed to guide the choice of which for which issues.
- The assessment of both the risk and benefit have to be performed under the same criteria for weighing the evidence and identifying uncertainties. The comparison of the results can be performed by the assessor, the manager or, even, the consumer.
- The aim of the RB analysis process is not a judgement on acceptability or safety!
- The presentation of the result of the RB analysis must fit the pre-defined purpose of the request.

9. Where is the borderline between risk-benefit analysis and risk management ?

- The borderline between RB analysis and risk management is not fixed and can shift with the nature of the output.
- Communication between assessors and managers, with possible inputs from stakeholders, is essential throughout the process *(formulation of the task determines the form of the output; continuous interaction between assessors and managers will help in a specific RB analysis for instance in choosing the common measurement scale).*
- The borderline is the delivery of the output of the RB analysis by the group of assessors to the risk manager.
- The output should include a clear narrative.

General recommendation

- A guidance document should be developed by e.g. EFSA with respect to methodology, approaches, tools and potential pitfalls in RB analysis.

DISCUSSION GROUP 2

NUTRIENT CONTENT OF FOOD VS TOXIC CONTAMINANTS/CONSTITUENTS

Day 1 and 2

Preamble remarks

- The Questions are interlinked, are not independent
- Problem formulation "why is the RB done" is pivotal
- We should clearly understand the RB question
- Each RB needs a narrative up-front; otherwise can be misunderstood
- The confidence in the outcome of a RB analysis
  - ▷ The assumptions for the RB analysis should be clear
  - ▷ Uncertainties should be clear

1a. What human health risk and human health benefits effects should be considered ?

- 1. Holistic way (cf NL) : diet as a whole.
- 2. More specifically (cf NO: fish, supplements, fufoods)
- Problem formulation: when do we need it?
  - ▷ 1 compound (eg micronutrients, eg medicines)
  - ▷ 1 food (eg fish: xenobiotics vs nutrients)

1b. What human health risk and human health benefits effects should be considered ?

- To help policy makers in their decisions: To inform consumer choices, no conflicting messages, nutritious food versus food safety makes confusion
- **Consumer** need indications to select proper food within a category (fruit, fish, meat, eggs ...); need more nutrients to reach RDI but cannot surpass TWI etc
- **Regulatory**: Measures from risk point of view: can prevent availability of food (health consequences of not eating a food)

2. What human health risks and human health benefits can be quantified ?

- Magnitude of effects is relevant; needed for quantification

- "none", only rarely sufficient data to quantify

- Health risks/benefits that are amenable to be studied by observational studies, intervention studies, animal data (need markers of exposure and effect)
- Can be quantified where you have good data. Need toxicologists and nutritionists (re health benefits), but can be difficult (re uncertainties of the relationships); use results from claims substantiation data

3. What tools/data do we currently have to quantify the human health risks and human health benefits ?

- Risk calculation (eg TDI is tool for safety assessment) (RDA is tool for nutritional intake): are NOT appropriate for quantitative RB (use animal dose-response data and transfer to human data; use the established tools)
- Uncertainty should be discussed in a narrative way
- Use available (national) data from human studies (epidemiology monitoring or intervention data)
- Exposure is crucial tool; but data often not available (fish ≠ fish)

4. What tools/data would be needed to quantify the human health risks and human health benefits ?

- Classification of hazards and of benefits
- Compare and prioritise
- Qualitative tools are there, but quantitative assessment is confronted with many uncertainties
- The more data are available the more quantitative the RB assessment can be done
- See also Q8: common scale of measurement

5. What type of risk-benefit analysis is needed ? (systematic qualitative assessment, semi-quantitative assessment, fully quantitative assessment)

- Overall dietary advise (eg RIVM report) and/or regulating food, food ingredients; is also problem formulation
- Advise to risk manager: impact has to be considered
- Use a tiered approach: start with categorisation
- Only when you have the question and political place: then decide on the type of RB analysis (full quantitative versus rapid answer)
- Difficult to compare quantitative assessment with an emerging qualitative assessment: task for risk manager
- RB of breast-feeding nice example to objectively weigh risks vs benefits, but entails more than mere scientific aspects (different per country/region)

6. Do we need risk-benefit analysis for different population groups ?

- Yes: different population groups have to be assessed (benefits as well as risks)
- Benefit in 1 population group vs risk in another population
- Set limits on the basis of decisions for public health?: one group perceiving the benefits and others the risks. Other (higher) limits (e.g. TUIL's) can have health impacts.
- Any choice is a choice, e.g. folic acid (NTD versus masking B12 deficiency)

7. When is it useful to carry out a risk-benefit analysis ?

- For regulated substances (e.g. additives) generally not needed but RB assessment can be worthwhile in certain situations.
- RB for economic and technology reasons (i.e. in food production chain) is outside scope of EFSA

Preamble remarks

- Guidance/ guidelines for performing RB analysis: Need some framework, but too premature to formulate guideline. Therefore narrative important (transparency)
- Need glossary / speak common RB language
- RB analysis is an iterative process; RB analysis paradigm involves:
  RB assessment, RB management, RB communication
- RB can improve our argumentation and understanding, and communication
- Mechanism / causality → confidence
- Requirement for RB communication in any form

*** TDI and RDA not appropriate for RB?**

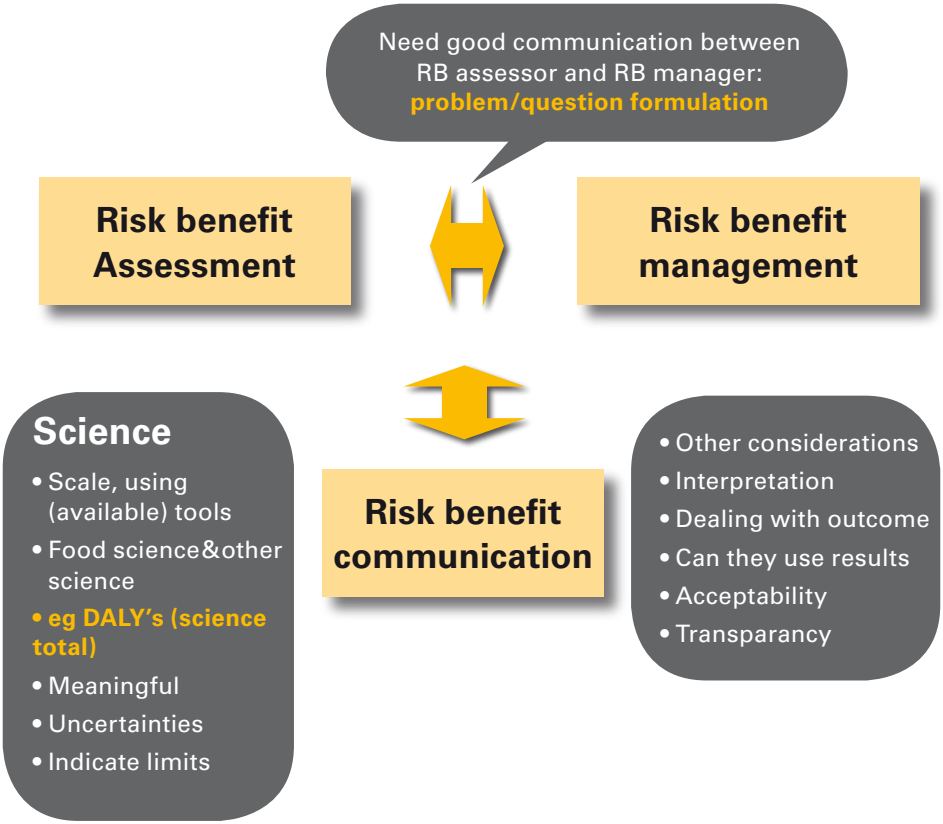
- TDI, RDA useful for identifying whether or not we need RB; can be used for qualitative consideration
- TDI and RDA are not appropriate **tools** for **quantitative** RB

8. What could be a common scale of measurement to compare human health risks and benefits ?

- Do we need a common metric?
  Depends on the question: **narrative!** (qualitative, quantitative)
- Difficult to compare the incomparable.
- Make clear where the uncertainties are. Compare relative confidence on benefits with uncertainties on risks
- Incidences -> 1 currency (DALY's, # days lost, ..) ->€€ /costs
- NL: DALY's and QALY's. Possible to apply DALY's? Are data available?
- DALY's are for societal considerations unlike for the individual <-> **when societal considerations are needed, RB with common currency needs to be performed**
- €€ instead of DALY's? Tricky: requires equal cost structures across countries, world; difficult to communicate

9. Where is the borderline between risk-benefit analysis and risk management ?

- Risk benefit analysis paradigm = iterative process



DISCUSSION GROUP 3

RISK AND BENEFIT ANALYSIS OF FOOD FORTIFICATION AND "FUNCTIONAL FOODS"

Day 1 and 2

1. What human health risk and human health benefits effects should be considered ?

- Consider folate as a case study to exemplify considerations (other useful cases: phytosterols, long-chain omega-3-fatty acids, iodine, iron, vitamin D, zinc, calcium)
- Benefits: NTD prevention, prevention of megaloblastic anaemia (in elderly?), possible CV benefits, possible reduction in cancer risk
- Risks: Masking of pernicious anaemia (vit B12), interactions with anti-folate drugs, possible increase in cancer risk
- Risks and benefits specific to particular groups in the population – separate analyses for different sub-groups
- Which effects should be considered will depend on the existence and quality of data, i.e. strength of evidence
- Long latency effects may be difficult to pick up

2. What human health risks and human health benefits can be quantified ?

- Those effects for which there is evidence for causality (epi, RCT, tox studies)
- Weight/strength of evidence for effects to consider (epi, mechanistic studies, etc)
- Risks – usually the available human data will be poor, may have to rely on tox data
- Dose-response data and shape of dose-response curve invaluable for quantification
- Sensitivity of endpoints in human studies (background, latency, at risk populations)?

- Biomarkers for earlier/more sensitive detection?
- Benefits: NTD prevention (but DR data not ideal)
- Other benefits and risks can only be estimated
    - ▷ Will require a number of assumptions and considerable uncertainty

3. What tools/data do we currently have to quantify the human health risks and human health benefits ?

- Importance of specification of nutrient form
- Information on dose-response relationship (epi, RCTs, medical records, tox studies)
- Need good data on dose (intake) and response
- Quantification of benefit at a range of fortification levels of folate(for NTDs) and in eliminating folate deficiency in the elderly (based on DR)
- Estimation of risks of masking of B12 deficiency
- Deterministic approaches, using PODs (NOAEL, LOAEL, BMDx) and SFs (possibility of CSAFs)
- Identification of population at risk or likely to benefit (numbers or proportion)
- Cannot compare risks with benefits directly

4. What tools/data would be needed to quantify the human health risks and human health benefits ?

- Data in relevant sub-populations for risks and for benefits
- Good quality DR data
  - ▷ Good quality exposure data
    - • *Intake data*
    - • *Validated, robust biomarkers of exposure*
  - ▷ Effect measures in humans on risks and benefits
    - • *Including validated, robust biomarkers*
      - *- Importance of animal studies in biomarker development*
    - • *Especially for long term outcomes*
- Probabilistic approaches to risk benefit assessment
  - ▷ On both exposure and effect measures
- Relevant animal data
  - ▷ Mechanistic studies
  - ▷ Biological comparability (PK and PD)
  - ▷ Characterisation of DR
- Some means to compare risks and benefits directly

5. What type of risk-benefit analysis is needed ?

(systematic qualitative assessment, semi-quantitative assessment, fully quantitative assessment)

- All of these. It will depend upon the needs of the risk manager
- Decide on a case-by-case basis
- Availability of the data
- Tiered approach may be helpful
  - ▷ If qualitative analysis indicates risk clearly outweighs benefit or vice versa, this may be sufficient

6. Do we need risk-benefit analysis for different population groups ?

- Yes, essential
- Even if final output is on a population basis (e.g. when considering mandatory fortification) it will be necessary to evaluate risks and benefits in the appropriate population groups
- Such information may be of value to risk manager both for policy and in communication
- Eventually, such information will be needed for a combined risk-benefit assessment

7. When is it useful to carry out a risk-benefit analysis ?

- When there is, or likely to be, a narrow margin of safety
- Prioritised when the risk or the benefit is thought to be very great (to check this assumption and to determine residual benefit or risk), case of need
- When dietary consumption changes significantly (qualitatively or quantitatively) as a consequence of fortification, introduction of functional foods, etc
- Risk-benefit analysis may be useful prior to launch or post-launch, with different objectives

8. What could be a common scale of measurement to compare human health risks and benefits ?

- Would need appropriate, relevant data on risks and benefits
- Health-related quality of life indices

- ▷ QALYs or DALYs
- ▷ Aggregate measure (population-based)
- ▷ Narrative on which sub-populations are relevant for risks and benefits, if different
- ▷ Useful for prioritisation and decision making by risk manager
- ▷ Quantification of QoL (which instrument), will need refinement
    - *Use of both human and animal data*
- ▷ Ability to compare dissimilar endpoints
- ▷ Can inform on whether or not to apply precautionary principle
- ▷ Communication issues

- EUROS
    - ▷ Substantial communication issues

- Quantification of specific risks and benefits
    - ▷ Benefit and risk to individual (probability and severity)
    - ▷ Importance of not just comparing probabilities of risks against benefits for dissimilar effects above or below limit values
    - ▷ Consumer choice when this is an option

- Probabilistic approaches to assessment of risks and benefits

- Incorporation of uncertainty
    - ▷ Output using different assumptions
        - *Sensitivity analysis*

9. Where is the borderline between risk-benefit analysis and risk management ?

- Need for clear problem formulation and that RB analysis addresses the needs of the risk manager, importance of dialogue
    - ▷ But need to ensure independence of processes

- Scientific tools are becoming available to allow the assessor to quantify risks and benefits, moving RB comparison from risk management into risk assessment

- Acceptability of QALYs or DALYs by risk managers
  - ▷ Need for accompanying narrative, including evaluation of uncertainty

- Weighting of HRQoLIs, by whom? Involvement of more than just scientific assessors – interface between RA and RM?

- Applicability of DALYs and QALYs across EU?
  - ▷ Harmonisation of derivation of DALYs and QALYs
  - ▷ Quality assurance of DALYs and QALYs

- Risk-benefit analysis should be extended to the extent possible, including presentation of alternative outputs based on sensitivity analysis

- Avoid conclusions that overlap into risk management

- Identify data deficiencies and their consequences for the RB analysis

DISCUSSION GROUP 4

FOOD PRESERVATION VS. MICROBIAL HAZARDS

Day 1 and 2

1. What human health risk and human health benefits effects should be considered ?

- **Food-borne microbiological health risk and benefit**
  Getting ill vs not getting ill
  - ▷ **Acute illness**, (outbreaks)
  - ▷ Also need to consider **long-term health effects** (e.g. campylobacter, starts with acute infection and later chronic disease)

- Preservation – can have also **negative effects on nutrition**

- Risk of chemical residues from use of preservatives (benzoates)

- Benefit: longer shelf-live and wider distribution (– risk is wider spread of disease)

- Benefit – ensuring confidence in food (regulators & consumer) - i.e. making choices based on nutrition without having to worry about MO

Examples:

- Minimally processed foods (fresh fruits and vegetables – 20-25% food-borne outbreaks)

- Nitrite in meat products

- Probiotics: benefit for parts of population can be risk for other parts

- Active chlorine used in food processing

- Salt: reduction of pathogenic bacteria – but too much salt increase other health risk (CVD)

- Preservation technologies, incl. packaging, have beneficial effects (Important: process of preservation)

2.+3. What human health risks and human health benefits can be quantified and what tools do we have?

- Number of **outbreaks** – measure of risk (population) (increase and decrease) – acute
  - ▷ Problem: can have other reasons than food preservation
  - ▷ Epidemiological link – food and people
  - ▷ Home prepared foods, retailers, food service
- **Background incidence** of disease – laboratory test (individuals)
- **Sentinel studies** (very expensive, but very informative if done properly)
- **Population studies** (very expensive, but very informative if done properly)
- Incidence of outbreaks – quantify impact of disease in population (burden of disease)
- Mandatory reporting of outbreaks (IHR) – when enforced can contribute to quantification of disease incidence etc.
- Nutritional status (in certain population) can be quantified
- Beneficial effects of food preservation – comparison with historical data (difficult) – decrease of outbreaks
- Days of work lost
- DALYs????????
- Reduction on cost for drugs (decrease in use of medicines to treat infections, works only if food borne outbreak known/confirmed)
- Cost of food-borne diseases (e.g. total health burden of salmonellosis, expressed as cost factor)

4. What tools/data would be needed to quantify the human health risks and human health benefits ?

- Moving from qualitative to quantitative MRA – but lots of data gaps
- Epidemiological studies – almost none for effects of chemical residues (preservatives)
- Epidemiological studies on MO (only for very few micro-organisms)

5. What type of risk-benefit analysis is needed ?(systematic qualitative assessment, semi-quantitative assessment, fully quantitative assessment)

- **All of the above**
- BUT: not possible because of data gaps
- Food orientated or agent oriented?

6. Do we need risk-benefit analysis for different population groups ?

YES

- E.g. YOPIs
- E. sakazakii –infants
- Hospital patients

7. When is it useful to carry out a risk-benefit analysis ?

All the time..... (done on single food item)

- Before implementing new measures
- Risk of treatment vs not having the food on the market
- If new knowledge emerges – trigger for RB analysis

BUT:

- Need appropriate data
- Waste of resource if benefit by far outweighs the risks(at least qualitative – e.g. pasteurization)

8. What could be a common scale of measurement to compare human health risks and benefits ?

- Money....based on e.g.
  - ▷ days of work lost,
  - ▷ cost of food-borne diseases (e.g. total health burden of salmonellosis)
- DALYs

Advantages:

- established procedure to compare different risks (e.g. acute micro vs chronic chemical, i.e. very different nature of risk)
- time-scale (includes whole life span)
- guidance to risk manager to prioritize
- direction on targeted intervention measures

Difficulties/Disadvantages:

- needs clear messages so that numbers are not taken out of context – long-term perspective (just consider individual 'numbers' and forget the whole picture)
- difficult to include preventive aspects (effects of preservation)
- absence of risk rather then benefit?
- can toxicological risk assessment (animal studies) be expressed as DALYs?
- QALYs
  - ▷ appears as quantitative - but still based on lots of assumptions
  - ▷ more difficult to measure

Other Option: (depending on the question and on the database)

- Not combine in common currency risks and benefit – detailed description and leave decision to risk manager
- Express as change in risk or benefit (increments) (risk+benefit differences)

9. Where is the borderline between risk-benefit analysis and risk management ?

What is the purpose of this question?????

- RBAssessor – presents options to RManager (if possible 'rated', i.e. (semi-) quantitative)
- RM – responsibility is to combine all aspects
- Guidance as to cost of 'actions' (e.g. cost of changes in dietary habit much higher than cost for intervention to reduce a specific food pathogen – linked to DALYs)
- Money – calculation by RBA (except economical aspects), cost of various interventions (objective way)

- Important (and obvious): good communication – mutual respect – interactive/ iterative process

Additional Remarks

- RB analysis has to be multidisciplinary (e.g. MDs)
  - ▷ Difficulty of different expert groups looking at different parts of the RB assessment

- Considered only microbiological risks – because chemical and physical preservation not considered a health risk.....(regulatory approval process before implementation, however may have some gaps);

  EXCEPTION – allergens

- In case of unintended/newly identified 'effects' (e.g. residues, nutritional impact) – RB assessment done on case-by-case basis (still often microbiological benefit outweighs chemical risk)

- Need to have clear question

- Holistic approach – complexity of issue, several questions to be addressed

- **Problem:** lack of transparency in final decision making by risk management

TM-AD-07-001-EN-C

ISBN 978-92-9199-031-3

Largo N. Palli 5/A
I-43100 Parma
Italy

Tel: +39 0521 036 111
Fax: +39 0521 036 110
info@efsa.europa.eu
www.efsa.europa.eu