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A review of Risk and Benefit Assessment procedures

– development of a procedure applicable for practical use at NFA

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Innehåll

Abbreviations

ADI	acceptable daily intake
AR	average requirement
BD	benchmark dose
CAC	Codex Alimentarius Commission
CHD	coronary heart disease
COI	cost of illness
DALY	disability adjusted life years
DRV	dietary reference value
EFSA	European Food Safety Authority
EHEC	Enterohemorrhagic E. coli
HALY	health adjusted life years
HBGV	health-based guidance value
LCPUFA	long chain polyunsaturated fatty acid
LI	lower intake level
LOAEL	lowest observed adverse effect levels
MCDA	multi-criteria decision analysis
MRA	microbiological risk assessment
NFA	National Food Agency
NOAEL	no observed adverse effect level
NRBA	nutritional risk-benefit assessment
OLF	other legitimate factors
QALY	quality adjusted life years
RDA	reference daily intake
RfD	reference dose (for health effect)
RI	recommended intake
RIVM	Dutch National Institute for Public Health and the Environment
TDI	tolerable daily intake
TRA	toxicological risk assessment
UL	safe upper limit of intake
WTP	willingness to pay
YLD	years lived with disability
YLL	years of life lost

Sammanfattning

Hittills har utvärderingen av risker och nyttor, som utförts av experter vid livsmedelsmyndigheter eller av internationella organisationer som WHO och FAO, i huvudsak varit separata processer där risker har haft den största betydelsen för livsmedelslagstiftningen. Eftersom ett livsmedel, och även samma livsmedelsingrediens, kan vara förenad med både gynsamma och skadliga hälsoeffekter är det viktigt att beakta både hälsorisker och nyttor i hanteringsprocesser. Följaktligen har ett ökat behov och krav för kombinerade bedömningar av risker och nyttor i livsmedel under senare år växt fram. Således behöver både potentiella risker och nyttor vägas, företrädesvis genom användandet av integrerade mått på hälsa, vilket i det ideala fallet uttrycker risker och nyttor enligt samma måttstock.

I Sverige är Risk-och Nyttovärderingsavdelningen vid Livsmedelsverket ansvarig för risk- och nyttovärderingar inom livsmedelssektorn och man har där sammanfört vetenskapliga dicipliner inom toxikologi, nutrition och mikrobiologi. Vid avdelningen initierades därför ett projekt med det övergripande målet att utveckla en generell procedur för risk-nyttovärderingar för att praktiskt kunna användas vid Livsmedelsverket. Som ett första steg i att utveckla en sådan procedur genomfördes en översikt och utvärdering av i dagsläget tillgängliga metoder/modeller avseende risk-nyttovärderingar som använts av nationella och internationella organ.

I vår översikt av litteraturen fann vi att den dominerande metoden/modellen för risk-nyttovärderingar var en stegvis utvärdering i olika nivåer. Integrerade risk-nyttovärderingar har utförts inom flera dicipliner som medicin, miljö-hälsa, livsmedelsmikrobiologi, livsmedel och nutrition, ekonomi, marknadsföring-ekonomi, och konsumentuppfattningar. Likheter och skillnader i de ovannämnda områdena för risk-nyttovärderingar identifierades. Hittills har man dock inte enats internationellt om generella principer eller metoder/modeller för hur risk-nyttovärderingar ska utföras inom livsmedelsområdet och för ämnen i livsmedel.

I projektet användes arbetsflödet som föreslagits av den Europeiska myndigheten för livsmedelssäkerhet (European Food Safety Authority, EFSA) som utgångspunkt för att ta fram en för Livsmedelsverket avsedd procedur för risk-nyttovärderingar. En stegvis utvärdering i olika nivåer bör vara den procedur som företrädesvis ska användas vid alla risk-nyttovärderingar. Detta beror på att, förutom typen av fråga/problem, är det tillgången och typen av data som bestämmer tillvägagångssättet, alltså huruvida bedömningen kan och behöver vara kvalitativ och/eller kvantitativ. Fördelen med en stegvis procedur är att den för utvärderaren är konceptuellt lätt att använda och främjar transparans i processen. Den föreslagna proceduren för risk-nyttovärderingar omfattar 3 steg, från kvalitativa skattningar av risker och nyttor var för sig, till kvantitativa skattningar av risker och nyttor enligt samma måttstock. Proceduren tillämpades i en pilotstudie som omfat-

tade en bedömning av om mängden nitrit och salt kan minskas i processat kött (charkprodukter) i kombination med en minskad maximal lagringstemperatur. De potentiella nyttorna för populationen i stort av ett minskat intag av nitrit och salt jämfört med risken att drabbas av *Clostridium botulinum* och *Listeria monocytogenes* infektioner bedömdes.

I pilotstudien kunde de inledande två stegen tillämpas. I huvudsak konstaterades att en minskning av nitrit och salt inte påverkar tillväxten av mikroorganismerna och bara har marginella effekter på folkhälsan om lagringtemperaturen hålls vid 5^{o}C. En minskning av lagringstemperaturen från 8^{o}C till 5^{o}C skulle emellertid resultera i en positiv effekt i form av minskad tillväxt av *L. monocytogenes*, medan ingen sådan effekt skulle uppnås för *C. botulinum*.

Summary

So far the assessments of risks and benefits, performed by experts at food agencies or in international organisations, such as WHO and FAO, have largely been separate processes, where risks have received the highest impact on food legislation. Since foods, and even the same food ingredient, may be associated with both beneficial and adverse health effects it is important to consider both health risks and benefits in management processes. Consequently, an increased demand for combined assessments of risks and benefits in food has evolved during recent years. Thus, both potential risks and benefits need to be balanced, preferably by the use of integrated measures of health, which ideally expresses risk and benefit on the same scale.

In Sweden risk-benefit assessments in the food sector are the responsibility of the Risk and Benefit Assessment Division at the National Food Agency (NFA), which brings together the scientific disciplines toxicology, nutrition and microbiology. A project was therefore initiated with the overall aim to develop a general procedure for risk-benefit assessment applicable for practical use at the NFA. As a start to develop such a procedure an overview and evaluation of current approaches in risk-benefit assessments used by national and international agencies was performed.

In our review of the literature, we found the dominating approach to risk benefit assessment to be tiered methods. Integrated risk-benefit assessments have been carried out, in several disciplines, such as medicine, environmental health, food microbiology, food and nutrition, economics, marketing-finance and consumer perception. Commonalities and differences in risk-benefit assessment in the abovementioned fields have been identified. However, international consensus on the general principles or approaches for conducting risk-benefit assessment for foods and food components has so far not been reached.

The workflow suggested by the European Food Safety Authority (EFSA) was used as a starting point for the development of the proposed NFA risk-benefit assessment procedure. A tiered, stepwise approach is proposed as a preferred procedure in all risk-benefit assessments, since in addition to the nature of the question/problem, the availability and type of data will determine the approach, e.g. whether the assessment can be and need to be qualitative, quantitative, or both. The advantage of a stepwise methodology is that it is conceptually easy to use by the assessors and promotes transparency of the process. The proposed procedure for risk-benefit assessment contains three steps, from a qualitative assessment of risks and benefits separately to a quantitative assessment expressing risks and benefits on the same scale. The procedure was applied in a case study to assess whether the content of nitrite and salt could be decreased in processed meat in combination with a decreased maximum storage temperature. The potential benefits for the general population of a decreased nitrite and salt intake versus risk of *Clostridium botulinum*

and *Listeria monocytogenes* infections were assessed. The two first steps of the procedure could be applied, and it was concluded that the reduction of salt and nitrite levels would not affect microorganism growth and would only have marginal effects on public health if the storage temperature was kept at 5 °C. The reduction of storage temperature from 8 °C to 5 °C would however result in a positive effect due to a reduction of growth of *L. Monocytogenes,* but no effect on growth of *C. botulinum.*

1. Background

Besides supplying nutrients and bioactive compounds needed for survival and function of human beings, food sometimes contain agents or substances that may have adverse effects on human health. These may be microorganisms, anti-nutrients or toxicants. Microorganisms may cause illness by infection or by intoxication via toxins pre-formed in food by the microorganism. Anti-nutrients are natural or synthetic compounds that interfere with the absorption of nutrients. Toxicants are chemical substances that have the potential to give rise to adverse effects when consumed in high amounts. Adding to the complexity, adverse health effects can also be the result of excessive intake of nutrients or energy. Furthermore, foods containing certain bioactive constituents may cause pharmacological effects in certain individuals.

Whereas the beneficial effect of a food needs to be considered in a total dietary context, the risks related to certain microorganisms, anti-nutrients and toxicants are frequently related to individual food products and much less related to the total diet. The potential positive or negative health effects that can be related to a particular food or diet depend on the pattern of consumption and the requirements and vulnerability of particular population groups. These factors also determine which questions about risk and/or benefit that are relevant to pose in a particular setting. A specific food item may supply nutritious compounds and be considered beneficial for specific groups of the population, and at the same time promote the development of adverse effects for other groups via its content of the same or other compounds.

So far the assessments of risks and benefits, performed by experts at food agencies or in international organisations, such as WHO/FAO, have largely been separate processes, where risks have received the highest impact on food legislation. Since food, and even the same food ingredient, may confer both beneficial and adverse effects it is important to consider both health risks and benefits in management processes. Consequently, an increased demand for combined assessments of risks and benefits in food and nutrition has evolved during recent years. It has been argued that, both hazardous and beneficial effects should be taken into account and potential risks and benefits balanced by the use of an integrated measure of health, which ideally expresses both risk and benefit on the same scale.

Aims and objectives

In Sweden risk benefit assessments are the responsibility of the Risk and Benefit Assessment Division at the National Food Agency (NFA), which brings together different scientific disciplines, i.e., toxicology, nutrition and microbiology. The overall aim of this pro-

ject was to develop a general procedure for risk-benefit assessment applicable for practical use at the NFA.

The first step in developing a risk-benefit assessment procedure to be used at the NFA was an overview of current methodological approaches. The second step was to compile a suitable procedure for performing risk-benefit assessment for use at NFA. The third step was to test the developed risk benefit assessment procedure in a relevant case study. The case study selected was an assessment of the risk and benefit associated with changes in storage temperature and different concentrations of sodium as salt and the food additive nitrite in processed meat. The fourth step, after the practical test (step 3), was to refine the procedure into a finalized document for practical use at NFA (Appendix 3).

2. Health risk-benefit assessment in the risk analysis process

Introduction

This section gives a description of the current state of the art regarding the process of health risk-benefit assessment within the risk analysis framework as it pertains to governmental food agencies and certain international organizations. Strong driving forces behind the development of a common international framework for risk analysis have been the globalization of food trade and food problems, such as the *mad cow disease* and the dioxin scandals in Europe. These and other health hazards were conceived by the public as being badly managed and were followed by demands for increased transparency and consistency in the risk assessment and management processes.

According to Codex Alimentarius, risk assessment is one of three cornerstones within the framework of the risk analysis of foods (FAO 2007). Whereas risk assessment is solely a scientific process, the two other components, risk management and risk communication, also takes into account other legitimate factors (OLFs), such as economics, cost-effectiveness, traditions, and consumer risk perception. Risk management entails the selection and implementation of the best available interventions to prevent or reduce the risk. Risk managers, whether working in government or in the private sector, may need to take also health benefits into account in the management decision and recently several studies developing a combined assessment of risk and benefit of food have been published (Havelaar et al., 2000; Hendrikssen et al., 2011; FAO/WHO 2011; Latte et al., 2011; Strom et al., 2011; VKM 2013). These endeavors have highlighted the need for methods and data that can assist in the demanding and complex process of simultaneously evaluating risks and benefits to human health

A similar terminology have been used internationally, and also at NFA, in microbiological risk assessment (MRA) and toxicological risk assessment (TRA), whereas the terminology in nutritional risk-benefit assessment (NRBA) differ somewhat in this context (see Appendix 1 and 2). This is mainly due to the fact that the purpose of assessment traditionally has differed between NRBA and TRA/MRA. In NRBA the assessor usually are trying to determine the intake of a nutrient/food component that is required for optimal health, whereas in microbiology and toxicology the most important outcome of the risk assessment is the relation between current exposure and negative health consequences. It should however be noted that within the framework of NRBA one of the outcomes is the safe upper level of intake (UL) of a nutrient/food component, similarly as in TRA (Appendix 2).

Within the framework of microbiological and toxicological risk analysis, the risk managers, in dialog with the risk assessors, take the decision if a risk assessment of a potential health hazard in food is possible and necessary. In certain cases a risk assessment is initiated by the risk assessors (self-tasking). If it is decided that a risk assessment is needed, it then follows the principle of food risk assessment developed under the concept of Risk Analysis by the Codex Alimentarius Commission (CAC) (FAO 2007; Codex 1999, 2007). No internationally agreed framework for NRBA exists, but some guidance regarding the processes and definitions used by the NFA in NRBA is given by the expert group behind the 5th edition of the Nordic Nutrition Recommendations (NNR 2012, 2014). Definitions of terms used in the following text have been compiled in Appendix 1.

Risk and benefit assessment as separate processes

Traditionally, risk assessment of hazards in food has focused on human health risks associated with exposure to various chemical (including nutrients), physical and biological agents in food (Codex 2007). The risk assessment is based on four steps; hazard identification, hazard characterization, exposure assessment and risk characterization (Codex 2007). The risk assessment should make use of the best scientific knowledge available.

Identification of toxicological/microbiological hazards or nutritionally induced positive health effects/reduced adverse effects

The hazard identification in risk assessment should describe the biological, chemical or physical agents capable of causing potential adverse health effects and at which levels they may be present in a particular food or group of foods. The hazard identification may already have been elucidated in the risk profiling of the potential hazard, performed by the risk managers in collaboration with the risk assessors. An elaborated risk profile should ideally precede the risk assessment and be used as a basis for a decision by the risk managers, whether to initiate a risk assessment or not. Hazard identification is predominately a qualitative process both in MRA and TRA. Examples of potential chemical food hazards are food additives, pesticides, contaminants (e.g. dioxins and cadmium), natural toxins (e.g. glycoalkaloids in potatoes or aflatoxins in peanuts) and veterinary drugs. Bacteria, such as *Listeria monocytogenes* and *Campolybacter* sp, viruses (e.g. Hepatit A virus and Norovirus) and parasites (e.g. *Cryptosporidium parvum*) are examples of well-known microbiological hazards. Radiation from radioactive cesium in contaminated food is an example of a physical health hazard. Similarly as in MRA and TRA, identification of a potential nutritionally induced positive health effect/reduced adverse effect is the first step of the NRBA. Vitamins, essential trace elements, fats, proteins, etc, are examples of potential nutritionally beneficial components in food, which also may be hazardous to health under certain circumstances.

Characterization of toxicological/microbiological hazards or nutritionally induced positive health effects/reduced adverse effects

During the MRA and TRA hazard characterization, risk assessors describe the nature and extent of the adverse health effects known to be associated with the specific hazard. If possible, a dose-response relationship is established between different levels of exposure to the hazard in consumed food and the likelihood of development of different adverse health effects. Types of data that can be used to establish dose-response relationships include animal toxicity studies, clinical human exposure studies, and epidemiological data on disease occurrence and outbreaks. In MRA, dose-response models are based on animal studies, data from surrogate pathogens, human volunteer studies, epidemiological studies or combinations of these data types.

The NRBA generally focuses on estimating metabolic and health effects of nutrient intakes in humans. In this process human data are used mainly derived from controlled intervention studies, prospective cohort studies and case-control studies. Animal (*in vivo*) and *in vitro* studies are used in cases when mechanistic information is important for the assessment. Included in MRA, and also in TRA and NRBA, is the identification of important human sub-populations showing increased sensitivity due to for instance genetic factors, developmental stage, age, pregnancy, dietary habits, medication status, etc. For more details regarding MRA/TRA hazard characterization and NRBA hazard/benefit characterization see Appendix 2.

The main goal of the TRA hazard characterization is to determine the specific intake level of a potentially hazardous substance that is safe, or not safe, from a health point-of-view, often by the determination of a toxicological “reference” intake. In MRA it is usually not possible to determine health-based reference intakes of microbes. This is partly due to the fact that the presence of a single infectious microbe in food may be enough to cause adverse health effects when ingested, since during favorable conditions they can increase their numbers by orders of magnitude. Thus, microorganisms can change their numbers in food along the food chain due to growth and inactivation, for instance during storage, transport and cooking. At the NFA less focus is put on developing MRA hazard characterisation (especially dose-response) and more on the exposure assessment part (see below).

In NRBA, characterization of nutritionally induced positive health effects/reduced adverse effecs, dietary reference values (DRVs) are determined. These are used as guidelines for planning and evaluation of nutrient intakes in populations and for groups of individuals (NNR 2012; 2014). DRVs generally refer to a set of values for essential nutrients. For details see Appendix 2.

Exposure assessment

The third step of the MRA and TRA, the exposure assessment, aims at characterizing the amount of a hazardous component that is ingested by consumers of the exposed population(s). Similarly, in NRBA the exposure of components causing positive health effects/reduced adverse effects is assessed. The assessment needs to consider the levels of the components in the raw materials and/or food ingredients added to the food, and the general food environment, in order to track changes in levels throughout the food production chain. These data are subsequently combined with the food consumption patterns of the target consumer population to assess exposure to the components over a particular period of time (acute or chronic exposure) from foods as actually consumed.

For some dietary hazards/nutritional components, intake may be associated with a single food, while others may be present in multiple foods, as well as in drinking water. Sometimes the general human environment may contribute with exposure, in a way that food accounts for only a portion of the total exposure. For instance, sunlight exposure affects the levels of vitamin D in the body. Ideally, the exposure assessment should consider all pathways of exposure for a hazardous component or a component causing positive health effects/reduced adverse effects. However, in many cases it is difficult to estimate the total intake/exposure. An alternative, complementary, approach to determine total exposure is to biomonitor levels of the components in question in human tissues. By combining biomonitoring methods with other types of exposure assessments, the relative contribution from different sources to the total exposure of a compound may be estimated.

Characterization of risk or benefit

In the final part of the risk assessment, risk characterization, information from the previous three steps of the risk assessment are brought together to estimate the risk. The risk characterization can be qualitative or quantitative. In qualitative risk characterizations, outputs can be expressed in descriptive terms such as high, medium or low risks. In quantitative risk assessments, the outputs can be expressed numerically and may include a numerical description of uncertainty. Quantitative risk assessments have the additional advantage of being able to model the effects of different interventions.

In TRA, the approach in determining toxicological reference intakes for hazards with mechanisms of toxic action considered to exhibit a threshold (see Appendix 2), has generally been considered to provide an adequate margin of safety when exposures are below the reference intake. Therefore, further characterization of the risk quantatively at exposures below the reference intake is rarely performed. In contrast, for genotoxic carcinogens quantitative risk characterization models have been applied by various expert bodies for effects that are judged to have no threshold of toxicity. These models employ mathematical extrapolations from observed animal cancer incidence data (usually derived from tests using high doses) to estimate the expected cancer incidence at the low levels typical

of ordinary human exposure. If epidemiological cancer data are available, they can also be used in quantitative risk characterization models.

In MRA, at the NFA, a tiered approach is used in the risk characterization where deterministic models are evaluated first, and if these do not give sufficient information, probabilistic models are if possible applied. The use of probabilistic models enables assessment of the impact of uncertainty (lack of knowledge) and the variability (property of the system under study). The probabilistic models developed have mostly been Monte Carlo simulation models. However, efforts to embrace other approaches such as Bayesian modelling have been initiated.

In NRBA intake estimates for nutrients can be compared with relevant dietary reference values for adequate intake or for potential risks of negative health effects for the population as a whole or for subgroups (Appendix 2). Similar evaluations, including assessment of positive health effects, can be done for specific foods, food groups or dietary patterns, although in these cases other types of data are needed, e.g. dose-response estimates, relative risks, for various health outcomes.

It is common that the supporting data needed to directly assess risks or benefits are inadequate. Indeed, identification of important knowledge gaps is one of the key outcomes of a risk and/or benefit assessment. Consequently, the ability to take uncertainty into consideration is crucial in order to use risk-benefit assessments as a basis for management decisions.

Integrated risk-benefit assessment

As described above, traditionally, the assessment of food-related health risks and benefits have been separate processes within NRBA, TRA and MRA. However, in line with the risk assessment process, the European Food Safety Authority (EFSA) have published a guidance document on human health risk-benefit assessment of foods (see below) (EFSA 2010a). This document is an effort to give guidance on steps forward towards an integrated risk and benefit assessment process. The aim is to weigh possible beneficial and adverse health effects of a food/food component against each other in order to assess the net effect on health. The EFSA activity was stimulated by a scientific colloquium on risk-benefit analysis of foods in which it was agreed that it, at present, might be premature to develop a prescriptive framework for risk-benefit assessment. It was however regarded as timely to give guidance with respect to methodology, approaches, tools and potential limitations in the risk-benefit assessment (EFSA 2010a).

Integrated risk-benefit assessments have historically been carried out, more or less fruitfully, in several disciplines, such as within the fields of medicine, environmental health, food microbiology, food and nutrition, economics, marketing-finance and consumer perception (BEPRARIBEAN, 2012). The commonalities and differences in the risk-benefit assessment have been identified between the abovementioned fields. However, interna-

tional consensus on the general principles or approaches for conducting risk-benefit assessment for foods and food components has so far not been reached. Because integrated risk-benefit assessments of food and substances in food involve different disciplines there is a need for a harmonization of some pivotal definitions, as presented in Appendix 1.

3. Comparing risks and benefits

Introduction

Risk management priorities and actions should according to the risk analysis concept be risk- and science-based. For risk assessors a key challenge in this respect is how to compare the risks associated with different hazards. A further complication is the introduction of health benefits into the comparisons. To enable risk/benefit-based approaches in risk assessment it is necessary to have methods and concepts for comparing risks and benefits, i.e. the probabilities for, and types of, adverse and beneficial health consequences associated with the consumption of the specific food. For food-related health issues, data and methods are needed to compare health consequences over a wide range, from diarrhea to cancer and death (Kuchenmüller et al., 2009).

If health risks and benefits to be compared are similar and can be expressed in the same metrics (e.g. the number of cases), the comparison may be straightforward once relevant health risks and benefits have been estimated. However, even in this case the comparison may not be straightforward if variability and uncertainty of the estimates of risk and benefit are taken into consideration. Further, how can many cases with mild symptoms, such as a few days of diarrhea, be prioritised or compared with a few cases with serious symptoms, such as meningitis or even death? For such comparisons, both scenarios would ideally require the use of standardized metrics for disease burden that are able to integrate the individual and societal impact of very different disease endpoints. In addition, methods are needed, preferably implemented in user friendly software, to evaluate the impact of uncertainty and variability of risk and benefit. Metrics that have been applied are the health adjusted life years (HALYs), including disability adjusted life years (DALYs) and quality adjusted life years (QALYs). Methods for weighing different hazards and criteria can be found within the field of decision analysis.

Metrics for comparing risk and benefit

Health-based guidance values (HBGV) are defined by Codex as “the quantitative expression of an oral exposure (either acute or chronic) that would be expected to be without appreciable health risk” (Codex 2011). These include e.g. Acceptable Daily Intake (ADI), Tolerable Daily Intake (TDI), and Safe Upper Level of Intake (UL). Dietary reference values for health-beneficial nutrient intakes, e.g. Average Requirement (AR) and Recommended Intake (RI), have a different background. For more details, see Appendix 2.

HBGV are thus set for various purposes and not primarily intended for comprehensive risk-benefit assessment, since they are based on different health outcomes and criteria. However, these can be used for initial estimates of potential risks and benefits resulting

from exposure from foods. For example, intake of long-chain n-3 polyunsaturated fatty acids (LCPUFA) and dioxins at various consumption levels of fish from the Baltic Sea can be estimated and compared with RI for the fatty acids or TDI for dioxins (Becker et al., 2007). The proportion of the population with intakes complying with the RI for n-3 LCPUFA or having a dioxin intake below the TDI can be calculated, which then can be used for judgments on acceptable/desireable consumption levels of fish.

Morbidity and mortality

Various disease outcomes and mortality are important endpoints in risk-benefit assesments. Usually data refer to probabilities, e.g. estimates of increased/decreased risk of disease incidence or death (relative risk, hazard ratio). Examples where such measures have been used include assessment of health effects of fish consumption (FAO/WHO 2011; Cohen et al., 2006), and include comparisons of outcomes such as effects on IQ depending on intake of n-3 PUFA and methylmercury, and, mortality from myocardial infarction and cancer mortality depending intake of n-3 LCPUFA and dioxins. Here exposure has been modelled using different concentrations of PUFA, methylmercury and dioxins at various consumption levels of fish.

HALYs – DALY and QALY

Quantification of disease burden in HALY (Health Adjusted Life Years) equivalents is increasingly used in public health research to inform priority setting processes, whereas COI (cost-of-illness) approaches are increasingly used in economic research (Gold et al., 2002; Havelaar et al., 2007). All methods have their specific strengths and weaknesses and represent, depending on the perspective taken, societal or specific stakeholders concerns regarding food safety (Havelaar et al., 2007). HALYs include DALYs (Disability Adjusted Life years) and QALYs (Quality Adjusted Life Years). Both combine mortality and morbidity into one single metric that can be used for quantifying disease burden. There are some differences but also many similarities between DALYs and QALYs (Gold et al., 2002), but focus in this report will be on DALYs.

A balanced quantitative assessment of the positive and negative health effects of food consumption requires that the supporting data in their entirety are comparable and that there are data that are applicable to different groups in the population. DALYs and QALYs are different measures of the health status in a population and also of the contribution of different diseases and risk factors to the total burden of disease (Peterson et al., 1998; Moradi et al., 2006; Allebeck et al., 2006).

The DALY is estimated by DALY = YLL + YLD, where YLL is the number of years of life lost due to mortality and YLD is the number of years lived with a disability weighted with a factor between 0 and 1 for the severity of the specific disability (Murray and Acharya, 1997). DALY is a composite health measure and attempts to combine mortality,

incidence, and sequelae, taking duration and severity into account. The DALY approach has been applied both nationally (Allebeck et al., 2006, Moradi et al., 2006) and internationally (e.g. by WHO) to integrate health consequences to enable comparisons between different problems and risk factors. Thus, in addition to the epidemiological information on the incidence of different morbidity and mortality outcomes information is needed on life expectancy for fatal cases (related to age and general survival tables in different countries) to calculate years of life lost. For morbidity, data are needed on severity weights and duration of illness. Weighting factors for severity of illness have been produced at international level and are based on combined assessments carried out by various groups of experts (Gold et al., 2002). Weighting factors are available for a range of ailments, both psychiatric and somatic.

Applying the DALY methodology involves making choices on the details of the analysis, e.g. the health outcomes considered in the analysis (van Lier et al., 2007), and the choices will most likely be related to the needs of decision-makers, the limitations of data, and the available resources. In a Swedish study the public health burden of illness due to Campylobacter and Enterohemorrhagic E. coli (EHEC) was compared using the DALY methodology (Toljander et al., 2012). Results indicate that the DALYs contributed by Campylobacter is at least three times that of EHEC and, contrary to EHEC, is mainly due to milder symptoms related to the illness.

The quality adjusted life years (QALY) measures the "total number of years with full health in a population by combining time lived with the functional capacity associated with that health state" (Gold et al., 2002). To calculate QALYs, data on life expectancy depending on age, gender and disease are required. In contrast to DALY, a value of 1 represents full health on the QALY scale and 0 represents the lowest possible health state (death). For QALY, and also DALY, health scales are created so that they have interval scale properties, i.e., changes of equal amount anywhere on a scale of 0 to 1.0 can be interpreted as equivalent to one another. QALYs were developed in the late 1960s primarily for use in cost-effectiveness analysis, for instance quantifying the incremental price of obtaining a unit of health effect from some kind of health intervention when compared with an alternative intervention (Gold et al., 2002). The relation between DALY and QALY is illustrated in Figure 1.

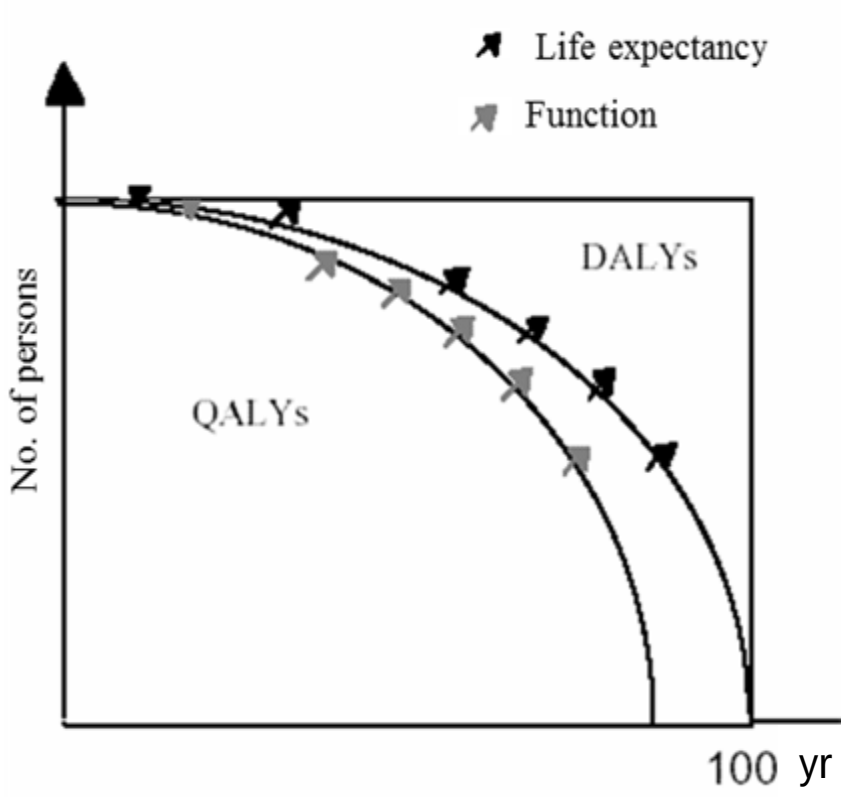

Figure 1. DALY represents the loss of healthy life-years, while QALY represents life-years with full health. The ultimate goal of public health policy is to minimize morbidity and extend longevity, hence moving the curves to the right, and minimizing the DALY area and maximizing the QALY area (Persson et al., 1998).

The metrics used for comparisons of health effects may strongly influence the results. In a pilot study the burden of seven infectious diseases in Europe was estimated (van Lier et al., 2007). Simple metrics such as incidence and mortality indicated that foodborne illnesses and tuberculosis, respectively, caused the greatest disease burden (van Lier et al., 2007). In comparison, based on DALY, a high burden of HIV-infection and tuberculosis, followed by campylobacteriosis, was indicated. The choice of metrics may influence also the results of comparisons between chemical hazards. This is a challenge since epidemiological data on the health incidence and health consequences associated with specific hazards are largely lacking. One approach to address this limitation when estimating public health burden of chemical hazards is to use default values for DALY by classifying different chemical hazards based on the health effects, for instance hazards with cancer and non-cancer effects, respectively (Crettaz et al., 2002; Pennington et al., 2002). These authors used an average of 6.7 DALY per cancer case based on data on several different types of cancers. The same authors used 0.67 DALY per case for health outcomes characterized by probably irreversible/life-shortening effects, and 0.067 DALY per case for health outcomes with reversible/non-life shortening effects. Such classifications are based on the hazard characterization of chemical hazards which has a long tradition in toxicolo-

gy and many elaborate schemes for classifying hazards exists (Hammerling et al., 2009), but these have to a limited extent been used in estimations of DALY.

Economic measures COI and WTP

The health impact may also be expressed in terms of monetary impact and two common measures are the cost of illness (COI) and the willingness to pay (WTP) (Kuchler and Golan, 1999). Each of these have their pros and cons; economists agree that COI understates the economic value of avoiding illness, whereas WTP may be a more complete health valuation measure but is labour intensive to derive (Kalogeras et al., 2012).

Decision analysis - other legitimate factors (OLF)

The approaches presented in this decision analysis section are used for estimating and weighing health risks and benefits as a basis for comparisons, but can also be applied for evaluating the effects of OLF than health as a basis for risk management decisions. This may be an advantage for development of a comprehensive and consistent risk management framework. However, framework development and risk management are outside the scope of the present report which focuses on the risk/benefit assessment part of the risk analysis framework.

Risk and benefit issues are complex by nature and in general decisions are taken under uncertainty, i.e. there is a lack of knowledge about the probabilities and/or consequences of the different decision alternatives. Decision analysis and decision theory has been applied in many different fields for careful quantitative deliberations preceding a decision. In short, the alternative decision options are listed with the mutually exclusive possible outcomes that may follow from each option. Decision analysis problems are often represented by graphical models, such as decision trees and influence diagrams, to facilitate understanding and analysis of the problem. Uncertainties about the possible outcomes and the associated consequences are expressed by probabilities or probability distributions. The consequences of the different outcomes are described in terms of values, e.g. DALYs, COI, to the decision maker in utility functions. Evaluation of the decision problem is done by evaluating the expected utility of the alternatives, where the utility may also reflect the preference of the decision maker as expressed in decision rules. For instance, the decision rule could be to maximize the expected value (e.g. the benefit), to minimize the expected loss (e.g. the risk), or to select alternatives resulting in returns of not less than a specific value. Thus, if negative (risks) and positive (benefits) health concequences can be expressed in the same units, e.g. DALY, the evaluation is a single-criterion problem. This means the only criteria to evaluate is the “cost” in terms of DALYs, and the task will be to select the option that optimizes the outcome, in this case minimizes the DALYs.

However, many decision problems are of a multi-criteria nature, i.e. multiple and sometimes conflicting criteria are necessary to consider when decisions are taken. For example, should flour be fortified with folic acid, and if so, at what level? Multi-criteria decision analysis (MCDA) has been applied in a variety of fields and is concerned with structuring and solving decision and planning problems involving multiple criteria. The task of striking an appropriate balance between often conflicting criteria, e.g. risk and benefit, is a multidisciplinary problem, and the purpose of MCDA is to generate support for decision makers in situations where no optimal solution exists since conflicting criteria are involved. Thus, a single unique optimal solution does not exist to a multiple criteria problem if decision criteria are conflicting. Instead the concept of an optimal solution is often replaced by the concept of choosing from a set of non-dominated solutions. A non-dominated solution has the property that it is not possible to move away from it to any other solution without sacrificing in at least one criterion.

Generally, problems become very complex and within the discipline of decision analysis structured processes, methods, and software tools have been developed to support in the analysis (Clemen and Reilly, 2001; Renn, 2005). This is especially helpful when uncertainties are associated with the risk and benefit estimates. Thus, software can be used to evaluate also single criteria problems, i.e. when variable or uncertain estimates of risk and benefit expressed in the same metrics are evaluated. One of the rare applications of this methodology, used within microbial food safety, can be found in Fazil et al. (2008) where multi-criteria decision analysis was applied to a food-safety decision-making problem.

Qalibra – a web-based tool

The model described in the EU research project Qalibra is conceptually a step forward in risk-benefit assessment (Hart et al., 2013). It uses the higher tiers of the BRAFO (see Section 4) proposed framework for risk-benefit assessment that present both potential risks and potential benefits to consumers (Hoekstra et al., 2012). The risks and benefits in these higher tiers are in the Qalibra method integrated quantitatively to estimate the net health impact measured in DALYs or QALYs. The flexible design of the Qalibra methodology makes it applicable to a wide range of dietary questions involving different nutrients, contaminants and health effects. It is a model for food risk-benefit assessment that also quantifies variability and uncertainty. Uncertainty in any input parameter may be quantified probabilistically, using probability distributions, or deterministically by repeating the assessment with alternative assumptions.

In addition, including described potential outputs of the model a case study on fish consumption has been used to illustrate the working procedure which increases the understanding and usability of the Qalibra model (Hart et al., 2013). The model is also available as a web-based software at www.qalibra.eu.

Comparisons of risk and benefit at the NFA

At the NFA, the DALY methodology have been applied in attempts to quantify the public health burden of microbiological (Lindqvist et al., 2011; Toljander et al., 2012) and chemical hazards (Lindqvist et al., 2011). These estimates have focused on risk and have not involved benefit assessments. In addition, extensive experience with hazard classification methods for chemical hazards exists at the NFA (Hammerling et al., 2009). Efforts to implement uncertainty and variability estimates in single and multiple criteria decision analysis (MCDA) in a case study comparing risk and benefits have been initiated.

Two risk and benefit assessments of fish consumption has been made by the NFA (Becker et al., 2007; Glynn et al., 2013). Both assessments were prompted by needs to update the scientific basis for risk management of dioxin-contaminated fish from the Baltic Sea. The assessment of Becker et al. (2007) also included an assessment of methylmercury-contaminated fresh water fish. In both assessments potential positive health effect of intake of n-3 fatty acids (DHA and EPA) and vitamin D from fish was assessed against possible negative health effects caused by intake of the contaminants. In both assessments intake calculations were made to evaluate how different fish consumption scenarios influenced the possibility of exceeding the TDI of dioxins and methylmercury and the RIs of n-3 fatty acids and vitamin D.

In the assessment of Becker et al. (2007) it was concluded that the health value of an increased fish consumption in line with the general dietary advice of 2-3 meals a week (250-375 g/week), varied between different species of fish. It is probable that an increased consumption would reduce the risk for cardiovascular disease, particularly with regard to risk groups and among people who eat little or no fish. It is also probable that an increased consumption among women of child bearing age (who has a low consumption) is beneficial with regard to foetal development. An increased consumption among those who eat little fish would significantly increase the vitamin D intake. However, consumption of certain fish from Baltic sea, and fish from methylmercury-contaminated waters could lead to that tolerable intake limits of environmental contaminants are exceeded; this primarily is of concern for children and women of child bearing age (dioxins/PCBs), and pregnant women (methyl mercury) (Becker et al., 2007).

Glynn et al. (2013) concluded that regular consumption of fatty Baltic Sea fish with high dioxin and PCB levels, especially herring from the northern part of the Baltic Sea (Bothnian Bay), would result in a significantly increased consumer risk of exceeding the health-based TDI of the contaminants in comparison with consumption of the same type of fish with levels below the ML. This increased risk would occur without any significant health benefits, since intake of n-3 fatty acids and vitamin D from herring is not expected to differ significantly between herrings with high and low levels of dioxins and PCBs.

A risk and benefit assessment of a decrease in nitrite and salt content in processed meat has also been published by the NFA (Darnerud et al., 2014). The specific question was whether a reduction of nitrite from 150 mg/kg to 60 mg/kg, and a 10 % or 25 % reduction of salt in processed food, would affect the health of the consumers or a concomitant risk for *Clostridium botulinum* and *Listeria monocytogenes* infection. Health risks and benefits were assessed at a storage temperature in the production-retail chain of 8°C (current recommended temperature) and 5°C. The assessment followed the step-wise (step 1 to 3) procedure developed at NFA which is described more in detail in chapter 7.

It was from published experimental studies concluded that nitrite levels close to the 60 mg/kg are effective in preventing growth of cold-resistant *C. botulinum* already at 8°C. Consequently, even with no reduction in temperature to 5°C there seems to be no risk for increased growth of *C. botulium* at 60 mg nitrite/kg products. Temperature modeling of *L. monocytogenes* growth showed that a decreased temperature from 8°C to 5°C caused a decreased growth both at 10 % and 25 % reduction of salt, compared to growth at 8°C at current salt levels. A sodium (salt) reduction with 25 % in processed meat was concluded to have a minor influence on the total sodium intake, but could have a limited beneficial health effect among high consumers. Similarly, a reduction of nitrite to Danish levels has a minor effect on the total intake of nitrite, as well as a limited influence on the risk of exceeding the ADI for nitrite among both children and adults. Overall it was concluded that the reduction of salt and nitrite levels would only have marginal effects on public health if the storage temperature was kept at 5°C. The reduction of storage temperature from 8°C to 5°C would however result in a positive effect due to a reduction of growth of *L. Monocytogenes.*

Risk and benefits associated with the consumption of nuts. Recognizing that nuts can be a part of a healthy dietary pattern the Nordic Nutrition Recommendations 2012 identified nuts as one of the type of foods to promote in the Nordic population (NNR, 2012). In an NFA assessment, health benefits associated with nut consumption in epidemiological studies and exposure to aflatoxin B1, acrylamide, *Salmonella* and other bacteria, were assessed in different scenarios of amount and type of nuts consumed (Bylund et al., 2014). Due to limitations in the possibility to quantify effects on cardiovascular disease, weight changes, cancer and salmonellosis, a common measure could not be applied. There also was a lack of data whether acrylamide and *Salmonella* are present in nuts. For aflatoxin B1, it is the rare high levels in some nuts that pose a potential threat to health.

It was concluded that while consumption of 30 or 65 g nuts per day may result in health benefits, such as maintenance of body weight and reduced risk of cardiovascular disease, negative health effects, such as increased risk for liver cancer and increased risk of salmonellosis, cannot be ruled out.

4. Procedures for risk-benefit assessment within the food sector

Procedures for integrated risk-benefit assessment have been described by various organisations and research institutes, including EFSA (EFSA 2010a), the Dutch National Institute for Public Health and the Environment, RIVM (van Kreijl, 2006) and FAO/WHO (FAO, 2010; FAO/WHO, 2011). Several international and national projects/efforts have been carried out using partly different approaches and methodologies.

Procedure suggested by EFSA

The Scientific Committee of EFSA has developed guidance for the procedure of risk-benefit assessments of food, although considering only health aspects (EFSA, 2010a). In this document, a stepwise (tiered) approach is described. Problem formulation before the risk-benefit assessor starts the work is critical to ensure that the assessment provides a useful and relevant outcome. The Terms of Reference for an assessment should specifically define the risk-benefit question, the diet or dietary element to be assessed, the population and potential subpopulations to be considered, the timetable and whether and which stakeholders should be involved. The Terms of Reference should be agreed upon by the risk-benefit assessor and the risk-benefit manager.

Risk-benefit questions are of two main types according to EFSA:

-What is the balance of risks and benefits in a population by a particular diet or dietary component?

-What would be the health impact in a population of a specified change in the diet (a comparison of alternative scenarios to the current situation)?

In all the steps of EFSA´s stepwise approach for risk-benefit assessment of both these types of questions, the level of evidence available and the rationale for selection of approach and parameters should be clearly stated. The outcome should be explained and assumptions and uncertainties well described.

Initial assessment (Step 1)

In the initial assessment all relevant factors related to a potential health risk and to a potential health benefit are considered separately. This could be done using either, a scenario where risks are estimated at a high dietary exposure and benefits at low dietary exposure, or risks estimated at low dietary exposure or benefits at high dietary exposure. Where the health benefits clearly outweigh the potential health risks or when the risks

clearly outweigh potential benefits, the risk-benefit assessor should report the result to the risk-benefit manager with suggestion to stop the assessment. The risk-benefit assessor and the risk-benefit manager should discuss whether sufficient information is provided by the initial assessment or if a new Terms of Reference should be reset in order to proceed to a refined assessment.

Refined assessment (Step 2)

If the risk-benefit assessment continues into step 2, the new Terms of Reference should include information about the endpoints and populations to be considered, what refinement is possible (for example probabilistic assessment or specific exposure scenarios) and the possibilities of quantifying hazards and positive health effects (for example with dose-response modeling).

The refined assessment should include a semi-quantitative or quantitative estimation of risk and benefits, depending on available data. If it is possible, a common metric such as for example incidence or mortality should be used in this step. The refinement may be of the exposure (for example a comparison of different scenarios), consideration of different populations or dose response-modeling. The Scientific Committee of EFSA provides some examples of outcomes of a refined assessment: an estimate of the proportion of population or relevant sub-group that is above health based guidance values or below a dietary reference value, estimates of disease incidence or mortality at a specified exposure level, probabilistic distribution of the health benefit and health risk with a quantification of the uncertainties. The outcome should also include an assessment whether it is possible to derive composite metrics.

Assessment using a composite metric (Step 3)

In the third step, composite metrics are used to combine two or more of the following: increase or decrease in morbidity, mortality, disease burden or quality of life, with the goal to result in a net health value. This value should however be considered together with the information obtained in the refined assessment (step 2). It is also possible that inherent uncertainties make it impossible to come to a conclusion in step 3. In such cases, the risk-benefit assessor report back to the risk-benefit manager that additional data are needed to reduce uncertainty.

Procedure suggested by RIVM

The Duch National Institute for Public Health and the Environment (RIVM) has suggested a tiered approach for performing risk-benefit assessment of foods (Fransen, 2010). The process is devided into part A-E of a decision tree and includes several check-points where the assessment can be stopped. The steps are the same as in the risk assessment paradigm, but not always performed in the same order as in the procedure suggested by EFSA (EFSA, 2010a). According to RIVM´s approach, exposure assessment should be performed before the characterization of a hazard and a benefit. An evaluation of the intake distribution early in the process gives the possibility to terminate the risk benefit

assessment at this stage in cases with no or limited exposure in the groups that would potentially be at risk or benefit of the exposure. Another difference from the approach suggested by EFSA is that RIVM suggests that the dose-response modeling is performed at a late stage in the phase of integrating risk and benefit. The reason for this view is that a dose-response analysis is only justified when the assessments proceeds beyond a stage where it is judged that risks and benefits do not clearly outweigh one another.

The RIVM approach includes options for termination of assessment at 5 stages:
1) After having formulated the risk-benefit question, it is found that there is no positive or negative effects on health, or no population at risk or having benefits;

2) Following the exposure assessment it is clear that there is no exposure in the population at risk or having benefits;

3) Following a comparison with safe level and recommended intake in all relevant population groups. If maximum safe level and recommended intake are reached in the population most at risk;

4) In consultation with policymaker if the maximum safe level is exceeded by a small percentage of a population group, or is exceeded very slightly;

5) If there is no data to perform a dose-response analysis

The RIVM approach provides a tool for performing a risk-benefit assessment, but like other suggested procedures there is limited practical use and evaluation of the model. RIVM's approach has been used in risk-benefit assessment of sugar sweetened beverages and was found useful (Henriksen et al., 2011).

BRAFO

The BRAFO project (Benefit–Risk Analysis for Foods), a European Commission funded Framework 6 project, developed a tiered approach for assessment of the benefits and risks when changing from a reference scenario to one or several alternative scenarios using risk estimates based on a common scale of measurement (Boobis et al., 2013). In Tier 1, benefits and risks are assessed separately. If results indicate a risk or a benefit only, assessment is stopped, otherwise assessment is continued. In Tier 2 risks and benefits are compared quantitatively in terms of disease incidence, severity of the health effects, duration of the disease, and any additional mortality resulting from the effect. Depending on the results, e.g. risks in the alternative scenario clearly exceeds the benefit, the assessment may be stopped. In Tier 3, health effects are compared using common metrics e.g. DALYs or QALYs. In a 4th Tier, a probabilistic approach can be applied, using the same common metrics as in Tier 3. A number of case studies was also carried out within the project.

Reports and projects

Several projects and research activities focusing on risk-benefit assessments of foods have been carried out at an international level. These include Beneris, BEPRARIBEAN, Our food – our health, and FAO/WHO fish, (refs., see below). The purpose of these projects has been to identify data needs, develop new, or improve existing tools for exposure assessment as well as for investigating tools to weigh risks and benefits from intakes of particular foods or food constituents using various health-based metrics.

The Beneris project in the EU 6th Framework Programme developed a framework for handling complicated risk-benefit situations, and applied it in a number of case studies of certain foods, e.g. fish (Pohjala and Tuomisto, 2011). The main products of Beneris are the improved methodology (open assessment) for risk-benefit assessments, including the web workspace Opasnet for performing them in a collaborative way, and the Opasnet Base database containing ready-to-use information needed in assessments. The method is described on the web workspace Opasnet (http://en.opasnet.org).

The BEPRARIBEAN project, had the aim to advance benefit-risk analysis in the area of food and nutrition by learning and comparing methodology from other fields, where such an analysis is performed (BEPRARIBEAN, 2012). A further aim was to integrate the best practices used in these fields into the field of food and nutrition (Tijhuis et al., 2012a). A series of reviews in a supplement to the journal "Food and Chemical Toxicology" provided an overview of principles, terminology, methods and framework for simultaneous weighing of human health risks against benefits in the risk-benefit assessment area. The commonalities and differences in risk-benefit analysis were identified between the food and nutrition field (Tijhuis et al., 2012b) and the fields of medicine (Luteijn et al., 2012), food microbiology (Magnusson et al., 2012), environmental health (Pohjola et al., 2012), economics and marketing-finance (Kalogeras et al., 2012) and consumer perception (Ueland et al., 2012). Within the BEPRARIBEAN project the term "Benefit" covers both improved function/well-being and reduced risk of health impairment, similar to the definition used by e.g. EFSA. However, in contrast to the definition of EFSA, risk-risk comparisons or examples where a microbiological intervention eventually lead to a benefit in terms of a generally reduced exposure to pathogenic microorganisms are presented as benefit-risk assessments. This illustrates that a flexible application of the EFSA guideline may be desirable since a too narrow definition of benefit may be counter productive.

The report "Our food, our health; healthy diet and safe food in the Netherlands", compiled by the National Institute for Public Health and the Environment (RIVM) in 2004 (van Kreijl, 2006), addressed a number of questions regarding risks and benefits of food consumption with regard to the Dutch diet and investigated five important dietary health determinants, i.e. saturated fatty acids, trans-fatty acids, fish, fruits and vegetables. In the analysis, two reference scenarios were defined. In one scenario it was assumed that all Dutch people follow the dietary recommendations with regard to the five factors considered. The outcome measure was DALY and, in addition to the above factors, included

estimates for food borne infections, and chemical constituents in food, including various proteins, mycotoxins, phycotoxins, phytotoxins, nitrate/nitrite, growth promoters, and process contaminants. In summary, the estimated health loss or potential health gain following improved diet and avoidance of exposure were as follows: 130,000-250,000 DALYs for unfavourable diet, in terms of the five health determinants considered (depending on scenario); 1,000-4,000 DALYs for food borne infections; and 1,500-2,000 DALYs for chemical contamination.

A framework for assessing the net health benefits or risks of fish consumption was developed and applied by FAO/WHO (2011) as a part of a joint expert consultation. The purpose of the framework was to provide guidance to national food safety authorities and Codex Alimentarius Commission in their work on managing risks, accounting for existing data on benefits of eating fish.

A recent Danish study reported on an integrated analysis of microbiological risks and nutritional benefits associated with consumption of cold-smoked salmon (Berjia et al., 2012). Two consumption scenarios were evaluated in terms of DALY and indicated that overall benefits of the fish consumption outweigh risk, especially by the effects on reduced coronary heart disease, mortality, and increased IQ. However, a sensitivity analysis suggested that risks may outweigh benefits at storage times of cold-smoked salmon in excess of five weeks.

5. Exposure assessment

Estimation of the dietary exposure represents a central step in any risk/benefit assessment of foods. When performed at national level, risk/benefit assessments normally focuses on the exposure assessment and risk characterization. This is because national authorities normally rely on international institutions, e.g. the European Food Safety Authority (EFSA) and WHO, with regard to the hazard identification and hazard characterisation, including the establishment of health based guidance values (in the case of chemicals and nutrients in foods).

The exposure assessment is traditionally performed by combining consumption data from national dietary surveys with concentration data derived from national monitoring programmes or total diet studies. Estimation of dietary exposure is complex, and the level of detail at which such an assessment is performed depends on various factors, including the purpose of the assessment (e.g., the exposure to a single food product or foods in general) as well as the data and resources available. Both the WHO and EFSA have developed guidelines for exposure assessments (WHO/IPCS, 2009; EFSA, 2011). Typically, a tiered approach is recommended that is “fit for purpose”. The NFA in Sweden has developed general guidelines for exposure assessment based on such considerations. More specifically, the NFA recommends the use of a “simple” or “developed” approach for exposure assessment. This guideline is intended to be a support for identifying which type of exposure assessment is most appropriate, mainly focusing on the level of detail in exposure estimates that is necessary for a particular task (Livsmedelsverket, 2014a and b).

6. Uncertainties in risk- and benefit assessment

Definitions of uncertainty may vary widely depending on context. In relation to food risk and benefit assessment uncertainty generally represents a lack of perfect knowledge, which may be reduced by further measurements or information (e.g. Sluijs et al., 2015; Hart et al., 2013; Bouwknegt et al., 2014). It is important to distinguish uncertainty from variability. Variability represents true heterogeneity of the study population. This heterogeneity is a consequence of the system under study and cannot be reduced by additional measurements or information.

Since risk and benefit assessments form the basis for risk management decisions, uncertainties in the assessments can have large impacts on the outcome and it is therefore important to evaluate and to communicate descriptions of uncertainty (Codex 2011). Further, the requirement for increased transparency in risk assessment to simplify the risk management and risk communication has also put focus on the explicit formulation and evaluation of uncertainties.

Many potential sources of uncertainty exist in risk- and benefit assessments (Hoekstra et al., 2012), ranging from quantitative and technical, e.g. statistical uncertainty in input parameters, to more qualitative, e.g. implicit assumptions or model boundaries (van der Sluijs et al., 2005). The treatment of uncertainties in published assessments varies depending on the scope, context and time constraints of the studies. Consequently, a tiered approach for risk and benefit assessment has been proposed, which is supported by the EFSA guidelines for exposure assessment (EFSA, 2006), and that includes steps to: 1) Document all identifiable sources of uncertainty, 2) Evaluate all of them at least qualitatively, 3) Quantify them to the extent that is necessary for decision making (Hart et al., 2013). This process is envisioned to include both qualitative and quantitative assessments of uncertainties until there is sufficient confidence for decision making.

There are a wide range of quantitative approaches to estimate uncertainties in risk- and benefit assessment, including deterministic, interval, and probabilistic. Qualitative or semi-qualitative approaches include uncertainty tables, weight of evidence procedures, evidence maps, subjective probabilities, pedigree analysis and social/participatory appraisal. Quantitative questions such as those related to benchmark dose might best express uncertainty in terms of how different the true value could be from the one given. Categorical questions, such as relevance of the effect to humans are frequently based on weight of evidence on a yes/no scale. Then uncertainties might best be expressed in terms of the probability of alternative outcomes.

However, many types of uncertainty, for example model uncertainty, are difficult to quantify. In some cases, only those uncertainties that can be reasonably quantified (statistical uncertainty) are incorporated in the assessment, and it is then incorrectly assumed that uncertainty has been quantified. Often this uncertainty is then assumed to be the only source of uncertainty, while others have simply been neglected. For quantitative assessments of uncertainties either deterministic or probabilistic methods may be used, e.g. scenario and sensitivity analysis. Methods for sensitivity analysis have been reviewed and evaluated in Frey and Patil (2002). As pointed out by Hart el al. (2013), although the overall magnitude of uncertainty associated with a risk–benefit assessment may often be large, this should not be regarded as implying a failure of the assessment process. On the contrary, it provides essential information for decision-making.

In recognition of all the different sources of uncertainties that may substantially impact the assessment, especially in controversial questions, structured approaches to identify and to assess also unquantifiable uncertainties have been proposed. In general, uncertainty typologies have been described that aims to identify and characterize sources of uncertainty (van der Sluijs et al., 2005; Knol et al., 2009). The identified uncertainties are then evaluated, e.g. using the NUSAP approach (Numerical, Unit, Spread, Assessment, Pedigree) with the objective of assessing the most important uncertainties impacting the assessment, i.e. those with little scientific rigor and a large influence on the outcome (van der Sluijs et al., 2005; Bouwknegt et al., 2014).

Exposure assessment. The part of the risk assessment where uncertainties have been most well defined and discussed is the dietary exposure assessment. Guidance related to uncertainty in this area was given by the Scientific Committee of EFSA already in 2006 (EFSA, 2006).

Terminology. It should be possible to harmonize terminology used within a specific risk assessment and possibly within each area of food safety, but it might be more difficult across the various areas of food safety. Introducing glossaries of definitions to improve the understanding and harmonising of terminology would be one way. The task of an agency involved in risk assessment and risk communication in several areas is not easy when the terminology is not always the same.

Terms used to express levels of risk and uncertainty should be consistent and well-defined, which require more quantitative expressions of risk and uncertainty whenever possible, i.e. quantitative expression of the probability of the adverse effect and of any quantitative descriptors of that effect (e.g. duration), or the use of verbal terms with quantitative definitions. The associated uncertainties should always be made clear, to reduce the risk of over-precise interpretation. Certain words such as “negligible”, “concern” and “unlikely”, may have risk management connotation in everyday language. When used in risk- and benefit assessments such words should be used carefully with as objective scientific criteria as possible.

Default values. In the absence of empirical data and when empirical data are to scattered, default values are often used to substitute for essential information. However, it is appropriate to stress that whenever specific data are available, these actual data should be used instead of default values. Default values will always introduce some uncertainty. As default assumptions may vary across expert groups, EFSA has produced guidance on selected default values to be used by its experts in the absence of actual measured data (EFSA, 2012b). Default values should be derived on the basis of existing data and be therefore scientifically justified.

In conclusion, how to address uncertainties in food risk and benefit assessments is a rapidly evolving field and EFSA among others is currently pursuing work in the Scientific Committee in order to develop guidelines for treatment of uncertainty. It is important to consider uncertainties in the risk and benefit assessments and to make this an integral part of the whole risk analysis process. At present it is premature to be prescriptive on how this should be carried out since different approaches exist and these may be more or less applicable depending on the nature of the assessment and the question. It will be important for NFA to follow the developments in the field and to integrate uncertainty assessment in the risk and benefit assessment process. As a minimum, assessments should contain a description of the most important uncertainties and an evaluation of their impact on the results that should be communicated to the risk managers.

7. Suggested procedure for risk-benefit assessment at NFA

During the last years, the NFA has observed an increasing demand of risk-benefit assessments, due to management issues. This increase led to the need to develop a structured procedure to performing risk-benefit assessments. As a start to develop such a procedure an overview and evaluation of current approaches in risk-benefit assessments used by national and international agencies was performed, as presented above.

In our review of the literature, we found the dominating approach to risk benefit assessment to be tiered methods. The advantages of stepwise methodology is that it is conceptually easy to use by the assessors and promotes transparency of the process. In this project, the workflow suggested by EFSA was used as a starting point for the development of our suggested procedure (EFSA, 2010a). The terms proposed by EFSA was used to describe the assessment (Table 1). The procedure suggested for use at NFA is described in detail in Appendix 3.

Table 1. Terms proposed by the Scientific Committee of EFSA for the assessment of the probability of harm (=risk) and the assessment of the probability of the positive health effects (=benefit) (EFSA, 2010a)

Risk Assessment	Benefit Assessment
Hazard identification	Positive health effect/reduced adverse effect identification
Hazard characterisation	Positive health effect/reduced adverse effect characterisation
Exposure assessment	Exposure assessment
Risk characterisation	Benefit characterisation

Risk-benefit assessments can be performed, for example, on individual agents (chemical substances, nutrients, microorganisms), combinations of agents, whole foods or diets, or different methods of food processing. Risk-benefit assessments can be carried out with varying levels of detail depending on the question and the availability of data. A simple exposure assessment is sometimes sufficient, comparing the result with previously established health-based reference values such as ADI (acceptable daily intake) and RI (recommended intake). In other cases, a more comprehensive assessment may be required. For individual substances in food, it is often a matter of determining whether the substance can itself constitute a risk and/or benefit, whereas the risk-benefit assessment for whole foods, diets or handling/preparation methods more often is expressed in relative or

comparative terms. According to the principles of risk analysis, the risk is assessed (risk characterisation) after the hazard has been identified and characterised and exposure to the hazard in question has been assessed. The benefit is assessed (benefit characterisation) after identification and characterisation of the positive health effect (including reduced adverse effect) of a substance/agent/food/diet and exposure assessment.

Before an assessment is initiated it is important that risk assessors and managers clearly define the terms of reference and describe the specific question, starting with what is included and what is not included in the question, as well as the boundaries that have been defined. As previously described our suggested procedure is based on a step-by-step workflow which is used to improve the effectiveness and quality of the assessment process, and to make it more transparent (Figure 2, Appendix 3). The procedure consists of three steps (step 1-3) moving from a simple assessment to a more advanced assessment, only if this is necessary and sufficient data are available in order to answer the question. Each step has decision points to determine whether the process can end or needs to continue. The steps are briefly described below and more in detail in Appendix 3.

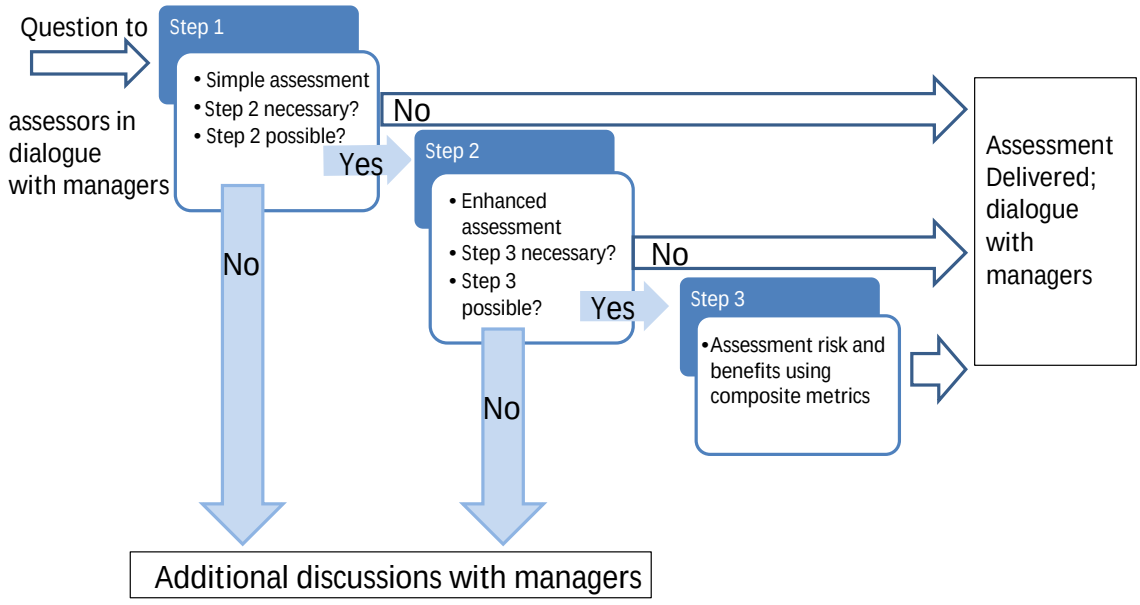

Figure 2. Overview of a step-by-step workflow, from a simple risk-benefit assessment to a more advanced one, if possible, and needed to answer the risk management question.

Step-by-step risk-benefit assessment

The first step (step 1) is an initial and simple assessment of risks and benefits in which different types of risk and benefit metrics are evaluated using a qualitative or semi-quantitative approach. It uses existing literature or includes a limited search/review of the relevant literature. Exposure assessment is based on consumption data at group level combined with point estimations of occurrence data regarding the content of substances in food/drinking water. For the characterization of hazards and positive health effects, existing and scientifically accepted health-based reference intakes and dose-response relationships are used. Risks and benefits are assessed separately, and aggregation of different metrics is performed for risks and benefits. If the assessment shows that the described risks and benefits are very close to each other, it may be appropriate, after consultation with the questioner, to proceed to step 2 for a more detailed assessment.

The second step (step 2) is an enhanced assessment of risks and benefits in which different types of risk and benefit metrics are evaluated using a semi-quantitative or quantitative approach. It may include an advanced search/review of the relevant literature. Exposure assessment used are consumption data at individual level combined with content data, i.e. point-estimations of variability in the content. Risks and benefits are assessed separately, and aggregation/weighting of different metrics for risks and benefits are performed. Step 2 may also include a more comprehensive hazard characterization if internationally accepted reference values or dose-response relationships are not available. If it is not possible in step 2 to obtain a satisfactory answer after weighing estimates of risks and benefits, the process moves on to step 3. However, to proceed to step 3 data must be available to estimate directly comparable metrics for comparing risks and benefits.

The third step (step 3) is a qualitative assessment of risks and benefits using the same metric. It uses more or less the same data on literature and exposure assessment as was obtained in step 2. Characterisation of risks and benefits uses aggregation of common directly comparable metrics for risks and benefits. The result of a step 3 assessment is therefore not merely a figure or a quantitative metric – instead, the result should be evaluated on the basis of all the uncertainties and in conjunction with all results in this. A risk-benefit assessment must always be reported and documented using quality-assured routines. This applies to all three steps. Assessments shall be searchable, making it easy to access and view the work that has been done on a particular substance/food/diet. One important part of the report is the description of how the risk-benefit assessment was performed and what deviations there were from this workflow. The conclusions must also contain an appraisal of the available data and must explain why – or why not – it is possible or necessary to perform a more comprehensive risk-benefit assessment (steps 2 and 3). In all assessments, data uncertainty must be estimated and described, or quantified to the extent possible. On the basis of the results obtained and their inherent uncertainty, an attempt should be made to evaluate the overall evidence of the established health effects through the following degrees of evidence: convincing, probable, possible and insufficient (FAO/WHO 2010).

8. Risk-benefit assessments – challenges and conclusions

Introduction

Integrated risk-benefit assessment in the food area is a relatively new field. General and more targeted procedures for carrying out assessments have been published (EFSA, 2010a; van Kreijl, 2006; FAO/WHO, 2007), and also applied to various extent. In this chapter some general comments and conclusions are outlined, based on a review of scientific papers and guidelines/documents dealing with proposed procedures and examples of how these have been applied and adapted to the specific questions.

Challenges

There are some general gaps of knowledge that need to be filled as the field progresses. In the present review issues related to health-based measures, grading of evidence and exposure data have been commented on. The project group has identified a number of additional major challenges in risk-benefit assessment.

Increased complexity of combined assessments

In risk assessments it is difficult to estimate actual health risks following exposure to specific compounds especially when exposure is above generally accepted safe levels e.g. a proposed TDI/ADI but below known levels associated with adverse health effects e.g. NOAEL/LOAEL. This problem is even greater when such risks are to be compared with estimated health benefits associated with nutrients or microbiological agents in food or food properties. In addition, it is easy to get the impression that a risk-benefit assessment gives a comprehensive picture of total risks and benefits of the food. This is not the case, since a risk-benefit assessment is always limited to the identified specific agents. Foods or whole diets contain a multitude of different agents (chemical substances, microorganisms, nutrients) with individual as well as combined effects.

Different metrics are often used to characterize risks and benefits

An important part in a risk-benefit assessment is the choice of relevant health-based metrics. There are various qualitative and quantitative metrics that can be used for estimating potential health effects of dietary intakes of food constituents. Depending on whether nutrients, anti-nutrients, microorganisms or toxicants are considered, these may include health-based guidance values (HBGV), such as ADI, TDI, BD and UL, which are based on toxicological data, and Dietary Reference Values (DRVs) for nutrients, e.g. RDA, AR and LI, which are based on nutritional data. For microorganisms in food there are no such reference values. Whereas a considerable amount of information is available on toxic and microbiological contaminants, there is very little information available for endogenous/ natural compounds in foods with a potential to cause adverse or positive health effects.

The above mentioned metrics are based on different types of data, applied to individuals or populations/groups, and some include different safety margins. Other metrics that have been used are morbidity and mortality and integrated metrics (composite metrics is EFSA´s terminology), such as DALYs and QALYs (see below).

Some previous risk-benefit assessments and our case study, regarding risk-benefit assessment of decreased nitrite and salt content of processed meat, show that it sometimes is possible to come to a reasonable certain weighing of health risks and benefits by using different metrics.

Data availability and data quality

The availability of scientific data is a general problem in risk-benefit assessments. Risk-benefit assessments require that data regarding positive and negative effects of food and substances in food are possible to compare in terms of potential health effects. There is in general more information available on dose-response data for toxicants and microorganisms relative to nutrients. On the other hand, dose-response information on nutrients are typically in dose intervals relevant to humans while the same type of data for toxicants in general are in dose intervals that are higher compared to the exposure experienced by the majority of the human population. Data need also to be applicable to different groups in the population, e.g. accounting for sensitivity due to gender, age, pregnancy, etc. In order to perform risk-benefit assessments, data on positive and negative health effects linked to a specific agent or food, data on composition and consumption of foods contributing to dietary intakes, need to be available.

Different types of data are used in risk versus benefit assessment

Chemical risk is typically defined from data derived either from laboratory animals, in vitro biochemical or in vitro cellular experimental settings, whereas benefit data mainly originate from human intervention trials or epidemiological studies.

Estimates of uncertainty associated with the risk-benefit assessment

A risk-benefit assessment may seem to result in clear results but it is important to communicate to the risk managers, information on the degree of uncertainty in the estimates. The strength of evidence for the association between the studied food/agent and health outcome should preferably be given (FAO/WHO 2011).

The separation between risk assessment and risk management

The use of different metrics for risk and benefit and the possibility that different populations may be affected by the risk and the benefits emphasize the importance that value-based inputs are supplied from risk managers prior to the assessment. This may relate to which population groups to assess and potential preferences for specific health endpoints.

Guidelines and approaches

In the present evaluation we identified a number of issues where available guidelines show a lack in some details when describing the process how to perform a risk-benefit assessment. With respect to application, the methods used for the risk-benefit assessment are not always stated in the papers. In addition, only few papers describe a full risk-benefit assessment with a common health metric comparing both risks and benefits. Thus, guidelines on how to perform a risk-benefit assessment of foods and their constituents need to be refined and possibly be adopted to apply for specific areas.

Conclusions

At NFA the overall aim has been to describe various approaches for performing risk-benefit assessment and from these develop an in-house procedure for practical use on issues where an assessment of risk-benefit is relevant. It is concluded that a tiered approach, as also suggested by EFSA, is preferred in all risk-benefit assessments, since the availability and type of data will determine how to approach a specific problem, e.g. whether the assessment can be and need to be qualitative, quantitative, or both. In addition, our developed three-step test procedure has been applied in a case study. In the case study potential risks and benefits of a decreased content of nitrite and salt in processed meat on population nitrite and salt intake and risk of *Clostridium botulinum* and *Listeria monocytogenes* infections were successfully assessed (Darnerud et al., 2014).

Some previous risk-benefit assessments and our case study show that it sometimes is possible to come to a reasonable certain weighing of health risks and benefits by using different metrics. Moreover a structural and tiered procedure for risk-benefit assessment is a valuable tool for more straight-forward and transparent presentation of the results and conclusions of risk- and benefit assessments within the food sector.

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Appendix I: Glossary

Adverse (health) effect: A change in morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences (IPCS, 2004; FAO/WHO, 2006).

Benefit: The probability of a positive health effect and/or the probability of a reduction of an adverse health effect in an organism, system, or (sub)population, in reaction to exposure to an agent (EFSA, 2010a).

Benefit-risk assessment: Science-based process intended to estimate the benefits and risks for humans following exposure (or lack of exposure) to a particular food or food component and to integrate them in comparable measures, thus facilitating better informed decisions by decision-makers (Tijhuis et al., 2012)

Composite metric: A combination of metrics that reflects a number of dimensions of health such as severity of disease, morbidity and mortality expressed in the same unit, for example DALYs or QUALYs (Gold et al., 2002).

Dose-Response Assessment: The determination of the relationship between the magnitude of exposure (dose) to a chemical, biological or physical agent and the severity and/or frequency of associated adverse health effects (response) (CAC, 2010).

Exposure Assessment: The qualitative and/or quantitative evaluation of the likely human intake of biological, chemical, and physical agents via food as well as exposures from other sources if relevant (Codex Alimentarus Commission 1999, 2007).

Hazard: A biological, chemical or physical agent in, or condition of, food with the potential to cause an adverse health effect (Codex Alimentarus Commission 1999, 2007).

Hazard Characterization: The qualitative and/or quantitative evaluation of the nature of the adverse health effects associated with biological, chemical and physical agents which may be present in food. For chemical agents, a dose-response assessment should be performed. For biological or physical agents, a dose-response assessment should be performed if the data are obtainable (Codex Alimentarus Commission 1999, 2007).

Hazard Identification: The identification of biological, chemical, and physical agents capable of causing adverse health effects and which may be present in a particular food or group of foods (Codex Alimentarus Commission 1999, 2007).

Metric (common metric): A measurement expressing risks and benefits in the same unit, for example incidence or mortality (Codex Alimentarus Commission 1999, 2007).

Risk: A function of the probability of an adverse health effect and the severity of that effect, consequential to a hazard(s) in food (Codex Alimentarus Commission 1999, 2007).

Risk Analysis: A process consisting of three components : risk assessment, risk management and risk communication (Codex Alimentarus Commission 1999, 2007).

Risk assessment: A scientifically based process consisting of the following steps: (i) hazard identification, (ii) hazard characterization, (iii) exposure assessment, and (iv) risk characterization (Codex Alimentarus Commission 1999, 2007).

Risk-benefit assessment: The probability of an adverse health effect or harm (both incidence and severity) as a consequence of exposure can be weighed against the probability of benefit, if both are known to be possible (EFSA 2010a).

Risk Characterization: The qualitative and/or quantitative estimation, including attendant uncertainties, of the probability of occurrence and severity of known or potential adverse health effects in a given population based on hazard identification, hazard characterization and exposure assessment (EFSA 2010a).

Risk Communication: The interactive exchange of information and opinions throughout the risk analysis process concerning risk, risk-related factors and risk perceptions, among risk assessors, risk managers, consumers, industry, the academic community and other interested parties, including the explanation of risk assessment findings and the basis of risk management decisions (Codex Alimentarus Commission 1999, 2007).

Risk Estimate: The quantitative estimation of risk resulting from risk characterization (Codex Alimentarus Commission 1999, 2007).

Risk Management: The process, distinct from risk assessment, of weighing policy alternatives, in consultation with all interested parties, considering risk assessment and other factors relevant for the health protection of consumers and for the promotion of fair trade practices, and, if needed, selecting appropriate prevention and control options (Codex Alimentarus Commission 1999, 2007).

Risk Profile: The description of the food safety problem and its context (Codex Alimentarus Commission 1999, 2007).

Appendix 2. Hazard characterization

In microbiology hazard characterization provides a qualitative or quantitative description of the severity and duration of adverse health effects that may result from the ingestion of a microorganism or its toxin in food. Data usually are derived from human studies of disease in connection to exposure to the organisms and/or toxins. Ideally a dose-response relationship between the exposure to the microorganism or toxin and disease should be established. Both infectious and non-infectious health effects should be considered. Data on infection, morbidity, hospitalization and death rates associated with different doses of microbes are commonly determined. If a dose-response relationship is not known, data on for instance infectivity could be important for the hazard characterization. Moreover, severity and duration of disease are important factors to consider.

In toxicological hazard characterization it is also common to determine dose-response relationships between exposure to the chemical hazard in question and adverse health effects. Commonly, data from animal studies are used, and the goal is to evaluate dose-response relationships for the most sensitive adverse effects reported in the available studies. This includes consideration of mechanistic aspects (e.g. whether the mechanism of action of the chemical observed in high-dose experimental studies is also relevant to human exposure at lower levels). Mechanistic considerations are also important determinants of which methods the risk assessors use in the risk characterization, i.e. wether the chemical hazards have a mechanistic threshold of exposure, below which no negative health effects are induced. For chemical hazards with a threshold, a no adverse exposure level (NOAEL) is established, which normally is the highest dose of the chemical that do not cause statistically significant increases in adverse health effects in the most sensitive animal species (see Figure 1 below).

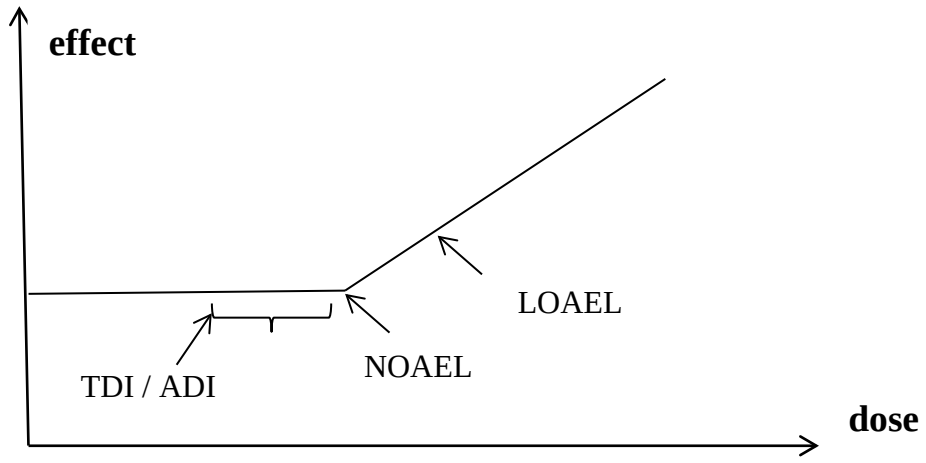

Figure 1, The dose response relationship for a chemical with a mechanistic threshold of exposure, i.e. in the very low doses the concentration of the chemical is too low to induce a measurable effect *in vivo*. TDI or ADI is established at a safe dose level of exposure, far below the obtained NOAEL, often hundred times lower.

In certain instances when no NOAEL can be established due to lack of scientific data, a lowest observed adverse effect level (LOAEL) can usually be established. The LOAEL represents the lowest dose of the chemical that produces an adverse effect in the most sensitive animal species. In certain cases, when human data is available from epidemiological studies of accidental human exposure or populations with high background exposures, NOAEL or LOAEL may be established from human data. An alternative approach to NOAEL/LOAEL may be to use benchmark modeling, in which dose-response modeling of experimental or epidemiological data is used to determine the lower-bound benchmark dose (BMDL) that is associated with a 5 % or 10 % increase in incidence of adverse effects in the experiment in question. The BMDL usually represents the lower-bound 95 % confidence interval.

By the use of the NOAEL, LOAEL or BMDL, characterization of a chemical hazard usually results in the establishment of a safe level of intake during long-term exposure, an acceptable daily intake (ADI), or tolerable daily intake (TDI) for contaminants (Figure 1). An ADI or TDI represents a crude but conservative approximation of an actual chronic safe daily intake. The conservatism considered to be inherent in such a safety evaluation is generally thought to ensure sufficient protection of human health. If scientific evidence for the contrary is lacking, humans are regarded as more sensitive to the hazard in question than the most sensitive animal species. Estimation of the ADI/TDI therefore includes the application of default “uncertainty factors” (UFs) to NOAEL/LOAEL/ BMDL, to account for uncertainties inherent in extrapolating from an animal model to humans and to account for inter-individual variability (Figure 1). The UF is frequently 100 for toxic effects that are not too severe, and encompass a factor of 10 for extrapolation of differences in sensitivity and metabolism of the chemical between the most sensitive animal species and humans. An additional factor of 10 is applied accounting for individual differences in sensitivity and metabolism within the human population. If a LOAEL or a BMDL is used in the derivation of a safe intake, or if severe adverse effects such as potential carcinogenicity are evident, additional UFs are commonly used. When enough scientific information is available, the UF can be replaced by data-derived chemical-specific extrapolation factors. The UFs usually becomes smaller if the assessment is based on human data.

Methods have also been developed for calculating reference doses for acute intakes of toxic chemicals when acute adverse health effects are plausible. For example, an acute reference dose (ARfD) may be calculated for a pesticide to take into account the possibility of occasional high intake of residues that may be acutely toxic.

Toxicological reference values used by different authorities for genotoxic carcinogenic chemicals vary. In this case it is assumed that there is no exposure to the chemical that is safe, i.e. in theory the risk for developing disease decreases with exposure down to a zero risk at zero exposure (see Figure 2 below).

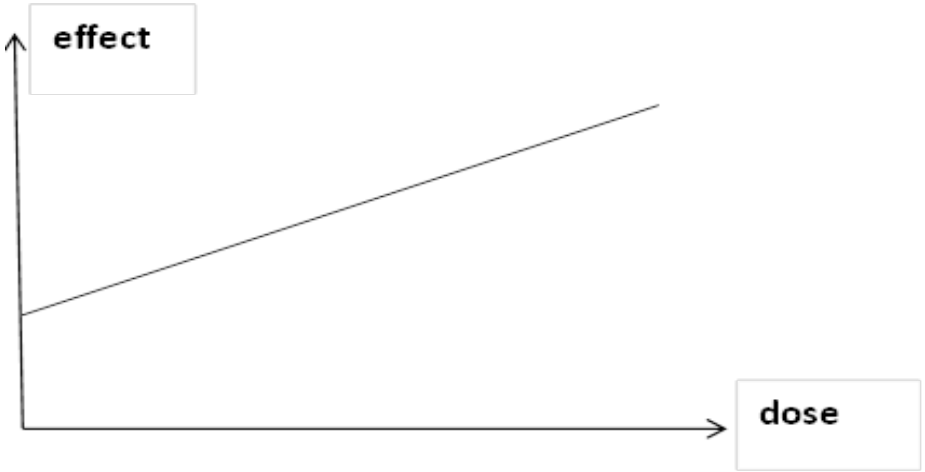

Figure 2, The dose response relationship for a chemical without a mechanistic threshold of exposure, i.e. there is an increased risk even in the lowest dose region. Examples of such chemicals are genotoxic substances with a potency to destroy the DNA and thereby increase the cancer risk.

Different mathematical models may be used to extrapolate risk estimates to low doses (Figure 2). These differences can lead to significant variability in cancer risk estimates for the same chemical. In some cases a combination of epidemiological and animal data are used, but most commonly modeling is based on animal data alone.

Nutritional risk-benefit characterization generally focuses on estimating metabolic and health effects of intake of various nutrients in humans. In this process, human data are used, mainly derived from controlled intervention studies, prospective cohort studies and case-control studies. Animal (*in vivo*) and *in vitro* studies are used in cases when mechanistic information is important for the assessment.

Dietary reference values (DRVs) are determined, which are used as guidelines for planning and evaluation of nutrient intakes in populations and for groups of individuals (NNR, 2011; NNR, 2012). DRVs generally refer to a set of values for essential nutrients:

- average requirement (AR).
- recommended intake (RI).
- upper safe intake level (UL).
- lower intake level (LI).
- recommended ranges of macronutrient intakes (e.g. fatty acids, protein).

AR is the lowest long-term intake level of a nutrient that will maintain a defined level of nutrient status in 50 % of a defined group of individuals, provided that the requirement is normally distributed. AR is generally applied to micronutrients and are usually based on data on biochemical markers of adequate nutritional status. AR is however also derived for certain macronutrients such as protein and essential fatty acids. RI is the amount of a nutrient that according to present scientific knowledge and information on dietary patterns can meet the known requirement and maintain good nutritional status among practically all healthy individuals in a certain life stage and gender group (NNR, 2012). When

an AR in a certain group is approximately normally distributed (or symmetrical) and a standard deviation (SD) can be determined, the RI is:

$RI = AR + 2\ SD_{AR}$

In cases when data on variability in AR are insufficient for a calculation of a SD, an approximate coefficient of variation (CV) of 10-15 % may be used to derive a RI. When intakes of nutrients are much higher than the RI the nutrient may cause toxic effects. The UL is the maximum level of long-term daily nutrient intake that is unlikely to pose a risk of adverse health effects in a certain group of individuals (NNR5). The procedure to determine an UL is similar as the determination of an ADI/TDI in TRA. NOAELs/ LOAELs/BMDLs are identified and the UL is derived by dividing the above threshold values with UFs. The UFs should account for uncertainties in individual variability, and in cases when animal data are used uncertainties about differences in sensitivity and metabolism between animals and humans. If there are other uncertainties or deficiencies in the data additional AFs can be used. LI is the cut-off intake below which an intake could lead to clinical deficiency symptoms in most individuals. LI is usually based on observations on individuals

All DRVs are expressed on a daily basis, except for the macronutrient ranges, which usually are expressed in percent of daily energy intake (E%). It should be noted that a certain DRV for a given nutrient is only applicable if the supply of other nutrients and energy is adequate.

Criteria for assessing nutrient adequacy include intakes necessary for prevention of clinical deficiency symptoms (LI), maintenance of optimal levels of body stores and functionality, e.g. enzyme function (used for setting AR and RI). Criteria for assessing health benefits include effects of intakes for maintaining/reducing established risk factors for disease (e.g. serum lipids, glucose, blood pressure), and preventing/reducing morbidity and mortality (used for setting RI and macronutrient ranges).

Figure 3 gives a schematic picture of the relation between the different reference values.

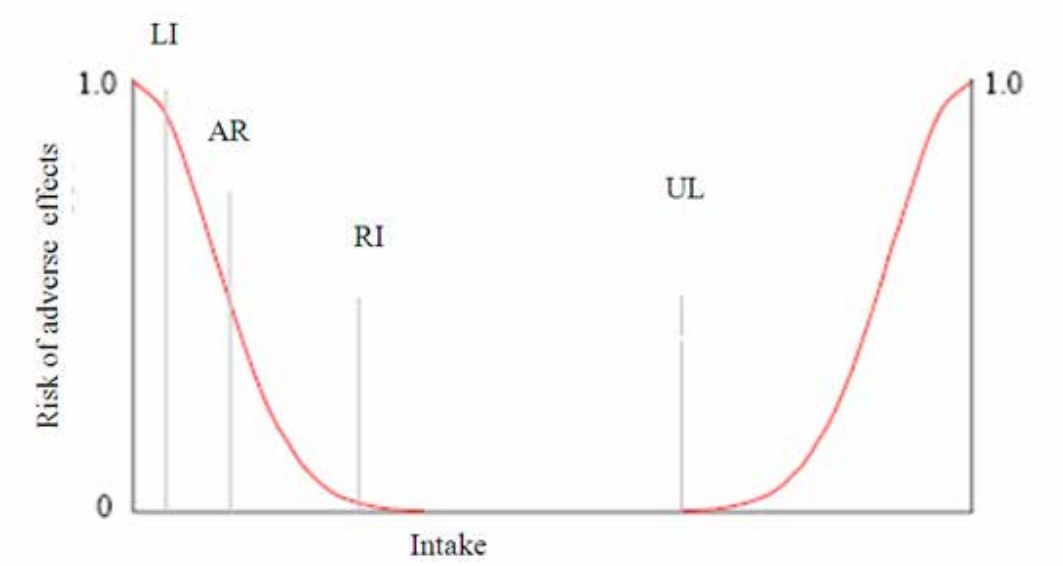

Figure 3. Schematic illustration of relation between dietary reference values for nutrients and risk of adverse health effects. Adapted from EFSA (EFSA 2010b).

AR: Average requirement
LI: Lower intake level
RI: Recommended intake
UL: Upper safe intake level

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Appendix 3. Instructions for risk-benefit assessments

Background

The Risk and Benefit Assessment Department (RN) at the National Food Agency (NFA) has developed a set of instructions for use in in-house work at NFA related to risk-benefit assessments. These include 1) a workflow for structured literature searches, 2) a workflow and a background document for exposure assessment of food and food constituents, and 3) a workflow for risk-benefit assessments. This document covers the workflow for risk-benefit assessments (3), which also builds on the other two documents.

Introduction

This document is intended to give assessors support in health-based risk-benefit assessments of food and agents occurring in food, using a step-by-step workflow that is conceptually easy to use by the assessors. The workflow is based on a procedure on human health risk-benefit assessment of foods outlined by the European Food Safety Authority (EFSA, 2010). Risk-benefit assessments can be performed, for example, on individual agents (chemical substances, nutrients, microorganisms), combinations of agents, whole foods or diets, or food processing. Risk-benefit assessments can be carried out with varying levels of detail depending on the question and the availability of data. A simple exposure assessment is sometimes sufficient, comparing the result with previously established health-based reference values, such as ADI (acceptable daily intake) and RI (recommended intake). In other cases, a full assessment is required (Figure 1). For individual substances in food, it is generally a matter of determining whether the substance can itself constitute a risk and/or benefit, whereas the risk-benefit assessment for whole foods, diets or handling/preparation methods more often are expressed in relative or comparative terms. For example, this could mean assessing the risks and benefits of consuming pasteurised milk compared to unpasteurised milk. According to the principles of risk analysis, the risk is assessed (risk characterisation) after the hazard has been identified and characterized, and exposure to the hazard in question has been assessed. The benefit is assessed (benefit characterisation) after identification and characterisation of the positive health effect (including reduced adverse effect) of a substance/agent/food/diet and exposure assessment. The purpose of this workflow is to simplify, standardise/harmonise and improve the effectiveness and quality of the assessment process, and to make it more transparent. The aim is to develop a risk-benefit assessment that can be used as a support for management decisions.

Problem formulation

An issue may be raised within NFA, and commissioned to RN. The issue is formulated jointly by the responsible manager and the assessor to clarify whether it is possible to answer a specific question. If it is agreed that the question is possible to answer, those involved proceed to formulate the question in more detail.

If it is decided, after consulting the manager, that the question as formulated cannot be answered, the issue is closed and a response is written indicating why. Further discussions with those who initiated the question may be needed to check if the question can be modified/specified, or if other measures are necessary before it is possible to proceed with a risk-benefit assessment.

If resources are needed from other departments/units at NFA, a decision is made whether the horizontal Risk Analysis Group at NFA needs to make an evaluation prior to decisions on how to proceed. This decision is made jointly with the concerned departments based on the extent of the issue and the resources required from the departments involved.

Specific question ("terms of reference")

The terms of reference should clearly describe the question, stating what is included and what is not included, as well as the limitations that have been defined. The scientific question is separate from practical matters such as the time, expertise and personnel available to perform the assessment (in certain cases external expertise may be brought in), although these issues should also be defined.

Overview of workflow for risk-benefit assessment, steps 1-3

The current workflow is based on the procedure outlined by EFSA (EFSA, 2010). A step-by-step workflow is used to simplify, standardise, harmonise and improve the effectiveness and quality of the assessment process, and to make it more transparent (Figure 1). The principle consists of moving in steps from a simple assessment to a more advanced assessment, only if this is necessary in order to answer the question (Table 1). Each step has decision points to determine whether the process can end or needs to continue. The procedure can also be used for a risk assessment or benefit assessment on its own.

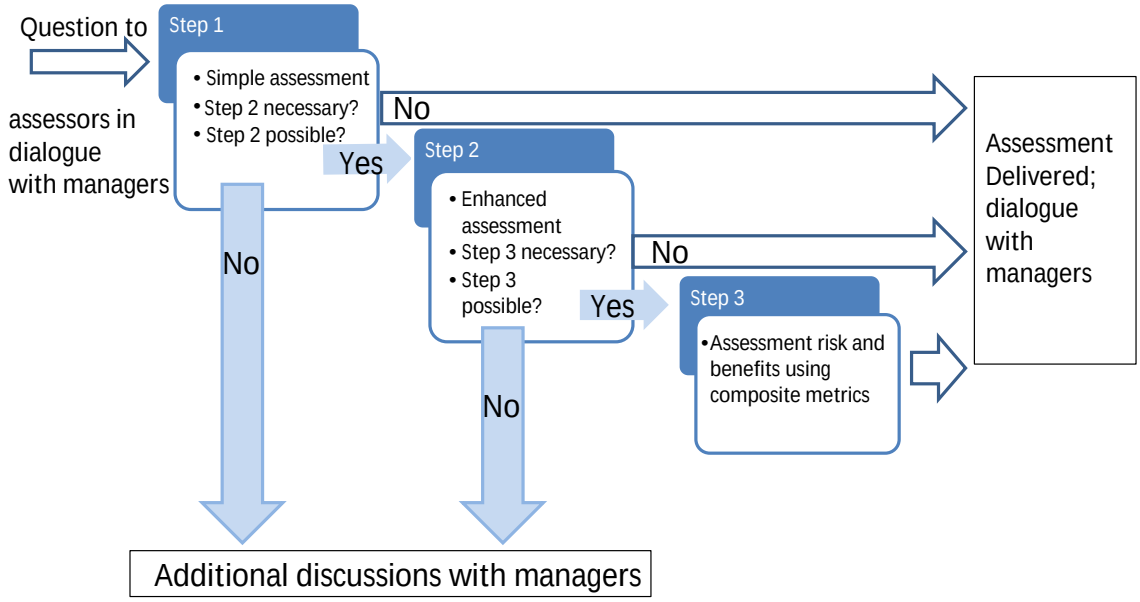

Figure 1. Overview of a step-by-step workflow, from a simple risk-benefit assessment to a more advanced one, if possible, and needed to answer the risk management question.

Step 1: Simple assessment: In step 1, a simple evaluation method is used to judge if the results are clear enough to show differences between risk an benefit that can be used as a basis for decision making. In step 1 it is also clarified if there is enough data that can be used for enhanced assessment in step 2 and 3. The simple assessment can be qualitative, semi-qualitative, or quantitative depending on the question. A simple quantitative assessment includes only deterministic (point) estimates of exposure, although the risk and benefit assessments have a quantitative approach.

Step 2: Advanced assessment: If the simple approach described in step 1 is not sufficient to answer the question, a more advanced assessment is carried out in step 2. Step 2 involves the use of more data relating to content/occurrence in food and consumption patterns in the exposure assessment. Step 2 may also include the development of health-based reference intakes if these are not already available. Additional calculations concerning intake and risk and/or benefit, for example probability modelling, may be performed to take account of variation and uncertainties.

Step 3: Assessing risks and benefits using composite metrics: If it was not possible in step 2 to obtain a satisfactory answer after weighing estimates of risks and benefits, the process moves on to step 3 if possible. In step 3, comparable metrics are used for the risks and benefits, such as morbidity, mortality, DALY (Disability Adjusted Life Years) and COI (Cost of Illness). This step assumes the availability of large amounts of data in order to calculate comparable metrics that can be used in a quantitative analysis.

Table 1. Steps and work-flow for risk-benefit assessments. The workflow can also be used for a risk assessment or benefit assessment separately.

Step	Literature search[a]	Exposure assessment[b]	Characterisation of hazards and positive health effect	Characterisation of risks and benefits	Type of assessment
1 Simple assessment	Use existing literature, or limited search	Consumption data at group level combined with point estimations of content.	Existing and scientifically accepted health-based reference intake and dose-response relationship used	Risks and benefits are assessed separately. Aggregation of different metrics for risks/benefits	Qualitative or semi-quantitative
2 Enhanced assessment	Advanced search	Consumption data at individual level combined with content data (point-estimations of variability in the content)	Health-based reference intake and dose-response relationship created after a literature review	Risks and benefits are assessed separately. Aggregation/ weighting of different metrics for risks/benefits	Semi-quantitative or quantitative
3 Assessing risks and benefits using the same metric	See step 2	See step 2	See step 2	Aggregation of common or directly comparable metrics for risks and benefits	Qualitative

a) Refers to the workflow for structured literature searches (see references)

b) Refers to the workflow and background document for exposure assessments (see references)

Step 1.
Initial assessment according to the principles of risk analysis (Initial assessment)

The step 1 assessment below describes the different items in the workflow. All the items are included, but the order in which they are carried out may vary depending on the question.

A. Literature review

A literature search must be included to determine whether scientific documentation exists concerning the negative or positive health effects. Details of how the search is performed are documented in terms of the relevant literature, databases and search strings. If there is no scientific data available, the question is closed. If the question is closed, an answer is written anyway, describing why the question could not be answered. A new question may be formulated if appropriate.

B. Identification of negative and positive health effects

Here, the food or diet in question is examined to confirm whether it really is a source of exposure to the substance(s) or agent(s) which the questioner suspects may give rise to negative or positive health effects. If negative or positive health effects can be identified, the process moves on to point C.

If there is a lack of data relating to the occurrence in food, the question is closed and reported. Similarly, the question is closed and reported if there is data showing that the food is not a source of intake/exposure. If it is only possible to identify a hazard but no benefit, or vice versa, the matter is closed and reported since it is not possible to balance the risk against the benefit. However, the procedure can be used for a risk assessment or benefit assessment on its own. The workflow is also effective for risk assessments and benefit assessments separately. In this case the process moves on to point C after the question has been reformulated in consultation with the questioner.

C. Exposure assessment

If negative or positive health effects have been identified and can be described, an assessment of the exposure is carried out. For example, an exposure assessment could be based on market basket data, providing a point estimation of per capita exposure (an approximate metric of a population's mean exposure). From here, the process moves on to point D.

If the exposure cannot be assessed, for example because of a lack of consumption data for the food in question or the absence of contents/quantities of agents in the food, the assessment is closed and reported. If data is available showing that the population is not exposed, the assessment is closed at this point and reported.

D. Characterisation of negative and positive health effects

Here it is described whether internationally recognized health-based guidance values (HBGV) or similar reference intakes are available, for example RI, ADI, Tolerable Daily Intake (TDI), Acute Reference Dose (ARfD), or Safe Upper Limit (UL), for the negative and positive health effects referred to in the question. The metric may also include an estimate of the risk of morbidity (prevalence and/or incidence) and mortality in relation to exposure in studied populations. Other metrics concerning health effects may also be used, for example grams of whole grain per day producing a certain percentage reduction in the risk of disease, or a change of cancer risk with a different intake of a substance/ food. If existing health-based reference values/ADI/TDI, etc. are available, they are described and the process moves on to point E. Certain guidance values are not based on optimum levels for health but instead take into account the composition of the diet. Examples include recommendations on added sugar and population-wide salt targets.

If there is no available reference value or other intake metric relating to risk or benefit, the question is closed at this point and reported. If relevant literature is available or if we have our own data, it is possible to develop a basis for estimating the ADI/TDI/reference

intake. In this case, the questioner must be contacted in order to formulate a new question. This new question requires a more detailed analysis for a more complete characterisation of negative and positive health effects, involving a more wide-ranging assessment, step 2 in this workflow.

Microbiological hazards and questions differ from nutritional or chemical hazards and questions, which is why reference values are rarely used. In this case, this item includes a description of negative and positive health effects, who they affect, and an identification of the dose-response relationship or comparable information about the relationship between exposure and risk. If any necessary information is lacking, an alternative strategy is discussed or the matter is closed and a report is sent to the questioner.

E. Characterisation of risks and benefits

The exposure of the agent/nutrient/food established in point C is compared with internationally recognised health-based reference intake values such as RI, ADI, TDI, ARfD, UL or another relevant measure of the relationship between exposure and health effects established in point D. In some cases where estimations of the exposure and reference value or the dose-response relationship are available, it may be possible to perform a preliminary assessment as to whether the risk outweighs the benefit or vice versa. In such cases the assessment is ended at this point and a report is sent to the questioner.

If an estimated exposure of a hazard is below the established health-based reference value (ADI, TDI, ARfD, UL) for the majority of the relevant population, the risk is generally considered to be minimal.

With regard to positive health effects, a number of reference values should be taken into account. If the mean intake of a nutrient (vitamin, mineral) for the relevant population is higher that the recommended intake (RI), the intake can generally be considered to be sufficient. However, since this is depending on the distribution of the intake in the population, the average requirement (AR) should always be used to assess the probability of insufficient intake. For energy-providing nutrients (e.g. fatty acids, added sugar, alcohol) and salt there are ranges or maximum values which the majority of that population should fall within/not exceed. If the population intake is within or under these values, the risk of negative health effects should generally be considered to be low.

If the assessment shows that the described risk and benefit are very close to each other, it may be appropriate, after consultation with the questioner, to proceed to step 2 for a more detailed exposure assessment.

F. Documentation

A risk-benefit assessment must always be recorded and documented using quality-assured routines in report forms designed for the purpose. This applies to all steps. Assessments can be made searchable, making it easy to see the work that has been done on a particular substance/food/diet. One important part of the report is the description of how the risk-

benefit assessment was performed and what deviations there were from this workflow. The conclusions must also contain an appraisal of the available data and must explain why – or why not – it is possible or necessary to perform a more comprehensive risk-benefit assessment (steps 2 and 3).

It will sometimes not be possible to state that the risk outweighs the benefit or vice versa. In cases where it is impossible to establish this, the report must include an explanation. The person commissioning the risk-benefit assessment is briefed on the result of the assessment and the reason why it cannot be completed.

G. New questions arise

If the questioner in consultation with RN considers it to be impossible to complete the risk-benefit assessment without more work being done, it may be necessary to reformulate the question. The question could be restricted in scope, for example only performing a full assessment for a particular risk group that has been identified. However, a reformulation of the question means that the original "terms of reference" are closed and a new "terms of reference" must be created.

Step 2. Advanced assessment of risks and benefits

Step 2 involves an enhanced, more detailed risk-benefit assessment in which different types of risk and benefit metrics are evaluated. In simple terms, there are three strategies/approaches that can be used in step 2, separately or in combination, in order to create a risk-benefit assessment.

i. Enhanced characterisation of negative and positive health effects: Based on an additional literature search from which health-based reference values are established. These reference values are compared with the point estimations of exposure created in step 1.
ii. Enhanced exposure assessment: The data obtained from the enhanced exposure assessment is evaluated in relation to reference intakes from the characterisation of negative and positive health effects created in step 1.
iii. Combination of i) and ii): The data obtained from the exposure assessment (ii) is compared with the result of the enhanced characterisation of negative and positive health effects (i).

The specific elements of an advanced assessment of risks and benefits are as follows:

A. Literature search

An extensive literature search is used to determine whether the risk significantly outweighs the benefit (risk>>benefit), or vice versa (benefit>>risk). If there is lack of relevant and sufficiently extensive literature, or that data is missing, the assessment is ended at this point and the result is recorded and reported to the manager. If there is enough data to establish health-related reference intakes, the assessment is continued. Alternatively, a decision is made about whether the "terms of reference" needs to be revised.

The literature search must be carefully documented, preferably by recording the research question, search strings and the databases accessed.

B. Exposure assessment

Extended and more detailed calculations are carried out. The question and the available data determine the most suitable approach and the level of detail that is desirable or achievable. As with other parts of the risk-benefit assessment, exposure assessments must be based on quality-assured background data and scientific methods.

The methods used for the exposure assessment must be clearly described. Information about the model and the data sources used, assumptions, limitations of scope and uncertainty must be documented. The workflow exposure assessments developed at RN helps clarify and identify which exposure assessment is most appropriate for the purpose and what quality assurance and documentation are necessary.

C. Characterisation of negative and positive health effects

The data obtained from the literature search is used to perform an enhanced analysis for a comprehensive characterization of negative and positive health effects. This enhanced analysis is carried out if internationally recognized health-based reference values are not available, and could involve developing a new reference intake, for example a basis for evaluating TDI, ADI, UL, or RI. The metrics used in step 2 may also include an estimate of the risk of morbidity (prevalence and incidence) and mortality.

D. Characterisation of risks and benefits

If there is good exposure data and internationally recognized health-based reference values or an in-house-developed health-based reference intake or dose-response relationship, it will be possible in step 2 to perform a semi-quantitative evaluation of different metrics of risk and benefit for a relevant exposure. Possible results:

- the proportion of the population or relevant subgroup whose intake exceeds the health-based guidance values or
- the intake does not reach the reference values or minimum intake for a positive health effect.

Other possible results include an estimation of the incidence of disease or mortality which occurs at a specific level of exposure, and the impact of altering the exposure, for example, through interventions like fortification or dietary advice.

If different health-based metrics with different units are used, the robustness of the conclusions must be evaluated by a suitable method. One option is to use multicriteria decision analysis (MCDA).

In all assessments, data uncertainty must be estimated and described, or quantified to the extent possible. On the basis of the results obtained and their inherent uncertainty, an attempt should be made to evaluate the evidential value of the established health effects through the following degrees of evidence: convincing, probable, possible, and insufficient (FAO/WHO, 2011).

Step 3. Quantitative assessment using aggregated (composite) metrics comparing risks and benefits

In this step, a quantitative comparison of risks and benefits is carried out using directly comparable and aggregated (composite) metrics. This presupposes the availability of adequate background data. Composite metrics of risk and benefit are a way of combining increases and decreases in morbidity, mortality, disease burden (DALY) and quality of life (QALY).

The result of a comparison using aggregated metrics with the same units can be directly expressed as a net value for negative and positive health effects. However, a net value should be treated with great care, and account must be taken of uncertainties in the assessment of risk or benefit. In the report, the values for risk and benefit should be broken down into relevant groups. It is also important to estimate and communicate the uncertainties in the established values.

The result of a step 3 assessment is therefore not merely a figure or a quantitative metric – instead, the result should be evaluated on the basis of the uncertainties and in conjunction with the result from step 3. If no conclusion can be drawn from the assessment due to excessive uncertainties, the manager should be given data collection recommendations to reduce the uncertainties.

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Rapporter som utgivits 2013

1. Contaminants and minerals in foods for infants and young children – analytical results, Part 1, by V Öhrvik, J Engman, B Kollander and B Sundström.

   Contaminants and minerals in foods for infants and young children – risk and benefit assessment, Part 2 by G Concha, H Eneroth, H Hallström and S Sand.

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17. Miljöpåverkan från animalieprodukter – kött, mjölk och ägg av M Wallman, M Berglund och C Cederberg, SIK.
18. Matlagningsfettets och bordsfettets betydelse för kostens fettkvalitet och vitamin D-innehåll av A Svensson, E Warensjö Lemming, E Amcoff, C Nälsén och A K Lindroos.
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