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Risk Benefit Assessment of foods: key findings from an international workshop

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Abstract

Whilst risk management measures, including food policy, are developed for the protection of public health and the environment, they may also lead to a reduction in health benefits. Policy decisions require then consideration of these necessary trade-offs, which leads to an increasing need to apply formal risk-benefit assessment (RBA) of foods. In this context, the European Food Safety Authority sponsored a Risk-Benefit Assessment Workshop on "past, current and future developments within the risk-benefit assessment of foods (RBA)" held in May 2017. The overall aims of the RBA Workshop were to discuss existing methods, challenges and needs within RBA, and to draft a roadmap for future development of RBA. The specific objectives were to i) identify RBA activities in Europe and globally; ii) discuss how to further develop and optimize RBA methodology; iii) identify challenges and opportunities within RBA; and iv) increase collaboration internationally. The two-day workshop gathered 28 participants from 16 institutions in 11 countries. It included technical presentations of RBA methods and case studies, and two break-out sessions for group discussions. All participants agreed that RBA has substantial potential to inform risk-management decisions in the areas of food safety, nutrition and public health. Several activities to optimize further developments within RBA were suggested. This paper provides a summary of workshop presentations, a discussion of challenges that limit progress in this area, and suggestions of next steps for this promising approach supporting a science-based decision process in the area of risk-benefit management of foods.

1. Introduction

1.1. History of RBA of foods

Risk-benefit assessment (RBA) of foods is a relatively new decision-support tool that assesses the combined beneficial and adverse health effects of consumption of foods in one integrated methodology. It integrates

knowledge on nutrition, toxicology, microbiology, chemistry and human epidemiology for comprehensive health impact assessments. RBA is part of the Risk-Benefit Analysis paradigm that combines RBA, risk-benefit management and risk-benefit communication, similar to the risk analysis paradigm (FAO, 2007). RBA is thus useful to inform food safety policies or to provide dietary advice based on an integration of the available scientific knowledge, with the ultimate aim of preventing food-associated diseases and promoting health and wellbeing of consumers.

Research to inform public health policies in the area of food and diets has been traditionally focused either on food safety, i.e. assessing risks and implementing strategies to limit the presence of microbiological or chemical hazards, or on nutritional assessments, i.e. assessing both risks or benefits of a lack or surplus of foods and nutrients. RBA is a conceptual and practical shift from the separate assessment of risks or benefits, typically within toxicology, microbiology and nutrition, to an integrated and multidisciplinary assessment of both risks and benefits. International organizations such as the World Health Organization (WHO) and Food and Agriculture Organization (FAO) have conducted RBA of foods to address risk-benefit questions (FAO/WHO, 2008, 2010). In the USA, several RBA studies have been performed on health risks and benefits of seafood consumption (FDA, 2014; Gochfeld & Burger, 2005; Malden C. Nesheim and Ann L. Yaktine, 2007; Rheinberger & Hammitt, 2012) Furthermore, the European Food Safety Authority (EFSA) started a discussion on RBA methodology in 2006, and in 2010 launched a scientific opinion on Guidance on human health risk-benefit assessment of foods (EFSA, 2006, 2010). Following these initial developments and discussions, important research and progress within RBA has been performed, for example within European research projects like BRAFO (Hoekstra et al., 2012), Qalibra (Hart et al., 2013), Beneris (Leino, Karjalainen, & Tuomisto, 2013), and BEPRARIBEAN (H. Verhagen et al., 2012). In these projects, important steps have been taken to develop RBA methodology, and first generation software tools were developed to facilitate RBA while taking relevant

66 uncertainties into account. In addition, a series of initial case studies was conducted (see e.g. Boobis et al.,
67 2013; Hart et al., 2013; Hoekstra et al., 2012; Hoekstra, Fransen, et al., 2013). These projects were also
68 important to identify main challenges and limitations of the implementation of RBA at that time. After the
69 termination of these EU projects, progress in RBA has been made by individual research groups, which have
70 addressed RBA questions in *ad-hoc* case studies in response to questions of food safety managers (Anonymous,
71 2017a; Eneroth, Wallin, Leander, Nilsson Sommar, & Åkesson, 2017; Steffensen et al., 2018) or to make further
72 progress in RBA method development (Berjia et al., 2014; Boué, 2017).
73

74 Several of the challenges identified as a result of the European RBA projects (Boobis et al., 2013) still remain, and
75 include data and knowledge gaps; methodological limitations; difficulties in aggregating/comparing risks and
76 benefits and in combining human data with data extrapolated from animal studies; lack of harmonization of
77 concepts; and complexities in communicating RBA results. Furthermore, new research questions and agendas
78 emphasize a need for assessments that include other societal impacts such as environmental, sustainability and
79 economic concerns, in addition to public health effects. Tackling these challenges and paving the way for further
80 development and implementation of RBA requires commitment and contribution of international experts in all
81 aspects of risk assessment, food safety and nutrition. International collaboration will be crucial for the
82 establishment and consolidation of RBA as a tool to evaluate scientific evidence to inform decision makers in
83 public health and food safety at national and international levels. Several research groups in different countries
84 are committed to further advance the field of RBA of foods, develop methodologies and provide evidence to
85 support risk-benefit management in food safety and nutrition at national and global level. Leveraging on these
86 research activities, EFSA sponsored a two-day workshop to gathered international RBA experts to pave the way
87 forward within the RBA area. This paper describes the structure, contents and overall conclusions of the
88 workshop. It starts by providing a brief overview of the RBA process and methodology (section 2), describes
89 examples of current developments of RBA that were presented at the workshop (section 3), as well as the most
90 important challenges within the field (section 4), and presents the opportunities and suggestions for next steps
91 within RBA discussed by the experts (section 5).1.2. Workshop objectives and structure
92 The overall aims of the RBA Workshop were to discuss methods, challenges and needs within RBA and to draft
93 a roadmap for its future development. The specific objectives were to i) identify RBA activities in Europe and
94 worldwide; ii) discuss how to further develop and optimize RBA methodology; iii) identify challenges and
95 opportunities within RBA; and iv) increase collaboration internationally. The two-day workshop gathered 28
96 participants from 16 institutions in 11 countries in Copenhagen, Denmark, May 2017. Participants and their

affiliations are presented in the appendix 1. The workshop included scientific presentations sharing past and current achievements in the area of RBA; break-out discussion sessions to identify challenges and to discuss opportunities for further developments in terms of data collection; methodologies and expansion of the scope of RBA to include other measures of impact; and an overall discussion to plan the future of RBA.

2. Risk-benefit assessment process and methodology

The process of an RBA is similar to the process of a traditional risk assessment. First, the risk-benefit question is defined by the risk manager, describing the purpose, scope and boundaries of the assessment including at what level (component, food or diet) the assessment is performed. As part of the problem formulation, the scenarios to be investigated are defined and the relevant subpopulations are identified. A reference scenario, which is usually current exposure or consumption, is compared to one or more alternative scenarios. The alternative scenarios serve to investigate the health impacts of a change in intake, and may be defined based on for example a worst-case exposure scenario or a recommended intake. Next, the RBA process can be divided into five steps, where the first four are common to the ones of traditional risk assessments but applied to risks and benefits separately (Boobis et al., 2013) (Figure 1). Lastly, risks and benefits are integrated to answer the risk-benefit question. Hence, the RBA process includes i) the identification of adverse and beneficial health effects associated with the consumption of food(s) and the exposure to food components considered; ii) the assessment of food consumption or exposure to food components; iii) the characterisation of the relevant health effects by determining the dose-response relationships for the food components or foods, describing the association between exposure and likelihood of an effect; and iv) the characterization of risks and benefits by integrating the information on dose-response relationships and the outcome of the exposure assessment. The conclusion of the risk-benefit characterization (i.e. step v) can be that a change in intake scenario is expected to lead to an increase or decrease in the incidence of the studied health effects. This conclusion may

be based on a qualitative assessment, stating that the health impact of one scenario is beneficial as compared to another without giving an estimate of the size of the health impact, but it can also be a quantitative estimate, expressing the health impact in terms of a common health metric such as incidence, mortality, disability adjusted life years (DALY) or quality adjusted life years (QALY) (Gold, Stevenson, & Fryback, 2002; Tijhuis et al., 2012). A quantitative assessment may be necessary if one scenario does not clearly stand out more beneficial or adverse compared to another in the qualitative assessment (Tijhuis et al., 2012); alternatively the aim of the RBA may be a quantitative outcome from the beginning.

RBA methods have evolved substantially over the years, allowing for improved evaluations of the health impact of foods. These developments have been equally evident in terms of data collection and analysis, and of method development and modelling (see 3.). As examples, while the first RBA studies focused on one single food (e.g. fish) (e.g Hoekstra et al., 2013; Skåre et al., 2015) or one single food component (e.g. folic acid (Hoekstra et al., 2008)) and investigated risks and benefits in the population as a whole, recent work has taken into account the health effects of substitution of foods in overall dietary patterns, or variation in the population in terms of susceptibility or dietary preferences (see 3.2. and 3.3.). The technical session of the workshop included presentations of past and present RBA case studies illustrating different approaches, some of which are summarized below.

3. Current developments in quantitative RBA of foods

3.1. RBA of single foods

The majority of published RBA in the area of food safety and nutrition focused on single foods (Berjia et al., 2014; Eneroth et al., 2017; Hoekstra, Fransen, et al., 2013; Hoekstra, Hart, et al., 2013), with fish being most

frequently evaluated (Boué, Guillou, Antignac, Bizec, & Membré, 2015). These RBA studies aimed to assess the overall impact of a food consumed while considering different levels of exposure and different factors affecting human health related to the fields of nutrition and/or microbiology and/or toxicology. Although many RBA performed recognize the broad impact of chemical hazards, nutrients and pathogens, most of them limited the analysis to only a few. For instance, the first RBA studies addressing fish consumption balanced potential nutritional benefits with chemical risks without considering potential microbiological effects, whereas another study on cold smoked salmon considered microbiological risks and nutritional benefits (Berjia et al., 2012). Only three out of more than 70 RBA studies included microbiological, chemical and nutritional concerns (ANSES, 2013; NAP, 2007; VKM, 2013), but these covered microbiology only with regard to hygiene practices recommendations.

Until recently, several studies have made efforts to address the challenges of including all potential types of risks and benefits of foods (Büchner, Hoekstra, & van Rossum, 2007; FAO/WHO, 2006; VKM, 2013), but none of them were comprehensive by including the three fields of research, nor were they quantitative to enable estimation of an overall health impact. A recent study that aimed to progress on RBA method development focused on infant milk consumption during the first months of life, considering breast milk and powdered infant formula (Boué et al., 2017). Methodological developments were investigated by taking into account a limited selection of five agents relevant to the case study (Boué et al., 2017). The model was built to quantify the risk of microbiological and chemical hazards (*Cronobacter sakazakii*, *Cryptosporidium*, dioxin like polychlorinated biphenyls (dl-PCBs) and arsenic), and the benefit of nutrients (docosahexaenoic acid (DHA)) by taking into account the variability in the population and data and model uncertainty (Boué et al., 2017). In addition, to progress further on RBA methodological development, variability and uncertainty were studied separately, using second-order Monte Carlo simulation.

This study's individual risk and benefit assessments components (microbiological, nutritional, and chemical) involved the use of different methods, highlighting the difficulty of using a single harmonized approach. Likewise, it was not possible to apply one common health metric for all health effects considered. Therefore, the assessment ended with different output measures (e.g. exposure or DALYs), which hampered the comparison of all health impacts in a single metric and thus restrained scenarios comparison. To overcome this limitation, a scoreboard table was suggested, which also facilitated communication of RBA results while providing a transparent and comprehensive overview. The RBA model developed was the first fully three-disciplinary and quantitative RBA performed for a single food and highlighted that the integration of different methods and the assessment and communication of variability and uncertainties are still some of the challenges that have to be tackled.

3.2. Health impact of substitution of foods

Changes in the intake of one food will lead to changes in the consumption of other foods, which will indirectly affect the overall health impact of the food under study. If the intake of a food product is increased or decreased, it either leads to a change in overall food intake, or it is compensated by a change of the rest of the diet. Hence, to obtain a more integrated and realistic assessment of the overall health impact of our diet, it is essential to consider the whole diet and the potential substitution of foods. Thus far, few studies have addressed food substitutions in RBA. Van der Voet et al. applied a probabilistic model to assess the health impact of substituting 10-100% of red meat (beef/pork) with fish in the Dutch diet (van der Voet, de Mul, & van Klaveren, 2007). The health impact was assessed in terms of probability of exposure being below the tolerable daily intake (TDI) of hazardous substances (dioxin) and above the adequate intake of beneficial components (n-3 long-chain polyunsaturated fatty acids, DHA and eicosapentaenoic acid (EPA)). By estimating individual probabilities, this approach allowed the authors to include variability of food consumption between consumers into the RBA. Hollander et al. 2018 (Hollander, De Jonge, Biesbroek, Hoekstra, & Zijp, 2018) assessed

qualitatively the health effects of a gram for gram substitution of meat by fish, and Temme et al. 2013 investigated the effects of replacing dairy and meat by plant based products (Temme et al., 2013). Substitutions on a nutrient level were also assessed as part of the BRAFO project, which included substitution of saturated fatty acids with mono-unsaturated fatty acids, substitution of saturated fatty acids with carbohydrates, and substitution of mono- and di-saccharides with low-calorie sweeteners (Hans Verhagen et al., 2012). However, none of the RBAs reached a quantitative health impact estimate, either due to the lack of a true risk-benefit question or inconclusive evidence. Others investigated the risk-benefit balance of substituting added sugar in beverages with artificial sweeteners, in terms of either risk of exceeding established reference doses (Husøy et al., 2008) or body mass index (BMI) (Hendriksen, Tijhuis, Fransen, Verhagen, & Hoekstra, 2011).

Current work at DTU Food investigates the health impact of changing from the current Danish diet to a diet that follows the Danish National Dietary Guidelines (Thomsen et al., 2018). The approach weighs nutritional benefits against nutritional and toxicological risks, and accounts for the substitution of foods. The model is based on a case study on substitution of red and processed meat with fish in the Danish adult diet. In this case study, the observed individual mean daily fish intakes for all adult individuals (> 15 years) in the Danish National Survey of Diet and Physical Activity are increased to 50 g/day as recommended in the guidelines (350 g/week). Using pre-defined substitution factors that take portion sizes and meal-specific differences into account, a corresponding decrease in the intake of red and processed meat was modelled. Four substitution scenarios addressing the impact of varying chemical and nutrient exposures on the final health impact were investigated and the net health gain or loss of the substitutions was measured in DALYs. Other foods could potentially be added to the model to reflect a more realistic substitution and the whole diet. The approach may account for changes in energy intake associated with substitutions, as well as the health impact of these

changes. To our knowledge, this is the first quantitative RBA that uses DALYs as health metric whilst taking substitution of foods into account.

3.3. Optimization of personalized dietary recommendations

Even though official dietary guidelines are developed to motivate the population to follow healthy food consumption patterns, repeated national surveys have shown that most individuals do not meet the intakes recommended by the food and health authorities (Pedersen et al., 2010; Tetens et al., 2013). To investigate how to inform dietary advice that has a higher adherence by individuals, recent studies have applied mathematical optimization techniques to propose personalized intake recommendations (Maillot et al., 2009; Maillot, Vieux, Amiot, & Darmon, 2010; Persson et al., 2018). Personalized recommendations may be perceived as more relevant, because they can account for individual preference, needs, and beliefs (Brug, Campbell, & van Assema, 1999).

In a case-study on consumption of fish in the Danish adult population, quadratic programming models were applied to generate personalized fish intake recommendations fulfilling pre-defined criteria in terms of intake recommendations for EPA, DHA, and vitamin D and tolerable intake levels for methyl mercury, dioxins, and dl-PCBs, while simultaneously deviating as little as possible from observed individual intakes (Persson et al., 2018). Such an approach has the potential to increase compliance with dietary guidelines by targeting the individual consumers and minimizing the need for large and potentially unrealistic changes in consumption patterns. The output is a range of intakes for different fish species that can be proposed as a personalized recommendation for each individual in the population.

The approach of optimization of a single food recommendation can be improved by taking into account individual exposures to nutrients and contaminants from other sources than the food of interest, which enable refined minimum and maximum exposure criteria. The approach can also be used to optimize whole diets

(Barre et al., 2016; Maillot et al., 2009, 2010). Environmental or other specific individual background exposures may still require consideration in both cases. Current research at DTU Food analyses the impact of individual exposures due to foods other than fish, dietary supplements and the environment, by expanding the case study of fish intake in Denmark (Persson et al., 2018) with individual data on this background exposure. Lastly, the optimization approach can be expanded to include other food-related issues beyond public health, such as sustainability (Horgan, Perrin, Whybrow, & Macdiarmid, 2016; Kramer, Tyszler, Veer, & Blonk, 2017), economic impact (Darmon, Ferguson, & Briend, 2002; Maillot, Vieux, Delaere, Lluch, & Darmon, 2017) or both (Van Dooren, Tyszler, Kramer, & Aiking, 2015)

4. Current challenges within RBA

Although significant progress has been made in the development of RBA, several challenges remain (Maarten J. Nauta et al., 2018). RBA has to face challenges of traditional risk assessment in the different disciplines, which are not specific for RBA, i.e. challenges related to data availability, variability between groups of consumers and individuals, strength of evidence and uncertainty in the dose response. In addition, there are challenges in defining how uncertainties should be presented to policymakers and the general public, and what guidance can be given to help policymakers make decisions based on uncertain evidence. Because of the parallel streams assessing adverse and beneficial impacts of foods or components, RBA faces additional challenges, including the integration of diverse data sources (e.g. from experimental animal studies and human epidemiological studies); heterogeneity of information between risks and benefits, classification of approaches for different types of risk-benefit questions (i.e. focusing on foods, food components or diets); scenario development including relevant policy options; and selection of metrics to evaluate and compare risks and benefits. Lastly, there are also challenges related to the current need to incorporate more than just health risks and benefits (e.g.: sustainability and economic consequences) to allow policymakers to make better informed decisions, and

the consequent requirement to further develop methodologies and approaches to perform those "expanded RBA". During the workshop, two categories of challenges were discussed in working groups, those related to "health RBA" and those specific to "expanded RBA".

4.1. Challenges related to RBA of health impact of foods

Aligning the Risk-Benefit question and the methodological approaches

The formulation of a risk-benefit question precedes the RBA and is of crucial importance to ensure that the RBA is focused, *fit for purpose*, and well-structured (Boobis et al., 2013; Hoekstra et al., 2012). The risk-benefit question will guide the choice of the RBA methodology and also the choice of risk-benefit metric. It is usually the risk-benefit manager that asks the RBA question, refined as necessary in dialogue with the risk-benefit assessors. Risk-benefit managers may be regulatory agencies such as national governments. However, policy makers with focus in the various aspects of food are often scattered in different regulatory bodies, with distinct interests, areas of action and potentially RBA questions. In addition, food companies and consumers may also have the "risk-benefit manager role" and will have different interests for such assessments. As an example, regulatory bodies may be primarily interested in defining safety criteria, priority setting and public health, whereas consumers may have more interest in their personal dietary choices and the anticipated health impacts of these choices. Hence, a broad range of risk-benefit questions and objectives are possible. For example, RBA may want to consider different levels of aggregation (e.g. a food component, food product or the whole diet), or the objective may be to compare specific scenarios and/or sub-populations to assess if the risk exceeds the benefit or vice versa (Hans Verhagen et al., 2012). The goal may also be to identify the most advantageous intake scenario (Berjia et al., 2014), or to provide a quantitative estimate of the overall health impact. RBA can include only health effects or be "expanded" to include non-health factors such as economy, sustainability and consumer preference (Ocké MC, Toxopeus IB, Geurts M, Mengelers MJB, Temme EHM, 2017;

Juliana M. Ruzante, Grieger, Woodward, Lambertini, & Kowalcyk, 2017; Seves et al., 2016; Temme et al., 2013; van de Kamp, Seves, & Temme, 2018).

Development of guidance on the approaches that can be adopted for different types of risk-benefit questions would facilitate the framing and the performance of RBA, and would support methodological harmonization in the future. Depending on the type of question, such guidance could for example assist in the selection of food components and foods as well as the health effects to be included in the RBA, and point out when quantitative approaches are needed. In general, clear and continuous communication between risk-benefit assessors and risk-benefit managers about the risk-benefit question and the methodological approach of choice is of crucial importance to ensure *fit for purpose* RBA.

Variability between groups of consumers and individuals

The inherent differences between individuals may lead to the risks and benefits differing between individuals and certain subpopulations (e.g. children, pregnant women, elderly). If this variability is ignored in RBA, certain (groups of) vulnerable individuals suffering from higher health risks may be ignored in its conclusions, even if an intake scenario, on average, is beneficial for the population. However, inclusion of variability demands knowledge on potential differences in health effects between groups of consumers and individuals, and this knowledge may not be available. Also, it increases the complexity of the RBA.

Variability is for example a concern for decisions on fortification, such as folic acid fortification of bread and iodine fortification of salt. This fortification may be considered beneficial for the majority of the population, or beneficial as expressed by overall population health gain, but may have negative health effects for subgroups (Hoekstra et al., 2008). Food policies such as fortification may lead to (health) winners and losers and it is an ethical political question whether such a policy should be implemented. However, it is the responsibility of the risk-benefit assessor to inform the policy maker of the effects on different subpopulations. Due to this different

susceptibility among the population groups, the application of folic acid fortification is still debated (Eckner, Bjørn, Lunestad, & Rosnes, 2014). Taking the variability into account is crucial in RBA and can reveal population groups that are at high risk or that will gain large benefit. It enables evaluation of the effect of specific interventions (i.e. assessing which groups gain the largest benefit and which population group might experience a health loss due to the intervention), thus enabling better informed policy decisions (Hart et al., 2013; Hoekstra, Hart, et al., 2013).

There are different levels at which the variability can be assessed in RBA. First, the entire distribution of exposures within the population can be used instead of a mean exposure estimate (Hart et al., 2013). This has been addressed by different methods in previous RBAs (Hart et al., 2013; Hoekstra, Hart, et al., 2013; van der Voet et al., 2007). Second, if detailed population statistics are available, variability between sub-population groups can also be taken into account explicitly. In such cases, RBAs are performed for each sub-population group and results are compared.

Risk-Benefit comparison metrics

There are several health metrics that can be used in RBA. Fransen et al (2010) divided risk-benefit comparison metrics into three categories: single outcome (e.g.: disease incidence, mortality); integrated (or summary) health (e.g.: DALY and QALY); and economically oriented measures such as WTP (willingness to pay). The choice of metric will depend on the type of question being asked by the risk-benefit manager and the complexity of the evaluation being done. For instance, in a situation where different components affect the same endpoint in an individual both positively and negatively, a net effect for the health outcome can be calculated, and integrated measures might not be needed (Fransen et al., 2010; Zeilmaker et al., 2013b). However, it is often the case that risk-benefit questions are more complex and involve multiple health effects, including different health effects for hazards and benefits, and therefore summary population measures such as disability

317 adjusted life year (DALY) can be helpful. For this reason, we focused our discussions during the workshop on
318 the use and challenges associated with integrated measures, more specifically DALY.

319 In recent years, the DALY has been frequently used in quantitative RBA as it is able to aggregate both mortality
320 and morbidity measures associated with several health outcomes (Murray, 1994). It is the metric of choice for
321 the Global Burden of Disease studies (Anonymous, 2017b), and has been shown to be a valuable instrument for
322 risk ranking of foodborne hazards (Havelaar et al., 2012, 2015). It has also been applied in RBA studies to
323 summarize the overall health impacts of foods (Berjia et al., 2014; Eneroth et al., 2017; Hoekstra, Fransen, et
324 al., 2013; Hoekstra, Hart, et al., 2013). While a single DALY estimate is usually the final estimate in burden of
325 disease studies, the difference in DALYs between a reference and an alternative scenario (ΔDALY) has been
326 used as the final estimate of RBA studies (Eneroth et al., 2017; Firew Berjia, Andersen, Hoekstra, Poulsen, &
327 Nauta, 2012).

328 Several limitations of the DALY have been identified, both in terms of how the metric is communicated and
329 perceived, and in the assumptions behind the method. Underlying the DALY metric is the idea that many
330 people suffering from a mild disease is as bad as few people suffering from a severe disease. The DALY provides
331 an expected value for the population and does not clearly reflect the two dimensions used for its calculation:
332 the probability of effect for individuals in the population and the severity of these effects. As an illustration,
333 consider a population of 100,000 people with a remaining life expectancy of 20 years, where all individuals get
334 infected by a pathogen. If the single effect of this infection is a probability of immediate death of one in a
335 million (0.0001%), this yields a loss of 100,000 * 0.000001 * 20 = 2 DALYs. If the single effect is that 10% of the
336 people get 1 day of mild diarrhea, with severity weight 0.074 (Salomon et al 2015), this also yields a loss of
337 100,000*1/365*0.074*0.1 = 2 DALYs. Despite the same DALY estimation, the two scenarios are clearly
338 different: in the first case, it is most likely that none of the 100,000 people involved will suffer from anything; in
339 the second case, 10% of the people get ill, so around 10,000 people will be affected. If risk managers are only

informed about the 2 DALY and not about this difference (about 10,000 ill people versus maybe one death), they may base their decisions on incomplete information. Hence, the advantage of an integrated metric, i.e. that it summarizes complex issues into one figure allowing direct comparison of multiple risks and benefits, may also be a disadvantage if improperly used or misinterpreted. Care should therefore always be given to presenting all of the relevant underlying information (such as the basic assumptions and estimates of incidence, mortality and attending uncertainty) to the decision makers. Likewise, because multiple health outcomes may be considered in the total DALY estimate, the impact on the net health of one subgroup may be clearly greater than for another subgroup in the population. Again, an example would be folic acid fortification in which one group benefits whereas another group experiences the risks (Hoekstra et al. 2008).

Quality adjusted life years (QALY) were not the focus of the discussions, but have also been used as integrated measures in RBA (EFSA, 2006; Ponce et al., 2000). QALY has similar advantages and disadvantages as the DALY and is also part of the Qalibra software tool (Hart et al., 2013).

The strength of evidence and uncertainty

Weighing and integrating evidence represents a substantial challenge because RBA involves various individual risks and benefits assessments, for which the current scientific strength of evidence might be different (Dorne et al., 2016). Consequently, evidence for each health is collected from different types of studies (e.g. epidemiological and toxicological studies). To date, all lines of evidence considered in RBA are reported only qualitatively, as advised by the EFSA guidance on RBA and the BRAFO approach (EFSA, 2010; Hoekstra et al., 2012). This qualitative integration does not allow for integrating the strength of evidence in the final output of quantitative RBA (e.g. DALY), which introduces an additional source of uncertainty.

The criteria for minimum weight of evidence are different in toxicology and nutrition. In general, the evidence accepted to refer to a toxicological hazard as “hazard” may be much weaker than the evidence needed to refer

362 to a benefit as “benefit”. In risk assessment, it is likely that a precautionary approach will be applied if there are
363 indications of a potential risk, even if the evidence is weak (Boobis et al., 2013; Hoekstra, Hart, et al., 2013; M.J.
364 Nauta et al., 2018; Tijhuis et al., 2012). In contrast, claims for beneficial or adverse health effects of a food or
365 nutrient need to be supported by convincing scientific evidence before they are acknowledged (Boobis et al.,
366 2013). If the established criteria for inclusion of adverse and beneficial health effects are used, toxicological
367 risks with a low level of evidence may be more likely to be included than nutritional benefits with the same low
368 level of evidence., This may lead to a skewed RBA. For example, the relative risk of colorectal cancer from
369 folate supplements is around 1, with an upper 95% confidence interval of around 1.2, but as high as 1.7 is some
370 studies (see (SACN, 2017)). The relative risk of a neural tube affected pregnancy is 0.29 after folic acid
371 supplements, with 95% CI of 0.12-0.71 (MRC Vitamine Study Research Group, 1991), An approach to assess an
372 upper bound risk of up to 77% increased incidence from a non-significant risk against a significant benefit of a
373 70% reduction, on average, in NTDs is still not available. This is clearly an area of RBA that needs further
374 development, such that risks and benefits can be weighted in some way for the respective levels of evidence
375
376 The characterization of the risks and benefits (i.e. the estimated health impact) is not necessarily affected by
377 this discrepancy, unless uncertainty factors that address the high uncertainty for low level evidence effects are
378 included in the dose response. However, if effects with a low level of evidence i.e. high uncertainty of
379 occurring, but potentially high health impact are ignored, the assessment could give a misleading suggestion.
380 Therefore, in communication with policymakers or risk managers, it is important to clearly address the
381 intentions of the RBA, and carefully demonstrate the assumptions in the inclusion and exclusion criteria of
382 adverse and positive health effects and their level of evidence. RBA should not be misused to play down health
383 risks associated with foods, nor should it overemphasize or ignore potential health benefits. This implies again
384 that transparency is of crucial importance for RBA, and that communication is an essential component of the

RBA process. Ultimately, it is the RBA manager that is responsible for the policy decision, and to support this decision, it is the role of the RBA assessor to provide all relevant information, including an assessment of the uncertainties, in as clear and transparent manner as possible, to support this.

Within RBA, strength of evidence is closely connected to the uncertainty assessment, which expresses the belief in the obtained results. Uncertainties are propagated for example via the derived dose-response models to the final DALY estimate and may, if not quantified, lead to misleading conclusions (Benford et al., 2018). This stresses the need for quantification, or at least a qualitative assessment, of uncertainties in RBA (Hart et al., 2013). For RBA, the EU project Qalibra has developed a tool to include uncertainty in stochastic quantitative models (Hart et al., 2013). The methodology of uncertainty assessment is still in development, it is not specific to RBA but inherent to any science-based decision: the lack of knowledge generates imprecision in the results. The impact of this imprecision has to be assessed before making decision. Sensitivity analysis is a powerful technique to assess this impact (Saltelli, 2002). In particular, it helps prioritizing additional data collection or research. However, when quantification is not possible, reporting a qualitative expression of uncertainty is still important as advised in the BRAFO tiered approach (Hoekstra et al., 2012) and illustrated in (Hoekstra, Hart, et al., 2013) and (Boué, 2017).

Uncertainty in the dose response

One of the major sources of uncertainty in RBA is the relationship between intake of a food or food component and a health effect. The ideal scientific studies to establish causality between exposure to a component and a health effect are randomized control trials with human participants. However, these are often not feasible for ethical and/or economic reasons. Other types of studies, such as (human or animal) observational studies that may reveal associations between intake of food components, contaminants, foods and diets and the likelihood of a health effect, may be used alternatively. Systematic reviews and meta-analyses of all available epidemiological evidence (e.g. derived by longitudinal cohort studies), which are suitable for ensuring a higher

level of evidence compared to using single studies available, are commonly used to describe the change in risk of health effects associated with dietary patterns and chronic exposure to chemicals (e.g. (Aune et al., 2015; Aune, Ursin, & Veierød, 2009; Hoekstra, Hart, et al., 2013)). Data from animal studies may be used to establish dose-response relations for chemical hazards, preferably supported by epidemiological studies.

For establishing the dose response relation, different types of evidence may be used in toxicology, microbiology and nutrition. Specifically in microbiological risk assessment, animal experiments are often not informative to establish a dose response relation, because the response to exposure to human pathogens is not comparable between humans and animals. The evidence often originates from either experimental studies with human volunteers, usually healthy young people that are not representative for the whole population (Teunis, Nagelkerke, & Haas, 1999), or outbreak studies that typically involve the more virulent strains or more vulnerable people (Teunis et al., 2010). In nutrition, whilst some data may be available from controlled clinical studies, more often reliance is on observational human epidemiological studies, which demand advanced statistical analysis, and interaction and confounding plays an important role: as only association can be studied, the evidence for causal relations may be weak (Tijhuis et al., 2012). In toxicological risk assessment, extrapolation/uncertainty factors are used to account for intra-species differences, and interspecies differences when translating observations from animal experiments into anticipated human health effects (van der Voet & Slob, 2007). . Another challenge is that adverse effects observed in animal studies may not be easily translated into human disease. Similarly, extracting the time of onset of a disease can be difficult, often requiring debatable assumptions. Examples of how in some cases exposure to chemicals is converted in DALYs can be found in (Gibb et al., 2015; Hoekstra, Hart, et al., 2013; Zeilmaker et al., 2013a).

The difference in methods for deriving dose response relations in RBA may be associated with different biases and systematic errors, and the attending uncertainties are of a different nature. Within a research discipline, these biases and errors may be relatively unimportant when risks or benefits that are derived by the same

methods are compared. But in RBA these differences may have a large impact on the output of the RBA. Currently, no established methods are available to overcome these differences. Performing a sensitivity analysis to highlight which sources contribute more to the overall uncertainty is recommended.

Data availability

The availability and quality of data is a common challenge in RBA, just as it is in traditional nutrition and risk assessments. Previous reviews have identified a number of data needs and general challenges, and most of these still remain (Boobis et al., 2013; EFSA, 2010; Maarten J. Nauta et al., 2018). There are different types of data to consider: data on food consumption, levels of nutrients and contaminants in foods, microbial contamination of food, background data on human disease (e.g. incidence, disability weights, pattern of disease progression), and dose-responses relationships. Food consumption data may be available from national dietary food surveys, which have been expanded and improved continuously (e.g. (ANSES, 2017; Pedersen et al., 2010)), but it may be difficult to compare them between countries, due to differences in their design. Regional databases such as the EFSA Comprehensive Food Consumption Database and harmonization guidance (e.g. the EFSA's general principles for the collection of national food consumption data in the view of a pan-European dietary survey, known as the EU Menu) are a valuable resource to overcome these limitations and ensure comparability (EFSA, 2011, 2014b). National food databases usually include information on nutrient content of foods, but national monitoring data on the concentration of contaminants in foods may not be available. Data from which dose-response relationships can be constructed are crucial to enable risks and benefits to be estimated quantitatively. The type of data and source of information greatly differ between microbiology, toxicology, nutrition, and epidemiology; and between foods, food components, and contaminants. If using an integrated metric such as the DALY to compare risks and benefits, data on life expectancy, disability weights and duration associated with the different health effects are needed

(Devleesschauwer et al., 2014; Hart et al., 2013). These data are specific to the sub-population of interest but rarely available at the national level. In addition, even though substantial amounts of data were published, these may be available in different formats or not directly suitable for use in RBA. Increased efforts to establish available, transparent and easily accessible database(s), with suitable contextual information i.e. the metadata, are needed to fill these data gaps for RBA. If observational or experimental data are lacking, another option is to gather information through expert elicitation (Cooke, 1991; EFSA, 2014a; EPA, 2009). This technique is already used in microbial risk assessment (Albert et al., 2012; Pujol, Johnson, Magras, Albert, & Membré, 2015; Van der Fels-Klerx, Cooke, Nauta, Goossens, & Havelaar, 2005) and more generally in food safety (Hald et al., 2016).

4.2. Challenges related to RBA including non-health related impact

RBA research has so far built on the principles of risk analysis for food safety, where the end-point is the human health impact of food intake scenarios. However, decision makers must take into consideration factors other than human health when making policy decisions (FAO/WHO, 2011; FAO, 2017). Thus, what the risk benefit manager needs is a comprehensive understanding and a way to consider and balance the health impacts of changes in food intake with effects on other factors such as sustainability, consumer preferences, the economy, and societal values. For clarity, the question whether other disciplines should be included in the RBA must be included in the risk-benefit question. Often, this question is in line with the general interests of society, e.g. discuss how risk and benefits are balanced in other disciplines, including pharmaceutical drugs (H. Verhagen et al., 2012) . There is consensus that, in the longer-term, RBA based only on health will not be sufficient to address risk management and societal questions, and including non-health factors is inevitable and necessary. This need is not unique to RBA and has been thoroughly discussed in different food-related policy areas such as food safety, agriculture, the environment and nutrition (Anonymous, 2018; FAO, 2017). Clear

priorities need to be identified at national and international levels in order to make best use of finite resources, and to ensure that decisions to ensure food safety do not negatively impact on other dimensions essential for development, e.g. trade, economics, food security, tourism, social well-being (FAO, 2017). An integrated approach requires an interdisciplinary procedure as well as exchange of data from the different disciplines involved. Bringing together data on safety (e.g. contamination), health aspects (e.g. nutrient composition), sustainability indicators (e.g. land use) and other characteristics (such as price) concerning the same products is important in order to facilitate interdisciplinary research. However, adding such factors makes the analysis more complex, potentially less transparent and harder to be updated as new data becomes available. Also, it increases the number of stakeholders involved, and requires a methodology in which those effects can be transparently weighted and compared. Multi-criteria decision analysis (MCDA) has been designed to address such complex decision problems, while making the analysis transparent and systematic. MCDA has been used in innumerous fields from emerging technologies (Bates et al., 2016) to establishing priorities for foodborne illness (Juliana Martins Ruzante et al., 2010). It is a robust decision analysis tool that integrates different factors (i.e. criteria), while considering the preference and values of policy makers as well as stakeholders (FAO, 2017). MCDA has been used to balance risk and benefits of pharmaceutical drugs (Hsu, Tang, & Lu, 2015; Tervonen, van Valkenhoef, Buskens, Hillege, & Postmus, 2011), emerging technologies (Tsang, Bates, Madison, & Linkov, 2014), and just recently a framework was proposed describing how it could be applied to foods (Juliana M. Ruzante et al., 2017). The challenges associated with incorporating other factors relevant to policy decision besides the typical RBA will not be related directly to the application of MCDA, but rather with the different magnitudes of uncertainty and the data availability to characterize those other factors. The field of medical products and drug development is more advanced in this area than food and nutrition, and has guidelines to gather and incorporate patient's perspective into their RBA analysis of future drugs (FDA, 2013; Nixon et al., 2016), which can be used as an example for RBA of foods.

At the workshop, sustainability was mentioned as being on the shortlist of aspects to include in the RBA. However, sustainability is not easily quantified by a single indicator. Several indicators in the area of food exist, such as greenhouse gas emission, water use, biodiversity, and others (Agovino, Cerciello, & Gatto, 2018; Chaudhary, Gustafson, & Mathys, 2018; Dora et al., 2015; Hallström, Carlsson-Kanyama, & Börjesson, 2015; Horgan, Perrin, Whybrow, & Macdiarmid, 2016; van Wagenberg et al., 2017). The choice for the most suitable indicator and/or weighing between them must be made depending on the assessment. Economic factors and consumer preferences were mentioned as other aspects that are important in a food policy assessment.

Sustainability factors have been incorporated in some studies (e.g. (Donati et al., 2016; Masset, Soler, Vieux, & Darmon, 2014)). In another example, Temme et al. 2013 investigated the health and sustainability effects if meat and dairy were to be replaced by plant derived foods. Health effects were expressed as saturated fatty acid (SFA) and iron (Fe) intake in women, and sustainability was expressed as land use. An integrative metric was not necessary as all indicators pointed in the same direction: replacement of meat and dairy foods by plant-based foods reduced land use for food consumption, and SFA intake of young females and did not compromise total Fe intake. Seves et al. 2015 examined the health and sustainability effects of the consumption of different fish species. Sustainability was measured by land use (by fish farms) and greenhouse gas emission, and having a sustainability label which was partly a measure for overfishing. The health benefits were expressed by the EPA and DHA (fish oil) content of the fish species. The study concluded that herring and salmon (cultivate and wild-caught with ASC/MSC logo) are species favorable in terms of beneficial for health and the environment. In 2017, RIVM published a large study involving the current and future Dutch diet (Ocké MC, Toxopeus IB, Geurts M, Mengelers MJB, Temme EHM, 2017) that attempted to disentangle and analyze the integrated complexity of safe, healthy and sustainable diets. It analyzes the population's diet according to microbial and chemical safety, nutritious value, cost, consumer preference, future trends in production, and sustainability factors. Ocké et al. (2017) discovered that the trio of safety, health and sustainability is not

enough when it comes to the actual behavioral motives related to food. Consumer motives like convenience, enjoyment and cost, as well as prosperity motives like employment and export and ethical issues like animal welfare are also involved. These are all issues that carry weight individually and in society. The report is concentrated on safe, healthy and sustainable diets without disregarding these other motives. Three extreme scenarios were developed qualitatively, focusing on safety, health or sustainability. The scenarios were analyzed and scored by exerts with a systematic group decision-support method. An attempt was made to use an MCDA method to weigh different scenarios (Ocké MC, Toxopeus IB, Geurts M, Mengelers MJB, Temme EHM, 2017; Saaty, 1994). Although the method proved promising, due to the uncertainties in quantifying underlying sub-criteria of indicators for sustainability, food safety and health, it was not possible to make the (subjective) weighing of the different aspects transparent and the final outcome was not used. Nevertheless, using expert-judgement and semi-quantification, the report concludes that opportunities to combine safety, health and ecological sustainability in an integrated food policy exist.

4.3. Communication of RBA results

The area of risk communication has been growing and has made great progress in better understanding consumer behavior, and how risk is perceived (Frewer et al., 2016). Despite remaining challenges and limitations, stakeholders are now better equipped to communicate risks to consumers. Under the risk-analysis paradigm, risk assessors have also made progress in communicating with risk managers and other stakeholders before, during and after a risk assessment is conducted and results are published. In most areas there is a demand for decisions to be transparent, and engaging with stakeholders early-on is key.

Communicating RBA messages is more complex than communicating risks or benefits separately. On one hand, the way risk is perceived is very different of how benefit is perceived by consumers. On the other hand,

because the overall process incorporates (at least) those two components' analyses, and their integration, the data, the uncertainty around it and the assumptions are more difficult to be described, which could potentially add confusion. It is important to understand the target population and establish trust by working in close collaboration with stakeholders and social scientists specialized in risk communication. More research is needed to understand consumer's trade-offs and values when it comes to risk and benefits of foods. Rideout and Kosatsky (2017) argue that also other factors than risks and benefits associated with physical health should be assessed when developing advice for specific populations (Rideout & Kosatsky, 2017). They suggest other factors to weigh in addition to health risks and benefits, such as socioeconomic and sociocultural factors, and to apply e.g. health impact assessment to evaluate external impacts of a consumption advice or policy (such as substitution of foods), and other qualitative tools for development of more comprehensive and effective advice.

In addition, it is crucial that the results and methods of RBA studies are transparent and that uncertainty, when possible, is taken into account and reported with the results. Likewise, it is important that the level of evidence for all effects is considered, and that the limitations in available data and assumptions made are communicated with the results. Especially when RBA studies are made for methodology development purposes, particular care should be taken in how any preliminary results are communicated, if they do not reflect a definitive RBA.

Moving towards an optimal communication of RBA results to all stakeholders requires a closer collaboration with social scientists. While these needs were considered and emphasized at the workshop, communication tools were not the scope of the discussions.

5. Opportunities and way forward

As a last step, the participants of the workshop discussed the practical way forward to take RBA to the next stage. Building on the challenges and opportunities identified, a number of needs and practical suggestions

were presented. In addition, activities that promote collaboration and integration of research efforts were put on the agenda for a RBA Network formally launched at the event.

It was generally agreed that the discussions on needs, methods and challenges should now be followed by the development of case studies, in which the identified challenges are addressed. Two options were identified: to develop new cases using the tools and frameworks that are now available; to re-open cases that have been performed previously, and apply new data and new methods to test the improvements that can be made and to evaluate their robustness. Examples include probabilistic approaches that allow for the assessment of variability and uncertainty and models that take substitution of foods into account. These case studies can also be applied to compare different health metrics (in parallel to the DALY). The latter should preferably be followed by research on the perception and communication of these different metrics to different stakeholders.

A categorization of RBA studies will be advantageous, for example by comparing the level of aggregation of the RBA (on food components, foods or diet), the risk-benefit question (which scenarios are to be compared, which consumer groups are included, what food components and contaminants associated with potential health effects are included), whether there is a need for a quantitative and/or stochastic approach, etc. (see section *Aligning Risk-Benefit question and methodological approaches,* section 4.1.). Ideally, these case studies would be performed by different research groups, and a platform to share and discuss their assessments should be created.

Another generally recognized challenge within RBA is the availability of data (section 4.1). To harmonize RBA internationally and to facilitate the application of RBA by national and international risk and benefit managers, it is important to establish and maintain shared databases with dietary intake data, concentration data on nutrients and contaminants, dose response data, data from observational studies and health data. These

databases should be transparent and easily accessible, and setting up and maintaining such a database(s) would be a community effort that requires broad international support.

In Europe, EFSA might expand its role as curator of such databases. RBA research groups should provide input to EFSA and other data providers on data needs. Furthermore, EFSA is already taking initiative to lead discussions on current challenges of the integration of evidence with very diverse and not readily comparable underlying evidence bases, and motivate stakeholders to address them (EFSA, 2018). Again, this should be a collaborative effort with broad international support.

As the challenges associated to RBA are complex, expertise required are numerous and the data needs are large, the workshop participants concluded that intensive international collaboration is a prerequisite for the development of this novel discipline. Formalizing an RBA international network will facilitate all future activities discussed and proposed in the workshop, and will help partners in consolidating and further developing current activities. Ideally, such a platform should be formed within a European or global international project, to ensure that harmonized approaches can be developed, and that these build on consensus in the international scientific community and can serve as a basis for global decision making. Due to the unique multidisciplinary character of RBA, it may be challenging to identify scientific associations and funding bodies that cover all its scientific and societal aspects. Still, networking initiatives can be established, for example via research applications and, at international level, with symposia organized at scientific conferences. With this in mind, participants have decided to launch the International Network for Risk-Benefit Assessment of Foods. The network is to be chaired by DTU Food and will be open to any group or individual with an active interest in the area. Among other overall goals, this network will serve as a forum for continuation of the discussions here described.

Overall, the workshop participants agreed that RBA is a promising and highly relevant research area that deserves increased attention worldwide. Because the broad range of public-health activities associated with

foods and diets brings a high degree of complexity to policy development and a need to involve various stakeholders to ensure synergy, international bodies such as the FAO have stressed that 'policy coherence' across ministries is key (FAO, 2017). RBA approaches, particularly when expanded to include non-health related impacts, can be a powerful tool to assist risk-managers defining policy that achieves the best societal outcomes.

RBA ultimately may show how integration of a variety of scientific disciplines and approaches can be used to address specific and general policy questions, and serve governmental regulatory bodies, food industry and individual consumers alike.

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References

Agovino, M., Cerciello, M., & Gatto, A. (2018). Policy efficiency in the field of food sustainability. The adjusted food agriculture and nutrition index. *Journal of Environmental Management*, *218*, 220–233. http://doi.org/10.1016/j.jenvman.2018.04.058

Albert, I., Donnet, S., Guihenneuc-Jouyaux, C., Low-Choy, S., Mengersen, K., & Rousseau, J. (2012). Combining Expert Opinions in Prior Elicitation. *Bayesian Analysis*, *7*(3), 503–532. http://doi.org/10.1214/12-BA717

632 Anonymous. (2017a). *Assessing the health benefits and risks of the introduction of peanut and hen's egg into*
633 *the infant diet before six months of age in the UK A Joint Statement from the Scientific Advisory*
634 *Committee on Nutrition and the Committee on Toxicity of Chemicals in*. Retrieved from
635 https://cot.food.gov.uk/sites/default/files/jointsacncotallergystatementfinal2.pdf

636 Anonymous. (2017b). Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and
637 injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2016: a systematic
638 analysis for the Global Burden of Disease Study 2016. *Lancet (London, England)*, *390*(10100), 1260–1344.
639 http://doi.org/10.1016/S0140-6736(17)32130-X

640 Anonymous. (2018). *The Economics of Ecosystems and Biodiversity (TEEB)*. Geneva. Retrieved from
641 http://teebweb.org/agrifood/wp-content/uploads/2018/06/Foundations_vJun26.pdf

642 ANSES. (2013). *AVIS de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du*
643 *travail relatif aux recommandations sur les bénéfices et les risques liés à la consommation de produits de*
644 *la pêche dans le cadre de l'actualisation des repères nutritionnels du PNNS*. Retrieved from
645 https://www.anses.fr/en/system/files/NUT2012sa0202.pdf

646 ANSES. (2017). *INCA 3: Changes in consumption habits and patterns, new issues in the areas of food safety and*
647 *nutrition | Anses - Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du*
648 *travail*. Paris. Retrieved from https://www.anses.fr/en/content/inca-3-changes-consumption-habits-and-
649 patterns-new-issues-areas-food-safety-and-nutrition

650 Aune, D., Navarro Rosenblatt, D. A., Chan, D. S., Vieira, A. R., Vieira, R., Greenwood, D. C., … Norat, T. (2015).
651 Dairy products, calcium, and prostate cancer risk: a systematic review and meta-analysis of cohort
652 studies. *American Journal of Clinical Nutrition*, *101*(1), 87–117. http://doi.org/10.3945/ajcn.113.067157

653 Aune, D., Ursin, G., & Veierød, M. B. (2009). Meat consumption and the risk of type 2 diabetes: a systematic
654 review and meta-analysis of cohort studies. *Diabetologia*, *52*(11), 2277–2287.
655 http://doi.org/10.1007/s00125-009-1481-x

656 Barre, T., Vieux, F., Perignon, M., Cravedi, J.-P., Amiot, M.-J., Micard, V., & Darmon, N. (2016). Reaching
657 Nutritional Adequacy Does Not Necessarily Increase Exposure to Food Contaminants: Evidence from a
658 Whole-Diet Modeling Approach. *Journal of Nutrition*, *146*(10), 2149–2157.
659 http://doi.org/10.3945/jn.116.234294

660 Bates, M. E., Grieger, K. D., Trump, B. D., Keisler, J. M., Plourde, K. J., & Linkov, I. (2016). Emerging Technologies
661 for Environmental Remediation: Integrating Data and Judgment. *Environmental Science & Technology*,
662 *50*(1), 349–358. http://doi.org/10.1021/acs.est.5b03005

663 Benford, D., Halldorsson, T., Jeger, M. J., Knutsen, H. K., More, S., Naegeli, H., … Hardy, A. (2018). Guidance on
664 Uncertainty Analysis in Scientific Assessments. *EFSA Journal*, *16*(1).
665 http://doi.org/10.2903/j.efsa.2018.5123

666 Berjia, F., Hoekstra, J., Verhagen, H., Poulsen, M., Andersen, R., & Nauta, M. (2014). Finding the Optimum
667 Scenario in Risk-benefit Assessment : An Example on Vitamin D. *European Journal of Nutrition and Food*
668 *Safety*, *4*(4), 558–576.

669 Boobis, A., Chiodini, A., Hoekstra, J., Lagiou, P., Przyrembel, H., Schlatter, J., … Watzl, B. (2013). Critical
670 appraisal of the assessment of benefits and risks for foods, "BRAFO Consensus Working Group." *Food and*
671 *Chemical Toxicology*, *55*, 659–675. http://doi.org/10.1016/j.fct.2012.10.028

672 Boué, G. (2017). *Public Health Risk-Benefit Assessment in Foods Géraldine BOUÉ*. ONIRIS, Nantes Atlantic
673 College of Veterinary Medicine, Food Science and Engineering. Retrieved from https://www6.angers-

674 nantes.inra.fr/secalim_eng/Master-to-postdoctoral-training/Defended-PhDs/2017/Geraldine-Boue

675 Boué, G., Cummins, E., Guillou, S., Antignac, J.-P., Le Bizec, B., & Membré, J.-M. (2017). Development and
676 Application of a Probabilistic Risk-Benefit Assessment Model for Infant Feeding Integrating
677 Microbiological, Nutritional, and Chemical Components. *Risk Analysis*, *37*(12), 2360–2388.
678 http://doi.org/10.1111/risa.12792

679 Boué, G., Cummins, E., Guillou, S., Antignac, J.-P., Le Bizec, B., & Membré, J.-M. (2018). Public health risks and
680 benefits associated with breast milk and infant formula consumption. *Critical Reviews in Food Science and*
681 *Nutrition*, *58*(1), 126–145. http://doi.org/10.1080/10408398.2016.1138101

682 Boué, G., Guillou, S., Antignac, J.-P., Bizec, B., & Membré, J.-M. (2015). Public Health Risk-benefit Assessment
683 Associated with Food Consumption–A Review. *European Journal of Nutrition & Food Safety*, *5*(1), 32–58.
684 http://doi.org/10.9734/EJNFS/2015/12285

685 Brug, J., Campbell, M., & van Assema, P. (1999). The application and impact of computer-generated
686 personalized nutrition education: A review of the literature. *Patient Education and Counseling*, *36*(2),
687 145–156. http://doi.org/10.1016/S0738-3991(98)00131-1

688 Büchner, F., Hoekstra, J., & van Rossum, C. (2007). *Health gain and economic evaluation of breastfeeding*
689 *policies Model simulation Contact: CTM van Rossum Centre for Nutrition and Health*. Bilthoven. Retrieved
690 from https://www.rivm.nl/dsresource?objectid=4412a3c2-bb52-4c7d-b72e-
691 c18d84f656e9&type=org&disposition=inline

692 Chaudhary, A., Gustafson, D., & Mathys, A. (2018). Multi-indicator sustainability assessment of global food
693 systems. *Nature Communications*, *9*(1), 848. http://doi.org/10.1038/s41467-018-03308-7

694 Cooke, R. (1991). *Experts in uncertainty : opinion and subjective probability in science*. Oxford University Press.

695 Retrieved from https://global.oup.com/academic/product/experts-in-uncertainty-
696 9780195064650?cc=dk&lang=en&

697 Devleesschauwer, B., Havelaar, A. H., Maertens De Noordhout, C., Haagsma, J. A., Praet, N., Dorny, P., …
698 Speybroeck, N. (2014). DALY calculation in practice: A stepwise approach. *International Journal of Public*
699 *Health*, *59*(3), 571–574. http://doi.org/10.1007/s00038-014-0553-y

700 Donati, M., Menozzi, D., Zighetti, C., Rosi, A., Zinetti, A., & Scazzina, F. (2016). Towards a sustainable diet
701 combining economic, environmental and nutritional objectives. *Appetite*, *106*, 48–57.
702 http://doi.org/10.1016/J.APPET.2016.02.151

703 Dora, C., Haines, A., Balbus, J., Fletcher, E., Adair-Rohani, H., Alabaster, G., … Neira, M. (2015). Indicators linking
704 health and sustainability in the post-2015 development agenda. *Lancet (London, England)*, *385*(9965),
705 380–91. http://doi.org/10.1016/S0140-6736(14)60605-X

706 Dorne, J. L. C. M., Bottex, B., Merten, C., Germini, A., Georgiadis, N., Aiassa, E., … Hardy, A. R. (2016). Weighing
707 evidence and assessing uncertainties. *EFSA Journal*, *14*. http://doi.org/10.2903/j.efsa.2016.s0511

708 Eckner, K., Bjørn, G. K., Lunestad, T., & Rosnes, J. T. (2014). Benefit and risk assessment of increasing potassium
709 by replacement of sodium chloride with potassium chloride in industrial food production. Retrieved from
710 https://vkm.no/download/18.a665c1015c865cc85bb73c4/1501777215648/b186a12b17.pdf

711 EFSA. (2006). *The EFSA's 6th Scientific Colloquium Report - Risk-benefit analysis of foods: methods and*
712 *approaches*. *EFSA Supporting Publications* (Vol. 4). http://doi.org/10.2903/sp.efsa.2007.EN-116

713 EFSA. (2010). *Guidance on human health risk benefit assessment of foods*. *EFSA Journal*.
714 http://doi.org/10.2093/j.efsa.20NN.NNNN.

715 EFSA. (2011). Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment.

716 *EFSA Journal*, *9*(3), 2097. http://doi.org/10.2903/j.efsa.2011.2097

717 EFSA. (2014a). Guidance on Expert Knowledge Elicitation in Food and Feed Safety Risk Assessment. *EFSA*
718 *Journal*, *12*(6), 3734. http://doi.org/10.2903/j.efsa.2014.3734

719 EFSA. (2014b). Guidance on the EU Menu methodology. *EFSA Journal*, *12*(12).
720 http://doi.org/10.2903/j.efsa.2014.3944

721 EFSA. (2018). EFSA Scientific Colloquium 23 – Joint European Food Safety Authority and Evidence-Based
722 Toxicology Collaboration Colloquium Evidence integration in risk assessment: the science of combining
723 apples and oranges 25–26 October 2017 Lisbon, Portugal. *EFSA Supporting Publications*, *15*(3).
724 http://doi.org/10.2903/sp.efsa.2018.EN-1396

725 Eneroth, H., Wallin, S., Leander, K., Nilsson Sommar, J., & Åkesson, A. (2017). Risks and Benefits of Increased
726 Nut Consumption: Cardiovascular Health Benefits Outweigh the Burden of Carcinogenic Effects Attributed
727 to Aflatoxin B1 Exposure. *Nutrients*, *9*(12), 1355. http://doi.org/10.3390/nu9121355

728 EPA. (2009). USEPA: Expert Elicitation Task Force White Paper. Retrieved from
729 https://yosemite.epa.gov/sab/sabproduct.nsf/0/F4ACE05D0975F8C68525719200598BC7/$File/Expert_Eli
730 citation_White_Paper-January_06_2009.pdf

731 FAO. (2007). *Food safety risk analysis - A guide for national food safety authorities*. Rome, Italy. Retrieved from
732 http://www.fao.org/docrep/012/a0822e/a0822e00.htm

733 FAO. (2017). Food Safety Risk Management Evidence-informed Policies and Decisions, Considering Multiple
734 Factors. *FAO Guidance Materials. Food Safety and Quality Series 4.* Retrieved from
735 www.fao.org/publications

736 FAO/WHO. (2006). WHO | Enterobacter sakazakii and Salmonella in powdered infant formula. *WHO*. Retrieved

from http://www.who.int/foodsafety/publications/micro/mra10/en/

FAO/WHO. (2008). *Benefits and risks of the use of chlorine-containing disinfectants in food production and food processing: report of a joint FAO/WHO expert meetingAND WORKSHOPS Benefits and Risks of the Use of Chlorine-containing Disinfectants in Food Production and Food Processing Use of Chlorine-containing Disinfectants in Food Production and Food Processing*. Ann Arbor, MI, USA. Retrieved from http://www.fao.org/docrep/012/i1357e/i1357e.pdf

FAO/WHO. (2010). *Report of the joint FAO/WHO expert consultation on the risks and benefits of fish consumption, 25–29 January 2010, Rome, Italy.* Rome, Italy. Retrieved from http://www.fao.org/docrep/014/ba0136e/ba0136e00.pdf

FAO/WHO. (2011). *Codex Alimentarius Commission. Definitions of Risk Analysis Terms related to Food Safety, Procedural Manual. Rome:* Retrieved from www.codexalimentarius.org

FDA. (2013). Strucutred Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making (Feb 2013). Retrieved from https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm329758.pdf

FDA. (2014). *A quantitative assessment of the net effects on fetal neurodevelopment from eating commercial fish (As Measured by IQ and also by Early Age Verbal Development in Children)*. Retrieved from https://www.fda.gov/downloads/Food/FoodborneIllnessContaminants/Metals/UCM396785.pdf

Firew Berjia, Andersen, R., Hoekstra, J., Poulsen, M., & Nauta, M. (2012). Risk-Benefit Assessment of Cold-Smoked Salmon: Microbial Risk versus Nutritional Benefit. *European Journal of Food Research & Review*, *2*(2), 49–68.

Fransen, H., De Jong, N., Hendriksen, M., Mengelers, M., Castenmiller, J., Hoekstra, J., … Verhagen, H. (2010). A

Tiered Approach for Risk-Benefit Assessment of Foods. *Risk Analysis*, *30*(5), 808–816. http://doi.org/10.1111/j.1539-6924.2009.01350.x

Frewer, L. J., Fischer, A. R. H., Brennan, M., Bánáti, D., Lion, R., Meertens, R. M., … Vereijken, C. M. J. L. (2016). Risk/Benefit Communication about Food—A Systematic Review of the Literature. *Critical Reviews in Food Science and Nutrition*, *56*(10), 1728–1745. http://doi.org/10.1080/10408398.2013.801337

Gibb, H., Devleesschauwer, B., Bolger, P. M., Wu, F., Ezendam, J., Cliff, J., … Bellinger, D. (2015). World Health Organization estimates of the global and regional disease burden of four foodborne chemical toxins, 2010: a data synthesis. *F1000Research*, *4*, 1393. http://doi.org/10.12688/f1000research.7340.1

Gochfeld, M., & Burger, J. (2005). Good Fish/Bad Fish: A Composite Benefit–Risk by Dose Curve. *NeuroToxicology*, *26*(4), 511–520. http://doi.org/10.1016/J.NEURO.2004.12.010

Gold, M. R., Stevenson, D., & Fryback, D. G. (2002). HALYs and QALYs and DALYs, Oh My: Similarities and Differences in Summary Measures of Population Health. *Annual Review of Public Health*, *23*(1), 115–134. http://doi.org/10.1146/annurev.publhealth.23.100901.140513

Hald, T., Aspinall, W., Devleesschauwer, B., Cooke, R., Corrigan, T., Havelaar, A. H., … Hoffmann, S. (2016). World Health Organization estimates of the relative contributions of food to the burden of disease due to selected foodborne hazards: A structured expert elicitation. *PLoS ONE*, *11*(1), 1–35. http://doi.org/10.1371/journal.pone.0145839

Hallström, E., Carlsson-Kanyama, A., & Börjesson, P. (2015). Environmental impact of dietary change: a systematic review. *Journal of Cleaner Production*, *91*, 1–11. http://doi.org/10.1016/J.JCLEPRO.2014.12.008

Hart, A., Hoekstra, J., Owen, H., Kennedy, M., Zeilmaker, M. J., de Jong, N., & Gunnlaugsdottir, H. (2013).

779 Qalibra: A general model for food risk–benefit assessment that quantifies variability and uncertainty. *Food*
780 *and Chemical Toxicology*, *54*, 4–17. http://doi.org/10.1016/j.fct.2012.11.056

781 Havelaar, A. H., Haagsma, J. A., Mangen, M. J. J., Kemmeren, J. M., Verhoef, L. P. B., Vijgen, S. M. C., … van Pelt,
782 W. (2012). Disease burden of foodborne pathogens in the Netherlands, 2009. *International Journal of*
783 *Food Microbiology*, *156*(3), 231–238. http://doi.org/10.1016/j.ijfoodmicro.2012.03.029

784 Havelaar, A. H., Kirk, M. D., Torgerson, P. R., Gibb, H. J., Hald, T., Lake, R. J., … Zeilmaker, M. (2015). World
785 Health Organization Global Estimates and Regional Comparisons of the Burden of Foodborne Disease in
786 2010. *PLoS Medicine*, *12*(12), 1–23. http://doi.org/10.1371/journal.pmed.1001923

787 Hendriksen, M. a, Tijhuis, M. J., Fransen, H. P., Verhagen, H., & Hoekstra, J. (2011). Impact of substituting added
788 sugar in carbonated soft drinks by intense sweeteners in young adults in the Netherlands: example of a
789 benefit-risk approach. *European Journal of Nutrition*, *50*(1), 41–51. http://doi.org/10.1007/s00394-010-
790 0113-z

791 Hoekstra, J., Fransen, H. P., van Eijkeren, J. C. H., Verkaik-Kloosterman, J., de Jong, N., Owen, H., … Hart, A.
792 (2013). Benefit–risk assessment of plant sterols in margarine: A QALIBRA case study. *Food and Chemical*
793 *Toxicology*, *54*, 35–42. http://doi.org/10.1016/j.fct.2012.08.054

794 Hoekstra, J., Hart, A., Boobis, A., Claupein, E., Cockburn, A., Hunt, A., … Chiodini, A. (2012). BRAFO tiered
795 approach for benefit–risk assessment of foods. *Food and Chemical Toxicology*, *50*, S684–S698.
796 http://doi.org/10.1016/j.fct.2010.05.049

797 Hoekstra, J., Hart, A., Owen, H., Zeilmaker, M., Bokkers, B., Thorgilsson, B., & Gunnlaugsdottir, H. (2013). Fish,
798 contaminants and human health: Quantifying and weighing benefits and risks. *Food and Chemical*
799 *Toxicology*, *54*, 18–29. http://doi.org/10.1016/j.fct.2012.01.013

800 Hoekstra, J., Verkaik-Kloosterman, J., Rompelberg, C., van Kranen, H., Zeilmaker, M., Verhagen, H., & de Jong,
801 N. (2008). Integrated risk–benefit analyses: Method development with folic acid as example. *Food and*
802 *Chemical Toxicology*, *46*(3), 893–909. http://doi.org/10.1016/j.fct.2007.10.015

803 Hollander, A., De Jonge, R., Biesbroek, S., Hoekstra, J., & Zijp, M. C. (2018). Exploring solutions for healthy, safe,
804 and sustainable fatty acids (EPA and DHA) consumption in The Netherlands. *Sustainability Science*, 1–11.
805 http://doi.org/10.1007/s11625-018-0607-9

806 Horgan, G. W., Perrin, A., Whybrow, S., & Macdiarmid, J. I. (2016). Achieving dietary recommendations and
807 reducing greenhouse gas emissions: modelling diets to minimise the change from current intakes.
808 *International Journal of Behavioral Nutrition and Physical Activity*, *13*(46), 1–11.
809 http://doi.org/10.1186/s12966-016-0370-1

810 Hsu, J. C., Tang, D. H., & Lu, C. Y. (2015). Risk-benefit assessment of oral phosphodiesterase type 5 inhibitors for
811 treatment of erectile dysfunction: a multiple criteria decision analysis. *International Journal of Clinical*
812 *Practice*, *69*(4), 436–443. http://doi.org/10.1111/ijcp.12548

813 Husøy, T., Mangschou, B., Fotland, T. Ø., Kolset, S. O., Nøtvik Jakobsen, H., Tømmerberg, I., … Frost Andersen, L.
814 (2008). Reducing added sugar intake in Norway by replacing sugar sweetened beverages with beverages
815 containing intense sweeteners - a risk benefit assessment. *Food and Chemical Toxicology : An*
816 *International Journal Published for the British Industrial Biological Research Association*, *46*(9), 3099–105.
817 http://doi.org/10.1016/j.fct.2008.06.013

818 Leino, O., Karjalainen, A. K., & Tuomisto, J. T. (2013). Effects of docosahexaenoic acid and methylmercury on
819 child's brain development due to consumption of fish by Finnish mother during pregnancy: A probabilistic
820 modeling approach. *Food and Chemical Toxicology*, *54*, 50–58. http://doi.org/10.1016/J.FCT.2011.06.052

Maillot, M., Vieux, F., Amiot, M. J., & Darmon, N. (2010). Individual diet modeling translates nutrient recommendations into realistic and individual-specific food choices. *American Journal of Clinical Nutrition*, *91*(2), 421–430. http://doi.org/10.3945/ajcn.2009.28426

Maillot, M., Vieux, F., Ferguson, E., Volatier, J.-L., Amiot, M. J., & Darmon, N. (2009). To Meet Nutrient Recommendations, Most French Adults Need to Expand Their Habitual Food Repertoire. *Journal of Nutrition*, *139*(9), 1721–1727. http://doi.org/10.3945/jn.109.107318

Malden C. Nesheim and Ann L. Yaktine, E. (2007). *Seafood Choices: Balancing benefits and risks*. Washington, D.C.: National Academies Press. http://doi.org/10.17226/11762

Masset, G., Soler, L.-G., Vieux, F., & Darmon, N. (2014). Identifying Sustainable Foods: The Relationship between Environmental Impact, Nutritional Quality, and Prices of Foods Representative of the French Diet. *Journal of the Academy of Nutrition and Dietetics*, *114*(6), 862–869. http://doi.org/10.1016/j.jand.2014.02.002

MRC Vitamine Study Research Group. (1991). Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. MRC Vitamin Study Research Group. *Lancet (London, England)*, *338*(8760), 131–7. http://doi.org/10.1016/0140-6736(91)90133-A

Murray, C. J. L. (1994). Quantifying the burden of disease: The technical basis for disability-adjusted life years. *Bulletin of the World Health Organization*, *72*(3), 429–445. http://doi.org/10.1016/S0140-6736(96)07495-8

NAP. (2007). *Seafood Choices*. Washington, D.C.: National Academies Press. http://doi.org/10.17226/11762

Nauta, M. J., Andersen, R., Pilegaard, K., Pires, S. M., Ravn-Haren, G., Tetens, I., & Poulsen, M. (2018). Meeting the challenges in the development of risk-benefit assessment of foods. *Trends in Food Science &*

842 *Technology*. http://doi.org/10.1016/j.tifs.2018.04.004

843 Nauta, M. J., Andersen, R., Pilegaard, K., Pires, S. M., Ravn-Haren, G., Tetens, I., & Poulsen, M. (2018). Meeting
844 the challenges in the development of risk-benefit assessment of foods. *Trends in Food Science and*
845 *Technology*, *76*. http://doi.org/10.1016/j.tifs.2018.04.004

846 Nixon, R., Dierig, C., Mt-Isa, S., Stöckert, I., Tong, T., Kuhls, S., … Thomson, A. (2016). A case study using the
847 PrOACT-URL and BRAT frameworks for structured benefit risk assessment. *Biometrical Journal*, *58*(1), 8–
848 27. http://doi.org/10.1002/bimj.201300248

849 Ocké MC, Toxopeus IB, Geurts M, Mengelers MJB, Temme EHM, H. N. (2017). *What is on our plate? Safe,*
850 *healthy and sustainable diets in the Netherlands*. Retrieved from
851 https://www.rivm.nl/dsresource?objectid=7f952231-c794-4eb2-bb61-
852 21314a39bdef&type=pdf&disposition=inline

853 Pedersen, A. N., Fagt, S., Velsing Groth, M., Christensen, T., Biltoft-Jensen, A., Matthiessen, J., … Trolle, E.
854 (2010). *Dietary habits in Denmark 2003-2008*.

855 Persson, M., Fagt, S., Pires, S. M., Poulsen, M., Vieux, F., & Nauta, M. J. (2018). Use of Mathematical
856 Optimization Models to Derive Healthy and Safe Fish Intake. *The Journal of Nutrition*, *148*(2), 275–284.
857 http://doi.org/10.1093/jn/nxx010

858 Ponce, R. A., Bartell, S. M., Wong, E. Y., LaFlamme, D., Carrington, C., Lee, R. C., … Bolger, M. (2000). Use of
859 quality-adjusted life year weights with dose-response models for public health decisions: a case study of
860 the risks and benefits of fish consumption. *Risk Analysis : An Official Publication of the Society for Risk*
861 *Analysis*, *20*(4), 529–42. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11051076

862 Pujol, L., Johnson, N. B., Magras, C., Albert, I., & Membré, J.-M. (2015). Added value of experts' knowledge to

863 improve a quantitative microbial exposure assessment model — Application to aseptic-UHT food
864 products. *International Journal of Food Microbiology*, *211*, 6–17.
865 http://doi.org/10.1016/j.ijfoodmicro.2015.06.015

866 Rheinberger, C. M., & Hammitt, J. K. (2012). Risk Trade-Offs in Fish Consumption: A Public Health Perspective.
867 *Environmental Science & Technology*, *46*(22), 12337–12346. http://doi.org/10.1021/es302652m

868 Rideout, K., & Kosatsky, T. (2017). Fish for Dinner? Balancing Risks, Benefits, and Values in Formulating Food
869 Consumption Advice. *Risk Analysis*, *37*(11), 2041–2052. http://doi.org/10.1111/risa.12769

870 Ruzante, J. M., Davidson, V. J., Caswell, J., Fazil, A., Cranfield, J. A. L., Henson, S. J., … Farber, J. M. (2010). A
871 Multifactorial Risk Prioritization Framework for Foodborne Pathogens. *Risk Analysis*, *30*(5), 724–742.
872 http://doi.org/10.1111/j.1539-6924.2009.01278.x

873 Ruzante, J. M., Grieger, K., Woodward, K., Lambertini, E., & Kowalcyk, B. (2017). The Use of Multi-criteria
874 Decision Analysis in Food Safety Risk-benefit Assessment. *Food Protection Trends*, *37*(2), 132–139.
875 Retrieved from https://www.foodprotection.org/publications/food-protection-trends/archive/2017-03-
876 the-use-of-multi-criteria-decision-analysis-in-food-safety-risk-benefit-assessment/

877 Saaty, T. L. (1994). How to Make a Decision: The Analytic Hierarchy Process. *Interfaces*, *24*(6), 19–43.
878 http://doi.org/10.1287/inte.24.6.19

879 SACN. (2017). *Update on folic acid. Scientific Advisory Committee on Nutrition.* Retrieved from
880 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/637
881 111/SACN_Update_on_folic_acid.pdf

882 Saltelli, A. (2002). Sensitivity Analysis for Importance Assessment. *Risk Analysis*, *22*(3), 579–590.
883 http://doi.org/10.1111/0272-4332.00040

884 Seves, S. M., Temme, E. H. M., Brosens, M. C. C., Zijp, M. C., Hoekstra, J., & Hollander, A. (2016). Sustainability
885 aspects and nutritional composition of fish: evaluation of wild and cultivated fish species consumed in the
886 Netherlands. *Climatic Change*, *135*(3-4), 597–610. http://doi.org/10.1007/s10584-015-1581-1

887 Skåre, J., Brantsæter, A., Frøyland, L., Hemre, G.-I., Knutsen, H., Lillegaard, I., & Torstensen, B. (2015). Benefit-
888 risk Assessment of Fish and Fish Products in the Norwegian Diet – An Update. *European Journal of*
889 *Nutrition & Food Safety*, *5*(4), 260–266. http://doi.org/10.9734/EJNFS/2015/18605

890 Steffensen, I.-L., Frølich, W., Dahl, K. H., Iversen, P. O., Lyche, J. L., Lillegaard, I. T. L., & Alexander, J. (2018).
891 Benefit and risk assessment of increasing potassium intake by replacement of sodium chloride with
892 potassium chloride in industrial food products in Norway. *Food and Chemical Toxicology*, *111*, 329–340.
893 http://doi.org/10.1016/j.fct.2017.11.044

894 Temme, E. H., van der Voet, H., Thissen, J. T., Verkaik-Kloosterman, J., van Donkersgoed, G., & Nonhebel, S.
895 (2013). Replacement of meat and dairy by plant-derived foods: estimated effects on land use, iron and
896 SFA intakes in young Dutch adult females. *Public Health Nutrition*, *16*(10), 1900–1907.
897 http://doi.org/10.1017/S1368980013000232

898 Tervonen, T., van Valkenhoef, G., Buskens, E., Hillege, H. L., & Postmus, D. (2011). A stochastic multicriteria
899 model for evidence-based decision making in drug benefit-risk analysis. *Statistics in Medicine*, *30*(12),
900 1419–1428. http://doi.org/10.1002/sim.4194

901 Tetens, I., Andersen, L. B., Astrup, A., Gondolf, U. H., Hermansen, K., Jakobsen, M. U., … Trolle, E. (2013).
902 *Evidensgrundlaget for danske råd om kost og fysisk aktivitet*.

903 Teunis, P. F. M., Kasuga, F., Fazil, A., Ogden, I. D., Rotariu, O., & Strachan, N. J. C. (2010). Dose–response
904 modeling of Salmonella using outbreak data. *International Journal of Food Microbiology*, *144*(2), 243–249.

http://doi.org/10.1016/j.ijfoodmicro.2010.09.026

Teunis, P. F. M., Nagelkerke, N. J. D., & Haas, C. N. (1999). Dose Response Models For Infectious Gastroenteritis. *Risk Analysis*, *19*(6), 1251–1260. http://doi.org/10.1023/A:1007055316559

Thomsen, S. T., Pires, S. M., Devleesschauwer, B., Poulsen, M., Fagt, S., Ygil, K. H., & Andersen, R. (2018). Investigating the risk-benefit balance of substituting red and processed meat with fish in a Danish diet. *Food and Chemical Toxicology*, *120*, 50–63. http://doi.org/10.1016/j.fct.2018.06.063

Tijhuis, M. J., de Jong, N., Pohjola, M. V., Gunnlaugsd??ttir, H., Hendriksen, M., Hoekstra, J., … Verhagen, H. (2012). State of the art in benefit-risk analysis: Food and nutrition. *Food and Chemical Toxicology*, *50*(1), 5–25. http://doi.org/10.1016/j.fct.2011.06.010

Tsang, M. P., Bates, M. E., Madison, M., & Linkov, I. (2014). Benefits and Risks of Emerging Technologies: Integrating Life Cycle Assessment and Decision Analysis To Assess Lumber Treatment Alternatives. *Environmental Science & Technology*, *48*(19), 11543–11550. http://doi.org/10.1021/es501996s

van de Kamp, M. E., Seves, S. M., & Temme, E. H. M. (2018). Reducing GHG emissions while improving diet quality: exploring the potential of reduced meat, cheese and alcoholic and soft drinks consumption at specific moments during the day. *BMC Public Health*, *18*(1), 264. http://doi.org/10.1186/s12889-018-5132-3

Van der Fels-Klerx, H. J., Cooke, R. M., Nauta, M. N., Goossens, L. H., & Havelaar, A. H. (2005). A Structured Expert Judgment Study for a Model of Campylobacter Transmission During Broiler-Chicken Processing. *Risk Analysis*, *25*(1), 109–124. http://doi.org/10.1111/j.0272-4332.2005.00571.x

van der Voet, H., de Mul, A., & van Klaveren, J. D. (2007). A probabilistic model for simultaneous exposure to multiple compounds from food and its use for risk-benefit assessment. *Food and Chemical Toxicology*,

926 *45*(8), 1496–1506. http://doi.org/10.1016/j.fct.2007.02.009

927 van der Voet, H., & Slob, W. (2007). Integration of Probabilistic Exposure Assessment and Probabilistic Hazard
928 Characterization. *Risk Analysis*, *27*(2), 351–371. http://doi.org/10.1111/j.1539-6924.2007.00887.x

929 van Wagenberg, C. P. A., de Haas, Y., Hogeveen, H., van Krimpen, M. M., Meuwissen, M. P. M., van Middelaar,
930 C. E., & Rodenburg, T. B. (2017). Animal Board Invited Review: Comparing conventional and organic
931 livestock production systems on different aspects of sustainability. *Animal*, *11*(10), 1839–1851.
932 http://doi.org/10.1017/S175173111700115X

933 Verhagen, H., Andersen, R., Antoine, J.-M., Finglas, P., Hoekstra, J., Kardinaal, A., … Chiodini, A. (2012).
934 Application of the BRAFO tiered approach for benefit–risk assessment to case studies on dietary
935 interventions. *Food and Chemical Toxicology*, *50*, S710–S723. http://doi.org/10.1016/j.fct.2011.06.068

936 Verhagen, H., Tijhuis, M. J., Gunnlaugsdóttir, H., Kalogeras, N., Leino, O., Luteijn, J. M., … Holm, F. (2012). State
937 of the art in benefit–risk analysis: Introduction. *Food and Chemical Toxicology*, *50*(1), 2–4.
938 http://doi.org/10.1016/j.fct.2011.06.007

939 VKM. (2013). *Benefit and risk assessment of Breastmilk for infant health in norway*. Retrieved from
940 https://vkm.no/download/18.2994e95b15cc5450716157e6/1501690194476/820a1a0bf8.pdf

941 Zeilmaker, M. J., Hoekstra, J., van Eijkeren, J. C. H., de Jong, N., Hart, A., Kennedy, M., … Gunnlaugsdottir, H.
942 (2013a). Fish consumption during child bearing age: A quantitative risk-benefit analysis on
943 neurodevelopment. *Food and Chemical Toxicology*, *54*, 30–34. http://doi.org/10.1016/j.fct.2011.10.068

944 Zeilmaker, M. J., Hoekstra, J., van Eijkeren, J. C. H., de Jong, N., Hart, A., Kennedy, M., … Gunnlaugsdottir, H.
945 (2013b). Fish consumption during child bearing age: A quantitative risk–benefit analysis on
946 neurodevelopment. *Food and Chemical Toxicology*, *54*, 30–34. http://doi.org/10.1016/j.fct.2011.10.068

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955 **Appendix 1: List of participants and affiliations**

Participant name	Affiliantion
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Bernhard Watzl	Max Rubner-Institut, Germany
David Senaeve	University of Ghent, Belgium
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Helga Gunnlaugsdottir	Matis ltd., Island
Inger Therese L. Lillegaard	VKM, Scientific Committee for Food Safety, Norway

Jacob van Klaveren	RIVM, The Netherlands
Jean-Luc Volatier	Anses, France
Jeanne-Marie Membré	INRA Secalim, France
Jeljer Hoekstra	RIVM, The Netherlands
Johannes Kruisselbrink	Wageningen University, Biometris, The Netherlands
Juliana Ruzante	RTI International, US
Kim Petersen	WHO/FOS
Marco Zeilmaker	RIVM, The Netherlands
Matthias Greiner	Federal Institute for Risk Assessment BfR), Germany
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Maarten Nauta	Technical University of Denmark
Rikke Andersen	Technical University of Denmark
Salomon Sand	National Food Agency, Sweden
Sara Monteiro Pires	Technical University of Denmark
Majken Ege	Technical University of Denmark
Lea Jakobsen	Technical University of Denmark
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