

GUIDANCE

Guidance on risk–benefit assessment of foods

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Correspondence:sc.secretariat@efsa.europa.eu**Abstract**

The EFSA Scientific Committee has updated its 2010 Guidance on risk–benefit assessment (RBA) of foods. The update addresses methodological developments and regulatory needs. While it retains the stepwise RBA approach, it provides additional methods for complex assessments, such as multiple chemical hazards and all relevant health effects impacting different population subgroups. The updated guidance includes approaches for systematic identification, prioritisation and selection of hazardous and beneficial food components. It also offers updates relevant to characterising adverse and beneficial effects, such as measures of effect size and dose–response modelling. The guidance expands options for characterising risks and benefits, incorporating variability, uncertainty, severity categorisation and ranking of different (beneficial or adverse) effects. The impact of different types of health effects is assessed qualitatively or quantitatively, depending on the problem formulation, scope of the RBA question and data availability. The integration of risks and benefits often involves value-based judgements and should ideally be performed with the risk–benefit manager. Metrics such as Disability-Adjusted Life Years (DALYs) and Quality-Adjusted Life Years (QALYs) can be used. Additional approaches are presented, such as probability of all relevant effects and/or effects of given severities and their integration using severity weight functions. The update includes practical guidance on reporting results, interpreting outcomes and communicating the outcome of an RBA, considering consumer perspectives and responses to advice.

KEYWORDS

benefit–risk, food safety, RBA, risk ranking, risk–benefit, risk–benefit assessment, risk–benefit communication

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SUMMARY

The EFSA Scientific Committee (SC) has updated its Guidance on risk–benefit assessment (RBA) of Foods, first published in 2010, to incorporate methodological developments since then and to meet the regulatory and risk management needs of the European Commission and Member States (MS). The EFSA 2010 SC RBA Guidance introduced a stepwise RBA approach that included the integration of risks and benefits using composite metrics, such as disability-adjusted life years (DALYs) and quality-adjusted life years (QALYs). The update was guided by input from MS that these composite metrics cannot always or easily be interpreted in terms that could support MS in defining dietary advice. An EFSA Scientific Colloquium (26th) was held in February 2022 to collect wider input from stakeholders involved in RBA methodologies, data generation and risk–benefit management. The scope of the updated Guidance includes relevant approaches for the characterisation and integration of risks and benefits focusing on chemical hazards and nutrients but does not replace procedures required by European legislation for regulated products. The methodologies presented may to some extent be applicable to biological hazards; environmental aspects of RBA would require additional considerations that remain out of the scope of this Guidance.

The updated guidance aims to provide a framework of principles that is applicable to a wide range of RBA scenarios to help harmonise the RBA process and meet the needs of regulators and policy makers. While the tiered approach and key aspects of the 2010 Guidance have been retained, the updated Guidance provides additional methodological options to address assessments of greater complexity, such as in the context of multiple chemical hazards, nutrients and health effects that may impact population subgroups differently. The Guidance aims to remain flexible and provides approaches for systematic and transparent identification, prioritisation and selection of hazardous and beneficial food components and relevant health effects to be included in the RBA and for systematically organising the available evidence. These are part of an iterative process and have an impact on the outcome of the assessment, its interpretation and implementation.

RBAs will differ depending on the level of complexity of the RBA question and the data and resources available. Therefore, the intention of the guidance is to provide several approaches that can serve as a basis for supporting a diverse set of continuously evolving RBAs.

The Guidance includes updates relevant to the characterisation of adverse and beneficial effects, mainly for more refined assessments, such as measures of effect size, or probability of gradual or binary effects and (benchmark) dose modelling of all relevant effects, which then feed into risk and benefit characterisation models. As levels of food intake change, the health effects (positive or negative) that may be observed may be not only quantitatively but also different in nature. Therefore, all identified health effects associated with diet, food or food components included in the RBA can be systematically mapped along the range of low-to-high food intakes and characterised for their relationship to dose. The options for characterisation of risks and benefits have been expanded with additional qualitative and quantitative approaches that incorporate variability, uncertainty, severity categorisation of effects within the continuum of biological progression over a relevant range of intakes, and ranking of different effects with a severity weight function.

The combined impact of different types of health effects on the health of the population overall is assessed either qualitatively or quantitatively depending on the problem formulation and the scope of the RBA question, but also on data availability. Comparative health impact assessment of risks and benefits often involves value-based judgements related to the severity and prioritisation of health effects. Value-based aspects should be performed in collaboration with the risk–benefit manager. When integration of risks and benefits adopts the commonly used composite metrics DALYs and QALYs, these should be reported together with other metrics such as number of cases, mortality, severity of effects and other relevant dimensions. Additional qualitative and quantitative methodologies for the integration of risks and benefits are provided. These build on the additional methods introduced for characterisation of risks and benefits and are based on the probabilities of all relevant effects and/or effects of given severities and their integration using severity weight functions.

The update also includes practical guidance on reporting the results of the assessment and on interpretation of the outcome. Lastly, guidance related to communication of the outcome of an RBA has been added, based on consumer perspectives, behaviour and response to advice.

1 | INTRODUCTION

Risk–benefit assessment (RBA) is a methodological framework, that forms an integral part of a broader risk–benefit analysis framework that consists essentially of three processes: risk–benefit assessment, risk–benefit management and risk–benefit communication. RBA is applicable across a variety of fields, of which human health is but one.¹ RBA of foods in relation to human health considers risks² from the presence of hazards in foods weighed against benefits³ from the diet, food and/or food components. RBA is inherently multidisciplinary, requiring a broad range of skills and collaboration across scientific disciplines, such as chemistry, nutrition, toxicology, microbiology, epidemiology and exposure science. Other kinds of expertise required include statistical modelling, data analysis and uncertainty analysis.

In 2010, the EFSA Scientific Committee (SC) (EFSA Scientific Committee, 2010) published a guidance document outlining the principles for conducting RBA of foods. The SC introduced a stepwise approach for the combined assessment of risks and benefits, mirroring the well-established risk assessment framework. Moreover, this approach included the integration of risks and benefits using composite metrics,⁴ thus providing a structured and systematic methodology for evaluating the overall impact of foods on human health.

At its 106th plenary meeting in November 2021, the SC discussed the need for an update to the Guidance. The need for the update was identified in anticipation of a draft request from the European Commission for an RBA related to fish consumption. This was based on a request from Member States (MS) for further guidance that would lead to RBA outcomes that would better serve their needs when developing food-based dietary guidelines (FBDG)⁵ at a national level. This is particularly the case when multiple food components⁶ (e.g. contaminants, nutrients) in a given food pose both risks and benefits. The SC agreed that an update of the 2010 Guidance was needed to incorporate methodological developments and improvements so that new RBAs could meet the regulatory and risk management needs of the European Commission and MS.

The SC therefore requested a mandate to update its 2010 Guidance for the RBA of Foods published in 2010. The updated Guidance supersedes the 2010 Guidance.

1.1 | Background and terms of reference of the self-task mandate, as provided by EFSA

In the 2018 EFSA Scientific Opinion, the Panel on Contaminants in the food chain (CONTAM Panel) performed a risk assessment related to the presence of polychlorinated dibenzo-*p*-dioxins and furans (PCDD/Fs) and dioxin-like polychlorinated biphenyls (DL-PCBs) in feed and food, and established a Tolerable Weekly Intake (TWI) of 2 pg WHO₂₀₀₅-TEQ/kg bw per week. The estimated human dietary exposure to PCDD/Fs and DL-PCBs was found to exceed the TWI for all age groups. The benefits of fish consumption were not assessed in this Opinion.

Previously, a 2005 EFSA Scientific Opinion on the human health risk assessment related to exposure to contaminants from consumption of wild and farmed fish relative to the benefits of fish consumption, was produced by the CONTAM Panel, with contributions from the Panel on Dietetic Products, Nutrition and Allergies (NDA Panel), the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP Panel) and the Panel on Animal Health and Welfare (AHAW Panel). This Scientific Opinion concluded that exposure to contaminants in fish, including PCDD/Fs and DL-PCBs, may counteract the benefits of fish consumption which were represented [mainly] by the content of long chain n-3 polyunsaturated fatty acids (LC n-3 PUFAs).

The EFSA Scientific Committee (SC) assessed the benefits of fish consumption in relation to risks specifically from methylmercury in a 2015 EFSA Statement, following the EFSA 2010 Guidance on human health Risk–Benefit Assessment (RBA) of foods. The 2005 EFSA assessment predates the 2010 EFSA RBA Guidance, while the 2015 SC Statement could not make general recommendations about fish consumption but recommended that each MS assess the risks and benefits relevant to fish species consumed in their respective countries.

Taking into account these previous risk/risk–benefit assessments and particularly the outcome of the 2018 CONTAM Panel Opinion on PCDD/Fs and DL-PCBs in food, the European Commission (EC) drafted a request for EFSA to prepare an updated RBA of fish consumption in relation to the presence of PCDD/Fs and DL-PCBs, and considering how the presence of other contaminants in fish, such as methylmercury, brominated flame retardants (BFRs) and perfluoroalkyl substances

¹RBA is applicable to other fields such as economy, politics, environmental assessments, and more.

²Risk is defined as ‘the probability of an adverse effect in an organism, system or (sub)-population caused under specified circumstances by exposure to an agent.’ (see EFSA glossary).

³Benefit is defined as ‘the probability of a positive effect and/or the reduction of the probability of an adverse effect on (1) normal biochemical and physiological functions of a tissue (e.g. muscular or nervous tissue), organ (e.g. heart, lung, kidney, liver), or system (e.g. immune system); or (2) the health of (sub) population.’

⁴<https://efsa.onlinelibrary.wiley.com/doi/abs/10.2903/j.efsa.2010.1673>.

⁵EFSA’s definition of FBDG is: ‘Science-based recommendations for healthy eating which translate numerical nutrition targets into lay advice on what foods to eat.’ (see EFSA glossary).

⁶The term ‘food component’ is used throughout the document to refer to nutrients, compounds of toxicological concern, other undesirable substances (EC definition), and other food constituents (e.g. non-nutrients) that are considered in an RBA. The term ‘chemical hazard’ refers to compounds of toxicological concern covering contaminants, residues, or any chemical that is present in food and presents toxicological concern. Nutrients characterised by an upper tolerable intake level may have both positive and negative health effects depending on intake.

(PFASs), influence the outcome of the RBA. An inter-Panel EFSA taskforce⁷ was convened to define the scope of the draft EC mandate. The proposal for an updated RBA was further discussed with Member States (MS), who are planning to issue recommendations for fish consumption at national level. In these discussions, MS expressed the need for an updated RBA that does not simply report the relative contribution of consumption of fish to the overall exposure to these chemical hazards, but that supports [them] to define fish consumption advice at national level and inform risk management decisions.

Based on the input from the EC and MS, the EFSA inter-Panel taskforce concluded that a substantive and fit-for-purpose update of the RBA for fish consumption that would serve the needs of MS is conditional upon additional updates that need to precede it, specifically: updated WHO₂₀₀₅ Toxic Equivalency Factors (TEFs), updated dietary exposure assessment, and updated EFSA RBA Guidance. The update of the RBA has been negotiated and agreed to be undertaken *after* the update of the WHO₂₀₀₅-TEFs for PCDD/Fs and DL-PCBs, as recommended in the 2018 CONTAM Panel Opinion. This work is outsourced and is currently underway, with EFSA assisting the World Health Organisation (WHO) in updating the toxicity database used to evaluate and revise the WHO₂₀₀₅-TEFs in a timely manner to facilitate their incorporation in the RBA within the timeframe of the EC mandate with anticipated deadline in 2025.⁸ As TEFs are significant inputs in the exposure assessment of PCDD/Fs and DL-PCBs, an updated dietary exposure assessment is planned, pending the completion of the TEF update and this activity is included in the Terms of Reference of the EC mandate.

The EFSA 2010 SC RBA Guidance aimed to produce commonly used composite metrics, such as disability-adjusted life years (DALYs) and quality-adjusted life years (QALYs), which are useful comparative measures of risk-benefit among various exposures. These are used in overall monitoring of population health status, but these parameters cannot be [easily] interpreted in terms that could support MS in defining fish consumption advice.

Terms of Reference of the Scientific Committee self-task mandate:

The Scientific Committee is asked:

- To update the 2010 EFSA Scientific Committee Guidance on the human health risk-benefit assessment of Foods (EFSA, Scientific Committee, 2010).

1.2 | Interpretation of the Terms of Reference

The update of the 2010 SC RBA Guidance aims to produce outputs that can better serve the needs of risk-benefit managers in issuing FBDG. Therefore, the update is primarily aimed at providing guidance on how to conduct a joint assessment of the risks and benefits that would better inform the risk-benefit managers when making decisions in cases of multiple risks and benefits. While aspects of the 2010 Guidance are likely applicable to less complex RBA situations, the updated Guidance integrates additional methodological aspects to address greater complexity, including the selection of appropriate metrics.

The 2010 RBA Guidance considered aspects related to the use of composite metrics and advised in their interpretation and embedded assumptions (see Appendix B.1). These aspects, alongside the associated recommendations, are utilised to guide the current update. Additionally, the update takes into account the accumulated experience in conducting RBAs of foods and the evolving methodologies and data types available for conducting RBA assessments. This ensures that the updated Guidance is relevant to, and aligned with, the advancements and experience gained since the publication of the 2010 Guidance.

The updated Guidance maintains the focus on the assessment of risks and benefits of food consumption to human health related to chemical hazards and nutrients. This Guidance does not address in detail the risks associated with biological hazards; however, the methodology may be applicable to such hazards. Incorporating environmental aspects in an RBA, while within the remit of scientific assessment, requires additional considerations which go beyond the scope of this Guidance.

It is to be noted that RBA fulfils a specific function and does not replace procedures required by existing European legislation applicable to regulated products, e.g. safety or risk assessment and authorisation of food additives, food supplements, novel foods, health claims, or any cases where safety and/or efficacy must be demonstrated. Therefore, the chemical hazards that fall within the scope of an RBA comprise mainly contaminants in the foods under assessment. However, it is possible that in addition to contaminants, other chemicals may become subject to RBA, such as compounds or processes intended to protect or enhance the safety of the food. The general term 'chemical hazard' is used to capture all relevant food components that may be subject to RBA.

It is acknowledged that effectors, such as socio-economic or cultural factors, are taken into account in risk-benefit management decisions. However, consideration of these effectors is outside the remit of EFSA. Notwithstanding, there is

⁷The taskforce consisted of EFSA staff providing scientific support to the Panel on Contaminants in the Food Chain (CONTAM), the Panel on Nutrition, Novel Foods and Food Allergens (NDA) and the Scientific Committee (SC).

⁸The work undertaken to assist the World Health Organization with the update of the WHO₂₀₀₅-TEFs for PCDD/Fs and DL-PCBs was completed in 2022. It was used at an expert meeting of the World Health Organization for the reevaluation of human and mammalian Toxic Equivalency Factors for Polychlorinated Dioxins, Dibenzofurans and Biphenyls, which was held from 17 to 21 October 2022 in Lisbon (DeVito et al., 2024). The completion of the EC mandate for the RBA of fish, with a tentative deadline at the end of 2025, is subject to both the updated WHO-TEFs for PCDD/Fs and DL-PCBs and the finalisation of the present Guidance update.

evidence from social research indicating that individuals and societal groups often conflate these other effectors with human health risks and benefits. Therefore, the updated Guidance includes advice on how social science can inform communication of human health RBA. Such consideration supports assessors and managers in fulfilling the Objectives and General Principles of risk communication in the 'Transparency Regulation'.⁹

Due to the multidisciplinary nature of the team engaged in RBA, interdisciplinary engagement is essential and must be supported by a common language and clear understanding of concepts and terminology. In the area of risk assessment, EFSA adopts definitions established by the International Program on Chemical Safety (IPCS) of the WHO and published in the Environmental Health Criteria (EHC) 240 (FAO/WHO, 2009). In the area of benefit assessment, EFSA adopts definitions established in existing guidance documents, EFSA glossary or WHO. A list of definitions pertinent to RBA in relation to human health is provided in Appendix A.

RBAs will differ depending on the level of complexity of the RBA question and the data and resources available. Therefore, the intention of the guidance is to provide several approaches that can serve as a basis for supporting a diverse set of continuously evolving RBAs.

1.3 | Consultations

In line with its policy on openness and transparency, EFSA consulted EU Member States and interested parties through an online public consultation held between 19 February 2024 and 2 April 2024. The comments received were considered by the working group and incorporated into the current guidance, where appropriate, before adoption of the opinion by the EFSA Scientific Committee. The outcome of the public consultation (EFSA-Q-2022-00211) is published as a technical report in Annex A.

2 | RISK-BENEFIT ASSESSMENT APPROACHES

The 2010 SC Guidance was the only such document at the time, published by a regulatory authority in the context of food risks and benefits. A similar framework was then published in 2012 and developed as an European Commission-funded project to compare benefits and risks (BRAFO¹⁰) (Hoekstra et al., 2012). Other activities, such as the Beneris,¹¹ Qalibra,¹² and Beparibeian¹³ projects were ongoing in parallel. In the last 10 years, some of RBAs have been conducted using a variety of approaches. An overview of currently available approaches and of activities that have taken place since the publication of the 2010 SC Guidance is provided in Appendix B. The SC reviewed these approaches and activities for their potential to improve the scientific process in conducting an RBA, especially for complex situations. The approaches and activities considered to advance the RBA methodology have been used here to update the 2010 SC Guidance.

RBA may be conducted at different levels of complexity, e.g. for specific foods (e.g. fish, eggs, apples, milk, etc.) or whole diets (e.g. vegan diet), few or multiple food components (e.g. nutrients, contaminants), single or multiple health effects in one or more population groups, and different pieces of evidence obtained from animal and/or human studies. Different methods may be appropriate or compatible depending on the data available. Associated metrics relate to disease probability and are applicable across areas. Collectively they can support different tasks, from prioritisation within the risk and benefit domains to the estimation of the overall quantitative trade-off using qualitative, semi-quantitative or quantitative approaches. Different methods that can support the RBA process are discussed in Sections 4 and 5. Increased awareness of the use of RBA in solving complex research questions has led to the development and integration of new approaches and methods, research collaborations across Europe and the engagement of international agencies such as WHO, FAO and EFSA (Alvito et al., 2019; Assunção et al., 2019).

Multiple national and international projects have considered the complexities of integrating the benefits and risks to human health linked to the consumption of foods or food components in order to understand the health impact of combined exposures to chemical hazards and nutrients.

⁹Regulation (EU) 2019/1381 of the European Parliament and of the Council of 20 June 2019 on the transparency and sustainability of the EU risk assessment in the food chain, revised Article 8a 'Objectives of risk communication' – 'Taking into account the respective roles of risk assessors and risk managers, risk communication shall pursue the following objectives: [...] (c) provide a sound basis, including, where appropriate, a scientific basis, for understanding risk management decisions'. Also, Article 8b 'General principles of risk communication' 'Taking into account the respective roles of risk assessors and risk managers, risk communication shall: [...] (b) provide transparent information at each stage of the risk analysis process from the framing of requests for scientific advice to the provision of risk assessment and the adoption of risk management decisions, including information on how risk management decisions were reached and which factors were considered.'

¹⁰BRAFO: Benefit-Risk Analysis of Foods; an EU supported program describing a tiered framework for risk and benefit assessment, similar to the step-wise approach of the EFSA 2010 Guidance.

¹¹Beneris: Benefit-Risk Assessment for Food: an Iterative Value-of-Information Approach; an EU-funded research project and co-funded by the Sixth Framework Programme of Research of the European Union, Food Quality and Safety Thematic Priority. <https://cordis.europa.eu/article/id/89760-better-assessment-of-food-safety-risks>.

¹²Qalibra: Quality of Life – Integrated Benefit and Risk Analysis Web-based Tool for Assessing Food Safety and Health Benefits; a research project supported by the European Commission's 6th Framework Programme on Food Quality and Safety. <https://cordis.europa.eu/project/id/22957/reporting>.

¹³Beparibeian: Best Practices for Risk-Benefit Analysis of Foods; a research project about benefit-risk assessment (BRA) of food and nutrition. It is based on lessons from other fields (food microbiology, economics and marketing-finance, environmental health, medicine and consumer perception). <http://en.opasnet.org/w/Beparibeian>.

2.1 | Input for the update of the risk–benefit assessment Guidance

The update of the 2010 SC Guidance is based on six lines of input:

(a) feedback from Member States (Section 1.1), (b) the aspects identified in the 2010 SC Guidance that call for caution in interpretation (Appendix B.1), (c) aspects of the Hoekstra et al. (2012) approach (Appendix B.2), (d) developments in the field since then (Appendix B.3), (e) the output of the 26th EFSA Scientific Colloquium (Appendix B.4) and (f) two systematic reviews on risk–benefit communication (Appendix G).

a. MS requested that outputs of RBA be more helpful to risk–benefit managers when issuing FBDG in the context of multiple chemical hazards, nutrients and health effects, that may impact population subgroups differently. Specifically, MS feedback indicated that a comparison of exposure to health-based guidance values (HBGVs)¹⁴ or dietary reference values (DRVs)¹⁵ is not sufficient, and reporting a single composite metric, such as the DALY, to capture the risks and benefits to the population would not help them to understand the overall health impacts and translate the risk–benefit output into FBDG.

b. Based on the aspects identified in the 2010 SC Guidance that need caution in interpretation, reporting the single composite metric together with other outcome parameters is recommended (Section 6), to not lose sight of the complexity embedded into a single value.

As noted in the 2010 SC Guidance, *'it is important that the risk-benefit manager is aware of the limitations of the different metrics used for measuring risks and benefits.'* Going beyond the 2010 SC Guidance, it is important that the uncertainties and assumptions are transparently documented and communicated to inform the risk–benefit manager in decision making.

c. The Hoekstra et al. (2012) approach offers helpful examples for output presentation, identification of RBA specific uncertainties and other aspects that are incorporated in this updated guidance.

d. Building on lessons learned from developments in the field of RBA, the updated Guidance takes into consideration experience reported in the literature. In the Thomsen et al. (2021) review, it was concluded among others, that there is heterogeneity in methods applied in the RBAs reviewed and there is a need for evidence-based, up-to-date and harmonised approaches. These authors also concluded that lack of harmonisation is still considered one of the main challenges for RBA.

A comprehensive analysis of the challenges in performing RBA along with proposals to meet them has been published by Nauta et al. (2018). The proposed approaches to meet the challenges are considered in the updated Guidance.

In these activities, different approaches are followed depending on the question and the purpose of the assessment. Importantly, lessons learned from implementing existing RBA approaches have led to improved procedures that are presented in the updated Guidance.

e. The outcome of the 26th EFSA Scientific Colloquium held in February 2022 re-emphasised the importance of clear problem formulation and highlighted that going beyond the 2010 SC Guidance can be achieved by exploring new approaches and possible refinements of existing methods. It was recommended that the updated Guidance remains flexible to capitalise on future developments in both methods and data.

f. Two outsourced systematic reviews of the social science literature were conducted to inform the risk–benefit communication considerations. The review by Jaskiewicz et al. (2023) covered relevant papers on food-related health risks and benefits from 2018 to 2022, while the report by Rodes-Sanchez et al. (2024) completed data gaps with a focus on consumer trade-offs related to risks and benefits.

3 | AIM OF THE GUIDANCE AND THE UPDATE

This Guidance document aims to provide guidance to scientists conducting RBA on how to address higher levels of complexity and improve consistency and harmonisation among independent assessments.

Guidance is provided for different RBA needs ranging from simple to more extensive assessments. Specifically, the updated Guidance aims to:

- Present the currently available methodological options relevant to comparisons of risks and benefits.
- Outline strategies for assessing multiple risks, e.g. from multiple chemical hazards, and/or multiple benefits that may be impacting different subgroups of the population.
- Allow flexibility for RBA application to different contexts (e.g. foods, novel foods, food replacement, interventions).
- Propose reporting templates to provide detailed information on health effects that assist the risk–benefit manager with prioritising public health needs.
- Include consideration of strength and weight of evidence.

¹⁴HBGV refers to reference values such as the tolerable daily/weekly intake (TDI or TWI) or acceptable daily intake (ADI), for chemical hazards, or the tolerable upper intake level (UL) for nutrients.

¹⁵DRV refers to reference values such as the average requirement (AR) population reference intake (PRI) or adequate intake (AI) for nutrients. UL is included in the definition of both DRVs and HBGVs.

- Include quality and reliability of evidence.
- With respect to risk benefit communication, to provide social science advice and tools to support assessors and managers to contextualise and plan communication of their respective assessment and management outcomes.

Considering the challenges identified and the heterogeneity of the RBA approaches adopted by the scientific community and reported in the literature, the updated Guidance aims to provide a framework of principles that is applicable to a wide range of needs. The specific context of the RBA question can be different, or the priorities may vary substantially among geographic areas. A systematic and transparent approach with adequate documentation and justification of the selections made can help harmonise the RBA process such that the outcomes are evidence-based, well documented and reproducible.

To achieve comparable and consistent RBA results across different contexts and priorities, international harmonisation of the principles for a systematic and transparent approach is needed. Although there are collaborative efforts within the EU, greater harmonisation and scientific cooperation are needed at an international level. At the time of the update of the EFSA Guidance, a parallel effort with similar goals is ongoing by the WHO. Despite different remit and needs, the two authorities aim for an alignment of RBA approaches in the respective Guidance on the basis of principles and methodological transparency.

3.1 | Situations where risk–benefit assessment is relevant

RBA is relevant when both risks and benefits are clearly associated with the consumption of foods. A few examples where an RBA may be applied are presented below. A distinction should be made between RBA and other situations assessing risk–trade-offs, or risk–risk assessments, even though the same methodology can be applied.

Some examples of where both risks and benefits are present are given below:

- Food: A specific food may itself be associated with both health risks and benefits (e.g. meat, brown rice).
- Component: A single component of the food (e.g. vitamin D, folic acid) has both positive and negative health effects.
- Component and food: Risks from the presence of specific contaminant(s) in a food weighed against the benefits of the food (or one or more of its components).
- Diet: A change of dietary patterns (e.g. increase in plant-based foods) or introduction of new foods (e.g. novel foods).

It should be noted that the assessment of nutrients, such as vitamins or minerals,¹⁶ is guided by principles of ‘Acceptable Range of Oral Intake’ (AROI) as described in a 2002 report of the IPCS/WHO (IPCS, 2002). The AROI concept also formed the basis for the development of the guidance for the derivation of HBGVs for regulated products that are also nutrients (EFSA Scientific Committee, 2021a). That guidance takes the range of beneficial effects into account but does not include an assessment of benefits.

In the assessment of foods and diets, it is relevant to include substitution. The changed intake of a food or diet as specified in the intake scenarios, will probably lead to a changed intake of other foods, which will indirectly affect the overall health impact of the food under study. It is, therefore, relevant to include the risks and benefits associated with the change in intake of these other foods in an RBA.

Additional situations where an RBA might be indicated could be:

- Before the start of an intervention, such as folic acid fortification, or fluoridation of drinking water.
- Before introducing a change in food processing procedures, e.g. to reduce microbial contamination, the risk and benefit of the applied heat treatment/UV-irradiation versus chemical treatment are compared.
- Where new knowledge emerges with major implications for either the risk(s) or the benefit(s) in a previous risk assessment, benefit assessment or RBA (e.g. presence of perfluorinated compounds in marine products).

3.2 | Retained and updated aspects of the Guidance

The updated Guidance maintains the overall framework for RBA as presented in Appendix B.1. It also maintains the step-wise approach developed in 2010 and provides additional information on available methodological options and tools for conducting RBAs for different needs. It provides approaches for increased transparency in the selections of hazards and beneficial components of the food to be included in the RBA and for systematically organising the available evidence. The Guidance aims to remain flexible and to guide assessors through different scenarios that may be encountered in the context of regulatory and non-regulatory assessments. The comparative nature of RBAs will require that the impact of different types of health effects is assessed in relation to each other, qualitatively or quantitatively. Since this part of the process involves value-based judgement, it should ideally be performed in collaboration with the risk–benefit manager (Box 1).

¹⁶The term ‘essential trace elements’ is sometimes used synonymously.

BOX 1 Elements of the RBA guidance that have been retained, revised or added compared with the 2010 SC Guidance

Retained:

- Overall RBA framework (Appendix B.1; Section 4.4 – 4.7)
- Tiered approach (“Step” → “Tier”) (§ 4.2)

Revised:

- Problem formulation considerations (Section 4.1; Figure 1)
- Account for severity with clarification on the role of weights in RBA (Section 4.7.3)
- Emphasis on transparency (throughout)
- Distinction of variability and uncertainty (Section 4.8)

Added:

- Approaches for selection and prioritisation of components and health effects (Section 4.3; Appendix C)
- Approaches for assessing multiple health effects (Section 4.6; Appendix D and E)
- Proposals for integrating risks and benefits while reflecting complexity (Section 4.7)
- Mapping stages of the RBA process with respective appropriate methods (Section 5)
- Templates for reporting results (Section 6; Appendix F)
- Communication recommendations (Section 7; Appendix G)

The term ‘Step’ used in the previous 2010 SC Guidance has been changed in this update to ‘Tier’ to harmonise the terminology with broadly recognised terms. This is consistent with the use of this term in other contexts where it implies increasing refinement, such as in exposure assessment (where Tier 1 is a simple assessment, often a worst-case scenario based on maximum limits, and higher tiers involve more refined data and analyses).

Section 4 of this updated Guidance is the main section providing guidance on conducting RBA and is structured in five distinct subsections discussing: (a) problem formulation, including all preparatory steps that refine the problem formulation; (b) description of the Tiered approach; (c) aspects of the RBA, including identification of positive and negative health effects, characterisation of adverse and beneficial effects, exposure assessment and characterisation of risks and benefits; (d) methodologies relevant to the integration of risks and benefits; and (e) variability and uncertainty assessment.

The updated Guidance puts emphasis on the adoption of additional approaches that have been developed since the 2010 SC Guidance and provides an overview of the methods applicable in each of the assessment areas (Section 5). The update also includes more practical guidance on reporting the results of the assessment and on the interpretation of the outcome (Section 6).

Guidance dedicated specifically to communication of the outcome of an RBA has been added (Section 7), based on recent social science projects evaluating consumer perspectives, behaviour and response to advice.

Application of other EFSA Guidance is advised as relevant to the context of the assessment, such as protocol development, combined exposure to multiple chemicals (Mixtures), Read-across, Benchmark Dose modelling, Uncertainty assessment, etc. (EFSA Scientific Committee, 2018, 2021b, 2022, 2023).

4 | CONDUCTING THE RISK-BENEFIT ASSESSMENT

There are several approaches to conducting an RBA. These depend on the context and scope and can range from qualitative to quantitative comparisons of risks and benefits. Before embarking on the assessment of risks and benefits, the assessor(s) is advised to clarify and define the scope of the assessment in the process of problem formulation. If RBA is performed in a regulatory context,¹⁷ the assessor should consult the risk-benefit manager in an iterative manner during this preparatory phase (EFSA Scientific Committee, 2023). In such a case, a tiered approach offers a versatile strategy to proceed through an RBA according to needs and data availability.

The time and resources available to carry out the assessment can impact its feasibility and need to be considered during problem formulation. Data needs and data availability for different aspects of the RBA question may be subjected to a preliminary assessment to help inform the problem formulation or be part of the assessment phase. This can be done with scoping reviews. Since different types of data and levels of refinement are needed in the different RBA tiers, data availability is likely to drive an iterative, problem re-formulation at several stages of the assessment.

Once the problem formulation is completed, the assessor may proceed with the assessment following a tiered approach. This iterative process of the preparatory phase and the progression to the tiered assessment are illustrated in Figure 1.

¹⁷Regulatory context, as used here, includes also policy development.

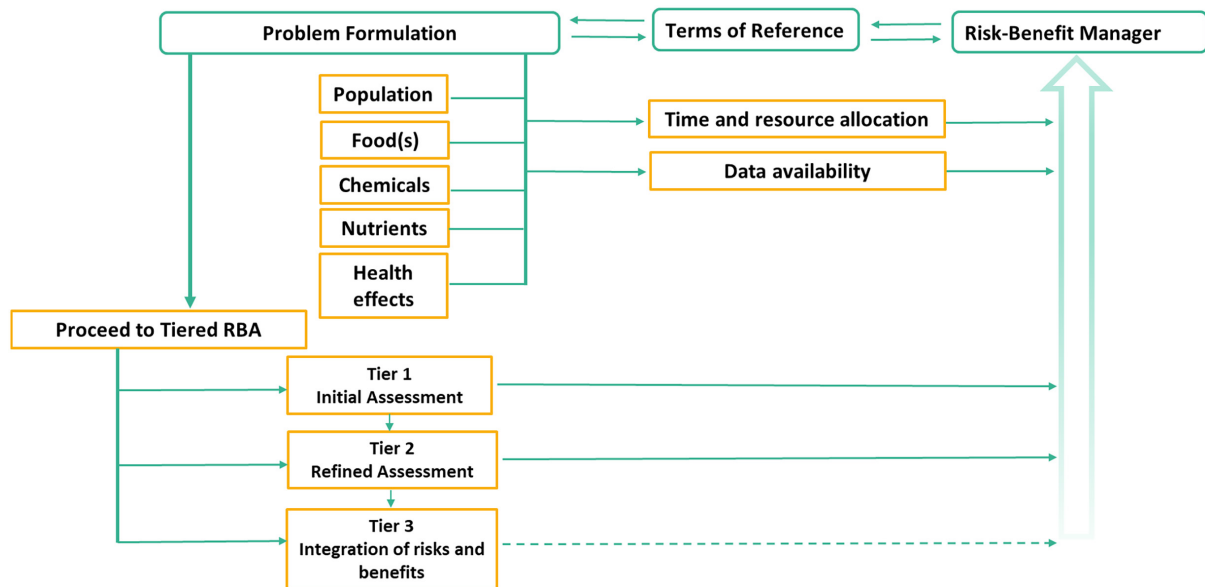


FIGURE 1 Iterative process of problem formulation in consultation with the risk-benefit manager in preparation for conducting an RBA.

4.1 | Problem formulation

The role of the problem formulation is to define the RBA question and the approach to be followed. Typically, when RBA is used within a regulatory framework, the RBA question is developed in a dialogue between the risk-benefit manager and risk-benefit assessor. In cases of RBA not performed in a regulatory framework (e.g. academic or other scientific purpose), the question is defined by the assessor.

The purpose of the RBA describes the overall objective. The scope of the RBA defines the target population (general or population subgroups), the level of aggregation at which it is performed (scale of diet, food(s), specific food components), the level of complexity, e.g. number of food components (e.g. contaminants, nutrients), foods to be assessed, as well as the intake scenarios, in line with EFSA Guidance on protocol development (EFSA Scientific Committee, 2023).

In a regulatory context, the compounds, foods or even the health effects of interest are defined by the requestor, e.g. the risk-benefit manager. In most cases, whether regulatory or not, the health effects relevant to the RBA are identified and characterised during the RBA process (see below).

The overall context and the scope as defined above, determine the methodological approaches that can be applied. The reasoning and considerations involved in the problem formulation, the selections of what is included in the assessment and assumptions made during the problem formulation should be transparently documented and justified as these aspects have an impact on the outcome of the assessment, its interpretation and implementation (Boué et al., 2022; Nauta et al., 2018; Ververis et al., 2024).

When embarking on an RBA, a number of questions should be addressed to frame a concise problem formulation. Table 1 provides some examples.

TABLE 1 Questions framing the problem formulation.

Questions that frame the problem formulation	Examples
What is the purpose of the assessment?	<ul style="list-style-type: none"> FBDG, dietary interventions, assessment of foods as part of a healthy diet, scoping before introducing a new food, change of food processing, assessment of whole diets, food replacement: substitution of one food with another, or one food component with another.
What is the scope of RBA?	<ul style="list-style-type: none"> Characterisation and specification of food components, foods or diets to be assessed. Definition of the target population (general population, or (sub)populations like elderly, women in the childbearing age, children, etc.). Definition of reference and alternative intake scenarios to be investigated and compared, where the reference scenario may be the current intake or a zero-intake level. Decision on whether to use individual data of dietary exposure or summary estimates. Decision on whether food substitution should be considered.
What are the boundaries and limitations of the RBA?	<ul style="list-style-type: none"> Inclusion or exclusion of specific population groups. Inclusion or exclusion of specific food components. Clear specification of assumptions made.

It is essential to identify, based on the needs of the risk–benefit manager, the type of RBA needed in terms of the level of refinement. If the risk–benefit manager wants to know if the risk–benefit balance as such is changed in response to one scenario or another, a qualitative outcome may be sufficient. Conversely, if the context is complex and quantitative information is needed, the RBA should identify not only if the risks outweigh the benefits or vice versa but also by how much the risks outweigh the benefits or vice versa.

In conclusion, a clear understanding of the overall purpose and scope of the RBA is needed and to list all the assumptions made. The problem formulation is an iterative process, and it is recommended to revisit it once a preliminary assessment has been conducted to refine the questions further, if necessary.

4.2 | Tiered approach to risk–benefit assessment

As in its previous Guidance on RBA in 2010, the SC recommends applying a tiered approach to the RBA to avoid complex assessments if not needed. More specifically, the different tiers relate to the level of detail needed to resolve a particular question, which may become more (or less) complex depending on the number of risks and benefits involved. For example, is a screening-level approach (Tier 1) enough? Are refinements using indirect (non-effect size based) measures of risks and benefits (Tier 2) adequate, or is an assessment of actual effect levels (Tier 3) at relevant exposures needed to conclude on the assessment question? Data requirements increase from low to high tiers. The use of internationally established methods and guidance applied within traditional chemical risk and nutrient assessments may not cover all aspects needed to perform an RBA. For example, approaches for comparing different types of health effects can be needed to balance the considered risks and benefits (Sections 4.6 and 4.7). Risks and benefits can be qualitatively or, ideally, integrated quantitatively (e.g. using a composite metric) at both Tiers 2 and 3. Below, a short description of the different tiers is given.

Tier 1 represents an initial RBA intending to see whether it is possible to conclude if the risks clearly outweigh the benefits (risks \gg benefits), i.e. when risks appear at low exposures (e.g. P5) while benefits are seen at high exposures (e.g. P95), or the benefits clearly outweigh the risks (risks \ll benefits), i.e. when benefits are seen at low exposures while risks are seen at high exposures (Figure 2). This is usually done using existing individual assessments for risks and benefits for relevant food components at upper and lower bounds of exposure. To make such a comparison, all relevant factors related either to a potential health risk or to a potential health benefit need to be considered (e.g. is it an apical effect or a biomarker of effect,¹⁸ what is the nature and severity of the effect, who is the affected (sub)population, etc.). If more than one risk and one benefit are to be assessed, risk ranking, and benefit ranking may help to conclude on the outcome. More details on ranking approaches and the typical approach to a Tier 1 assessment are given in Sections 4.3 and 4.6, respectively. If this initial assessment leads to a clear conclusion, then no further action is needed. However, if it is inconclusive, a refinement is needed and the assessment proceeds to Tier 2 (Figure 3).

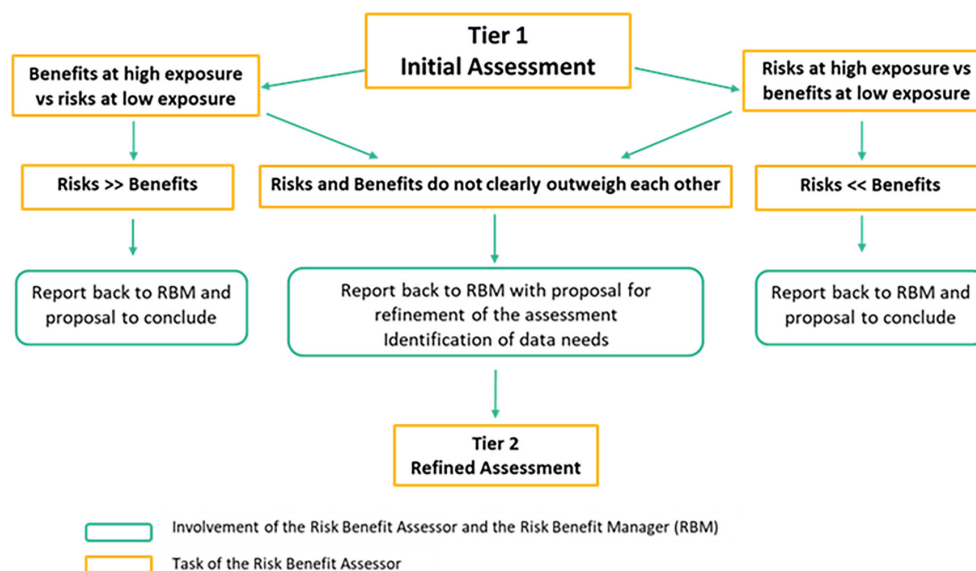


FIGURE 2 Tier 1 process of risk–benefit assessment.

¹⁸According to the definition by the WHO, a biomarker of effect refers to a measurable biochemical, physiological, behavioural or other alteration within an organism that, depending upon the magnitude, can be recognised as associated with an established or possible health impairment or disease (EFSA Scientific Committee, 2017a; WHO/IPCS, 1993). A biomarker may be associated with a risk or a benefit. It is the direction of the association that determines whether the relationship reflects an adverse or beneficial outcome. See EFSA's ongoing work on developing a guidance for the use of biomarkers of effect: <https://open.efsa.europa.eu/study-inventory/EFSA-Q-2023-00583>.

Tier 2 aims to refine the assessment using indirect (non-effect size-based) measures of risks and benefits. For example, the number of individuals with exposure to food components above or below HBGVs and DRVs can be characterised, accounting for population variability and/or uncertainty (see Section 4.6.1). Tier 2 can also be used to derive semi-quantitative or quantitative estimates of risks and benefits at relevant exposures. This would need the use of a common or a composite metric. In Tier 2 the latter could, for example, be a comparative margin of exposure (see Section 4.6.1), or in case of multiple effects, severity-standardised approaches for a combination of data can be consulted (see Section 4.6.2). Alternatively, if risks and benefits are in different non-comparable quantitative units, a qualitative approach for their integration is needed (see Section 4.7.1). This includes the case of risks and benefits at different tiers, e.g. a margin of exposure describing indirect risk (Tier 2) compared with reduced disease incidence or mortality describing benefit (Tier 3). If a conclusion on the problem formulation cannot be reached on the basis of this refined assessment, e.g. the outcome of this refined assessment does not clearly indicate that the risks outweigh the benefits (risks >> benefits) or vice versa (risks << benefits), the assessment proceeds to Tier 3 (Figure 3).

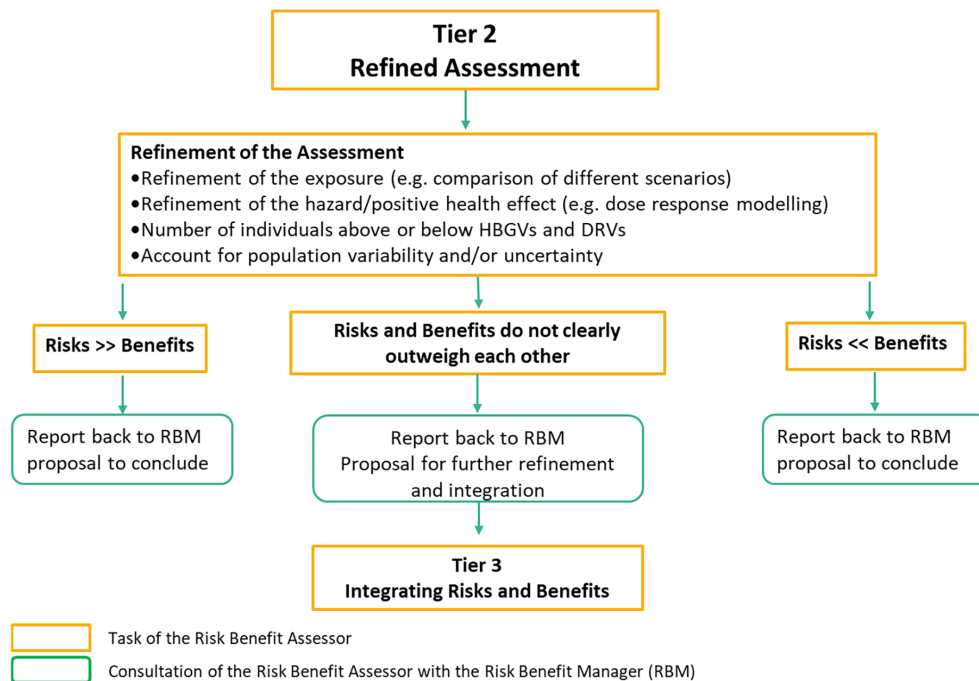


FIGURE 3 Tier 2 process of risk–benefit assessment.

Tier 3 aims to refine the assessment further using direct (effect size-based) measures of risks and benefits, i.e. the probability of a health effect/disease or the mean response for a continuous health effect. This generally requires more detailed data than at Tier 2, but similar to Tier 2, population variability and/or uncertainty may be accounted for, and a common or composite metric is applied. Typical Tier 3 composite metrics account for several dimensions of a health effect, e.g. incidence, severity, duration and mortality (Hoekstra et al., 2012) as described by the DALY. Composite metrics like the DALY might be applied in the case of single or multiple risks and benefits (Section 4.7.2). For assessments involving multiple effects, severity standardised approaches for a combination of data, covering disease endpoints, as well as related risk factors can be considered (Sections 4.6.2 and 4.7.2). As an alternative to using common or composite metrics, a more straightforward approach would be to list the evidence on the risks and the benefits in a qualitative integration approach. It should be noted that quantitative Tier 3 approaches require detailed data describing disease and/or other risk factors that might not be readily available, and new data may need to be generated. Sections 4.6 and 4.7 on characterisation and integration of risks and benefits provide more information on methods and approaches related to Tiers 1–3. It should be noted that while Tiers 2 and 3 describe different levels of detail in the data/metrics used, the resources needed to conduct an assessment are also likely to be determined by the level of complexity, e.g. in terms of how many risks and benefits need to be considered as part of the assessment. In all cases, the strength of the evidence together with the uncertainties in the estimations should be described and quantified to the greatest extent possible (see Section 4.8). This is particularly relevant when the quality of the data differs between hazards and benefits.

The SC emphasises that for regulatory assessments, after the completion of each tier by the risk–benefit assessor, a discussion should take place with the risk–benefit manager on whether sufficient information and detail supporting the outcome has been provided and whether the assessment can stop. If this is not the case, new terms of reference need to be agreed upon in order to proceed with the next tier.

While the risk–benefit assessor is responsible for evaluating the evidence available for both risks and benefits, the risk–benefit manager concludes whether the outcome is adequate to make decisions.

For all the tiers in the RBA, the rationale for following a certain approach and for selecting specific parameters should be clearly described. The RBA should include a description of the assumptions and uncertainties and explain the outcome. This will help the risk-benefit manager to understand its relevance in relation to the management decisions made.

4.3 | Selection of components and health effects relevant to the risk-benefit assessment

When conducting an RBA, the identification and selection of diet, and/or food, and/or food components with their associated possible health effects (see Appendix A – Glossary) are the key first steps. The RBA question and terms of reference will shape the scope of the assessment. This includes the selection of foods, components and health effects, the relationship of which is shown in Figure 4.

In certain situations, the RBA question and the terms of reference will directly include the foods and/or components to be considered. If this is not the case, it will first be necessary to clarify the level at which the RBA is carried out, i.e. whether it considers a diet, foods and/or components (Figure 4). At the diet level, foods that make up the diet will have to be defined, and then the components of each food. For specific foods, the identification of food components, nutrients and potential hazards is also needed. The health effects associated with either the diet or foods or components selected have to be defined.

When conducting RBA of specific foods or diets, it may be relevant to establish a reference food comparator or define a reference diet, considering that changes in the consumption of specific foods rarely occur without modifications to the rest of the diet. Understanding the resulting changes in dietary consumption patterns helps establish a comparative basis for evaluating the associated risks and benefits (Ibsen et al., 2021).

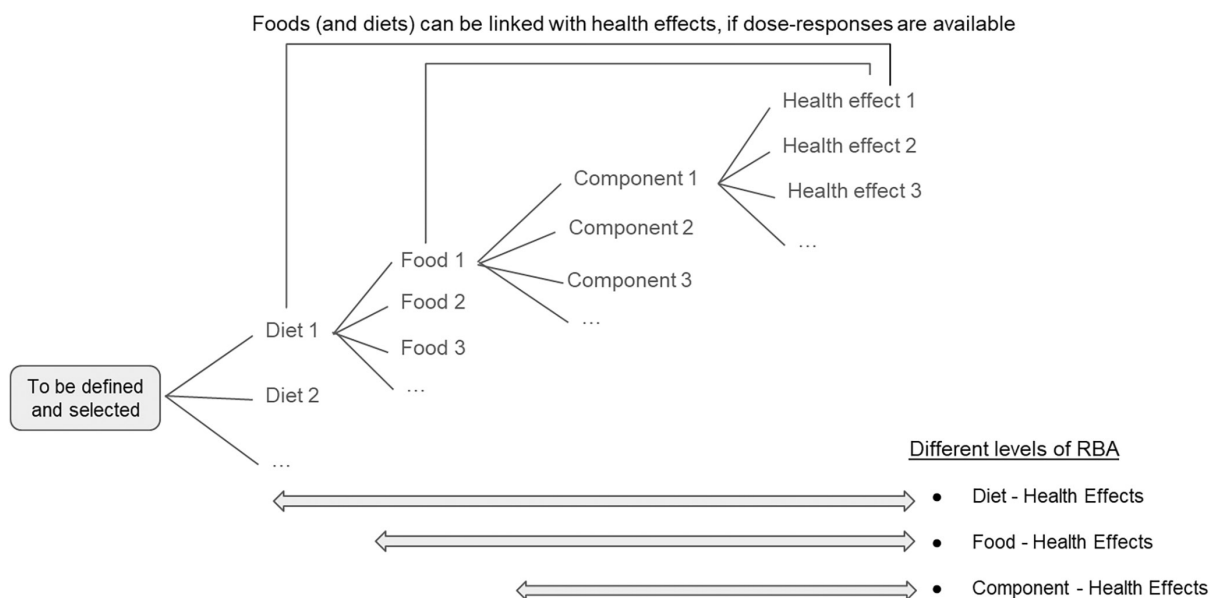


FIGURE 4 Representation of the different levels of RBA and links between 'diet – food – components – Health effects' to be defined and selected.

4.3.1 | Identification of foods, components and health effects

The stage of identification of food components may apply differently to benefits and risks. In the context of nutrition, the nutrients in various foods may be well defined, but in the context of toxicology, it is important to specify which chemical hazards are identified as relevant to the RBA.

When identifying health effects for an RBA, the first step should be to consult existing assessments of diet, foods or food components. These assessments are typically carried out by entities such as EFSA, national authorities, WHO or other recognised national and international agencies and health authorities. Assessments done by such authorities can typically lead to establishing DRVs for nutrients and HBGVs for chemical hazards and they generally provide robust assessments for health benefits and risks, respectively.

4.3.2 | Data sources

The identification of food components and health effects depends on data availability and requires expert judgement and decisions. It is stressed to report clearly and transparently any choice. Different sources may include:

- Existing assessments from national and international authorities;
- Systematic literature reviews from individual research groups and institutions;
- Original research articles (literature search and appraisal, synthesis of evidence...);
- Data repositories (individual data, synthesis of evidence...).

Focused systematic literature reviews carried out by individual research groups or institutions (e.g. IARC, NASEM) addressing either risks or benefits can be used as initial screening tools for identifying possible risks and benefits. When relying on existing systematic reviews, it is important to thoroughly evaluate both the original research question and the resulting inclusion/exclusion criteria. Furthermore, the methodological quality of the systematic review needs to be checked carefully, ideally through the use of critical appraisal tools (e.g. AMSTAR 2, ROBIS, ROB-ME). If well conducted, systematic reviews may be particularly helpful for identifying the health effects related to food intake. This approach is often necessary when established health effects cannot be directly attributed to one or several specific nutrients. For instance, assessing the potential benefits of consuming legumes in terms of reduced cardiovascular disease risk (Mendes et al., 2023) may require considering the holistic impact of the entire food rather than isolated individual nutrients.

If it is judged that existing opinions and assessments from public health authorities or available systematic reviews do not provide sufficient information on possible risks and benefits, it may become necessary to conduct independent assessments, e.g. when existing assessments or opinions from public health authorities require updating. It is acknowledged that such new literature searches and evidence syntheses are both time-consuming and resource-intensive.

In summary, the use of existing assessments from public health authorities is encouraged. Existing systematic reviews can also be a valuable source of information. Before use, systematic reviews need to be appraised for methodological quality. New literature review and evidence synthesis may be needed in cases when it is known that substantial new literature is available that has not been considered in previous assessments.

Unlike the process of establishing HBGVs based on the most sensitive endpoint in the most sensitive population group, all potential effects that may occur within a relevant range of exposure(s) are relevant for RBA. To address potential risks that may occur in a wider segment of the population, other adverse effects at higher doses could serve as candidate endpoints in the RBA. For example, in the case of PCDD/Fs and DL-PCBs (EFSA CONTAM Panel, 2018), the HBGV is based on the effects of decreased sperm concentration in males, taking exposure through breastfeeding into consideration. At higher doses, other effects such as changes in sex ratio and developmental enamel defects in teeth may occur as well. These effects may be also considered in the RBA. Similarly, DRVs usually provide robust assessments of well-established nutrient benefits for a specific health outcome. When expressed in terms of average-nutrient requirements (AR), such values allow for a direct quantitative assessment for risk of deficiency if exposure assessment is available, thereby providing a direct measure of risk at specific intake. For other DRVs such as adequate intake (AI), the applicability of such values for quantitative assessment is less clear. Similar to the example on PCDD/Fs and DL-PCBs, assessments on DRVs usually include a thorough assessment of several health endpoints that can also be used for RBA assessment. For example, for vitamin D, the upper intake level (UL) is based on all population groups above the age of 1 year on persistent hypercalciuria (EFSA NDA Panel, 2023) while different considerations were made for infants < 1 year (EFSA NDA Panel, 2018).

4.3.3 | Ranking and selection of foods, components and health effects

For transparency, the assessor is advised to document clearly and justify how the selection of food, food components and associated health effects is made. The documentation should include details of the specific criteria and rationale upon which these ranking and selections are made. One example of such prioritisation is the 'Risk Thermometer' developed by the Swedish Food Agency (SFA, 2015). This approach is based on a severity-adjusted margin of exposure approach, for prioritising chemical hazards (see Appendix D). In the context of RBA, a systematic stepwise approach was developed by Boué et al. (2022), starting with a compilation of a 'long list' of food components identified through systematic literature search of nutrients, chemical and biological hazards. Then, the ranking and selection of relevant components are applied in a structured way based on predefined criteria. Through iterative revisions, a 'final list' of food components is selected considering, for instance, strength of evidence, dose-response and levels of intake (Boué et al., 2022; Ververis et al., 2024) (see Appendix C). A similar prioritisation methodology is published by the national food safety authority in France (ANSES, 2020).

4.4 | Characterisation of adverse and beneficial health effects

Characterisation of adverse and beneficial effects refers to the evaluation of their dose-response relationship. For binary (yes/no) health outcomes, this relates to their probability of occurrence across the range of measured (observational) or assigned (experimental) exposures. For continuous health effects (e.g. blood pressure or blood lipid levels), the dose-response reflects the magnitude of change associated with higher or lower exposure. When characterising risks and benefits, relevant guidance documents should be consulted. These may include guidance on benchmark dose modelling, biological relevance, the weight of evidence (WoE) and assessment of combined exposure to multiple chemicals (EFSA Scientific Committee, 2017a, 2017b, 2021b, 2022). From the side of nutrition, comprehensive guidance also exists on approaches for establishing DRVs including ULs (EFSA NDA Panel, 2010, 2022).

Deviating from such guidance needs to be justified (see Section 4.4.1). Furthermore, dose–response relationships may, by convention, be performed differently for risks and benefits. This is due to the different sources and nature of the evidence being used (e.g. human versus animal studies) and the size of the evidence base.

Similar to the risk assessment process, characterising beneficial effects in RBA results in recommended minimum or maximum thresholds that protect from deficiency or toxicity, respectively. However, it is recognised that as exposure levels change, the health effects (positive or negative) that may be observed at high exposure levels may be not only quantitatively (higher frequency or severity of the same effect) but also qualitatively different from those observed at low levels. Each of these effects can have a dose–response relationship with a food component or a food. Therefore, the nature of all potential effects along the range of relevant doses or exposures may also be characterised. Whether positive or negative, these health effects associated with food components or foods included in the RBA can be systematically mapped along the range of low- to high dose levels (or exposures) and characterised for their relationship to dose, e.g. by categorical regression or methods in Sand et al. (2018) and Sand (2022) (see Figure 5; Appendix D).

4.4.1 | Characterisation of adverse health effects

For chemical hazards, hazard characterisation is usually based on a few key studies judged sufficiently robust to assess dose–response relationships. The source data can generally be from either human or animal studies. Human observational studies usually cover a continuum of exposure levels, but the observed dose–response relationship may be, to varying degrees, affected by biases that can occur in an observational setting.

When performing a quantitative RBA at Tier 3 to estimate the size of the health impact following a change in food consumption, the aim is to compare the observed adverse and beneficial health effects. Under such an approach the HBGV is not used directly but the data underlying its establishment are considered. The HBGV can be helpful in a qualitative/quantitative RBA at Tier 1 and 2 where the aim is to assess the number of individuals above the HBGV, or similar.

The EFSA Guidance on benchmark dose modelling (EFSA Scientific Committee, 2022) describes dose–response modelling approaches for identifying the reference point (RP), for establishing HBGVs. In the case of RBA, some deviation of the use of that guidance may be needed compared with its intended application for identifying an RP for establishing a HBGV. When the aim is to compare benchmark doses across risks and/or benefits, the central estimate (i.e. the benchmark dose, BMD) is a more appropriate measure than the lower bound of the BMD. The upper and lower confidence intervals (e.g. BMDL–BMDU) then provide a direct measure of uncertainty around the BMD.

Another important aspect that may require deviation from procedures used for establishing HBGV is the use of default uncertainty factors when, e.g. adverse effects are characterised using animal studies. Default uncertainty factors are used to minimise risk taking into consideration the uncertainty of the animal to human extrapolation and interindividual variability. The objective of the RBA is to accurately quantify and compare risks and benefits. When relying on animal data, more accurate animal-to-human extrapolation (than the default uncertainty factor, UF, of 100) may be achieved through the use of toxicokinetic data and/or physiologically based pharmacokinetic (PBPK) modelling.

In the absence of reliable dose–response data or when extrapolating dose–response data from animal studies to corresponding adverse effects in humans is uncertain, existing HBGV may be used as an indirect or qualitative measure of adverse effects.

4.4.2 | Characterisation of beneficial health effects

The characterisation of beneficial health effects may refer to individual nutrients, other food components or the whole food. For nutrients, the beneficial health effects are usually characterised by assessing the dose–response relationship of effects resulting from nutrient deficiency (see Appendix A for the definition of benefit). By convention, data obtained from experimental and observational studies in humans are most often used for the benefit characterisation of either food components or whole foods. Several approaches for assessing evidence of beneficial effects, tailored to different purposes, have been developed (Aggett et al., 2005; WCRF/AICR, 2007; WHO/FAO, 2003).

In contrast with chemical hazards, dose–response assessment for nutritional benefits often relies more on dose–response meta-analysis or merging of several data sets. Modelling individual studies can also be applied. Due to the U-shaped dual risk relationships of most nutrients, the use of the BMD approach is not directly applicable (EFSA NDA Panel, 2022; EFSA Scientific Committee, 2022).

As mentioned before for DRV, the AR (i.e. the level of a nutrient in the diet that meets the daily needs of half the people in a typical healthy population) and the corresponding population reference intake (PRI, i.e. the level of nutrient intake that is enough for virtually all healthy individuals in a group) provide quantifiable measure in terms of risk of deficiency. However, if the underlying data are not robust enough to establish an AR, the resulting DRV can be set on the basis of risk reduction. This includes the AI (i.e. average nutrient level consumed daily by a typical healthy population that is assumed to be adequate for the population's needs). The AI is set to ensure sufficient intake, but it does not usually provide a quantifiable measure in terms of risk of deficiency or other health effects. The tolerable upper intake level (UL) is the maximum level of total chronic daily nutrient intake from all sources which is judged unlikely to pose a risk of adverse health effects to humans. For nutrients for which there are no, or insufficient, data on which to base an UL, a safe level of intake can give

an indication of the highest level of intake where there is reasonable confidence in data on the absence of adverse effects (EFSA NDA Panel, 2022). However, the application of safe levels of intake for risk assessment and risk management is more limited than an UL because the proportion of people at risk of adverse effects in a population cannot be estimated, as the intake level at which the risk of adverse effects starts to increase is not defined. At intakes between the PRI and the UL, the risks of inadequacy and of excess are both considered to be close to zero. As with HBGV for chemical hazards, the underlying health endpoints used to establish DRVs often provide a logical first step in prioritising relevant health effects for nutrient benefits.

4.4.3 | New approach methodologies for identification and characterisation of health effects

New approach methodologies (NAMs) have the potential to add value in both hazard identification and hazard characterisation. They provide more specific or detailed biological information than traditional animal models. They can provide relevant information to substantiate the biological relevance of exposure–effect associations. Therefore, they can also be adapted to the identification and the characterisation of adverse and beneficial effects within RBA. With respect to the identification of effects, NAMs have the potential to predict the effects of chemical substances in the organism based on their activity, employing in chemico, in silico or in vitro methods (Cattaneo et al., 2023). An important advantage of NAMs is their capacity to provide a mechanistic understanding of the chemical–biological interactions across various levels of biological organisation (Blaauboer et al., 2016; Karmaus et al., 2020).

Although substantial efforts have been made to incorporate data from NAMs into chemical risk assessments, their application in the context of RBA, especially for the purpose of identifying and characterising benefits, still requires further demonstration and validation.

4.5 | Exposure assessment

Exposure assessment is a key component of any RBA. Usually, the term exposure assessment is used in relation to chemical hazards and most often the interest is in consumers with high exposures. The term intake assessment is usually used in relation to nutrients, where the interest is in consumers with both high and low intakes. In this guidance, the term exposure assessment relates to both chemical hazards and nutrients. As for all exposure assessments, data on food consumption and food component concentrations are minimum requirements. Food consumption data are usually obtained from national dietary surveys. The EFSA Comprehensive European Food Consumption Database (EFSA Comprehensive Database) provides a compilation of existing national information on food consumption at the individual level and was first built in 2010 (EFSA, 2011b; Huybrechts et al., 2011; Merten et al., 2011). Details on how the Comprehensive Database is used are published in the Guidance of EFSA (EFSA, 2011b). These individual consumption data allow modelling distributions for consumption and the associated uncertainties, but the access to those data is restricted. EFSA therefore developed a set of dietary exposure tools (e.g. DietEx, FAIM), which are based on the data from the EFSA Comprehensive Database. Nutrient and chemical concentration data are typically obtained from national or regional monitoring, which are collected and compiled into EFSA databases. When specific data are not available to EFSA, targeted data requests may be needed. Concentration data may also be found in the peer-reviewed literature, but care must be taken to assess their representativeness and their reliability. In all cases, validated data and details of the analytical methodologies used are needed.

In low tier exposure assessment, using conservative screening methods, food consumption is evaluated using aggregate data at the population group level in combination with point estimates of the occurrence of hazardous or beneficial food components of interest (e.g. chemical hazards, nutrients, etc.) (EFSA, 2011a). If available, biomonitoring data at population group level can also be used to strengthen the understanding of the relationship between external and internal doses. In a refined exposure assessment, however, detailed, individual-level data are needed for consumption and/or biomonitoring data. In addition, more detailed occurrence data of the components of interest are needed, including, e.g. their variability in foods of different origin, production methods, processing, etc. (e.g. occurrence of chemical hazards and nutrients in different types of fish, in farmed or wild-caught, location of catch, origin of fish, seasonal variability, etc.). Several uncertainties and sources of variability may be quantified in probabilistic models of exposure due to multiple hazards in multiple foods, accounting for correlations in the multivariate distributions (Ranta et al., 2021). For Tier 2 or 3 assessments, more detailed data and refined exposure assessment should be prioritised.

The assessor can consult guidance documents and tools to conduct an exposure assessment. Exposure assessment guidance has been published by IPCS (FAO/WHO, 2009), while EFSA makes publicly available exposure tools that are updated over time.¹⁹ Depending on the scope of the RBA, exposure assessment may be conducted for the reference scenario and alternative exposure scenarios, provided that concentration or food consumption data are available for both scenarios, selected by the risk–benefit assessor and risk–benefit manager.

¹⁹EFSA's Assessment Tools and Resources available at <https://www.efsa.europa.eu/en/science/tools-and-resources>.

The risk–benefit assessor should consider all relevant food components for varying amounts of a given food consumed and prioritise each compound in a stepwise manner. EFSA's guidance on chemical mixtures may be a useful reference in some cases (EFSA Scientific Committee, 2021b).

4.6 | Characterisation of risks and benefits

An overview of the methods and approaches discussed in this section is provided in Tables 2 and 3 (Section 5).

As a starting point, within the Tier 1 assessment, the characterisation of risks and benefits can be performed on the basis of existing HBGVs and DRVs, i.e. an approach similar to that taken in traditional risk assessment. The HBGVs are typically established using a conservative approach, i.e. overestimating risks to ensure the protection of the population. The conservative nature of the HBGV arises, e.g. from the application of uncertainty, adjustment or extrapolation factors. Under a Tier 1 assessment, generally, conservative estimates of the human dietary exposure are then compared with the HBGV. An apparent advantage is the possibility to rely on already established HBGVs. Besides supporting a Tier 1 assessment, this standard approach can also assist in the identification of the most important, or practically relevant, risks and benefits, along with methods discussed in Section 4.1 (Boué et al., 2022; SFA, 2015).

For chemical risks, in cases where an HBGV cannot be established (e.g. due to lack of appropriate data) or is not appropriate (as for genotoxic carcinogens),²⁰ the principles of the margin of exposure (MOE) approach may be applied. MOE is the ratio of an RP to the population exposure, and the higher it is, the lower the risk concern.

On the other hand, a Tier 3 assessment involves the direct characterisation of risks and benefits independently based on specific morbidity or mortality rates (reflecting the number of cases or deaths), probability of effect or effect levels at relevant exposures in a population or subpopulation. In cases where the risk–benefit question requests a quantitative estimate of the magnitude of the health impact of a change in food consumption, using either a common or composite metric is needed. A common metric describes a specific single health effect that may improve or worsen as a result of exposure, while a composite metric has a multidimensional basis, e.g. accounting for the fact that risks and benefits may represent different health effects. Depending on the considered health effects, these approaches also enable the estimation of the burden of disease. Composite metrics related to such analysis are further discussed in Section 4.7 on the integration of risks and benefits.

In order to broaden the options for risk and benefit characterisation, the methods discussed in the subsections below may be considered. These approaches can also provide a type of composite metric, since they account for the nature/severity of the health effects considered, supporting Tiers 2 and 3.

4.6.1 | Methods that address variability and uncertainty

A refinement to Tier 1 assessment is to take into account population variability and/or uncertainty in the HBGV and/or the exposure. This refinement can be introduced at Tier 2 and helps to clarify if there is a relevant exceedance of the HBGV. For example, the WHO/IPCS (2014) recommends a 'probabilistic HBGV' and proposes a 'target human dose', HD_M^I , defined as the dose at which a fraction I of the population experiences an effect of magnitude/severity M , or greater, for the critical effect. The uncertainty in the RP and the adjustment factors are quantified and combined, resulting in an uncertainty distribution for the HD_M^I . The WHO/IPCS (2014) presents three different approaches; i.e. a non-probabilistic approach, an approximate probabilistic approach (implemented in a spreadsheet tool, 'APROBA') or a fully probabilistic approach to derive HD_M^I . The fraction I in the HD_M^I refers to the population variability in the HBGV, and M describes the response (i.e. the benchmark response, BMR) associated with the RP when it is estimated using the BMD method.

The WHO/IPCS approach, focusing on uncertainty is based on work by van der Voet and Slob (2007), for example. They have described how both variability and uncertainty may be accounted for in both the HBGV and the exposure. These principles for addressing variability and/or uncertainty may also be used more broadly to refine other methods related to both Tier 2 and 3 discussed in this guidance (Appendix D gives one example of this).

There are differences in how variability and uncertainty are quantified (EFSA Scientific Committee, 2018). Quantification may be assumption-based (e.g. distributions anchored to common default uncertainty factors based on expert choice) or data-based (e.g. frequentist confidence distributions or Bayesian uncertainty distributions derived explicitly from data). Also, variability can have several nested levels, some of which could be quantified with empirical data or assumptions.

The WHO/IPCS (2014) attempts to make the choice of the BMR associated with the HBGV more explicit and transparent. Similarly, EFSA Scientific Committee (2022) and WHO (2020) argue that the value of the BMR should be endpoint-specific. Using BMRs that account for the nature of the underlying health effect, in order for associated HBGVs and DRVs to represent similar (absolute) severity levels, would further refine this type of Tier 2 assessment. This allows a form of composite MOE metric to be derived as the health effects involved would be considered. For example, it has been argued that the type of development proposed by the WHO can support risk–risk and cost–benefit analysis (Chiu et al., 2018).

²⁰<https://www.efsa.europa.eu/en/topics/topic/margin-exposure>.

4.6.2 | Methods for addressing multiple effects

While an RBA may be based on one risk and one benefit, there will be cases when it is necessary to cover several effects that may also refer to different food components. This can be done by considering each effect separately using any of the approaches discussed earlier in this section. In addition, there are methods that allow for the combination of data for different effects across the dose continuum. Such methods can help to assess various outcomes in a systematic manner, such as allowing for estimating the probability related to several types of health effects for a given exposure and the consequence of a gradual increase in exposure can be broadly characterised. Figure 5 shows an example of modelling the range of benchmark doses for interrelated effects associated with a mixture of food components. Standardised scoring systems (Figure 5, y-axis) by which data are combined enable comparison of results (probabilities) between chemical hazards, and can support comparison to separately derived results for other food components (see Section 4.7.2 on integration). These approaches also facilitate the combination of data from multiple studies in a single analysis (meta-analysis). This can, for example, be useful when an individual study provides limited dose–response information.

Categorical regression has been used to combine data, from both toxicological and epidemiological studies, describing different health effects by developing a severity scoring system (Section 4.7.3 for weighting of effects) to place the various outcomes on a common scale. While its application in RBA has been limited so far, this method can estimate the likelihood of different categories of severity for given exposure conditions. The severity categorisation of the effect data that populates this model is generally a function of both the nature of the health effect as well as the level of response observed (e.g. a certain per cent increase in the incidence of some lesion). Categorical regression is regarded to apply to Tier 3 since effect levels are typically considered to be part of this method (see Section 4.7). The US-EPA has developed a software package called CatReg (US EPA, 2017) and categorical regression has, for example, been applied to estimate the dose–response for manganese (Milton et al., 2017).

Sand et al. (2018) describe another approach for a combination of data for which the nature of the health effect and the level of response are treated as two distinct variables (Figure 5). In this case, severity is a relative term that refers to the nature of the health effect only, and the model may be evaluated at a particular response level (Tier 2), i.e. at the same BMR, or across the whole response domain (Tier 3). In the former case, the method is a form of generalisation of a traditional approach that considers RPs for multiple effects in a joint fashion. It can be part of an extended Tier 2 assessment that evaluates the probability of exceeding these RPs at given exposures. As part of the method, the RPs which are associated with lower to higher order effects, are organised according to a categorical (relative) severity scale (Figure 5, severity categories C1–C9). A summary response can also be estimated by integrating contributions across effects. As described in Sand et al. (2018), by adding a model for the dose–response curve, a generalisation is obtained so that the response metric describes the probability of effect/s rather than the probability of exceeding associated RPs. This extension of the model applies to Tier 3 (see Section 4.7). The method was first illustrated for traditional animal data and later adapted to allow the combination of BMDs from short-term toxicogenomic studies in rodents (Sand, 2022). See Figure 5 and Appendix D for more information, including a case study for application within RBA that uses human (epidemiological) data.

While the methods discussed have been proposed for assessing chemical risks, the model outputs may, due to their standardised nature, also help to quantify and characterise benefits. This is further discussed in the section below on integration of risk and benefits. Also, work more broadly in the area of risk ranking (Chen et al., 2013; Lindqvist et al., 2020; Van der Fels-Klerx et al., 2018) can be consulted in the process of characterising multiple risks and benefits. In this context, the conclusion from an international workshop noted, e.g. that both probability and severity are important aspects to be included in a risk comparative framework (Sand, 2022).

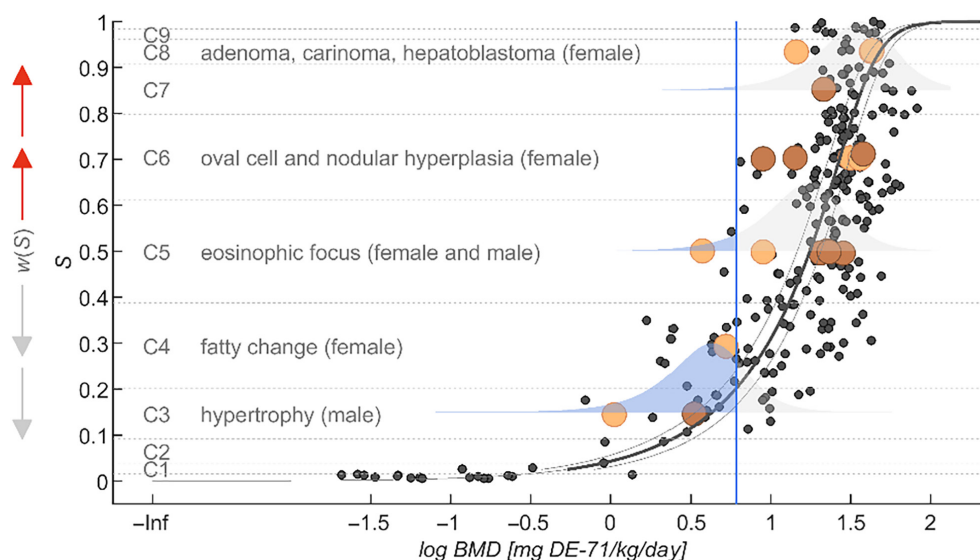


FIGURE 5 Joint assessment of multiple effects.

Combination of BMDs for several long- and short-term effects of pentabromodiphenyl ether mixture (DE-71) in rats. Large orange circles are BMDs based on long-term data from the NTP (National Toxicology Program) (2016) – light circles are BMDs for liver lesions, and dark circles are BMDs for effects in other organs. Small black circles are gene-level BMDs from liver transcriptomic data in the same rat strain (Dunnick et al., 2018). BMDs correspond to a 10% excess probability of response ($BMR = 0.10$).²¹ In this example, data are described by a common model – the solid curve with associated blue/grey distribution. For the long-term data, it characterises the relation between BMD and relative severity (category C1–C9, mapped to S). For the short-term data, it portrays BMD variability within (solid curve) and between (blue/grey distribution) gene sets. The probability of exceeding the BMD (blue areas) can be evaluated at a given exposure/s (vertical line). Probabilities across S (y -axis) may also be integrated/summarised by utilising the attached weight function, $w(S)$. This function can be used to modify relations between the severity categories (long-term data) or genes/gene sets (short-term data), e.g. to support sensitivity analysis of the integrated probability. See Appendix D for the generalised model. Details can be found in Sand (2022) [Note: compared with (Sand, 2022), the (blue/grey) distribution is generalised logistic rather than normal, and the model is fitted with the maximum likelihood rather than the least squares method].

4.7 | Integration of risks and benefits

4.7.1 | Qualitative methods

The methods discussed for the characterisation of risks and benefits (Section 4.6) can potentially be applied across both risk and benefit domains. However, depending on the selected metric the integration of risks and benefits may need to be qualitative in nature. In this context, the term qualitative implies that the integration of risks and benefits relies on value-based judgement without using any weights or similar. Combining risk and benefits qualitatively does not place any constraint on the metric used within each domain. For example, in a qualitative integration, it may be assessed that the number of reduced disease cases (benefit, Tier 3 metric) under a certain exposure scenario outweighs the number of individuals above an HBGV (risk, Tier 2 metric) at the same exposure level. A qualitative assessment may also involve risks and benefits expressed in terms of the same type of metric (at the same tier) but related to different health effects. Assessment of the gradual change in risk/benefit depending on exposure, e.g. by providing detailed information on how the response or incidence for given effects change, or how multiple effects appear as the dose increases could enrich the basis for qualitative integration.

Qualitative integration is valuable not only when different metrics are present but also when data are limited or uncertain, making it a useful approach for assessing scenarios in risk–benefit analysis where quantitative integration may not be feasible.

4.7.2 | Quantitative methods

As discussed in Section 4.1, risks and benefits are ideally integrated quantitatively. A qualitative RBA can more clearly provide an overall answer to the risk–benefit question on whether the risks or benefits dominate. Quantitative integration is applicable in the case of both indirect (non-effect size-based) Tier 2, and direct (effect size based) Tier 3 measures of risks and benefits. When performed at Tier 3, a further advantage is that it can predict the magnitude of the human health risks and benefits, providing a better interpretation, and can then be more easily used when the human health impact is weighted against costs and sustainability indicators in a holistic assessment. It can provide the basis for generating FBDG including the identification of optimum dietary solutions.

4.7.2.1 | Quantitative health impact metrics

If the risk–benefit question requests an estimate of the size of the health impact, a risk–benefit comparison based on threshold values such as a reference dose, MOE or UL are not sufficient to quantify the health impact. In this case, risks and benefits should be expressed in terms of either a common or composite metric (Thomsen et al., 2018).

Common metrics are single outcome measures used to consider both positive and negative health effects. They express only a single dimension such as disease incidence, prevalence or mortality, or a specific endpoint e.g. cholesterolaemia, or cognitive performance (Boué et al., 2015; Fransen et al., 2010; Tijhuis et al., 2012). If the number of new cases or the incidence of disease X is much lower than the number of prevented cases or incidence of disease Y, then the outcome of the assessment could be straightforward. Conversely, if disease X and Y differ in terms of health impacts, then other dimensions of the diseases, including their severity and duration, as well as subpopulations at risk, should be considered and this can be handled with use of composite metrics (Hoekstra, Hart, et al., 2013).

Composite metrics are integrated measures and combine information about disease into one measure, and in contrast with common metrics reflect several dimensions of health. Due to the higher complexity of composite metrics, they require

²¹A BMR of 10% is applied to all endpoints.

more data input than common metrics (Boué et al., 2015; Fransen et al., 2010; Tjihuis et al., 2012), which in some cases can be a challenge. Examples of composite metrics are the Willingness to Pay, Cost of Illness, DALY and QALY (Havelaar et al., 2015; Jakobsen et al., 2016; Oberoi et al., 2014).

DALYs and QALYs combine aspects that characterise the magnitude of the health impact: number of people affected, severity, duration and mortality. The most used composite metric in quantitative RBA is the DALY (Berjia et al., 2012; FAO/WHO, 2011; Hoekstra et al., 2008; Hoekstra, Hart, et al., 2013; Van Kreijl et al., 2006), which is also the preferred metric in the GBD study (GBD 2016 DALYs and HALE Collaborators, 2017) and the WHO estimates of the global burden of food-borne diseases (Devleesschauwer et al., 2015).

DALY is a measure of healthy life lost, whereas QALY is a measure of healthy life gained (Gold et al., 2002). DALY measure health loss compared with an ideal life, and express years lost caused by premature death and health loss due to disease. The use of DALY allows for a comparison across diseases, and the difference in the sum of DALYs between a given reference scenario and one or more alternative scenarios thereby providing information on an overall health gain or loss by a theoretical intervention in a population.

When reporting DALY estimates, a detailed description of the interpretation should follow along with other measures, such as comparison of chemical and nutrient exposures with HBGVs and DRVs, respectively, number of cases of disease and characterisation of unquantified uncertainties. More details are provided in Appendix E.

4.7.2.2 | *Other quantitative metrics*

Similar to health impact metrics described above, the nature of the effect can also be taken into account using the additional methods discussed in Subsections 4.6.1 and 4.6.2. These methods, in conjunction with metrics like DALY, can assist in enabling a semiquantitative or quantitative integration of risks and benefits at Tier 2 or 3. For example, at Tier 2, HBGVs and DRVs may be better mapped (or compared) by calibrating the associated benchmark responses to represent similar levels of severity (i.e. severity in terms of the combination of the nature of the effect behind the HBGV/DRV and the selected BMR). The approaches discussed for the combined assessment of multiple effects in Section 4.6.2 may also be applicable for benefits expressed as risk reductions, provided that there is a relationship between dose and severity (categorical regression) or dose and relative severity (Sand, 2022; Sand et al., 2018) for such effects. This requires further consideration and development since the methods so far have primarily focused on chemical risks.

However, in specific exposure scenarios, the observed levels of risk reductions can be compared separately with the likelihood of various severity categories resulting from a categorical regression approach employed to assess the risks. The integration may be semiquantitative or quantitative at Tier 3 depending on how well observed levels of risk reductions are mapped to the severity levels in the categorical regression approach.

Similarly, for given exposures, the generalised version of Sand et al. (2018) provides the probability of effect/severe effect, which can be semiquantitatively or quantitatively integrated with the associated probability of effect/disease reductions that may be derived separately at Tier 3. As illustrated in Appendix D, results from this method can be derived at specific severity levels between 0 and 1 (i.e. relative severity, relating to the nature of effect) or in terms of an integrated/summary response accounting for the whole severity (effect) domain. Consideration of where the separately derived benefit-related effects or diseases (risk reductions) are classified on the same severity scale between 0 and 1 can help in the process of integrating the risks and benefits more quantitatively (see Appendix D, Section D.1.3).

As an extended Tier 2 approach, the simpler version of Sand et al. (2018) that evaluates the probability of exceeding RPs/adjusted RPs (applying to a particular BMR) may be compared with (separately) derived probabilities of exceeding DRVs (preferably using the same BMR). Similar to the discussion above, consideration of effects behind the DRVs in relation to the severity scale attached to the risk model could aid in the comparison of the risk and benefit related results for given exposure scenarios.

There may be situations when it is difficult to categorise effects by severity and/or develop a composite metric within a risk/benefit assessment framework. Estimates of the magnitude or probability of effect for considered risks and benefits at relevant exposures may then serve as input for decision analysis (Smith, 2010). Developments related to the latter issue would more exclusively focus on risk management, requiring either explicit ranking or weighted preferences of multiple effects as part of a formal decision analysis, or application of multicriteria decision analysis to arrive at an optimised overall conclusion. Approaches for the estimation of probabilities of the various effects to be used as input may utilise methods discussed or exploit modern Bayesian multilevel modelling for evidence synthesis with multiple uncertainties simultaneously.

Future efforts in the area could envision more precise and context specific dose–response models for risk and benefit estimation that may support RBA broadly. Such approaches would involve probabilistic integration of dose–response functions over exposure distributions for directly addressing the probable magnitude of (positive or negative) effects or cases in a population over specified times. A focus on data needs would be an important element as part of such developments.

4.7.3 | Weighting of health effects

A fundamental challenge in RBA is the need to balance various types of health effects since it will generally not be possible to describe relevant risks and benefits by the same endpoint/s only. The disability weights developed by the WHO are the most established factors that address this issue, and they exist for a number of health effects that generally relate to different

diseases, including subgroups (WHO, 2020). These disability weights were developed for assessing the impact of different diseases in a population, within a burden-of-disease context and account for both disability and premature death. The WHO weights are part of the estimation of DALYs but could potentially also support other approaches with weightings. As the disability weights are disease-specific, they do not cover the entire spectrum of effects that may be relevant for RBA. As the global burden of disease may not always be applicable to the specific national or regional context under consideration, disability weights have also been developed for regions, including the European region and individual countries (GBD 2019 Diseases and Injuries Collaborators, 2020; Global Burden of Disease Collaborative Network, 2022; Schwarzingler et al., 2003).

As part of other approaches presented in this Guidance, new weighting schemes are also presented. For example, in Boué et al. (2022), a severity weight is assigned in the identification of food components and health effects based on a 3-graded scale, as detailed in Appendix C. Also, as part of the Risk Thermometer (SFA, 2015), a 5-graded severity scale is used, which is attached to a hierarchical health effect classification scheme covering effects ranging from lower order, such as biochemical markers, to higher order endpoints, such as diseases. This scheme has been further refined and extended by Sand et al. (2018) (see Appendix D). Similarly, in the context of categorical regression, more specific weighting schemes for given chemicals have been developed (e.g. Milton et al., 2017). Besides their application within associated methods, such schemes might, together with other considerations, also more broadly support the comparison of multiple (positive and negative) effects in a risk-benefit context.

It should be noted that ranking and weighting effects include both scientific and value-based aspects. For example, effects associated with an organ-specific adverse outcome or disease might be hierarchically organised based on scientific considerations of severity, e.g. changes of biochemical markers, organ weight, histopathological presentation, functional impairment, malignancy, that may be linked in a continuum of increased toxicological consequences and may be ranked for increasing severity based on scientific criteria.

Assigning weights, quantitatively, to effects within and across different adverse outcomes not only entails scientific considerations but also involves societal considerations on which effect is expected to have a larger impact on the population. Therefore, the selection of weights should be performed in consultation with risk management authorities. The initial severity-based ranking of effects would constrain the subsequent selection of weights such that the weight for a high-severity category would need to be larger than that for a low-severity category. In this process, sensitivity analyses may also be considered, investigating how a result may change depending on the weights selected.

4.8 | Consideration of variability and uncertainty

Variability and uncertainty are distinct and important to consider within all assessments. In relation to the Guidance for RBA, consideration of variability and uncertainty is an important component of Tiers 2 and 3 assessments. However, assessment of variability and uncertainty would generally not be a major focus at Tier 1 where point estimates, worst-case scenarios or similar, are considered. Characterisation of the uncertainty and variability is part of the RBA assessment while the impact these may have on decisions is part the RBA management.

4.8.1 | Sources and characterisation of variability

Variability is inherent in biological systems and can be estimated to various degrees of accuracy depending on the data and methods used. Various modelling approaches can be used to estimate inter- and intraindividual variability, both in the context of exposure and in the biological response to nutrients or chemical hazards. Variability cannot be reduced but better characterised with additional data.

In exposure assessment, more information on the between-person variability can be obtained by assessing the distribution of exposures in a population. Depending on the characteristics of data collection and the availability of raw data, various approaches exist to model the variability of individual servings or variability of long-term average (usual) intakes between individuals. Analysis of variability in consumption patterns e.g. within Member States may be performed using summary data, such as from the EFSA Comprehensive Food Consumption Database. However, modelling among individuals or correlations between food types is not possible when only summary data are available. Furthermore, data are usually not available to assess within person patterns of exposure considering that people do not eat the same food every day. The intermittent exposure patterns are not easily represented in estimates of usual intake. Also, an additional complexity is that nutritional composition of food and hazard contamination may potentially vary according to time and cooking practices.

In biological terms, variability impacts the kinetics of a given substance, i.e. how a substance is handled in the organism, and its dynamics, i.e. the response of the biological system to the substance in question. This translates to variability of dose-response relationships associated with considered risks and benefits. Interspecies or intraspecies variability (i.e. inter-individual) can be accounted for either with specific data, if available, or by the use of default factors (EFSA Scientific Committee, 2012) or default probability distributions. Interspecies variability is typically addressed using default factors only, when extrapolating evidence from animal studies to humans, although more information is becoming available thanks to targeted studies or high throughput studies using cells, tissues or macromolecules (e.g. receptors, enzymes) from different species in direct comparisons. In general, intraindividual variability is more difficult to assess and to account for, typically due to lack of relevant data, unless a study is designed to collect such data (e.g. multiple time points, different

conditions, etc.). In epidemiological studies, interindividual and intraindividual variability in kinetics and dynamics are the main sources of variability and can be estimated and accounted for various degrees depending on study design and data collected (EFSA Scientific Committee, 2024).

4.8.2 | Sources and characterisation of uncertainty

Uncertainties are generated mostly from lack of knowledge or data either in the exposure assessment or in the evidence of health effects for the assessment of risks and benefits. The EFSA Guidance on Uncertainty Analysis (EFSA Scientific Committee et al., 2018) describes a broad range of principles and methods for uncertainty analysis in risk assessment, which are also applicable to RBA. According to the EFSA guidance, the sources of uncertainty should be identified, and their overall impact on the assessment conclusions should be characterised. For RBA, the latter would concern conclusions regarding the overall trade-off between considered risks and benefits. In the case of a quantitative health impact assessment, this may be captured by a single metric like DALY.

The consideration of individual uncertainties, and their overall impact may be performed qualitatively or quantitatively. Ideally, conclusions on overall uncertainty in Tier 2 or 3 assessment are expressed quantitatively in terms of probability, e.g. the likelihood that an assessed exposure scenario/s is associated with a net-benefit or a net-risk. However, as a starting point, sources of uncertainty may, for example, be communicated through a table listing each uncertainty, noting its potential magnitude and direction of influence (e.g. see Hoekstra, Fransen, et al., 2013). Uncertainties that are typical for individual risk and benefit assessments will also be important in RBA. In addition, there are uncertainties that are unique for RBA, e.g. characterisation of disease severity.

In a quantitative analysis, the sources of uncertainty may be described by probability distributions. A quantitative approach can, however, never be fully exhaustive. Uncertainty analysis for RBA is more complex than for an individual risk assessment, e.g. due to potential identification of several relevant chemical hazards and nutrients. Therefore, a quantitative analysis may be performed, e.g. considering the most important uncertainties, besides a qualitative one that provides complementary and comprehensive information (Hoekstra et al., 2012; Naska et al., 2022). As noted in EFSA (2018), a quantitative characterisation is conditional on assumptions made for the uncertainties that could not be quantified. Uncertainty in the overall assessment must be communicated clearly to the risk-benefit manager, including the conditions under which the results apply.

4.8.3 | Probabilistic approaches and sensitivity analysis

In risk assessment as well as in RBA both variability and uncertainty can be considered using probabilistic approaches. This allows inputs related to exposure and dose-response to be described by a range of values that can be defined by probability distributions. Besides methods referenced in Section 4.6.1, several approaches to probabilistic assessment that are relevant for RBA have been presented and discussed (FDA US, 2009; Gao et al., 2015; Groth, 2017; Hoekstra, Fransen, et al., 2013; Hoekstra, Hart, et al., 2013; Naska et al., 2022; Schütte et al., 2012; Seal et al., 2008; Verwer et al., 2024; Zeilmaker et al., 2013). Under a fully quantitative RBA approach, variability and uncertainty can be separated using second-order Monte Carlo simulations (e.g. Boué et al., 2017). An example of a probabilistic approach is illustrated as part of the case study in Appendix D (Section D.1).

Sensitivity analysis can be used to investigate how different inputs influence the RBA result/s. Different methods are available in the literature (Frey et al., 2004; Frey & Patil, 2002), including the case of second order assessments (Busschaert et al., 2011; Mokhtari & Frey, 2005; Roelofs & Kennedy, 2011). These studies relate to risk assessment but there are also examples specific for RBA (e.g. Berjia et al., 2012; Leino et al., 2013). Also, the Food and Drug Administration (FDA US, 2009) analysed the effect of different levels of methylmercury exposure in fish, as was also done by Ponce et al. (2000). It is necessary to define at what level the sensitivity analysis should be conducted. For example, it can be done for the output from each individual risk or benefit assessment model, or with respect to the overall results of the RBA. The choice depends on the purpose of the analysis, e.g. if it is to support model understanding and validity, or find optimums for management. Performing a sensitivity analyses specific for each risk and benefit assessed can be a first stage for understanding the model and guiding interpretation. In this context, Appendix D exemplifies how the risk is influenced by severity considerations, and whether or not correlation in BMD uncertainty is accounted for (Section D.1.3; Table D.1). More extended analyses may also be conducted that focuses on the aggregated result describing the overall trade-off between risks and benefits (e.g. in terms of DALY).

5 | OVERVIEW OF RISK-BENEFIT ASSESSMENT APPROACHES

Table 2 provides an overview of the minimum characteristics, data sources, methods and other aspects of the RBA process that are necessary for application of each tier of assessment. In Table 3, the methods and approaches discussed in Sections 4.3–4.8 are summarised to provide an overview of their uses within RBA including the required input parameters and associated metrics.

TABLE 2 Overview of aspects of the RBA process at each tier.

	Tier 1	Tier 2	Tier 3
Detail level	Screening	Indirect measures	Direct effects comparison
Number of components in the assessment	One or multiple prioritisation	One or multiple prioritisation	One or multiple prioritisation
Reference scenario	Yes/no	Yes/no	Yes/no
Data for positive and negative health effects	HBGV/DRV	HBGV/DRV Dose–response modelling Variability and/or uncertainty	Effect size Dose–response modelling Variability and/or uncertainty
Exposure assessment	Conservative screening methods (summary data: median, 95%)	Refined preferred (probability; variability; uncertainty; subgroups; geographic areas)	Refined (probability; variability; uncertainty; subgroups; geographic areas)
Health effects	Most sensitive adverse endpoint (for each hazard component) Endpoint defining benefit (for each beneficial component)	Most sensitive adverse endpoint (for each hazard component) with refinements Endpoint defining benefit (for each beneficial component) with refinements	All adverse effects along relevant exposure range All positive effects along relevant exposure range
Data type	Summary data Indirect	Summary data Indirect Variability Uncertainty	Individual data Direct (effect size) Variability Uncertainty
Data sources	Existing assessments Systematic literature reviews	Existing assessments Systematic literature reviews Original research articles	Existing assessments Systematic literature reviews Original research articles Data repositories Original data
Characterisation of positive and negative health effects	Existing HBGV/DRV	HBGV/DRV No/Lowest-observed-adverse-effect level (NOAEL, LOAEL) Benchmark dose (BMD)	Effect size, or probability of gradual or binary effect
Integration methods	Qualitative based on value judgement	Qualitative or quantitative	Qualitative or quantitative

TABLE 3 Summary of methods that can be considered in the process of risk–benefit assessment.

Application within RBA	Method/approach	Input parameters/data	Output/metric	Purpose	Example
Identification, selection and prioritisation of food components	Score-based ranking	<ul style="list-style-type: none"> – Scores for occurrence – Scores for severity of health effect 	<ul style="list-style-type: none"> – Overall score based on scores for occurrence and health effect 	To provide a rough prioritisation of components to be considered in the RBA using data requirement that are the same/similar to that for traditional risk or benefit assessment.	Boué et al. (2022)
	Margin of exposure-based ranking	<ul style="list-style-type: none"> – Exposure estimate or scenario – HBGV or RP – Severity weight (1–100) 	<ul style="list-style-type: none"> – Severity-adjusted margin of exposure for ranking of chemical hazards 		Risk Thermometer (SFA, 2015)
Exposure assessment	Conservative screening methods	<ul style="list-style-type: none"> – Summary consumption data at group level in combination with point estimate of occurrence – Biomonitoring summary data at group level 	<ul style="list-style-type: none"> – Summary estimates of exposure, conservative scenario or similar 	To provide exposure information relevant for Tier 1, and which may also be used for initial prioritisation of risks and benefits.	EFSA (2011a)
	Refined assessment	<ul style="list-style-type: none"> – Consumption data at individual level in combination with occurrence data, – Biomonitoring data at individual level 	<ul style="list-style-type: none"> – Full distributions of exposure estimates, including variability and/or uncertainty 		To provide exposure assessments relevant for Tier 2 and 3.
Characterisation of adverse and beneficial effects	Dose–response models	Animal or human data NAMs data	<ul style="list-style-type: none"> – No observed adverse effect level or similar (NOAEL, LOAEL) – Benchmark dose (BMD) – Effect size, or probability of gradual or binary effect 	To support Tiers 1 and 2 (NOAEL, LOAEL, BMD) or Tier 3 (effect sizes or probabilities) assessments.	Thomsen et al. (2021) EFSA Scientific Committee (2022)
Characterisation of risks and benefits	Traditional chemical risk assessment or nutrient assessment	<ul style="list-style-type: none"> – Exposure estimates or scenario – RP/HBGV or DRV/UL 	<ul style="list-style-type: none"> – Margin of exposure, per cent of HBGV or DRV, or similar- Qualitative integration across risk and benefit domains 	Risk and benefit characterisation at Tier 1.	FAO/WHO (2009) EFSA NDA Panel (2010, 2022)
	Refined chemical risk assessment or nutrient assessment	<ul style="list-style-type: none"> – Exposure estimates – RP/HBGV or DRV – Account for variability and/or uncertainty – May be advanced by biologically-based BMRs 	<ul style="list-style-type: none"> – Number of individuals above/below RP/HBGV or DRV/UL – Qualitative or quantitative integration across risk and benefit domains 	Risk and benefit characterisation at Tier 2.	WHO/IPCS (2014)
	Categorical regression	<ul style="list-style-type: none"> – Exposure estimates or scenarios – Dose–response data – Severity categorisation 	<ul style="list-style-type: none"> – Probability of different severity categories – Qualitative or quantitative integration across risk and benefit domains 	Risk (and benefit) characterisation at Tier 3. This approach facilitates combination of data from multiple studies in a single analysis (meta-analysis). This can be useful when an individual study provides limited dose–response information.	US EPA (2017) Milton et al. (2017) Hertzberg and Dourson (1993)

(Continues)

TABLE 3 (Continued)

Application within RBA	Method/approach	Input parameters/data	Output/metric	Purpose	Example
	Combination of dose–response information across health effects ^a	<ul style="list-style-type: none"> – Exposure estimates or scenarios – RPs or adjusted RPs – Severity categorisation, and severity weight function – Model for dose–response curve may be added 	(A) Probability of exceeding RPs/adjusted RPs at given (relative) severity, or integrated probability using severity weight function (B) Probability of effect at given (relative) severity, or integrated probability using severity weight function <ul style="list-style-type: none"> – Quantification of variability and/or uncertainty – Qualitative or quantitative integration across risk and benefit domains 	Risk (and benefit) characterisation at Tier 2 (A) and 3 (B). Purpose is similar to that for categorical regression. These methods also enable that the various effects caused by a food component can be jointly assessed in a systematic manner. Standardised effect scoring systems enable comparison of outputs between chemical hazards, and support comparisons to other food components.	Sand et al. (2018); Sand (2022)
	Methods for estimation of disease burden	<ul style="list-style-type: none"> – Estimates of no. of cases or adverse effects at exposure/s of interest – Disease duration and disability 	<ul style="list-style-type: none"> – Disease probability/mortality – Burden of disease – Disability adjusted life years (DALY) – Quantitative integration – Across risk and benefit domains 	Risk and benefit characterisation at Tier 3. The use of a composite metric like the DALY facilitates quantitative integration of considered risks and benefits.	Outzen et al. (2024)
	Probabilistic decision analysis of both risks and benefits, ^b multicriteria methods.	<ul style="list-style-type: none"> – Dose–response and exposure data for each effect. 	<ul style="list-style-type: none"> – Probability of incidence for each effect – Quantification of variability and uncertainty – Qualitative or quantitative integration across risk and benefit domains e.g. using multicriteria decision analysis 	Risk and benefit characterisation at Tier 3. For example, this approach may provide an alternative when derivation of composite metrics and/or combined analysis of data/effects is not straight-forward.	Ruzante et al. (2017); Li et al. (2018); Ali et al. (2022)

^aIn categorical regression, observed effect levels, e.g. associated with different exposures, are categorised by severity. This categorisation considers the nature of the health effect as well as the level of response in the effect. In Sand et al. (2018), the nature of effect and the level of response are treated as two distinct variables. In this case, severity is a relative term that refers to the nature of the health effect, and the model may be evaluated at a particular response or across the whole response domain. The possibility to *quantitatively* integrate outputs from these two approaches with benefits considers the case when benefits are described as risk reductions, evaluated under the same model/s (if possible) or otherwise expressed in similar metrics.

^bConsidering benefits that may not only be expressed as risk reductions but genuine health improvements too, and when no common metrics readily exist.

6 | REPORTING AND INTERPRETING RESULTS OF RISK-BENEFIT ASSESSMENT

When reporting on the outcome of an RBA assessment, it is important to list all the relevant points starting from the question(s) at hand. First, the outcome of the problem formulation should be outlined in a short form: ‘What did the RBA consider?’ Second, there should be a clear explanation of the ‘scenario(s)’ assessed. Does the RBA provide information on a current situation, such as the risks and benefits of consuming red meat? Or does it compare a current dietary pattern (reference scenario) with another one (alternative scenario) that describes a different pattern? Third, the available data used in the RBA should be described in terms of the type of data, their adequacy and their quality. Fourth, a description of the tier in which the assessment was possible and/or was selected for the specific assessment. Fifth, the methodological approach that was used should be outlined. Finally, the outcome of the RBA should be provided, accompanied by a description of the uncertainties (Table 4).

TABLE 4 Reporting template for the RBA approach.

The RBA question	State the question received from the risk-benefit manager (and possible adjustments after consultation) including the time and resources allocated.
Problem formulation	Describe the outcome of the problem formulation, including any restriction to certain geographical areas, age groups, specific population groups, determination of chemical hazards and nutrients included in the assessment, etc.
Data	Describe the available data compared with the data needed in terms of amount, availability, adequacy and quality. Also indicate the cut-off date, if any, for the literature search.
Approach	Describe the tier under which the assessment falls, and the qualitative or quantitative approach applied to arrive at an RBA outcome
Method	Describe the methodology applied (see Section 4.7 and Appendices D and E)
Outcome	Report the outcome of the RBA assessment including qualitative and/or quantitative format (see examples in Appendices D-F)
Uncertainty analysis	Describe any uncertainties of the RBA assessment and the impact on the outcome in accordance to the respective EFSA Guidance.-
Comments	List any data or methodological needs that would add value to the RBA assessment (feasible vs comprehensive assessment)

The output (type of results) of the RBA depends on the methodology applied and may be expressed in composite metrics such as DALY or other metrics, such as probability of effect, as presented in Section 4.7.

To capture the whole dimension of the RBA and report the outcome in a practical and comprehensive way, it is advised (in Tier 3) to address and report the following in tabular format: intake scenarios (alternative vs. reference), health effect, level of evidence (e.g. probable, convincing), population affected, a brief description of the outcome metric [e.g. change in incidence (No. of individuals), effect severity ($w=0-1$), years lived with disease (YLD) per affected person, change in mortality, years of life lost (YLL), change in DALYs] (Hoekstra et al., 2012). For further details related to the application and interpretation of these composite metrics, see Appendix E.

When other methods are adopted in Tier 3 (see Sections 4.7 and 5), it is advised to report appropriately relevant metrics and data for a comprehensive presentation of the results of the assessment, such as the probability of effect for each endpoint (adverse effect or beneficial effect) and for each subpopulation. An example of a Tier 3 assessment and further details with interpretation of these metrics are also provided in Appendix D and reported data are presented in Table D.1. Examples of possible reporting tables are provided in Appendix F.

7 | RISK-BENEFIT COMMUNICATION

The SC recognises that communication of RBA outcomes plays an important role in the dialogue between assessors and managers, their interaction with civil society stakeholders, and in providing dietary advice to the public. The challenges faced by national public health authorities in formulating and delivering FBDGs to the public are recognised in the terms of reference above as a prime motive for the update of this Guidance document. Moreover, the dual nature of RBA (simultaneous assessment of both risk and benefits) represents an additional challenge in communicating the RBA results (Boehm et al., 2021). Social science evidence and expertise can help identify and characterise key factors that may lie behind these challenges and develop communication strategies to overcome them. They range from cognitive factors (i.e. knowledge, awareness, perceptions), to information-seeking and processing behaviours, as well as to individual, socio-economic and environmental characteristics. The literature provides insights and approaches that, building on the experience of EFSA, the European Commission and national partners, communicators can employ to develop strategies for structured, evidence-based risk-benefit communication.

Appendix G of this Guidance document summarises these key factors and provides strategic advice for communicators. The Guidance document focuses on RBA; therefore, the main target of this communication advice is communicators at risk assessment and other scientific advisory bodies who are required to communicate science-based RBA outcomes. Nevertheless, the Scientific Committee notes that the advice and tools for risk-benefit communication described here can

also be of use in planning and carrying out communication of management decisions and actions, which follows RBA. EFSA has recent experience in providing technical assistance in the field of risk communication to the European Commission (EFSA, 2021) and to national competent authorities in EU Member States (e.g. EFSA, 2022a). This contribution and future use in EU risk-benefit communication can be seen as a continuation of this type of support and cooperation.

Appendix G includes some recommendations for future research and collaboration that could further support and improve risk benefit communication in the food safety area.

8 | FOOD-RELATED RISKS AND BENEFITS BEYOND HUMAN HEALTH RISK-BENEFIT ASSESSMENT

This guidance deals exclusively with the health risks and benefits of food. There are other factors that may be considered in the wider evaluation of the RBA for decision-making, FBDG and risk-benefit communication. These factors include societal and economic issues (such as the cost of food and the cost of healthcare), the environmental impact of agriculture, the long-term sustainability of the food production chain, animal welfare related to the production of food and legal aspects. These considerations are increasingly important to both consumers and decision makers but in order to take these into account in an RBA, subjective aspects and value judgements such as acceptability and desirability criteria would be required. Multicriteria decision support (MCDS) approaches have been proposed for these more holistic RBAs (Pitter et al., 2015; Ruzante et al., 2017; van der Voet & Slob, 2007). However, these issues are beyond the scope of this guidance.

ABBREVIATIONS

AI	adequate intake
AR	average-nutrient requirements
AROI	Acceptable Range of Oral Intake
BFRs	brominated flame retardants
BMD	benchmark dose
BMDL	benchmark dose lower
BMDU	benchmark dose upper
BMR	benchmark response
BRAFO	Benefit-Risk Analysis of Foods
DALYs	disability-adjusted life years
DRV	dietary reference values
EHC	Environmental Health Criteria
FAO	Food and Agriculture Organisation of the United Nations
FBDG	food-based dietary guidelines
FDA	Food and Drug Administration
HBGVs	health-based guidance values
IARC	International Agency for Research on Cancer
IPCS	International Program on Chemical Safety
MCDS	multicriteria decision support
MOE	margin of exposure
MS	Member States
NAMs	new approach methodologies
PBPK	physiologically-based pharmacokinetic
PFASs	perfluoroalkyl substances
PRI	population reference intake
QALYs	quality-adjusted life years
RBA	risk-benefit assessment
RP	reference point
SC	Scientific Committee
SEYLL	standard expected years of life lost
TEFs	Toxic Equivalency Factors
TWI	Tolerable Weekly Intake
UF	uncertainty factor
UL	upper intake level
WHO	World Health Organisation
WoE	weight of evidence
YLD	years lived with disease
YLL	years of life lost

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CONFLICT OF INTEREST

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REFERENCES

- Adamczyk, D., & Maisson, D. (2021). Ecology or health-how to successfully promote palm oil free products: A comparison between Spain and Poland. *Food*, 10, 2380–2389. <https://doi.org/10.3390/foods10102380>
- Aggett, P. J., Antoine, J. M., Asp, N. G., Bellisle, F., Contor, L., Cummings, J. H., Howlett, J., Müller, D. J., Persin, C., Pijls, L. T., Rechkemmer, G., Tuijelaars, S., & Verhagen, H. (2005). PASSCLAIM: Consensus on criteria. *European Journal of Nutrition*, 44(Suppl. 1), i5–i30. <https://doi.org/10.1007/s00394-005-1104-3>
- Ali, B. M., Andersson, M. G., van den Borne, B. H. P., Focker, M., & van der Fels-Klerx, H. J. (2022). Multi-criteria decision analysis in food safety risk management: The case of dioxins in baltic fish. *Food*, 11, 1059.
- Alvito, P., Brazão, R., Carmona, P., Carvalho, C., Correia, D., Fernandes, P., Jakobsen, L. S., Lopes, C., Martins, C., Membré, J.-M., Monteiro, S., Nabais, P., Thomsen, S. T., Torres, D., Pires, S. M., Boué, G., & Assunção, R. (2019). RiskBenefit4EU – Partnering to strengthen risk-benefit assessment within the EU using a holistic approach. *EFSA Supporting Publications*, 16, 1768E. <https://doi.org/10.2903/sp.efsa.2019.EN-1768>
- Amin, L., Azad, M. A. K., Gausman, M. H., & Zulkifli, F. (2014). Determinants of public attitudes to genetically modified salmon. *PLoS One*, 9, e86174. <https://doi.org/10.1371/journal.pone.0086174>
- Amzal, B., Julin, B., Vahter, M., Wolk, A., Johanson, G., & Akesson, A. (2009). Population toxicokinetic modeling of cadmium for health risk assessment. *Environmental Health Perspectives*, 117, 1293–1301. <https://doi.org/10.1289/ehp.0800317>
- ANSES (Agence nationale de sécurité sanitaire de l'alimentation de l'environnement et du travail). (2010). *Avis de l'Agence française de sécurité sanitaire des aliments relatif aux bénéfices/risques liés à la consommation de poissons*. <https://www.anses.fr/fr/system/files/RCCP2008sa0123.pdf>
- ANSES (Agence nationale de sécurité sanitaire de l'alimentation de l'environnement et du travail). (2014). *Avis de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail relatif à « Evaluation du risque et du bénéfice liés à la consommation de produits alimentaires enrichis en phytostérols ou en phytostanols »*. <https://www.anses.fr/fr/system/files/NUT2010sa0057Ra.pdf>
- ANSES (Agence nationale de sécurité sanitaire de l'alimentation de l'environnement et du travail). (2015). *Évaluation des bénéfices et des risques nutritionnels des édulcorants intenses*. <https://www.anses.fr/fr/system/files/NUT2011sa0161Ra.pdf>
- ANSES (Agence nationale de sécurité sanitaire de l'alimentation de l'environnement et du travail). (2019). *Avis de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail relatif « aux risques et bénéfices associés à la consommation de poissons pélagiques contaminés par le mercure en Nouvelle-Calédonie »*. <https://www.anses.fr/fr/system/files/ERCA2016SA0041.pdf>
- ANSES (Agence nationale de sécurité sanitaire de l'alimentation de l'environnement et du travail). (2020). *Méthodologie de hiérarchisation des dangers biologiques et chimiques dans les aliments*. <https://www.anses.fr/en/system/files/BIORISK2016SA0153Ra.pdf>
- Assunção, R., Pires, S. M., & Nauta, M. (2019). Risk-benefit assessment of foods. *EFSA Journal*, 17, e170917. <https://doi.org/10.2903/j.efsa.2019.e170917>
- Bearth, A., Cousin, M.-E., & Siegrist, M. (2014). The consumer's perception of artificial food additives: Influences on acceptance, risk and benefit perceptions. *Food Quality and Preference*, 38, 14–23. <https://doi.org/10.1016/j.foodqual.2014.05.008>
- Bearth, A., Kaptan, G., & Kessler, S. H. (2022). Genome-edited versus genetically-modified tomatoes: An experiment on people's perceptions and acceptance of food biotechnology in the UK and Switzerland. *Agriculture and Human Values*, 39, 1117–1131. <https://doi.org/10.1007/s10460-022-10311-8>
- Berjia, F., Andersen, R., Poulsen, M., Hoekstra, J., & 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.
- Blaauboer, B. J., Boobis, A. R., Bradford, B., Cockburn, A., Constable, A., Daneshian, M., Edwards, G., Garthoff, J. A., Jeffery, B., Krul, C., & Schuermans, J. (2016). Considering new methodologies in strategies for safety assessment of foods and food ingredients. *Food and Chemical Toxicology*, 91, 19–35. <https://doi.org/10.1016/j.fct.2016.02.019>
- Boehm, E., Borzekowski, D., Ververis, E., Lohmann, M., & Böhl, G. F. (2021). Communicating food risk-benefit assessments: Edible insects as red meat replacers. *Frontiers in Nutrition*, 8, 749696. <https://doi.org/10.3389/fnut.2021.749696>

- Bolek, S. (2020). Consumer knowledge, attitudes, and judgments about food safety: A consumer analysis. *Trends in Food Science and Technology*, 102, 242–248.
- Boué, G., Cummins, E., Guillou, S., Antignac, J. P., Le Bizec, B., & Membré, J. M. (2017). Development and application of a probabilistic risk-benefit assessment model for infant feeding integrating microbiological, nutritional, and chemical components. *Risk Analysis*, 37, 2360–2388. <https://doi.org/10.1111/risa.12792>
- Boué, G., Guillou, S., Antignac, J.-P., Le Bizec, B., & Membré, J.-M. (2015). Public health risk-benefit assessment associated with food consumption – A review. *European Journal of Nutrition & Food Safety*, 5, 32–58. <https://doi.org/10.9734/EJNFS/2015/12285>
- Boué, G., Ververis, E., Niforou, A., Federighi, M., Pires, S. M., Poulsen, M., Thomsen, S. T., & Naska, A. (2022). Risk-benefit assessment of foods: Development of a methodological framework for the harmonized selection of nutritional, microbiological, and toxicological components. *Frontiers in Nutrition*, 9, 951369. <https://doi.org/10.3389/fnut.2022.951369>
- Busch, G., Kassas, B., Palma, M. A., & Risius, A. (2020). Perceptions of antibiotic use in livestock farming in Germany, Italy and the United States. *Livestock Science*, 241, 104251. <https://doi.org/10.1016/j.livsci.2020.104251>
- Busschaert, P., Geeraerd, A. H., Uyttendaele, M., & Van Impe, J. F. (2011). Sensitivity analysis of a two-dimensional quantitative microbiological risk assessment: Keeping variability and uncertainty separated. *Risk Analysis*, 31, 1295–1307. <https://doi.org/10.1111/j.1539-6924.2011.01592.x>
- Cattaneo, I., Astuto, M. C., Binaglia, M., Devos, Y., Dorne, J. L. C. M., Fernandez Agudo, A., Fernandez Dumont, A., Garcia-Vello, P., Kass, G. E. N., Lanzoni, A., Liem, A. K. D., Panzarea, M., Paraskevopoulos, K., Parra Morte, J. M., Tarazona, J. V., & Terron, A. (2023). Implementing new approach methodologies (NAMs) in food safety assessments: Strategic objectives and actions taken by the European Food Safety Authority. *Trends in Food Science & Technology*, 133, 277–290. <https://doi.org/10.1016/j.tifs.2023.02.006>
- Chen, Y., Dennis, S. B., Hartnett, E., Paoli, G., Pouillot, R., Ruthman, T., & Wilson, M. (2013). FDA-iRISK—A comparative risk assessment system for evaluating and ranking food-hazard pairs: Case studies on microbial hazards. *Journal of Food Protection*, 76, 376–385. <https://doi.org/10.4315/0362-028x.Jfp-12-372>
- Chiu, W. A., Axelrad, D. A., Dalajamts, C., Dockins, C., Shao, K., Shapiro, A. J., & Paoli, G. (2018). Beyond the RfD: Broad application of a probabilistic approach to improve chemical dose-response assessments for noncancer effects. *Environmental Health Perspectives*, 126, 067009. <https://doi.org/10.1289/EHP3368>
- de Oliveira, G. A., Domingues, C. H. F., & Borges, J. A. R. (2021). Analyzing the importance of attributes for Brazilian consumers to replace conventional beef with cultured meat. *PLoS One*, 16, e0251432. <https://doi.org/10.1371/journal.pone.0251432>
- DeVito, M., Bokkers, B., van Duursen, M. B. M., van Ede, K., Feeley, M., Antunes Fernandes Gáspár, E., Haws, L., Kennedy, S., Peterson, R. E., Hoogenboom, R., Nohara, K., Petersen, K., Rider, C., Rose, M., Safe, S., Schrenk, D., Wheeler, M. W., Wikoff, D. S., Zhao, B., & van den Berg, M. (2024). The 2022 world health organization reevaluation of human and mammalian toxic equivalency factors for polychlorinated dioxins, dibenzofurans and biphenyls. *Regulatory Toxicology and Pharmacology*, 146, 105525. <https://doi.org/10.1016/j.yrtph.2023.105525>
- Devleeschauwer, B., Haagsma, J. A., Angulo, F. J., Bellinger, D. C., Cole, D., Döpfer, D., Fazil, A., Fèvre, E. M., Gibb, H. J., Hald, T., Kirk, M. D., Lake, R. J., Maertens de Noordhout, C., Mathers, C. D., McDonald, S. A., Pires, S. M., Speybroeck, N., Thomas, M. K., Torgerson, P. R., ... Praet, N. (2015). Methodological framework for World Health Organization estimates of the global burden of foodborne disease. *PLoS One*, 10, e0142498. <https://doi.org/10.1371/journal.pone.0142498>
- Devleeschauwer, B., Havelaar, A. H., Maertens de Noordhout, C., Haagsma, J. A., Praet, N., Dorny, P., Duchateau, L., Torgerson, P. R., Van Oyen, H., & Speybroeck, N. (2014a). Calculating disability-adjusted life years to quantify burden of disease. *International Journal of Public Health*, 59, 565–569. <https://doi.org/10.1007/s00038-014-0552-z>
- Devleeschauwer, B., Havelaar, A. H., Maertens de Noordhout, C., Haagsma, J. A., Praet, N., Dorny, P., Duchateau, L., Torgerson, P. R., Van Oyen, H., & Speybroeck, N. (2014b). DALY calculation in practice: A stepwise approach. *International Journal of Public Health*, 59, 571–574. <https://doi.org/10.1007/s00038-014-0553-y>
- DunnGalvin, A., Roberts, G., Regent, L., Austin, M., Kenna, F., Schnadt, S., Sanchez-Sanz, A., Hernandez, P., Hjorth, B., Fernandez-Rivas, M., Taylor, S., Baumert, J., Sheikh, A., Astley, S., Crevel, R., & Mills, C. (2019). Understanding how consumers with food allergies make decisions based on precautionary labelling. *Clinical and Experimental Allergy*, 49, 1446–1454. <https://doi.org/10.1111/cea.13479>
- Dunnick, J. K., Shockley, K. R., Pandiri, A. R., Kissling, G. E., Gerrish, K. E., Ton, T. V., Wilson, R. E., Brar, S. S., Brix, A. E., Waidyanatha, S., Mutlu, E., & Morgan, D. L. (2018). PBDE-47 and PBDE mixture (DE-71) toxicities and liver transcriptomic changes at PND 22 after in utero/postnatal exposure in the rat. *Archives of Toxicology*, 92, 3415–3433. <https://doi.org/10.1007/s00204-018-2292-y>
- EFSA (European Food Safety Authority). (2009). Cadmium in food – Scientific Opinion of the Panel on Contaminants in the Food Chain. *EFSA Journal*, 7, 980. <https://doi.org/10.2903/j.efsa.2009.980>
- EFSA (European Food Safety Authority). (2011a). Overview of the procedures currently used at EFSA for the assessment of dietary exposure to different chemical substances. *EFSA Journal*, 9, 2490. <https://doi.org/10.2903/j.efsa.2011.2490>
- EFSA (European Food Safety Authority). (2011b). Use of the EFSA comprehensive European food consumption database in exposure assessment. *EFSA Journal*, 9, 2097. <https://doi.org/10.2903/j.efsa.2011.2097>
- EFSA (European Food Safety Authority), Maxim, L., Mazzocchi, M., Van den Broucke, S., Zollo, F., Robinson, T., Rogers, C., Vrbos, D., Zamariola, G., & Smith, A. (2021). Technical assistance in the field of risk communication. *EFSA Journal*, 19, e06574. <https://doi.org/10.2903/j.efsa.2021.6574>
- EFSA (European Food Safety Authority). (2022a). *Food safety in the EU – Report, Publications Office of the European Union*.
- EFSA (European Food Safety Authority), Maxim, L., Mazzocchi, M., Van den Broucke, S., Zollo, F., Rasche, M., Ortega, P., Robinson, T., Rogers, C., Vrbos, D., Zamariola, G., & Smith, A. (2022b). EU insights study on consumers and dietary sugars. *EFSA Supporting Publications*, 19(3), EN-7213. <https://doi.org/10.2903/sp.efsa.2022.EN-7213>
- EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain), Knutsen, H. K., Alexander, J., Barregård, L., Bignami, M., Brüschweiler, B., Ceccatelli, S., Cottrill, B., Dinovi, M., Edler, L., Grasl-Kraupp, B., Hogstrand, C., Nebbia, C. S., Oswald, I. P., Petersen, A., Rose, M., Roudot, A.-C., Schwerdtle, T., Vleminckx, C., ... Hoogenboom, L. (2018). Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food. *EFSA Journal*, 16, 5333. <https://doi.org/10.2903/j.efsa.2018.5333>
- EFSA NDA Panel (EFSA Panel on Nutrition, Novel Foods and Food Allergens). (2010). Scientific Opinion on principles for deriving and applying dietary reference values. *EFSA Journal*, 8, 1458. <https://doi.org/10.2903/j.efsa.2010.1458>
- EFSA NDA Panel (EFSA Panel on Nutrition, Novel Foods and Food Allergens), Turck, D., Bresson, J.-L., Burlingame, B., Dean, T., Fairweather-Tait, S., Heinonen, M., Hirsch-Ernst, K. I., Mangelsdorf, I., McArdle, H. J., Naska, A., Nowicka, G., Pentieva, K., Sanz, Y., Siani, A., Sjödin, A., Stern, M., Tomé, D., Loveren, H. V., ... Neuhäuser-Berthold, M. (2018). Update of the tolerable upper intake level for vitamin D for infants. *EFSA Journal*, 16, e05365. <https://doi.org/10.2903/j.efsa.2018.5365>
- EFSA NDA Panel (EFSA Panel on Nutrition, Novel Foods and Food Allergens), Turck, D., Bohn, T., Castenmiller, J., De Henauw, S., Hirsch-Ernst, K. I., Knutsen, H. K., Maciuk, A., Mangelsdorf, I., McArdle, H. J., Peláez, C., Pentieva, K., Siani, A., Thies, F., Tsabouri, S., Vinceti, M., Aggett, P., Crous Bou, M., Cubadda, F., ... Naska, A. (2022). Guidance for establishing and applying tolerable upper intake levels for vitamins and essential minerals. *EFSA Journal*, 20, e200102. <https://doi.org/10.2903/j.efsa.2022.e200102>

- EFSA NDA Panel (EFSA Panel on Nutrition, Novel Foods and Food Allergens), Turck, D., Bohn, T., Castenmiller, J., de Henauw, S., Hirsch-Ernst, K.-I., Knutsen, H. K., Maciuk, A., Mangelsdorf, I., McArdle, H. J., Pentieva, K., Siani, A., Thies, F., Tsbouri, S., Vinceti, M., Lanham-New, S., Passeri, G., Craciun, I., Fabiani, L., ... Naska, A. (2023). Scientific opinion on the tolerable upper intake level for vitamin D, including the derivation of a conversion factor for calcidiol monohydrate. *EFSA Journal*, 21, e08145. <https://doi.org/10.2903/j.efsa.2023.8145>
- EFSA Scientific Committee. (2010). Guidance on human health risk-benefit assessment of foods. *EFSA Journal*, 8(7), 1673. <https://doi.org/10.2903/j.efsa.2010.1673>
- EFSA Scientific Committee. (2012). Guidance on selected default values to be used by the EFSA scientific committee, scientific panels and units in the absence of actual measured data. *EFSA Journal*, 10, 2579. <https://doi.org/10.2903/j.efsa.2012.2579>
- EFSA Scientific Committee, Hardy, A., Benford, D., Halldorsson, T., Jeger, M. J., Knutsen, H. K., More, S., Naegeli, H., Noteborn, H., Ockleford, C., Ricci, A., Rychen, G., Schlatter, J. R., Silano, V., Solecki, R., Turck, D., Benfenati, E., Chaudhry, Q. M., Craig, P., ... Younes, M. (2017a). Guidance on the use of the weight of evidence approach in scientific assessments. *EFSA Journal*, 15, e04971. <https://doi.org/10.2903/j.efsa.2017.4971>
- EFSA Scientific Committee, Hardy, A., Benford, D., Halldorsson, T., Jeger, M. J., Knutsen, H. K., More, S., Naegeli, H., Noteborn, H., Ockleford, C., Ricci, A., Rychen, G., Schlatter, J. R., Silano, V., Solecki, R., Turck, D., Younes, M., Bresson, J.-L., Griffin, J., ... Alexander, J. (2017b). Guidance on the assessment of the biological relevance of data in scientific assessments. *EFSA Journal*, 15, e04970. <https://doi.org/10.2903/j.efsa.2017.4970>
- EFSA Scientific Committee, Benford, D., Halldorsson, T., Jeger, M. J., Knutsen, H. K., More, S., Naegeli, H., Noteborn, H., Ockleford, C., Ricci, A., Rychen, G., Schlatter, J. R., Silano, V., Solecki, R., Turck, D., Younes, M., Craig, P., Hart, A., Von Goetz, N., ... Hardy, A. (2018). Guidance on uncertainty analysis in scientific assessments. *EFSA Journal*, 16, e05123. <https://doi.org/10.2903/j.efsa.2018.5123>
- EFSA Scientific Committee, More, S., Bampidis, V., Benford, D., Bragard, C., Halldorsson, T., Hougaard Bennekou, S., Koutsoumanis, K., Machera, K., Naegeli, H., Nielsen, S., Schlatter, J., Schrenk, D., Silano, V., Turck, D., Younes, M., Aggett, P., Castenmiller, J., Giarola, A., ... Hernández-Jerez, A. (2021a). Statement on the derivation of health-based guidance values (HBGVs) for regulated products that are also nutrients. *EFSA Journal*, 19, e06479. <https://doi.org/10.2903/j.efsa.2021.6479>
- EFSA Scientific Committee, More, S. J., Bampidis, V., Benford, D., Bragard, C., Hernández-Jerez, A., Bennekou, S. H., Halldorsson, T. I., Koutsoumanis, K. P., Lambré, C., Machera, K., Naegeli, H., Nielsen, S. S., Schlatter, J. R., Schrenk, D., Silano, V., Turck, D., Younes, M., Benfenati, E., ... Hogstrand, C. (2021b). Guidance document on scientific criteria for grouping chemicals into assessment groups for human risk assessment of combined exposure to multiple chemicals. *EFSA Journal*, 19, e07033. <https://doi.org/10.2903/j.efsa.2021.7033>
- EFSA Scientific Committee, More, S. J., Bampidis, V., Benford, D., Bragard, C., Halldorsson, T. I., Hernández-Jerez, A. F., Bennekou, S. H., Koutsoumanis, K., Lambré, C., Machera, K., Mennes, W., Mullins, E., Nielsen, S. S., Schrenk, D., Turck, D., Younes, M., Aerts, M., Edler, L., ... Schlatter, J. (2022). Guidance on the use of the benchmark dose approach in risk assessment. *EFSA Journal*, 20, e07584. <https://doi.org/10.2903/j.efsa.2022.7584>
- EFSA Scientific Committee, More, S., Bampidis, V., Benford, D., Bragard, C., Hernández-Jerez, A., Bennekou, S. H., Koutsoumanis, K. P., Lambré, C., Machera, K., Mullins, E., Nielsen, S. S., Schlatter, J., Schrenk, D., Turck, D., Younes, M., Kraft, A., Naegeli, H., Tsaïoun, K., ... Halldorsson, T. I. (2023). Guidance on protocol development for EFSA generic scientific assessments. *EFSA Journal*, 21, e08312. <https://doi.org/10.2903/j.efsa.2023.8312>
- EFSA Scientific Committee, More, S., Bampidis, V., Benford, D., Bragard, C., Hernández-Jerez, A., Bennekou, S. H., Koutsoumanis, K., Lambré, C., Machera, K., Mennes, W., Mullins, E., Nielsen, S. S., Schlatter, J., Schrenk, D., Turck, D., Younes, M., Fletcher, T., Greiner, M., ... Halldorsson, T. I. (2024). Scientific Committee guidance on appraising and integrating evidence from epidemiological studies for use in EFSA's scientific assessments. *EFSA Journal*, 22(7), e8866. <https://doi.org/10.2903/j.efsa.2024.8866>
- FAO/WHO (Food and Agriculture Organization of the United Nations and World Health Organization). (2009). *Principles and methods for the risk assessment of chemicals in food. Environmental health criteria*, 240. ISBN:9789241572408. <https://www.who.int/publications/i/item/9789241572408>
- FAO/WHO (Food and Agriculture Organization of the United Nations and World Health Organization). (2011). *Report of the joint FAO/WHO expert consultation on the risks and benefits of fish consumption*, 25–29 January 2010, Rome, Italy. Food and Agriculture Organization and World Health Organization. 63 pp.
- FAO/WHO (Food and Agriculture Organization of the United Nations and World Health Organization). (2023). *Summary report of the Joint FAO/WHO FAO/WHO expert consultation on risks and benefits of fish consumption*. <https://www.fao.org/3/cc8503en/cc8503en.pdf>
- FDA US (United States Department of Health and Human Services, Food and Drug Administration). (2009). *Draft report of quantitative risk and benefit assessment of consumption of commercial fish, focusing on fetal neurodevelopmental effects (measured by verbal development in children) and on coronary heart disease and stroke in the general population*.
- Florin, M.-V., & Bürkler, M. T. (2017). *Introduction to the IRGC risk governance framework* (revised ed.). EPFL International Risk Governance Center. <https://doi.org/10.5075/epfl-irgc-233739>
- Florin, M.-V., & Parker, S. D. (2020). *Involving stakeholders in the risk governance process*. EPFL International Risk Governance Center. <https://doi.org/10.5075/epfl-irgc-282243>
- Fontalba-Navas, A., Zafra Aparici, E., Prata-Gaspar, M. C., Herrera-Espejo, E., Company-Morales, M., & Larrea-Killinger, C. (2020). Motivating pregnant and breastfeeding women in Spain to avoid persistent toxic substances in their diet. *International Journal of Environmental Research and Public Health*, 17.
- Fontalba-Navas, A., Zafra Aparici, E., Prata-Gaspar, M. C., Herrera-Espejo, E., Company-Morales, M., & Larrea-Killinger, C. (2020). Motivating pregnant and breastfeeding women in Spain to avoid persistent toxic substances in their diet. *International Journal of Environmental Research and Public Health*, 17(23), 8719 (13 pages). <https://doi.org/10.3390/ijerph17238719>
- Fransen, H., de Jong, N., Hendriksen, M., Mengelers, M., Castenmiller, J., Hoekstra, J., van Leeuwen, R., & Verhagen, H. (2010). A tiered approach for risk-benefit assessment of foods. *Risk Analysis*, 30, 808–816. <https://doi.org/10.1111/j.1539-6924.2009.01350.x>
- Frey, H., Mokhtari, A., & Zheng, J. (2004). *Recommended practice regarding selection, application, and interpretation of sensitivity analysis methods applied to food safety process risk models*. US Department of Agriculture.
- Frey, H. C., & Patil, S. R. (2002). Identification and review of sensitivity analysis methods. *Risk Analysis*, 22, 553–578.
- Füzesi, I., Lengyel, P., & Felföldi, J. (2018). Significance of food industry trademarks and product traceability from a customer perspective. *Journal of Agricultural Informatics*, 9, 66–75. <https://doi.org/10.17700/jai.2018.9.2.452>
- Galati, A., Tulone, A., Moavero, P., & Crescimanno, M. (2019). Consumer interest in information regarding novel food technologies in Italy: The case of irradiated foods. *Food Research International*, 119, 291–296. <https://doi.org/10.1016/j.foodres.2019.01.065>
- Gao, Y. X., Zhang, H. X., Li, J. G., Zhang, L., Yu, X. W., He, J. L., Shang, X. H., Zhao, Y. F., & Wu, Y. N. (2015). The benefit risk assessment of consumption of marine species based on benefit-risk analysis for foods (BRAFO)-tiered approach. *Biomedical and Environmental Sciences*, 28, 243–252. <https://doi.org/10.3967/bes2015.035>
- GBD 2016 DALYs and HALE Collaborators. (2017). Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2016: A systematic analysis for the Global Burden Of Disease Study 2016. *The Lancet*, 390, 1260–1344. [https://doi.org/10.1016/s0140-6736\(17\)32130-x](https://doi.org/10.1016/s0140-6736(17)32130-x)
- GBD 2019 Diseases and Injuries Collaborators. (2020). Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden Of Disease Study 2019. *The Lancet*, 396, 1204–1222. [https://doi.org/10.1016/S0140-6736\(20\)30925-9](https://doi.org/10.1016/S0140-6736(20)30925-9)
- Global Burden of Disease Collaborative Network. (2022). *Global Burden of Disease Study 2019 (GBD 2019) disability weights*. <https://ghdx.healthdata.org/record/ihme-data/gbd-2019-disability-weights>

- 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, 115–134. <https://doi.org/10.1146/annurev.publhealth.23.100901.140513>
- Groth, E., 3rd. (2017). Scientific foundations of fish-consumption advice for pregnant women: Epidemiological evidence, benefit-risk modeling, and an integrated approach. *Environmental Research*, 152, 386–406. <https://doi.org/10.1016/j.envres.2016.07.022>
- Hakim, M. P., Zanetta, L. D., de Oliveira, J. M., & da Cunha, D. T. (2020). The mandatory labeling of genetically modified foods in Brazil: Consumer's knowledge, trust, and risk perception. *Food Research International*, 132, 109053. <https://doi.org/10.1016/j.foodres.2020.109053>
- Hansen, J., Holm, L., Frewer, L., Robinson, P., & Sandøe, P. (2003). Beyond the knowledge deficit: Recent research into lay and expert attitudes to food risks. *Appetite*, 41, 111–121. [https://doi.org/10.1016/s0195-6663\(03\)00079-5](https://doi.org/10.1016/s0195-6663(03)00079-5)
- Hartmann, C., Hübner, P., & Siegrist, M. (2018). A risk perception gap? Comparing expert, producer and consumer prioritization of food hazard controls. *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association*, 116, 100–107. <https://doi.org/10.1016/j.fct.2018.04.006>
- Havelaar, A. H., Kirk, M. D., Torgerson, P. R., Gibb, H. J., Hald, T., Lake, R. J., Praet, N., Bellinger, D. C., de Silva, N. R., Gargouri, N., Speybroeck, N., Cawthorne, A., Mathers, C., Stein, C., Angulo, F. J., & Devleesschauwer, B. (2015). World Health Organization global estimates and regional comparisons of the burden of foodborne disease in 2010. *PLoS Medicine*, 12, e1001923. <https://doi.org/10.1371/journal.pmed.1001923>
- Hertzberg, R. C., & Dourson, M. L. (1993). *Using categorical regression instead of a NOAEL to characterize a toxicologist's judgment in noncancer risk assessment*. Proceedings of the 1993 (2nd) international symposium on uncertainty modeling and analysis, 25–28 April 1993s, 254–261 pp.
- Ho, S. S., Leong, A. D., Looi, J., Chen, L., Pang, N., & Tandoc, E., Jr. (2019). Science literacy or value predisposition? A meta-analysis of factors predicting public perceptions of benefits, risks, and acceptance of nuclear energy. *Environmental Communication*, 13, 457–471. <https://doi.org/10.1080/17524032.2017.1394891>
- Hoekstra, J., Fransen, H. P., van Eijkeren, J. C., Verkaik-Kloosterman, J., de Jong, N., Owen, H., Kennedy, M., Verhagen, H., & Hart, A. (2013). Benefit-risk assessment of plant sterols in margarine: A QALIBRA case study. *Food and Chemical Toxicology*, 54, 35–42. <https://doi.org/10.1016/j.fct.2012.08.054>
- Hoekstra, J., Hart, A., Boobis, A., Claupein, E., Cockburn, A., Hunt, A., Knudsen, I., Richardson, D., Schilter, B., Schütte, K., Torgerson, P. R., Verhagen, H., Watzl, B., & Chiodini, A. (2012). BRAFO tiered approach for benefit-risk assessment of foods. *Food and Chemical Toxicology*, 50(Suppl. 4), S684–S698. <https://doi.org/10.1016/j.fct.2010.05.049>
- Hoekstra, J., Hart, A., Owen, H., Zeilmaker, M., Bokkers, B., Thorgilsson, B., & Gunnlaugsdottir, H. (2013). Fish, contaminants and human health: Quantifying and weighing benefits and risks. *Food and Chemical Toxicology*, 54, 18–29. <https://doi.org/10.1016/j.fct.2012.01.013>
- Hoekstra, J., Verkaik-Kloosterman, J., Rompelberg, C., van Kranen, H., Zeilmaker, M., Verhagen, H., & de Jong, N. (2008). Integrated risk-benefit analyses: Method development with folic acid as example. *Food and Chemical Toxicology*, 46, 893–909. <https://doi.org/10.1016/j.fct.2007.10.015>
- Hu, L., Liu, R., Zhang, W., & Zhang, T. (2020). The effects of epistemic trust and social trust on public acceptance of genetically modified food: An empirical study from China. *International Journal of Environmental Research and Public Health*, 17, 7700 (20 pages) <https://doi.org/10.3390/ijerph17207700>
- Huang, T., Ko, C., Hooper, K., & Smith, B. (2022). An updated review of published human health risk-benefit assessment studies in the scientific literature. *Archives of Food and Nutritional Science*, 6, 62–67. <https://doi.org/10.29328/journal.afns.1001039>
- Huybrechts, I., Sioen, I., Boon, P. E., Ruprich, J., Lafay, L., Turrini, A., Amiano, P., Hirvonen, T., De Neve, M., Arcella, D., Moschandreas, J., Westerlund, A., Ribas-Barba, L., Hilbig, A., Papoutsou, S., Christensen, T., Oltarzewski, M., Virtanen, S., Rehurkova, I., ... Van Klaveren, J. D. (2011). Dietary exposure assessments for children in Europe (the EXPOCHI project): rationale, methods and design. *Archives of Public Health*, 69, 4. <https://doi.org/10.1186/0778-7367-69-4>
- Ibsen, D. B., Laursen, A. S. D., Würtz, A. M. L., Dahm, C. C., Rimm, E. B., Parner, E. T., Overvad, K., & Jakobsen, M. U. (2021). Food substitution models for nutritional epidemiology. *The American Journal of Clinical Nutrition*, 113, 294–303. <https://doi.org/10.1093/ajcn/nqaa315>
- IPCS (International Programme on Chemical Safety). (2002). *Principles and methods for the assessment of risk from essential trace elements*. World Health Organization.
- Ito, T. A., Larsen, J. T., Smith, N. K., & Cacioppo, J. T. (1998). Negative information weighs more heavily on the brain: The negativity bias in evaluative categorizations. *Journal of Personality and Social Psychology*, 75, 887–900. <https://doi.org/10.1037/0022-3514.75.4.887>
- Jacobs, S., Sioen, I., Pieniak, Z., De Henauf, S., Maulvault, A. L., Reuver, M., Fait, G., Cano-Sancho, G., & Verbeke, W. (2015). Consumers' health risk-benefit perception of seafood and attitude toward the marine environment: Insights from five European countries. *Environmental Research*, 143, 11–19. <https://doi.org/10.1016/j.envres.2015.02.029>
- Jakobsen, L. S., Granby, K., Knudsen, V. K., Nauta, M., Pires, S. M., & Poulsen, M. (2016). Burden of disease of dietary exposure to acrylamide in Denmark. *Food and Chemical Toxicology*, 90, 151–159. <https://doi.org/10.1016/j.fct.2016.01.021>
- Jahn, S., Tsalis, G., & Lähteenmäki, L. (2019). How attitude towards food fortification can lead to purchase intention. *Appetite*, 133, 370–377. <https://doi.org/10.1016/j.appet.2018.11.022>
- Jaskiewicz, K., Taylor, O., Senior, B., & Maestre, M. (2023). Communication of food-related health risks and benefits – A systematic review (2018–2022). *EFSA Supporting Publications*, 20, 8203E. <https://doi.org/10.2903/sp.efsa.2023.EN-8203>
- Ji, X., Zhou, Y., Xiao, Y., Lyu, W., Wang, W., Shao, K., & Yang, H. (2024). A tiered approach of hazard-prioritization and risk-ranking for chemical hazards in food commodities: Application for selected mycotoxins. *Food Research International*, 178, 113946. <https://doi.org/10.1016/j.foodres.2024.113946>
- Jones, C. L., Jensen, J. D., Scherr, C. L., Brown, N. R., Christy, K., & Weaver, J. (2015). The health belief model as an explanatory framework in communication research: Exploring parallel, serial, and moderated mediation. *Health Communication*, 30, 566–576. <https://doi.org/10.1080/10410236.2013.873363>
- Karmaus, A. L., Bialk, H., Fitzpatrick, S., & Krishan, M. (2020). State of the science on alternatives to animal testing and integration of testing strategies for food safety assessments: Workshop proceedings. *Regulatory Toxicology and Pharmacology*, 110, 104515. <https://doi.org/10.1016/j.yrtph.2019.104515>
- Kiliç, O., İsmet, B. O. Z., & Eryılmaz, G. A. (2020). Determination of consumers' behaviors in food purchasing, conservation, consumption and food safety. *Journal of Management and Economics Research*, 18(2), 29–40.
- Kim, R. (2012). Consumer attitude of risk and benefits toward genetically modified (GM) foods in South Korea: Implications for food policy. *Engineering Economics*, 23(2), 189–199. <https://doi.org/10.5755/j01.ee.23.2.1548>
- Kumpulainen, T., Vainio, A., Sandell, M., & Hopia, A. (2018). The effect of gender, age and product type on the origin induced food product experience among young consumers in Finland. *Appetite*, 123, 101–107. <https://doi.org/10.1016/j.appet.2017.12.011>
- Kuttschreuter, M., & Hilverda, F. (2019). "Listen, did you hear...?" A structural equation model explaining online information sharing on the risks of nanotechnology in food. *Food Quality and Preference*, 76, 118–132.
- Labrecque, J., & Charlebois, S. (2011). Functional foods: An empirical study on perceived health benefits in relation to pre-purchase intentions. *Nutrition & Food Science*, 41, 308–318. <https://doi.org/10.1108/00346651111170905>
- Lamonaca, E., Cafarelli, B., Calculli, C., & Tricase, C. (2022). Consumer perception of attributes of organic food in Italy: A CUB model study. *Heliyon*, 8, e09007. <https://doi.org/10.1016/j.heliyon.2022.e09007>
- Langerholc, T., Lindqvist, R., & Sand, S. (2018). Risk ranking of chemical and microbiological hazards in food. *EFSA Journal*, 16, e160813. <https://doi.org/10.2903/j.efsa.2018.e160813>
- Leino, O., Karjalainen, A. K., & Tuomisto, J. T. (2013). Effects of docosahexaenoic acid and methylmercury on child's brain development due to consumption of fish by Finnish mother during pregnancy: A probabilistic modeling approach. *Food and Chemical Toxicology*, 54, 50–58. <https://doi.org/10.1016/j.fct.2011.06.052>

- Li, K., Yuan, S. S., Wang, W., Wan, S. S., Ceessay, P., Heyse, J. F., Mt-Isa, S., & Luo, S. (2018). Periodic benefit-risk assessment using Bayesian stochastic multi-criteria acceptability analysis. *Contemporary Clinical Trials*, 67, 100–108. <https://doi.org/10.1016/j.cct.2018.02.016>
- Lindqvist, R., Langerholm, T., Ranta, J., Hirvonen, T., & Sand, S. (2020). A common approach for ranking of microbiological and chemical hazards in foods based on risk assessment – Useful but is it possible? *Critical Reviews in Food Science and Nutrition*, 60, 3461–3474. <https://doi.org/10.1080/10408398.2019.1693957>
- Loh, Z., & Hassan, S. (2021). Consumers' attitudes, perceived risks and perceived benefits towards repurchase intention of food truck products. *British Food Journal*, 124, 1314–1332. <https://doi.org/10.1108/BFJ-03-2021-0216>
- Lusk, J. L., & Briggeman, B. C. (2009). Food Values. *American Journal of Agricultural Economics*, 91, 184–196. <https://doi.org/10.1111/j.1467-8276.2008.01175.x>
- Merten, C., Ferrari, P., Bakker, M., Boss, A., Hearty, A., Leclercq, C., Lindtner, O., Tlustos, C., Verger, P., Volatier, J. L., & Arcella, D. (2011). Methodological characteristics of the national dietary surveys carried out in the European Union as included in the European Food Safety Authority (EFSA) Comprehensive European Food Consumption Database. *Food Additives & Contaminants. Part A, Chemistry, Analysis, Control, Exposure & Risk Assessment*, 28, 975–995. <https://doi.org/10.1080/19440049.2011.576440>
- Mendes, V., Niforou, A., Kasdagli, M. I., Ververis, E., & Naska, A. (2023). Intake of legumes and cardiovascular disease: A systematic review and dose-response meta-analysis. *Nutrition, Metabolism, and Cardiovascular Diseases*, 33, 22–37. <https://doi.org/10.1016/j.numecd.2022.10.006>
- Milton, B., Krewski, D., Mattison, D. R., Karyakina, N. A., Ramoju, S., Shilnikova, N., Birkett, N., Farrell, P. J., & McGough, D. (2017). Modeling U-shaped dose-response curves for manganese using categorical regression. *Neurotoxicology*, 58, 217–225. <https://doi.org/10.1016/j.neuro.2016.10.001>
- Minnens, F., Marques, A., Domingo, J. L., & Verbeke, W. (2020). Consumers' acceptance of an online tool with personalized health risk-benefit communication about seafood consumption. *Food and Chemical Toxicology*, 144, 111573. <https://doi.org/10.1016/j.fct.2020.111573>
- Mokhtari, A., & Frey, H. C. (2005). Sensitivity analysis of a two-dimensional probabilistic risk assessment model using analysis of variance. *Risk Analysis*, 25, 1511–1529. <https://doi.org/10.1111/j.1539-6924.2005.00679.x>
- Mondelaers, K., Verbeke, W., & Van Huylenbroeck, G. (2009). Importance of health and environment as quality traits in the buying decision of organic products. *British Food Journal*, 111, 1120–1139. <https://doi.org/10.1108/00070700910992952>
- Morgan, M. G., Fischhoff, B., Bostrom, A., & Atman, C. J. (2002). *Risk communication: A mental models approach*. Cambridge University Press.
- Nagler, R. H. (2014). Adverse outcomes associated with media exposure to contradictory nutrition messages. *Journal of Health Communication*, 19, 24–40. <https://doi.org/10.1080/10810730.2013.798384>
- NASEM (National Academies of Sciences Engineering, and Medicine). (2023). *The role of seafood in child growth and development*. <https://www.nationalacademies.org/our-work/the-role-of-seafood-in-child-growth-and-development>
- Naska, A., Ververis, E., Niforou, A., Pires, S. M., Poulsen, M., Jakobsen, L. S., Becker, N., Lohmann, M., Tesson, V., Federighi, M., & Boué, G. (2022). Novel foods as red meat replacers – An insight using risk benefit assessment methods (the NovRBA project). *EFSA Supporting Publications*, 19, 7316E. <https://doi.org/10.2903/sp.efsa.2022.EN-7316>
- 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 & Technology*, 76, 90–100. <https://doi.org/10.1016/j.tifs.2018.04.004>
- Neuwirth, K., Dunwoody, S., & Griffin, R. J. (2000). Protection motivation and risk communication. *Risk Analysis*, 20, 721–734. <https://doi.org/10.1111/0272-4332.205065>
- NTP (National Toxicology Program). (2016). NTP technical report on the toxicology studies of a Pentabromodiphenyl ether mixture [DE-71 (technical grade)] (CASRN 32534-81-9) in F344/N rats and B6C3F1/N mice and toxicology and carcinogenesis studies of a Pentabromodiphenyl ether mixture [DE-71 (technical grade)] in Wistar Han [Cr:WI(Han)] rats and B6C3F1/N mice (gavage studies). *National Toxicology Program Technical Report Series*, 589, 369 pages <https://doi.org/10.22427/ntp-tr-589>
- Oberoi, S., Barchowsky, A., & Wu, F. (2014). The global burden of disease for skin, lung, and bladder cancer caused by arsenic in food. *Cancer Epidemiology, Biomarkers & Prevention*, 23(7), 1187–1194. <https://doi.org/10.1158/1055-9965.Epi-13-1317>
- Orkusz, A., Wolańska, W., Harasym, J., Piwowar, A., & Kapelko, M. (2020). Consumers' attitudes facing entomophagy: Polish case perspectives. *International Journal of Environmental Research and Public Health*, 17, 2427.
- Outzen, M., Thomsen, S. T., Andersen, R., Jakobsen, L. S., Jakobsen, M. U., Nauta, M., Ravn-Haren, G., Sloth, J. J., Pilegaard, K., & Poulsen, M. (2024). Evaluating the health impact of increased linseed consumption in the Danish population. *Food and Chemical Toxicology*, 183, 114308. <https://doi.org/10.1016/j.fct.2023.114308>
- Pires, S. M., Boué, G., Boobis, A., Eneroth, H., Hoekstra, J., Membré, J. M., Persson, I. M., Poulsen, M., Ruzante, J., van Klaveren, J., Thomsen, S. T., & Nauta, M. J. (2019). Risk benefit assessment of foods: Key findings from an international workshop. *Food Research International*, 116, 859–869. <https://doi.org/10.1016/j.foodres.2018.09.021>
- Pitter, J., Jozwiak, A. B., Martos, E., Kaló, Z., & Vokó, Z. (2015). Next steps to evidence-based food safety risk analysis: Opportunities for health technology assessment methodology implementation. *Studies in Agricultural Economics*, 117, 155–161. <https://doi.org/10.7896/j.1524>
- Ponce, R. A., Bartell, S. M., Wong, E. Y., LaFlamme, D., Carrington, C., Lee, R. C., Patrick, D. L., Faustman, E. M., & Bolger, M. (2000). Use of quality-adjusted life year weights with dose-response models for public health decisions: A case study of the risks and benefits of fish consumption. *Risk Analysis*, 20, 529–542. <https://doi.org/10.1111/0272-4332.204050>
- Poortinga, W., & Pidgeon, N. F. (2004). Trust, the asymmetry principle, and the role of prior beliefs. *Risk Analysis*, 24, 1475–1486. <https://doi.org/10.1111/j.0272-4332.2004.00543.x>
- Ranta, J., Mikkilä, A., Suomi, J., & Tuominen, P. (2021). BIKE: Dietary exposure model for foodborne microbiological and chemical hazards. *Food*, 10, 2520.
- Rodes-Sanchez, M., Pozzi, F., Sunyer-Vidal, J., Puppo, F., Griepink, M., Santuccio, F., Stillitano, P., Folkvord, F., & Lupianez-Villanueva, F. (2024). Development of a roadmap for action on evidence-based risk communication in the EU food safety system. *EFSA Supporting Publications*, 21(6), EN-8863. <https://doi.org/10.2903/sp.efsa.2024.EN-8863>
- Rodríguez-Entrena, M., Salazar-Ordóñez, M., & Becerra-Alonso, D. (2016). An assessment of the barriers to the consumers' uptake of genetically modified foods: A neural network analysis. *Journal of the Science of Food and Agriculture*, 96, 1548–1555. <https://doi.org/10.1002/jsfa.7247>
- Roelofs, V. J., & Kennedy, M. C. (2011). Sensitivity analysis and estimation of extreme tail behavior in two-dimensional Monte Carlo simulation. *Risk Analysis*, 31, 1597–1609. <https://doi.org/10.1111/j.1539-6924.2011.01599.x>
- Ruzante, J. M., Grieger, K., Woodward, K. L., Lambertini, E., & Kowalczyk, B. (2017). The use of multi-criteria decision analysis in food safety risk-benefit assessment. *Food Protection Trends*, 37, 132–139.
- Sand, S. (2022). A novel method for combining outcomes with different severities or gene-level classifications. *ALTEX-Alternatives to Animal Experimentation*, 39, 480–497. <https://doi.org/10.14573/altex.2004212>
- Sand, S., Lindqvist, R., von Rosen, D., & Ilbäck, N. G. (2018). Dose-related severity sequence, and risk-based integration, of chemically induced health effects. *Toxicological Sciences*, 165, 74–89. <https://doi.org/10.1093/toxsci/kfy124>
- Sand, S., Ranta, J., & Lindqvist, R. (2023). Risk ranking of chemical and microbiological hazards in foods – research project and international workshop. *EFSA Supporting Publications*, 20, E210201E. <https://doi.org/10.2903/sp.efsa.2023.e210201>
- Schütte, K., Boeing, H., Hart, A., Heeschen, W., Reimerdes, E. H., Santare, D., Skog, K., & Chiodini, A. (2012). Application of the BRAFO tiered approach for benefit-risk assessment to case studies on heat processing contaminants. *Food and Chemical Toxicology*, 50(Suppl. 4), S724–S735. <https://doi.org/10.1016/j.fct.2012.01.044>

- Schwarzinger, M., Stouthard, M. E. A., Burström, K., Nord, E., & European Disability Weights Group. (2003). Cross-national agreement on disability weights: The European disability weights project. *Population Health Metrics*, 1, 9. <https://doi.org/10.1186/1478-7954-1-9>
- Seal, C. J., de Mul, A., Eisenbrand, G., Haverkort, A. J., Franke, K., Lalljie, S. P., Mykkänen, H., Reimerdes, E., Scholz, G., Somoza, V., Tuijelaars, S., van Boekel, M., van Klaveren, J., Wilcockson, S. J., & Wilms, L. (2008). Risk-benefit considerations of mitigation measures on acrylamide content of foods – a case study on potatoes, cereals and coffee. *The British Journal of Nutrition*, 99(Suppl. 2), S1–S46. <https://doi.org/10.1017/S0007114508965314>
- Segrè Cohen, A., Love, N. G., & Árvai, J. (2020). Communicating the risks and benefits of human urine-derived fertilizer. *Sustainability*, 12, 9973.
- Smith, J. Q. (2010). *Bayesian decision analysis: Principles and practice*. Cambridge University Press.
- Song, X., Pendenza, P., Díaz Navarro, M., Valderrama García, E., Di Monaco, R., & Giacalone, D. (2020). European consumers' perceptions and attitudes towards non-thermally processed fruit and vegetable products. *Food*, 9, 1732.
- Steenis, N. D., & Fischer, A. R. H. (2016). Consumer attitudes towards nanotechnology in food products: An attribute-based analysis. *British Food Journal*, 118, 1254–1267. <https://doi.org/10.1108/BFJ-09-2015-0330>
- Suwazono, Y., Sand, S., Vahter, M., Filipsson, A. F., Skerfving, S., Lidfeldt, J., & Akesson, A. (2006). Benchmark dose for cadmium-induced renal effects in humans. *Environmental Health Perspectives*, 114, 1072–1076. <https://doi.org/10.1289/ehp.9028>
- Suwazono, Y., Sand, S., Vahter, M., Skerfving, S., Lidfeldt, J., & Akesson, A. (2010). Benchmark dose for cadmium-induced osteoporosis in women. *Toxicology Letters*, 197, 123–127. <https://doi.org/10.1016/j.toxlet.2010.05.008>
- Swedish Food Agency (SFA). (2015). *The risk thermometer: A tool for risk comparison*. Swedish National Food Agency report 8.
- Swedish Food Agency (SFA). (2017). *Swedish market basket survey 2015: Per capita-based analysis of nutrients and toxic compounds in market baskets and assessment of benefit or risk*. Swedish Food Agency Report 26.
- Swedish Food Agency (SFA). (2022). *Risk and benefit assessment of whole grain intake in the Swedish adult population*. Swedish Food Agency report 11.
- Tessitore, S., Iraldo, F., Apicella, A., & Tarabella, A. (2020). *The link between food traceability and food labels in the perception of young consumers in Italy*. <https://doi.org/10.18461/ijfsd.v11i15.65>
- Thomsen, S. T. (2018). *Risk-benefit assessment of food substitutions*. Technical University of Denmark, National Food Institute.
- Thomsen, S. T., Nauta, M., Jakobsen, L. S., Jakobsen, M. U., Mejborn, H., Outzen, M., Poulsen, M., Ravn-Haren, G., & Andersen, R. (2021). Approaches for health effect characterization in risk-benefit assessment of foods: A comparative case study. *Frontiers in Nutrition*, 8, 607929. <https://doi.org/10.3389/fnut.2021.607929>
- Thomsen, S. T., Pires, S. M., Devleeschauwer, 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. <https://doi.org/10.1016/j.fct.2018.06.063>
- Tijhuis, M. J., de Jong, N., Pohjola, M. V., Gunnlaugsdóttir, H., Hendriksen, M., Hoekstra, J., Holm, F., Kalogeris, N., Leino, O., van Leeuwen, F. X., Luteijn, J. M., Magnússon, S. H., Odekerken, G., Rempelberg, C., Tuomisto, J. T., Ueland, Ø., White, B. C., & Verhagen, H. (2012). State of the art in benefit-risk analysis: Food and nutrition. *Food and Chemical Toxicology*, 50, 5–25. <https://doi.org/10.1016/j.fct.2011.06.010>
- Tiozzo, B., Pinto, A., Mascarello, G., Mantovani, C., & Ravarotto, L. (2019). Which food safety information sources do Italian consumers prefer? Suggestions for the development of effective food risk communication. *Journal of Risk Research*, 22, 1062–1077. <https://doi.org/10.1080/13669877.2018.1440414>
- U.S. Environmental Protection Agency (EPA). (2017). *Categorical regression (CATREG) user guide*. Version 3.1.0.7. EPA/600/R-17/236.
- Valente, M., & Chaves, C. (2018). Perceptions and valuation of GM food: A study on the impact and importance of information provision. *Journal of Cleaner Production*, 172, 4110–4118. <https://doi.org/10.1016/j.jclepro.2017.02.042>
- Van der Fels-Klerx, H. J., Van Asselt, E. D., Raley, M., Poulsen, M., Korsgaard, H., Bredsdorff, L., Nauta, M., D'Agostino, M., Coles, D., Marvin, H. J. P., & Frewer, L. J. (2018). Critical review of methods for risk ranking of food-related hazards, based on risks for human health. *Critical Reviews in Food Science and Nutrition*, 58, 178–193. <https://doi.org/10.1080/10408398.2016.1141165>
- van der Voet, H., & Slob, W. (2007). Integration of probabilistic exposure assessment and probabilistic hazard characterization. *Risk Analysis*, 27, 351–371. <https://doi.org/10.1111/j.1539-6924.2007.00887.x>
- van Dijk, H., Fischer, A. R., & Frewer, L. J. (2011). Consumer responses to integrated risk-benefit information associated with the consumption of food. *Risk Analysis*, 31, 429–439. <https://doi.org/10.1111/j.1539-6924.2010.01505.x>
- Van Kreijl, C., Knaap, A., & van Raaij, J. (2006). *Our food, our health: healthy diet and safe food in the Netherlands*. National Institute for Public Health and the Environment (RIVM). English translation of Ons eten gemeten: Gezonde voeding en veilig voedsel in Nederland (RIVM, 2004). www.rivm.nl/en
- Vellinga, R. E., Sam, M., Verhagen, H., Jakobsen, L. S., Ravn-Haren, G., Sugimoto, M., Torres, D., Katagiri, R., Thu, B. J., Granby, K., Hoekstra, J., & Temme, E. H. M. (2021). Increasing seaweed consumption in the Netherlands and Portugal and the consequences for the intake of iodine, sodium, and exposure to chemical contaminants: A risk-benefit study. *Frontiers in Nutrition*, 8, 792923. <https://doi.org/10.3389/fnut.2021.792923>
- Verbeke, W., & Liu, R. (2014). The impacts of information about the risks and benefits of pork consumption on Chinese consumers' perceptions towards, and intention to eat, pork. *Meat Science*, 98, 766–772. <https://doi.org/10.1016/j.meatsci.2014.07.023>
- Ververis, E., Niforou, A., Poulsen, M., Pires, S. M., Federighi, M., Samoli, E., Naska, A., & Boué, G. (2024). Substituting red meat with insects in burgers: Estimating the public health impact using risk-benefit assessment. *Food and Chemical Toxicology*, 189, 114764. <https://doi.org/10.1016/j.fct.2024.114764>
- Viscecchia, R., De Devitiis, B., Carlucci, D., Nardone, G., & Santeramo, F. G. (2018). On Consumers' acceptance of nanotechnologies: An Italian case study. *International Journal on Food System Dynamics*, 9, 321–330. <https://doi.org/10.18461/ijfsd.v9i4.943>
- VKM (Norwegian Scientific Committee for Food and Environment). (2022). *Benefit and risk assessment of fish in the Norwegian diet*. Scientific opinion of the scientific steering Committee of the Norwegian Scientific Committee for food and environment. VKM Report 2022:17, ISBN: 78-82-8259-392-2, ISSN: 2535–4019. Norwegian Scientific Committee for Food and Environment (VKM), Oslo, Norway.
- Vrbos, D., Zamariola, G., Maxim, L., Nicolini, G., Ortega, P., Ramsay, J., Rasche, M., Rogers, C., Schombert, L., Smith, A., & Gallani, B. (2023). Societal insights in risk communication planning – A structured approach. *Journal of Risk Research*, 26, 841–854. <https://doi.org/10.1080/13669877.2023.2197613>
- Wang, E. (2015). Effect of food service-brand equity on consumer-perceived food value, physical risk, and brand preference. *British Food Journal*, 117, 553–564. <https://doi.org/10.1108/BFJ-09-2013-0260>
- WCRF/AICR (World Cancer Research Fund/American Institute for Cancer Research). (2007). *Food, nutrition, physical activity, and the prevention of cancer: A global perspective*. AICR. <http://www.dietandcancerreport.org/>
- WHO (World Health Organization). (1946). *Constitution of the World Health Organization*. www.who.int/about/accountability/governance/constitution
- WHO (World Health Organization). (2017). *WHO methods and data sources for global burden of disease estimates 2000–2015*. Global Health estimates technical paper WHO/HIS/IER/GHE/2017.1. World Health Organization.
- WHO (World Health Organization). (2020). *WHO methods and data sources for country-level causes of death 2000–2019*. Global Health Estimates Technical Paper WHO/DDI/DNA/GHE/2020.2. https://cdn.who.int/media/docs/default-source/gho-documents/global-health-estimates/gho2019_cod_methods.pdf?sfvrsn=37bcfacc_5
- WHO/FAO (World Health Organisation/Food and Agriculture Organisation of the United Nations). (2003). *Diet, nutrition and the prevention of chronic diseases*. Report of a joint WHO/FAO expert consultation. 149 pages. Geneva. <https://www.who.int/publications/i/item/924120916X>
- WHO/IPCS (World Health Organization/International Programme on Chemical Safety). (1993). *Biomarkers and risk assessment: Concepts and principles/published under the joint sponsorship of the United Nations environment Programme, the International Labour Organisation, and the World Health Organization*. World Health Organization.

- WHO/IPCS (World Health Organization/International Programme on Chemical Safety). (2014). *Guidance document on evaluating and expressing uncertainty in hazard characterization*. Harmonization project document no. 11.
- Zeilmaker, M. J., Hoekstra, J., van Eijkeren, J. C., de Jong, N., Hart, A., Kennedy, M., Owen, H., & Gunnlaugsdottir, H. (2013). Fish consumption during child bearing age: A quantitative risk-benefit analysis on neurodevelopment. *Food and Chemical Toxicology*, 54, 30–34. <https://doi.org/10.1016/j.fct.2011.10.068>
- Zorell, C. V. (2022). Central persons in sustainable (food) consumption. *International Journal of Environmental Research and Public Health*, 19(5), 17 pp. <https://doi.org/10.3390/ijerph19053139>

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX A

Glossary

A.1 | RISK

The 2010 SC RBA Guidance included the following terms under risk: risk assessment, risk, hazard, adverse (health) effect and used IPCS (2004)²² and FAO/WHO (2006)²³ as references. These terms were essentially the same as in a 42-page glossary in Annex 1 of EHC 240 (FAO/WHO 2009).²⁴

Adverse effect is a ‘change in the morphology, physiology, growth, development, reproduction or lifespan 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.’

Benchmark dose (BMD): A dose of a substance associated with a specified low incidence of risk, generally in the range of 1%–10%, of a health effect; the dose associated with a specified measure or change of a biological effect.

Biomarker is a measurable biochemical, physiological, behavioural or other alteration within an organism that, depending upon the magnitude, can be recognised as associated with an established or possible health impairment or disease (EFSA Scientific Committee, 2017a; WHO/IPCS, 1993). A biomarker may be associated with a risk or a benefit. It is the direction of the association that determines whether the relationship reflects an adverse or beneficial outcome. See EFSA's ongoing work on developing a guidance for the use of biomarkers of effect: <https://open.efsa.europa.eu/study-inventory/EFSA-Q-2023-00583>.

Exposure is defined as the ‘concentration or amount of a particular agent that reaches a target organism, system or (sub) population in a specific frequency for a defined duration.’

Exposure assessment is the ‘evaluation of the exposure of an organism, system or (sub)population to an agent (and its derivatives). Exposure assessment is one of the steps in the process of risk assessment.’

Exposure, Aggregated: ‘The combined exposures to a single chemical across multiple routes (oral, dermal, inhalation) and across multiple pathways (food, drinking water, residential).’

Exposure scenario is defined as ‘a set of conditions or assumptions about sources, exposure pathways, amounts or concentrations of agents involved and exposed organisms, systems or (sub)populations (i.e. numbers, characteristics, habits) used to aid in the evaluation and quantification of exposures in a given situation.’

Hazard is an ‘inherent property of an agent or situation having the potential to cause adverse effects when an organism, system or (sub)population is exposed to that agent.’

Hazard assessment is ‘a process designed to determine the possible adverse effects of an agent or situation to which an organism, system or (sub)population could be exposed. The process includes hazard identification and hazard characterisation. The process focuses on the hazard, in contrast with a risk assessment, where exposure assessment is a distinct additional step.’

Hazard characterisation is ‘the qualitative and, wherever possible, quantitative description of the inherent properties of an agent or situation having the potential to cause adverse effects. This should, where possible, include a dose-response assessment and its attendant uncertainties. Hazard characterisation is the second stage in the process of hazard assessment and the second step in risk assessment.’

Hazard identification is ‘the identification of the type and nature of adverse effects that an agent has an inherent capacity to cause in an organism, system or (sub)population. Hazard identification is the first stage in hazard assessment and the first step in the process of risk assessment.’

Health-Based Guidance Value (HBGV) is ‘a numerical value derived by dividing a point of departure (a no-observed-adverse-effect level, benchmark dose or benchmark dose lower confidence limit) by a composite uncertainty factor to determine a level that can be ingested over a defined time period (e.g. lifetime or 24 h) without appreciable health risk.’ UL for nutrients are included in the definition of both DRVs and HBGVs.

Lowest-observed-adverse-effect level (LOAEL): Lowest concentration or amount of a substance, found by experiment or observation, that causes an adverse alteration of morphology, functional capacity, growth, development or lifespan of the target organism distinguishable from those observed in normal (control) organisms of the same species and strain under the same defined conditions of exposure.

No-observed-adverse-effect level (NOAEL): Greatest concentration or amount of a substance, found by experiment or observation, that causes no adverse alteration of morphology, functional capacity, growth, development or lifespan of the target organism distinguishable from those observed in normal (control) organisms of the same species and strain under the same defined conditions of exposure.

²²IPCS (International Programme on Chemical Safety), 2004. Harmonisation Project Document No. 1 – IPCS risk assessment terminology. WHO, Geneva. <https://www.who.int/publications/i/item/9241562676>.

²³FAO/WHO (Food and Agriculture Organization of the United Nations/World Health Organization), 2006. A Model for Establishing Upper Levels of Intake for Nutrients and Related Substances: Report of a Joint FAO/WHO Technical Workshop on Nutrient Risk Assessment. WHO, Geneva, Switzerland. <http://www.who.int/ipcs/methods/en>.

²⁴Annex 1 Glossary of Terms of FAO/WHO (2009). Principles and methods for the risk assessment of chemicals in food. Environmental health criteria 240 (updated in 2020). See [link](#). A comprehensive 42-page document.

Reference point (or point of departure): The point on a dose–response curve identified from experimental data used to derive a safe level.

Risk is defined as ‘the probability of an adverse effect in an organism, system or (sub)-population caused under specified circumstances by exposure to an agent.’

Risk assessment is defined as ‘a process intended to calculate or estimate the risk to a given target organism, system or (sub)population, including the identification of attendant uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system. The risk assessment process includes four steps: hazard identification, hazard characterisation (related term: dose–response assessment), exposure assessment and risk characterisation. It is the first component in a risk analysis process.’

Risk characterisation is defined as ‘the qualitative and, wherever possible, quantitative determination, including attendant uncertainties, of the probability of occurrence of known and potential adverse effects of an agent in a given organism, system or (sub)population, under defined exposure conditions. Risk characterisation is the fourth step in the risk assessment process.’

Risk communication is the ‘interactive exchange of information and opinions about hazards (health or environmental) and risks among risk assessors, risk managers, consumers, feed and food businesses, the academic community and other interested parties, including the explanation of risk assessment findings and the basis of risk management decisions.’

Risk estimation is the ‘quantification of the probability, including attendant uncertainties, that specific adverse effects will occur in an organism, system or (sub)population due to actual or predicted exposure.’

Risk management is the ‘decision-making process involving considerations of political, social, economic and technical factors with relevant risk assessment information on a hazard to develop, analyse and compare regulatory and non-regulatory options and to select and implement appropriate regulatory response to that hazard.’

A.2 | BENEFIT

Adequate Intake (AI) is ‘the value estimated when a Population Reference Intake (PRI) cannot be established because an average requirement (AR) cannot be determined. An AI is the average observed daily level of intake by a population group (or groups) of apparently healthy people that is assumed to be adequate.’

Average Requirement (AR) is the level of nutrient intake that is adequate for half of the people in a population group, given a normal distribution of requirements.

Benefit is defined as ‘the probability of a positive effect and/or the reduction of the probability of an adverse effect on (1) normal biochemical and physiological functions of a tissue (e.g. muscular or nervous tissue), organ (e.g. heart, lung, kidney, liver), or system (e.g. immune system); or (2) the health of (sub) population.’

Deficiency is defined as ‘the lack of a necessary factor in, for example, the diet or the environment which results in harm to the growth of an organism.’

Dietary reference values (DRV) are ‘the complete set of nutrient reference values.’ DRV comprise PRI, AR, AI, RI, and UL. UL is included in the definition of both DRVs and HBGVs

Disease is ‘a pathological process, acute or chronic, inherited or acquired, of known or unknown origin, having a characteristic set of signs and symptoms, which are used for its diagnosis.’ The diagnosis of a disease relies on widely accepted, well-defined criteria (i.e. the criteria used for diagnosis are widely accepted by the medical community and can be verified by a physician)

Endpoint is ‘the qualitative or quantitative expression of a specific factor with which a risk may be associated as determined through an appropriate risk assessment.’

The endpoints related to the consumption of nutrients, other food components, foods, or a diet can be ranked as follows (from the most to the less robust):

- Diseases (e.g. hypertension, stroke, renal insufficiency, Alzheimer's disease).
- Surrogate markers/proxies of disease (e.g. blood pressure or LDL-cholesterol and cardiovascular disease).
- Biomarkers of effect (e.g. urinary beta-2 microglobulin and tubular function).
- Fulfilment of DRV for nutrients, e.g. an intake above the AR or AI and below the UL.

Food-based dietary guidelines (FBDG) are defined as ‘science-based recommendations for healthy eating which translate numerical nutrition targets into lay advice on what foods to eat.’

Health is defined by the WHO as ‘a state of physical, mental and social well-being and not merely the absence of diseases or infirmity.’

Health effect is ‘a change in the morphology, or physiology, growth, development, reproduction or life span in humans that results in a change in human health.’

Novel food is ‘a foodstuff or food ingredient that was not used for human consumption to a significant degree within the European Union before 15 May 1997.’

Nutrient is ‘an element or compound needed for normal growth, development, and health maintenance. Essential nutrients cannot be made by the body and must, therefore, be consumed from food.’

Population Reference Intake (PRI) is ‘the level of nutrient intake that is adequate for virtually all people in a population group.’

Reference intake range (RI) is ‘the value set for energy-yielding macronutrients. It is expressed as the proportion (%) of energy derived from that macronutrient. RIs represent ranges of intakes that are adequate for maintaining health. A calorie-containing component of food (e.g. fat, protein, carbohydrate) which is needed in significant quantities for normal growth, development and maintenance of health.’

Safety is ‘the practical certainty that adverse effects will not result from exposure to an agent under defined circumstances. It is the reciprocal of risk.’

Safe level of intake for nutrients is defined as ‘the highest level of intake where there is reasonable confidence in data on the absence of adverse effects’ when no or insufficient data are available on which to base an UL.’

(Sub)population is ‘an identifiable subdivision of a population; for example, infants.’

Tolerable Upper Intake Level (UL) is ‘the maximum level of total chronic daily intake of a nutrient (from all sources) which is not expected to pose a risk of adverse health effects to humans.’

A.3 | RISK-BENEFIT COMMUNICATION

Risk-benefit communication is the ‘interactive exchange of information and opinions about hazards (including human or animal health/welfare, socioeconomic, environmental), risks and benefits among assessors, managers, consumers, feed and food businesses, the academic community and other interested parties, including the explanation of risk benefit assessment findings and the basis of risk benefit management decisions.’

A.4 | RISK-BENEFIT INTEGRATION

Common metric refers to measurements expressed in the same unit, for example, incidence of disease, morbidity or mortality.

Composite metrics integrate multiple components or dimensions into a single numerical value and are commonly used for disease burden. The most commonly used composite metrics are disability-adjusted life years (DALYs) and quality-adjusted life years (QALYs).

DALY stands for ‘disability-adjusted life years’ and was developed by the WHO as part of the effort to estimate global disease burden. DALYs for a disease or injury cause are calculated as the sum of the years of life lost due to premature mortality (YLL) in the population and the years lost due to disability (YLD) for incident cases of the disease or injury.

Disability weights represent an assigned magnitude of health loss associated with specific health outcomes and are commonly used to calculate years lived with disability (YLD) for these outcomes in a given population. The weights are measured on a scale from 0 to 1, where 0 equals a state of full health and 1 equals death.²⁵

Disease burden is the impact of a health problem on a given population and can be measured using a variety of indicators such as mortality, morbidity or financial costs.

Health impact, as used in this guidance, refers to the overall consequences on health as a result of combined or integrated positive and negative health effects.

Non-composite metrics are single-dimensional and are used to assess a specific parameter.

QALY stands for ‘quality-adjusted life years’ and provides a composite metric for disease burden adjusted for the quality of life. Hence the metric is a complement to the DALY concept. It takes into account both the quantity and the quality of life generated by a given intervention, which may have a positive or negative effect on health. A QALY is the arithmetic product of life expectancy and the QALY valuation of the health state for the remaining life years.

Quality of life is defined as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.²⁶ It refers to consequences of morbidity and health impact not captured by disease, e.g. physical and mental health.

²⁵See <https://ghdx.healthdata.org/record/ihme-data/gbd-2019-disability-weights> and <https://www.who.int/data/gho/indicator-metadata-registry>.

²⁶WHO Quality of Life: <https://www.who.int/tools/whoqol>.

APPENDIX B

The risk–benefit assessment approaches

B.1 | 2010 EFSA SCIENTIFIC COMMITTEE GUIDANCE

The focus of the EFSA Guidance on RBA of foods published in 2010²⁷ was on the risks and benefits to human health and excluded other aspects such as social, cultural, economic and environmental considerations. The 2010 SC Guidance proposed the development of a benefit assessment to parallel that of risk assessment namely identifying the positive health effect, characterisation of the positive effect (dose response assessment), exposure assessment and finally characterisation of the benefit (Figure B.1). The EFSA 6th Scientific Colloquium was organised in 2007²⁸ to collect input from experts on RBA methods and approaches to be considered in the development of the Guidance.

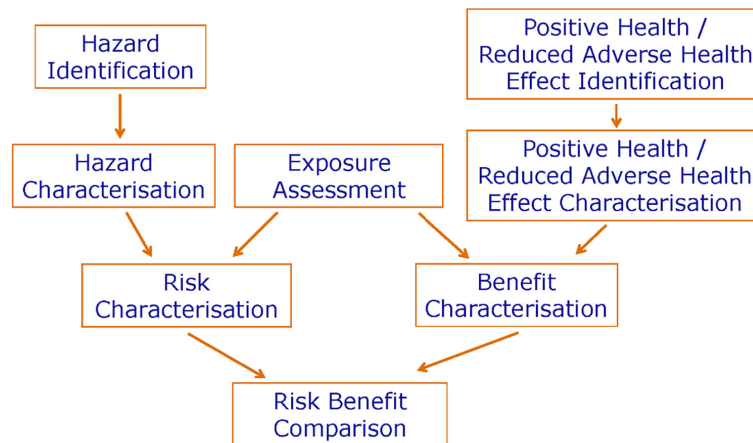


FIGURE B.1 The RBA paradigm, as recommended by the EFSA Scientific Committee (2010) and based on the discussions of the 6th EFSA scientific colloquium on risk–benefit analysis of foods (2007).

To address the assessment part, a stepwise approach was formulated and a narrative describing each step was recommended to indicate the strengths and weaknesses of the evidence.

1. In Step 1, an initial assessment to determine whether the benefit significantly outweighs the risk or vice versa.
2. In Step 2, a refined assessment aiming to provide semi-quantitative or quantitative estimates of risks and benefits using common metrics.²⁹
3. In Step 3, a comparison of the risks and benefits using composite metrics³⁰ (e.g. DALYs or QALYs) to provide a single net health impact value.

RBA is usually performed at the population level, but where pertinent sensitivities are apparent it may be necessary to consider (sub)populations such as the elderly or infants.

The 2010 SC Guidance recommended a close collaboration between the risk–benefit assessor and the risk–benefit manager in order to meet the risk–benefit goals efficiently. Despite this interaction, the overall uncertainty associated with the RBA may be large. Evaluation of the uncertainties helps to identify data gaps while still providing relevant information for decision making.

The 2010 SC Guidance described a number of metrics that can be used for RBA and emphasised the need for a clear definition and international agreement on these and on any other factors used in the assessment. The need for the development of relevant biomarkers of effect for both risk and benefit was stressed.

The EFSA 2010 SC Guidance concluded with the identification of a few cautionary aspects in the proposed approach of using composite metrics such as DALYs or QALYs for direct comparison of effects. It was noted, e.g. that not all relevant dimensions are captured, such as whether the effect is in children or adults (estimate of ‘years saved’ or ‘years lost’); comparing the incidence of a minor ailment with that of a major disability is not helpful; or that comparing the incidence of the same outcome may not include differences in severity or age group affected. It was also noted that mortality metrics are

²⁷Risk is defined as ‘the probability of an adverse effect in an organism, system or (sub)-population caused under specified circumstances by exposure to an agent.’ (see EFSA glossary).

²⁸European Food Safety Authority (EFSA), 2007. The EFSA’s 6th Scientific Colloquium Report – Risk-benefit analysis of foods: methods and approaches. EFSA Supporting Publication 2007; 4(3):EN-116, 157 pp. [10.2903/sp.efsa.2007.EN-116](https://doi.org/10.2903/sp.efsa.2007.EN-116).

²⁹Common metrics refer to a measurement expressed in the same unit, for example, incidence or mortality.

³⁰Composite metrics combine two or more of the following elements: increases or decreases in morbidity, mortality, disease burden and quality of life (see Appendix of EFSA 2010 Guidance).

more directly comparable, but do not capture the total number of people affected (e.g. when risks and benefits occur in different subpopulations of different sizes). In addition, the mortality rate does not take into account the severity of the cases, e.g. death may occur suddenly or only after a prolonged period of ill health, and that mortality rate standardised for population size does not indicate age groups.³¹

B.2 | OTHER RISK–BENEFIT ASSESSMENT FRAMEWORK

Another framework, similar to that of EFSA 2010, was published in 2012 (Hoekstra et al., 2012) and proposed a tiered approach for the comparison of the benefits and risks of foods. In this approach, also known as BRAFO, Tiers 1, 2 and 3 mirror Steps 1, 2 and 3 of the EFSA 2010 process, whereas an additional Tier 4 is included that refers exclusively to probabilistic analysis (which is part of Step 3 in the 2010 EFSA guidance). As described in this update (Section 4.1), deterministic or probabilistic assessments may be performed within both Tier 2 and Tier 3. As before, the EFSA approach does not structure this in terms of additional tiers or sub-tiers within Tier 2 and Tier 3. Unlike the EFSA framework that leaves open the assessment of a specific scenario or comparison of different scenarios, the BRAFO approach is structured to compare relative effects between a reference scenario and alternative scenarios. Of note, exposure is estimated from all sources in this framework.

In Tier 1, risks and benefits are assessed separately but only changes between reference and alternative scenarios are assessed. Any changes (positive or negative) that are minimal or negligible do not move to the next tier.

In Tier 2, assessment of risks and benefits can be quantitative or even probabilistic but the integration remains qualitative without a common metric and justification of the assessment is important (not self-evident).

As in the EFSA 2010 guidance, if positive or negative health effects neither ‘dominate’ nor ‘clearly outweigh’ each other, refinements are made at a higher tier assessment. It is acknowledged that comparing effects involves expert judgement (which one is ‘more important’, ‘more severe’, etc.) and must be done with caution.

When there are both positive and negative health effects and neither is dominant, they are combined in a composite metric in Tier 3, using a deterministic analysis (fixed estimates of each parameter) or Tier 4 with probabilistic analysis, which has been the focus of other EU projects (see www.qalibra.eu and www.beneris.eu). Probabilistic analysis at Tier 4 also helps resolve some of the uncertainties.

The assessment of each health effect accounts for incidence, severity, duration, mortality (a product of incidence × severity) and lost years by population subgroup. The outputs of the assessments at each tier present the relevant health effects together with these pertinent characteristics that are helpful to the interpretation of the results of the assessment. The severity of health effects in Tier 2 assessments is described using DALY metrics. At higher tiers, the DALY is used as a composite metric for comparing the impact of each health effect on each population subgroup and the overall impact on the population.

A detailed guide to the assessment of uncertainties associated with different input sources of the RBA has also been provided.

B.3 | DEVELOPMENTS IN THE FIELD OF RISK–BENEFIT ASSESSMENT

Many papers have been published since the 2010 SC Guidance that use variations of the RBA methodology. The Horizon 2020 programme³² funded several projects related to the RBA of foods. In addition, a Risk-Benefit Assessment International Network has been developed to provide a platform for knowledge exchange and collaboration (Pires et al., 2019).

In a review of the literature between 1999 and 2014, Boué et al. (2015) found that 70% of the 70 publications retrieved were RBAs of fish and commented on the different approaches used. Of those, 62% applied a threshold approach (comparing exposure to reference values), 20% applied a composite metric (DALY or QALY) and 21% compared risks and benefits by endpoint. An updated review of the literature, by Huang et al. (2022) reported that among 50 RBA publications between 2014 and 2022, 60% assessed fish or seafood ($n = 17$ and 13 , respectively) and the scope remained limited to specific chemical hazards and nutrients. Of these, 70% applied a threshold approach (of which 24% applied a ‘risk-benefit quotient’, RBQ, and the rest simply compared exposure to an HBGV or a DRV), 22% applied integration into a common metric (DALY) and 8% compared risks and benefits on a common health effect.

A scoping review of the literature focusing only on the RBA of fish and seafood assessed the approaches used in 106 publications between 2000 and 2019 (Thomsen et al., 2021). Authors found that 25 of these studies quantified the health impact by integrating risks and benefits into a composite health metric; 63 studies applied a threshold approach, characterising risks and benefits by comparing nutrient and contaminant exposures with DRVs and HBGVs, respectively (including six studies that characterised risks and benefits using threshold-approach with other scales); 14 studies used mixed methods, comparing risks and benefits on different measurement scales; and four studies that mathematically optimised fish consumption to such that meets both nutritional and toxicological recommendations of reaching and not exceeding DRVs and HBGVs, respectively. Some studies presented several separate RBAs each using different measures. About half of the studies addressed specifically the (sub)population of women of child-bearing age.

³¹Standardised mortality is used either due to lack of age-specific data or when age-specific mortality is not of interest.

³²Horizon 2020 was the EU’s research and innovation funding programme from 2014 to 2020 with a budget of nearly €80 billion; https://research-and-innovation.ec.europa.eu/funding/funding-opportunities/funding-programmes-and-open-calls/horizon-2020_en.

EFSA-supported activities through partnering grants (within the EU) resulted in a workshop in Copenhagen in 2017, an EFSA summer school in 2019, the 'Risk Ranking of Chemical and Microbiological Hazards in Foods – Research project and international workshop' (Sand et al., 2023), the project 'RiskBenefit4EU: Partnering to strengthen the Risk-Benefit Assessment within the EU using a holistic approach' (Alvito et al., 2019), the 'Novel foods as red meat replacers – an insight using Risk-Benefit Assessment methods (NovRBA)' project (Naska et al., 2022) and the 'Alternative protein sources in the European diets – integrating health risk-benefit and sustainability' (Alternativa) project. Novel foods (NF) is a new area where RBA has been applied (Naska et al., 2022; Vellinga et al., 2021; Ververis et al., 2024) where the benefits of the NF are taken into consideration when assessing risks and are compared with the benefits and the risks of the food replaced for a more comprehensive assessment of both nutritional value and risk to the consumer from the presence of specific hazards.

One of the projects funded by Horizon 2020 resulted in the development of a digital communication tool³³ that allows the calculation of intake of nutrients and chemical hazards to assist in dietary choices specifically for seafood consumption based on scientific information on a list of nutrients according to the latest EFSA recommendations and data on risks from pollutants from the literature. The tool includes consideration of the sustainability of seafood consumption.

Lastly, several RBAs have been published by national authorities (ANSES, 2010, 2014, 2015, 2019; Outzen et al., 2024; VKM, 2022) while, presently, an RBA of fish consumption is being performed by the WHO (FAO/WHO, 2023) as well as an RBA on seafood in association with child development by the National Academies of Science, Engineering and Medicine (NASEM, 2023).

B.4 | 26TH EFSA SCIENTIFIC COLLOQUIUM

EFSA organised the 26th Scientific Colloquium³⁴ in February 2022 to obtain input from experts on existing and potential new approaches to conducting RBA of foods. The colloquium included an opening plenary session with presentations on the current state of RBA and future RBA needs followed by break-out sessions, each aimed at exploring one of the following areas: (a) understanding the needs of the risk–benefit managers for current and future RBA of foods in European countries, (b) assessing the strengths and weaknesses of existing and possible new approaches to RBA and (c) assessing the data available and new data needed to enable RBA approaches that can meet risk–benefit manager needs.

The conclusions of the scientific colloquium can be summarised as follows:

- *Clear problem formulation and iterative refinements involving risk assessors and risk managers are key.*
- *Current methodologies are useful but should be improved.*
- *More work is needed to identify fit-for-purpose common metrics.*
- *Mechanistic information (NAMs and other) can improve RBA.*
- *More (and targeted) population-based and harmonised data are required.*
- *Collaboration on data generation, exchange and use is needed.*
- *Application of outcome pathways for toxicity as well as for benefits would facilitate the use of data at various levels.*
- *Overall, methodologies should remain flexible.*

³³www.fishchoice.eu.

³⁴26th EFSA Scientific Colloquium: <https://www.efsa.europa.eu/en/events/efsa-scientific-colloquium-26-risk-benefit-assessment-combined-exposure-nutrients-and>.

APPENDIX C

Identification and prioritisation of relevant food components and relevant hazards and benefits

A three-step tiered approach to standardise the prioritisation of food components (nutrients, microbiological hazards and chemical hazards) under assessment has been developed (Boué et al., 2022) in the context of an EFSA-supported project (Naska et al., 2022; Ververis et al., 2024). It applies a similar framework in the three domains (nutrition, microbiology and toxicology) following the same steps, with adaptation of criteria definitions to serve principles of these different domains. In practice, it includes the establishment of three lists of food components: the 'long', the 'short' and the 'final' list (Figure C.1).

The 'long list' of all components in the food is assembled based on an exhaustive literature search, data available from national food composition databases, and from national food safety authorities. A set of criteria addressing the occurrence of food components and the severity of established associated health effects, specific to nutrition, microbiology and toxicology are subsequently considered and prioritised according to their relevance for the assessment in order to compile the ranking and selection of components included in the RBA as the 'short list' (Section C.1). Food components prioritised in the short list are further reviewed for inclusion in the 'final list' of components to be considered for the RBA model based on data availability for a feasible RBA. It is, however, important to note that the final list, which is usually the one communicated in RBA studies, is the list of food components and health effects that can be included in the model, whereas the short list is the one including all the food component-health effect pairs which have been identified as relevant and important to be evaluated with respect to the level of evidence. The aspects missing from the final list are therefore essential and should also be communicated with the results obtained. A detailed description of the criteria used to select food components related to chemical, microbiological hazards and nutrients to be considered in the RBA is provided below. Given the focus of the guidance document on nutrients and chemical hazards, the criteria proposed to select microbiological agents are not presented.

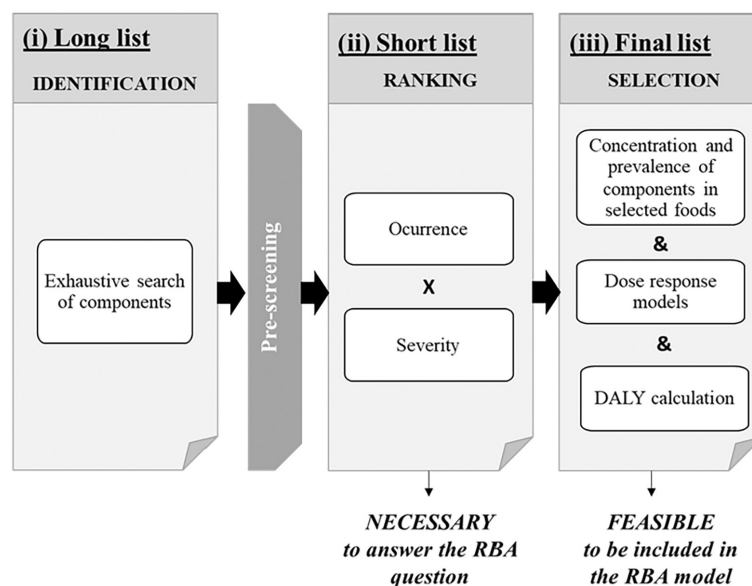


FIGURE C.1 Selection and prioritisation of food components and associated effects, in the context of a case study of a substitution scenario (Boué et al., 2022).

C.1 | DEFINITION OF SUBCRITERIA OF OCCURRENCE AND SEVERITY IN NUTRITION AND TOXICOLOGY TO DEVELOP THE 'SHORT LIST'

C.1.1 | General ranking calculation (common in the fields of nutrition and toxicology)

For the identification of food components to be included in the short list, items in the long list are ranked on the basis of a set of standardised criteria taking into account data on the occurrence (criterion 1) and the severity of the associated health effect(s) (criterion 2) with specific definitions applied in nutrition and toxicology. Each nutrient and chemical hazard receives a grade estimated by the product of the score achieved in each criterion.

C.1.2 | Definition of criteria in nutrition

Occurrence (criterion 1) is defined taking into consideration the concentration of each nutrient in the raw material together with the effect of processing on concentration levels.

The public health nutrition considerations (criterion 2) include: (a) whether the components of interest are included in current food policy measures; (b) the contribution of the food under consideration to the intake of the component of interest from the diet; and (c) how the food matrix could impact the bioavailability of the nutrient.

C.1.3 | Definition of criteria in toxicology

For the selection of chemical hazards, criterion 1 includes two subcriteria: 'the presence relative to reference doses' and 'the contribution to total exposure' (occurrence), while criterion 2 considers the 'impact of associated health effects' (severity).

With respect to criterion 1 on 'occurrence', the sub-criterion 'presence relative to reference doses' is defined considering the concentration of the hazard in the food, whether it is above the limit of detection/limit of quantitation (LOD or LOQ) and whether the total exposure to the hazard exceeds the HBGV (for non-genotoxic carcinogens) or the MOE is below 10,000 (for genotoxic carcinogens). The second subcriterion on 'contribution to total exposure' relies on whether the food is a major (> 50%), a significant (10%–50%) or a minor source of exposure to the hazard, including the possibility of not being a source (< 10%).

Criterion 2 considers the severity of the health effects associated with exposure to the chemical hazard. The severity is evaluated qualitatively and considers the following input parameters.

- (a) Is the incidence of the associated disease/condition high in the population under study?
- (b) Is the disease fatal?
- (c) Is the disease associated with lifelong disability?
- (d) Is the disease associated with high disability (rounded disability weight (DW) > 0.4)?

For each component, criteria 1 and 2 are multiplied and the obtained rankings in each field (nutrition and toxicology) are analysed to set a limit of inclusion in the short list.

C.2 | FINAL LIST

The final selection of food components primarily relies on data availability on dose–response associations at a range of intakes of interest. If a component cannot be further considered in the quantitative estimate (RBA modelling) due to lack of data, this should be clearly denoted as a source of uncertainty and as a priority for future model improvement.

APPENDIX D

Multiple effects assessment

For chemical hazards, a set of approaches that differ in complexity has been developed to support risk characterisation and prioritisations using the traditional framework as a starting point (Sand, 2022). They address that chemical exposures may be associated with different types of health effects. More specifically, the methods are based on the ideas that the amount of effects (e.g. occurring in a target organ) for a given exposure increases with dose and that the severity of these events, or that the severity overall, gradually increases across the dose continuum. Some background and additional information about these approaches are given below. Next, a case study (Section D.1) is provided as one example of how they may support risk-benefit assessments.

SFA (2015) proposed that a severity-adjusted margin of exposure approach could improve the comparison of chemical exposures; i.e. the Risk Thermometer. Compared with Boué et al. (2022) the relation between the exposure and HBGV is assessed quantitatively, and in similarity to Boué et al. (2022), this output is weighted by severity. The overall risk metric, the severity-adjusted MOE (SAMOE), is derived for specified exposure scenarios, e.g. the mean/median or a percentile of exposure to a chemical from foods or food groups in a given population.

SFA (2015) uses a 5-graded severity scale and the selection of weights, i.e. a severity factor of 1, 3.2, 10, 32 or 100, is guided by a health effect classification scheme. This scheme was refined and harmonised across toxicities in Sand et al. (2018). Under the new scheme the 5-graded scale, describing broad effect groups, still applies to the Risk Thermometer, while a connected and overlapping 9-graded refined scale relates to further developments of the model in Sand et al. (2018) described below. The classification scheme/s with associated factors/weights was initially developed as a practical alternative to refining the HBGV using endpoint-specific BMR values, e.g. discussed in WHO/IPCS (2014) and EFSA Scientific Committee (2022). While the scheme is based on toxicological considerations, representing a broader take on the 'dose makes the poison', the quantitative values of associated severity factors for the risk thermometer are value based and were selected in consultation with the SFA risk management. The new scheme can be regarded as a tool that may help guide and harmonise the severity classification of specific effects according to a 5- or 9-graded scale.

A risk classification system is attached to the Risk Thermometer method, which has also been consulted with risk management, where the SAMOE value is classified in one of five 'Risk Classes'. SFA (2015) also describes a quantitative approach for the assessment of uncertainty in the SAMOE, which is partly data-driven (for the RP and the exposure), and partly based on expert assessment (for adjustment factors, including the severity factor). The Risk Thermometer has been used for ranking chemicals (e.g. Langerholm et al., 2018; SFA, 2017) and as part of risk prioritisation in the initial stage of an RBA (SFA, 2022). Also, Ji et al. (2024) implements the SAMOE metric in the Risk Thermometer under the use of a probabilistic HBGV (discussed in Section 4.6.1). As a case example, the resulting MOE-based metric was used for ranking mycotoxins.

Sand et al. (2018) advance the idea behind the Risk Thermometer by the combination and integration of toxicity data to cover a/the domain of effects (i.e. effects across the classification scheme discussed earlier) caused by a compound. A reference point profile (RPP) is defined as the relation between BMDs for considered effects, and either a severity score (for traditional effects) or a rank score (for bioactivity measures) determined for these effects. Similar to traditional risk assessment, adjustment/uncertainty factors can be applied to the RPP, which results in an adjusted RPP (a form of HBGV equivalent based on several effects). In a given analysis, the BMDs and consequently the RPP applies to a standardised benchmark response (BMR) between 0 and 1. Therefore, the RPP represents a cross section of a dose-severity/rank-response volume. The latter may be characterised by adding a model for the shape of the underlying dose-response curve/s. The relation between the RPP and dose-severity/rank-response volume is illustrated and discussed in Figure D.1.

Under the Tier 2 version of the model that applies to a given BMR, the probability of exceeding all BMDs (i.e. the whole RPP) can be assessed for given exposure scenarios (Figure D.1). An overall toxicological response can also be estimated by integrating contributions across effects, i.e. summarising probabilities of exceeding the BMD to a single value by utilising the attached weight function. Under the generalised (Tier 3) model that accounts for the whole BMR domain this response metric describes the probability of effect/s rather than the probability of exceeding associated BMDs. See Figure D.1 for more details.

The uncertainty in the BMD across the different effects may be more or less correlated. To address this issue, the iterative approach for estimating the RPP described in detail in Sand et al. (2018) and Sand (2022) has been further developed. Besides simulating BMDs from estimated uncertainty distributions independently across effects, all individual distributions can also be combined to define a multivariate BMD uncertainty distribution. BMD values may then be simulated from this multivariate uncertainty distribution after specifying a correlation between 0 and 1.

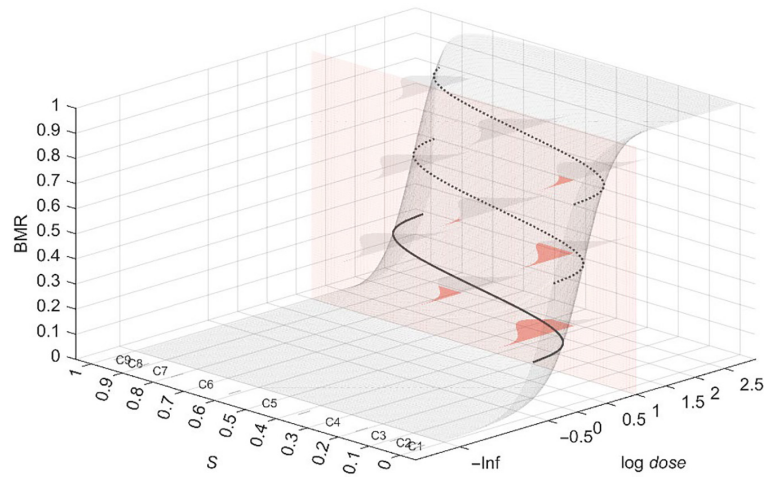


FIGURE D.1 Illustration of the reference point profile (RPP) and the dose-severity/rank-response volume.

For a given chemical hazard or mixture, the RPP describes the relation between BMDs for considered health effects and a relative severity score (S) determined for these effects. The RPP is associated with a normalised benchmark response (BMR). Generalisation across BMRs gives the dose-severity/rank-response volume. RPPs at BMRs of 21%, 50% and 79% are highlighted. The RPP associated with a BMR=0.21 is taken from Sand et al. (2018) describing the BMD profile for liver effects (classified in severity categories C2 to C8 mapped to S) in rodents caused by dioxin-like chemicals. Sand et al. (2018) present an approximate approach for derivation of RPPs across the BMR domain by using a given RPP as a starting point and adding a dose–response model. In this example, a Hill dose–response model with a common shape (Hill coefficient=1.66) across effects was used. This is an average representation of the dose–response shapes obtained in the analysis of the individual liver effects (see Sand et al. (2018) for details). When evaluating the model as illustrated by the vertical (red) plane at log dose=1, probability profiles (red areas) associated with BMRs of 0 through 1 are obtained. For example, at a given relative severity, S , the probability of exceeding the BMD can be derived for each BMR. Integration of these probabilities provides a result equal to the average probability on the BMR interval (0 through 1) at S . This corresponds to the probability of effect at S for the given exposure (e.g. log dose=1). If the RPP variability (red/grey distribution/s) is zero, this integration across BMRs becomes equivalent to directly evaluating the response from the Hill dose–response curve at S . Besides evaluating the model at a given S -value, an integrated response can be derived that summarises the probability profiles (at the different BMRs) to single values (see Sand, 2022; equation 3 in Sand et al., 2018). This collapses the S -axis, resulting in a weighted average of the probability of exceeding the BMD at each BMR. Then, a second integration over BMR will provide a result equal to the average probability on the BMR interval, which corresponds to the probability of (weighted) effect at the given exposure (see Sand, 2022; equation 4 in Sand et al., 2018).

D.1 | CASE STUDY

The risks and benefits associated with the consumption of whole grain are used as one example of how the Sand et al. (2018) method may be used as part of a Tier 2 or Tier 3 assessment. This exercise is limited to consideration of one prioritised risk component (cadmium) and one prioritised benefit (i.e. reduced risk of myocardial infarction, MI) in the assessment by the Swedish Food Agency (SFA, 2022).

D.1.1 | Reference Point Profile (RPP) characterisation

Several effects of cadmium exposure have been identified in epidemiological studies. The TWI established by EFSA (2009) is based on a kidney marker (β -2-microglobulin). Besides effects related to kidney function, bone and cardiovascular effects have also been observed. The multiple effects approach by Sand et al. (2018) is illustrated here using results from benchmark dose analysis of a set of renal and bone effects presented by Suwazono et al. (2006) and Suwazono et al. (2010), respectively. These effects have been assessed in the same group of middle-aged Swedish women part of the Women's Health in the Lund Area (WHILA) study. The data are used for illustrative purposes without consideration of how relevant they would be for an actual RBA. The performed severity classification of effects would also need to be re-visited for an actual assessment.

In the two studies, BMDs corresponding to benchmark responses (extra risks) of 5% and 10% were derived for nine endpoints. These BMDs correspond to an increased probability of 5% or 10% (extra risk) that levels in the respective endpoint are above/below defined cut-off values describing some degree of abnormal change. In this regard, the three bone effects (classified at C5–C7 in Figure D.2) describe three different cut-off values for low bone mineral density. One of these cut-off values corresponds to the definition of osteoporosis, and the other two describe less and more serious reductions in bone mineral density, respectively. A reference point profile based on BMDs associated with a BMR=0.05 was estimated, which after the application of an adjustment factor and population variability resulted in the adjusted RPP shown in Figure D.2.

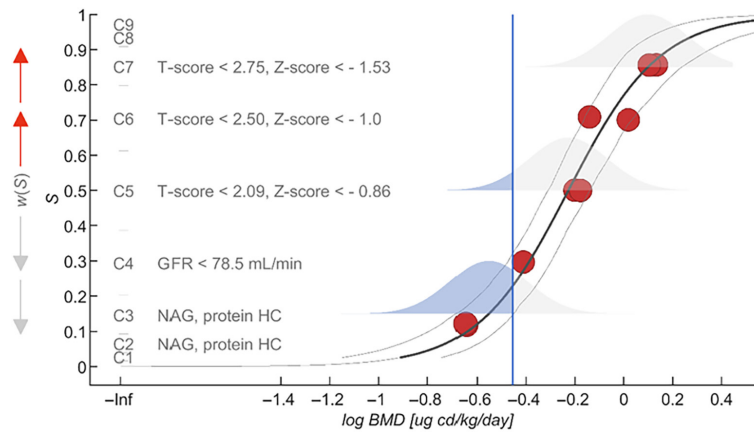


FIGURE D.2 Adjusted reference point profile (RPP) for cadmium renal and bone toxicity.

Circles are BMDs associated with a BMR=0.05 for nine health effects classified at C2 to C7. NAG and protein HC are assigned to either C1 or C2, rather than just a single category. Before fitting the RPP model, as described by Sand et al. (2018), BMDs (in $\mu\text{g/g}$ creatinine) were converted to dietary intake (in $\mu\text{g/kg}$ bw per day) by the multiplication of a factor 0.7906. Amzal et al. (2009) provide information on population variability in the dietary exposure associated with urinary cadmium concentrations of 0.5, 1 and 2 $\mu\text{g/g}$ creatinine. In SFA (2022) normal distributions with mean, $\mu = \log(0.7906 \times \text{urinary concentration})$ and a common standard deviation, $\sigma = 0.483$ (logarithmic scale), were used to approximate the modelled intakes in Amzal et al. (2009). The standard deviation of 0.483 (log scale) describes population variability, which in combination with the dose adjustment (the factor of 0.7906) is used to define the adjusted RPP. The vertical line corresponds to the upper 95th percentile of the cadmium exposure (0.35 $\mu\text{g/kg/day}$; SFA, 2022), which approximates to the EFSA cadmium TWI. The adjusted RPP in the figure represents the lower 5th percentile of the variability distribution. This illustration describes one example of a model evaluation. For the assessed exposure of 0.35 $\mu\text{g/kg}$ bw per day, the integrated probability of exceeding the adjusted RPP (Tier 2 metric) is 0.09 (0.05–0.16). Assuming an underlying Hill dose–response curve with Hill coefficients in the range of 1.4–2.1, the integrated probability of effect (Tier 3 metric) is 0.02 (0.01–0.03). Details related to the derivation of these metrics can be found in Sand et al. (2018) and Sand (2022). By repeating calculations across the whole range of possible exposures and adjusted RPPs an overall population average may be estimated. Table D.1 presents such results based on Monte Carlo simulations accounting for population variability (inner loop) and BMD uncertainty (outer loop).

D.1.2 | Tier 2 assessment

In SFA (2022), the number of reduced cases of MI between the present situation and a scenario where 100% of cereals are consumed as whole grain was about 7000 per year (uncertainty: 4000–11,000). This result was compared qualitatively to the change in the number of individuals exceeding their ‘critical cadmium exposure’, accounting for both population variability in the exposure and in the EFSA TWI, which was 3000 per year (uncertainty: 0 to 18,000). See SFA (2022) for details. Application of the Tier 2 version of the Sand et al. (2018) method enables the type of risk metric used in SFA (2022) to be generalised across several health effects.

In Table D.1, the probability of exceeding the adjusted RPP is given (columns 3–5). Besides the derivation of an integrated probability metric (probabilities integrated across the severity domain, S), the model may be evaluated at any relative severity, S , between 0 and 1. Across the two scenarios (present situation vs. 100% cereals consumed as whole grain), the increase in the number of individuals above the critical cadmium exposure decreases from about 10,000 (severity category 2–3) to below 100 (severity category 7) per year. For the integrated metric, the change is between 600 and 3000 individuals, accounting for the uncertainty and sensitivity analysis performed (Table D.1). Results at the higher severity categories, including the integrated metric, may in this example provide better points of comparisons to the change in MI cases as this is a disease (MI may classify in the range of C7–C8) compared with results at C2–C4.

Considering the population size of 10,230,000 in SFA (2022) used for assessing cadmium risk, a case probability of 0.034 is required to match the 7000 benefit cases (point estimate) per year (assuming 50 years). The adjusted RPP corresponds to a BMR of 0.05, which is not so different from the required case probability of 0.034. Therefore, in order to match the change in benefit cases (describing disease), the integrated probability of exceeding the adjusted RPP or the probability of exceeding the adjusted RPP at a high severity category would need to significantly increase versus the present situation. For example, if the integrated metric in the whole grain scenario were 0.5 (i.e. 50% of the population exceeding), the average disease probability would be equal to or larger than the BMR of 0.05 (assuming sigmoidal dose–response on a log scale). The change in disease cases per year would then be in the range of 10,000 or more, which would then exceed the 7000 benefit cases. As is shown in Table D.1, the integrated probability of exceeding the adjusted RPP in the whole grain scenario is far from 50%, i.e. only about 1%–2% (point estimate).

D.1.3 | Tier 3 assessment

The result from the Tier 3 version Sand et al. (2018) is also given in Table D.1 (columns 6–8). This describes the probability of effect/s rather than the probability of exceeding the adjusted RPP. The results related to different severity categories, and the integrated metric, are more or less quantitatively comparable to the number of reduced MI cases. The latter (4000–11,000 per year) can be contrasted to an increase in the number of risk cases per year that range between about 100 (C7)

and 2000 (C2–C3) depending on the health effect and severity category. Considering the integrated metric the increase is about 200–600 cases, accounting for the uncertainty and sensitivity analysis performed (Table D.1). This would be quantitatively comparative to the number of MI cases after the application of a weight to the latter using the same severity scale (MI may classify in the range of C7–C8). These types of results may further clarify the trade-off between the considered benefit and risks.

As can be seen from the results in Table D.1 for the integrated metric, the selection of weights may not necessarily have a large impact if the RBA focuses on differences between scenarios rather than absolute risks and benefits. Also, in this example, the consideration of correlated BMD uncertainty does only slightly increase the uncertainty in the integrated metric (Table D.1). More generally, the Tier 3 metric may be more stable and less uncertain than the Tier 2 metric, e.g. when evaluated at high relative severities (5). If the benefit side does not represent a Tier 2 metric, the Tier 3 version may be considered directly by assuming a dose–response model.

As part of the analysis the Tier 3 results were contrasted to a more conventional approach of estimating the probability of response for each health effect separately (Table D.1 columns 9 and 10). A Hill model was used to describe all underlying dose–response relationships. The parameter values of this model (i.e. the ED50 and the Hill coefficient) were derived for each health effect by superimposing the curve to both of the reported BMDs (corresponding to BMRs of 5 and 10%, respectively) for each health effect. The slope (Hill coefficient) ranged between 1.4 and 2.1 across the nine health effects. The effect-specific slope values were used in the conventional analysis and under the Sand et al. (2018) method results were derived by using a slope value in the observed range (1.4–2.1) that was randomly sampled (assuming a uniform distribution) as part of each uncertainty iteration (i.e. as part of the outer loop in the Monte Carlo simulation). Comparison of results for the different severity categories indicates consistency between approaches (Table D.1). For example, the Sand et al. (2018) model estimate at category C6 is 0.002 (present situation), which lies between the estimates of 0.001 and 0.003 from the conventional analyses (Table D.1). This is in line with Figure D.2 showing that the BMDs at C6 are on either side of the central estimate of the adjusted RPP. Also, in this example, a simple weighted average of results from the conventional analyses became very similar to the integrated metric. More generally, however, this may depend on the RPP variance, how the data cover the severity domain and are situated relative to the model, as well as the setting of the weight function. In this standardised comparison, for most effects/categories, the uncertainty in estimated probabilities from the combined model is lower than the uncertainty in corresponding results from the conventional analysis (according to the confidence intervals in Table D.1). The generalisability and significance of this, however, requires further analysis.

TABLE D.1 Risks associated with cadmium exposure under present exposure (present) and increased consumption of whole grain (scenario).

Health effect	Relative severity, S (category)	Probability of exceeding adjusted RPP ^a based on RPP for a BMR=0.05			Probability of effect ^b based on combining RPPs (BMRs=0–1)			Probability of effect ^c based on individual dose–response curves	
		Present	Scenario	Difference (cases)	Present	Scenario	Difference (cases)	Present	Scenario
N-acetyl-β-D-glucosaminidase NAG > 3.6 U/g creatinine	0.12 (C2–C3)	0.073 (0.03–0.14)	0.13 (0.06–0.23)	11,000 (700–19,000)	0.017 (0.01–0.03)	0.026 (0.02–0.04)	1800 (1100–3000)	0.018 (0.01–0.02)	0.025 (0.02–0.03)
Human complex forming protein Protein HC > 6.8 mg/g creatinine								0.018 (0.01–0.03)	0.026 (0.02–0.04)
Glomerular filtration rate GFR < 78.5 mL/min	0.29 (C4)	0.017 (0.005–0.03)	0.035 (0.01–0.06)	3800 (1700–6100)	0.008 (0.005–0.01)	0.011 (0.007–0.02)	700 (500–1000)	0.009 (0.004–0.02)	0.013 (0.006–0.02)
Bone mineral density T-score < 2.09	0.50 (C5)	0.004 (0.001–0.01)	0.01 (0.003–0.02)	1200 (400–2300)	0.004 (0.002–0.006)	0.006 (0.003–0.009)	400 (200–500)	0.004 (0.001–0.008)	0.006 (0.002–0.01)
Bone mineral density Z-score < –0.68								0.004 (0.001–0.009)	0.006 (0.002–0.01)
Osteoporosis T-score < 2.50	0.71 (C6)	0.001 (0–0.003)	0.003 (0.0002–0.007)	330 (40–800)	0.002 (0.001–0.004)	0.003 (0.002–0.005)	200 (100–400)	0.001 (0.0003–0.003)	0.002 (0.0004–0.004)
Osteoporosis Z-score < –1.0								0.003 (0.0008–0.007)	0.004 (0.001–0.01)
Bone mineral density T-score < 2.75	0.85 (C7)	0.0002 (0–0.0009)	0.0005 (0–0.002)	60 (0–200)	0.001 (0.0004–0.002)	0.002 (0.0007–0.003)	100 (50–200)	0.0005 (0.0001–0.001)	0.0008 (0.0002–0.002)
Bone mineral density Z-score < –1.53								0.0005 (0.0001–0.001)	0.0009 (0.0002–0.002)
Integrated/weighted metric Linear weight, a = b = 1	-	0.006 (0.002–0.01)	0.013 (0.006–0.02)	1200 (700–1900)	0.003 (0.002–0.005)	0.005 (0.003–0.007)	400 (200–500)	0.003	0.005
Integrated/weighted metric Weight, a = 0.75, b = 1	-	0.013 (0.006–0.02)	0.024 (0.01–0.04)	2100 (1300–3100)	0.005 (0.003–0.007)	0.007 (0.005–0.01)	500 (300–600)	-	-
Integrated/weighted metric Linear weight, correlation = 0.5	-	0.006 (0.002–0.01)	0.012 (0.005–0.02)	1200 (600–2100)	0.003 (0.002–0.005)	0.005 (0.003–0.008)	400 (200–500)	-	-

Note: For 'present' and 'scenario' the mean cadmium exposure is 0.18 and 0.23 µg/kg/day, respectively. The population variability in the exposure and RPP was assumed to be normal on the log scale (standard deviations of 0.39 and 0.48, respectively), as well as the uncertainty in reported BMDs (BMR=0.05). Probabilities in the table have been calculated using Monte Carlo simulations accounting for population variability (inner loop) and BMD uncertainty (outer loop). Results are presented in terms of the population average with a 90% confidence interval. The differences in the no. of cases across scenarios are based on a population size of 10,230,000, and is presented on a per year basis (divided by 50) in line with SFA (2022).

^{a,b,c}Probability of exceeding the adjusted RPP (column 3–5), probability of effect according to generalised response metric in Sand et al. (2018) (columns 6–8), and probability of effect based on separate analysis of the health effects (columns 9 and 10). The integrated response metric is presented for a linear and a non-linear severity weight, and for a scenario where the BMD uncertainty is correlated. For the separate analysis of health effects, the integrated metric is a simple weighted average using S-values in column 2 as weights.

APPENDIX E

Application and interpretation of the Disability Adjusted Life Years (DALYs)

In a quantitative risk–benefit assessment, the health impact of going from the reference scenario to the alternative scenarios is quantified on a common scale of measurement for each individual health effect.

Such a scale can be disease incidence or mortality. However, the most commonly used health metric in RBA is the disability adjusted life years (DALY), which is an integrated composite health metric, as it allows inclusion of incidence and duration of disease, severity of disease and mortality, for all health endpoints considered.

The DALY is a measure, which compares a given health state with an ideal state of health and well-being. The DALY measures health loss due to morbidity and mortality as a result of a health outcome, where one DALY is equal to one healthy life-year lost.

In addition, it allows for a comparison across diseases and disabilities and combines information on incidence, severity and duration of a health outcome (Years Lived with Disability, YLD) with the Years of Life Lost (YLL) due to premature death (Devleeschauwer et al., 2014a, 2014b; WHO (World Health Organization), 2017). A basic approach of calculating DALY is presented below.

$$\text{DALY} = \text{YLD} + \text{YLL}$$

where:

$$\text{YLD} = \text{AC} \times D \times \text{DW}$$

$$\text{YLL} = \text{AD} \times \text{SEYLL},$$

where AC is the annual number of incident cases of a given health outcome in a population; D is the duration of the health outcome in years from onset until remission or death; DW is the disability weight for the health outcome. The DWs can be found in the scientific literature, WHO or the Institute for Health Metrics and Evaluation (see Section 4.7.3); AD is the annual number of deaths due to the health outcome; and SEYLL is the Standard Expected Years of Life Lost.

The DALY incorporates severity of disease or disability by use of the DWs, which reflect the relative reduction in health on a scale from zero to one, where zero implies perfect health and one is equivalent to death. The DWs are socially derived values based on how the majority of people perceive living with a disease or condition and thus also reflect the relative severity of diseases and disease stages.

DWs have been developed for a limited range of diseases. Thus, to calculate DALYs for conditions or health effects where no DW exist, these health effects should be identified and characterised during the previous steps of the RBA. The purpose is then to translate the health effect into a defined disease or disability for which a DW exists. An example is the case where a decrease in sperm concentration due to a given chemical exposure could be translated into a risk of infertility at population level.

Duration of disease or disability is also required to calculate YLD, and can be estimated based on data from the literature, hospital registries or expert elicitations. For diseases and disabilities that persist until death, the duration is calculated as the difference between the age of onset of the disease and the life expectancy for the given age and sex as obtained by national population registries.

Residual life expectancy is required for calculating YLL. According to the WHO methods for global burden of disease estimates 2000–2015 (WHO, 2017), SEYLL should be based on the frontier national life expectancy projected for the year 2050 for Japanese women, should be applied as the residual life expectancy for calculating YLL, rather than national life expectancies.

The last step of the risk–benefit assessment process is the integration of risks and benefits and the comparison of scenarios. If the outcome of the RBA is expressed in terms of DALYs, a difference in DALYs between an alternative scenario and a reference scenario should be reported. The DALY difference, ΔDALY_d , for health outcome d is calculated as follows:

$$\Delta\text{DALY}_d = \text{DALY}_{d,\text{alt}} - \text{DALY}_{d,\text{ref}}$$

where $\text{DALY}_{d,\text{alt}}$ and $\text{DALY}_{d,\text{ref}}$ are the estimated disease burden in the alternative scenario and the reference scenario, respectively, for health outcome d . Estimation of the overall health impact, the DALY difference over all diseases and health outcomes is calculated as:

$$\Delta\text{DALY} = \Sigma (\Delta\text{DALY}_d).$$

A positive DALY difference implies a health loss, whereas a negative DALY difference implies a health gain. The total DALY difference can be expressed for the total population but for comparison DALYs are often expressed per 100,000 individuals.

The DALY approach can be implemented in different ways, depending on data availability and the assessment objective, see for example (Hoekstra et al., 2008; Hoekstra, Hart, et al., 2013; Naska et al., 2022; Thomsen et al., 2018; Ververis et al., 2024).

An example of how the DALYs are interpreted are presented in Thomsen (2018). In this study, the health impact of substituting red and processed meat with fish in the diet of the adult Danish population was quantified using DALYs as health metric. The following scenarios were compared to the current Danish consumption of fish (reference scenario):

- Alternative scenario 1: consumption of 350 g of a mix of lean and fatty fish per week.
- Alternative scenario 2: consumption of 350 g of fatty fish per week.
- Alternative scenario 3: consumption of 350 g of lean fish per week.
- Alternative scenario 4: consumption of 350 g of tuna per week.

To quantify the health effect of each health outcome in terms of DALYs for these scenarios, YLD for health outcome d , sex s and age a was defined as:

$$YLD_{d,s,a} = AC_{d,s,a} \cdot D_d \cdot DW_d$$

where $AC_{d,s,a}$ is the annual number of cases with health outcome d for sex s and age a , D_d is the duration of health outcome d until remission or death and DW_d is the disability weight for health outcome d .

YLL for health outcome d , sex s and age a was defined as:

$$YLL_{d,s,a} = AD_{d,s,a} \cdot SEYLL_{s,a}$$

where $AD_{d,s,a}$ is the annual number of deaths due to health outcome d for sex s and age a and $SEYLL_{s,a}$ is the standard expected years of life lost for sex s and age a (WHO (World Health Organization), 2017). Finally, the disease burden for health outcome d was summed over sex and age:

$$DALY_d = \sum_s \sum_a (YLD_{d,s,a} + YLL_{d,s,a}).$$

The outcome of the calculations, expressed in DALY for the Danish population ≥ 15 years (4.7 million individuals), can be seen in Figure E.1, and shows the health impact of the substitution in terms of the total DALY difference for each alternative scenario compared to the reference scenario. An overall health gain was observed in the alternative scenarios 1, 2 and 3 (note the negative numbers), whereas a health loss (positive number) was observed for the alternative scenario 4.

The DALY difference estimates were significantly different from zero in all alternative scenarios ($p < 0.001$).

The outcome shows that approximately 7000 healthy life years could be gained each year in Denmark if the adult population substituted some of the red and processed meat in the diet with fish to reach the recommended intake of 350 g of fish per week (a mix of fatty and lean, or only fatty fish). In contrast, a smaller health gain was estimated when consuming only lean fish in the recommended amounts and an overall health loss was estimated when consuming only tuna.

To assess the significance and magnitude of the observed DALY differences, they can be compared with the outcome of other RBAs, risk ranking and burden of disease estimates where the output is also quantified in DALY.

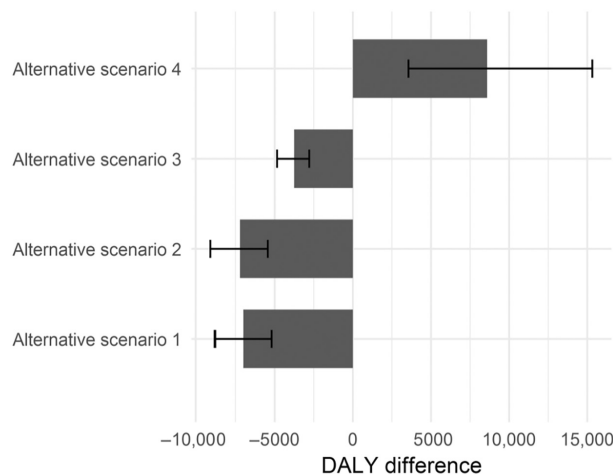


FIGURE E.1 Difference in Disability-Adjusted Life Years (DALYs) by scenario. DALY difference between the current consumption (reference scenario) and the four alternative scenarios for the total Danish adult population (≥ 15 years; 4.7 million individuals). The bars represent the DALY differences between each of the four alternative scenarios and the current consumption as a measure of the health impact of the substitution. Error bars indicate 95% uncertainty intervals.

APPENDIX F

Templates for risk–benefit assessment data and outputs of risks and benefits

The complexity of risk–benefit assessments, when involving multiple hazards and nutrients, different food scenarios, populations and other dimensions, calls for clear, comprehensive and transparent presentation of data and results in summary tables (Tables F.1–F.6). These may present the elements included in the assessment (e.g. Table F.1), or the output(s) of the assessment in different formats depending on the approach followed and the tier of the assessment. A few examples of templates are provided in the appendix, including in format of a heat map (e.g. Table F.3) that may be useful to convey the overall picture of complex outputs.

Additionally, the reader is referred to tables 3 and 4 in Hoekstra et al. (2012) as examples of outputs from Tier 2 and Tier 3 assessments, respectively. In this publication, Table 3 summarises dimensions of two different health effects, a beneficial and an adverse, the corresponding common metrics in terms of life years lost per mortality and the net health impact in qualitative terms. Table 4 presents a quantitative integration of different health effects resulting from an example of food fortification, the corresponding DALY for each health effect and the net health impact as a sum of DALYs.

TABLE F.1 Characterisation of the exposure to hazardous and beneficial food components by level of consumption (e.g. mean \pm SD, or range).

Food component	Intake of food		
	10 g	100 g	200 g
Hazardous			
A	... μ g/g		
B	... ng/g		
C			
D	No data	No data	No data
Beneficial			
A	... mg/g		
B			
C			
D			

TABLE F.2 Template for reporting composite metrics for different effects impacting different populations.

Risk	(Q)DALYs			
	Critical effects (risk ranking)	Population 1	Population 2	Population 3
Intake				
1	Obesity			
2	High blood pressure			
3	Colorectal cancer			
...	...			
Benefit	(Q)DALYs			
	Critical effects	Population 1	Population 2	Population 3
Intake				
1	Iron deficiency anaemia			
2	Cardiovascular disease			
3				
...	...			

TABLE F.3 Template for reporting different effects impacting different populations by means of different metrics, such as per cent population above or below a BMD or other threshold; as probability of an effect occurring at various intake scenarios in a given population; heat map.

Risk		>/< BMR P(effect) P(severe effect)		
Intake	Critical effects (apply risk ranking)	Population 1	Population 2	Population 3
1	A
2	B (+C)
3	(B+)C
...	...			
Benefit		>/< DRV P(deficiency) P(risk not averted)		
Intake	Critical effects	Population 1	Population 2	Population 3
1	A
2	B
3	C
...	...			

Note: A heat map can be constructed to present results for several endpoints by populations, using separate colour for risks and benefits (here orange and green, respectively). The heatmap may include measures of incidence, severity, duration, mortality and other assessed features. Such aspects are combined in calculations of composite metrics. However, each of the aspects (incidence, severity, duration, mortality) may have a different scale (and different distribution) that may be represented with a simple scoring scheme without agglomerating into a single metric, e.g.: severity: 5-point scale (Sand); duration: 3-point scale (short, intermediate, long); incidence: 10-point scale (1–10); contribution to mortality. The intensity of the respective colour indicates a scale of risks and benefits from low (lighter shade) to high (darker shade). No shade may be used if data are not available, or health effect is not applicable.

TABLE F.4 Template for reporting risks by means of probability of each effect and their possible cumulative occurrence at increasing intakes, together with associated uncertainties.

Compound	Age/pop. group	Effect	Intake 1 (dose)	Intake 2 (dose)	Intake 3 (dose)	Uncertainty
A	Children	Neurobehaviour	$P(S1)$	$P(S1) + P(S2)$	$P(S1) + P(S2) + P(S3)$...
		Thyroid		$P(S1)$	$P(S1) + P(S2)$...
		Delayed puberty		
	Adult	Liver		$P(S1)$	$P(S1) + P(S2)$	
		Thyroid			$P(S1)$	
		Cardiovascular				
	Women reproductive age	Infertility				
B						
C						
D						

Note: $P(S)$: probability (P) of each effect over a range of severity levels (S) for effects 1, 2, 3, etc. ($S1, S2, S3$, etc.) (or probability > BMDx). Another metric that may be used is integrated response (RTR) across effects x severity, at each level of intake, in each subpopulation.

TABLE F.5 Template for reporting benefits by means of probability of each effect and their possible cumulative occurrence at increasing intakes, together with associated uncertainties.

Compound	Age/population group	Positive effect	Intake (dose) median	Intake (dose) 95%	Intake (dose) 200 g	Uncertainty
A	Children	A		
		B		
		C		...		
	Women reproductive age					
	Adults					
B						
C						
D						

TABLE F.6 Template for reporting outcomes as probabilities of effects.

Health effect	Relative severity, S (category)	Probability of exceeding adjusted RPP ^a based on RPP for a selected BMR			Probability of effect ^b based on combining RPPs (BMRs = 0–1)			Probability of effect ^c based on individual dose-response curves	
		Present	Scenario	Difference	Present	Scenario	Difference	Present	Scenario
A									
B									
C									
D									
Integrated/weighted metric									
Linear weight (a, b values)									

APPENDIX G

Risk-benefit communication guidance

This section describes the basis for EFSA's definition of risk-benefit communication and summarises social science literature relevant to food-related risk-benefit communication that was reviewed for this Guidance document. These are structured in three sections: (1) consumer perceptions of food-related risks and benefits, (2) characteristics of risk-benefit trade-offs, and (3) information seeking and processing. Based on these findings, it provides advice for contextualising risk-benefit analysis both when framing requests for risk benefit assessments, and for communicating assessment and management outcomes to the public. It concludes with recommendations for testing the proposed advice and for further research to fill gaps in the literature.

The SC considers (see Appendix A.2) that, 'In RBA, a benefit can be defined as the probability of a positive effect and/or the reduction of an adverse effect [...]'. The WHO defines health as a state of physical, mental, and social well-being and not merely the absence of diseases or infirmity (WHO, 1946). The EU Food Law Regulation (178/2002) focuses primarily on the protection of human life and health, as well as the rights of consumers. However, Article 22 states that EFSA shall provide 'scientific advice and scientific and technical support on human nutrition' and Article 14 stipulates that when 'determining whether any food is unsafe, regard shall be had: [...] (b) to the information provided to the consumer, including information on the label, or *other information generally available to the consumer concerning the avoidance of specific adverse health effects* from a particular food or category of foods.'

Risk benefit communication is not explicitly defined in Regulation 178/2002, but it can be inferred from the definition of 'risk communication' (see Appendix A.1) which states that this involves the 'interactive exchange of information and opinions about hazards and risks among risk assessors, risk managers, consumers, feed and food businesses, the academic community and other interested parties, including the explanation of risk assessment findings and the basis of risk management decisions'. Taken together with the above-mentioned articles, as both nutrition (although not advice to consumers, which is a national competence) and risk reduction information is within EFSA's remit, their communication can be considered objectives of EFSA's risk benefit communication. Lastly, many studies indicate that people confound health risks and benefits with non-health related risks and benefits, e.g. environmental impact, animal welfare, and socioeconomic (see e.g. Lusk & Briggeman, 2009). Social psychological theoretical models (e.g. the Health Belief Model) have been developed on the premise that people often undertake health-related behaviours for seemingly non-health reasons (Jones et al., 2015). Effective communication planning, therefore, requires the identification of these non-health related risks and benefits so that they can be taken into account, as far as possible, in developing communication strategies and messaging.

In summary, the SC considers for this Guidance document, that 'risk benefit communication' involves the 'interactive exchange of information and opinions about hazards (including human or animal health/welfare, socioeconomic, environmental), risks and benefits among assessors, managers, consumers, feed and food businesses, the academic community and other interested parties, including the explanation of risk benefit assessment findings and the basis of risk benefit management decisions.'

G.1 | CONSUMER PERCEPTIONS OF FOOD-RELATED RISKS AND BENEFITS

In the 2022 Eurobarometer on food safety in the EU (NB significant differences exist across countries and should always be considered in developing tailored communication) over 2 in 5 respondents (46% and 41%) declare themselves to be almost equally concerned about a healthy diet and food risks, a third (31%) are more concerned about a healthy diet than about food risks, leaving 1 in 5 reporting that food safety concerns them more than a healthy diet (EFSA, 2022b). In a systematic review carried out for EFSA by Jaskiewicz et al. (2023), studies showed that consumer perceptions of food safety and health benefits vary widely and are shaped by several internal and external factors. For example, the perception of highly beneficial foods was found to rely more on individual personal beliefs and cultural background (e.g. nationality, religion) than consumer awareness of specific health issues (Adamczyk & Maison, 2021; Jahn et al., 2019; Kuttschreuter & Hilverda, 2019; Zorell, 2022). Also, consumer perceptions of risks and benefits to health often do not necessarily motivate them to purchase or consume differently. Other factors play an important role; for example, in the above-mentioned 2022 Eurobarometer more respondents indicated cost (54%) and taste (51%) above safety (46%) or nutrient content (41%), as factors influencing their food purchases (EFSA, 2022b).

Factors influencing risk (and to a lesser extent benefit) perceptions are well documented in the literature on the psychometric approach of Slovic and others, and in subsequent research (for a comprehensive review see EFSA, 2021): individuals combine their knowledge or perceptions of 'naturalness', 'convenience', 'tradition', 'origin', 'fairness', 'appearance' with other criteria such as 'taste', 'cost', 'nutrition' and their 'values'. These combinations can be made based on different dimensions that may be weighed against each other, e.g. increased tastefulness may require food additives, or increased fairness may imply increased costs. Depending on what people value more, a different evaluation of risk versus benefit will emerge (Lusk & Briggeman, 2009). In response to a request from the European Commission for technical assistance in the field of risk communication EFSA developed a 'concern assessment' framework (referred to in the report as 'risk profiling') that clusters the various factors in four groups by characteristics of the hazard, the individual, socio-cultural, and source of information (EFSA, 2021). The concern assessment framework and a pre-assessment tool consisting of a checklist are used in EFSA's risk communication planning to define audiences, objectives and strategies (Vrbos et al., 2023) (see Section G.5.2 below).

In addition, the review conducted for EFSA by Rodes-Sanchez et al. (2024) analysed papers and grouped the key factors that increase or decrease risk perceptions and benefit perceptions. These are summarised in Figure G.1 below, augmented with papers from Jaskiewicz et al. (2023) or identified as relevant by EFSA's social science experts. Trust in science can both decrease risk perception and increase benefit perception (Boehm et al., 2021; Viscecchia et al., 2018), while a lack of trust in industry as a source of information would have the opposite effect (Boehm et al., 2021; van Dijk et al., 2011). Lack of knowledge, and confusing or conflicting information were all associated with increased risk perception (Nagler, 2014; van Dijk et al., 2011), but some studies showed it had no effect on behaviour (Rodríguez-Entrena et al., 2016).

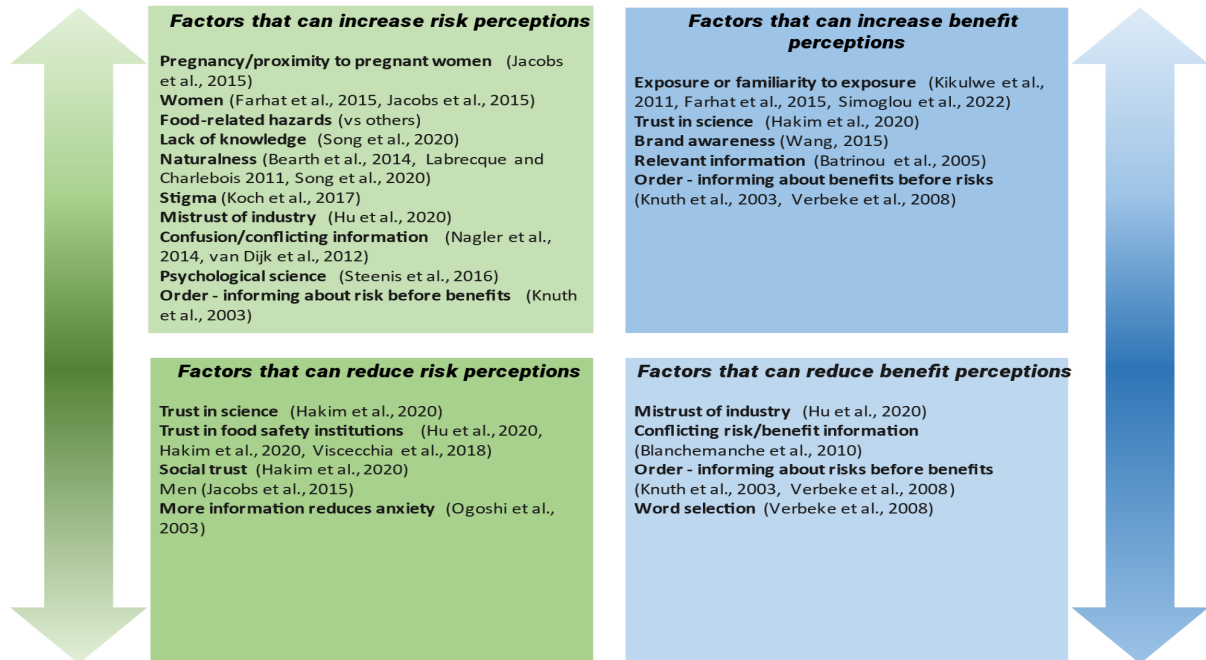


FIGURE G.1 Schematic of influences on risk and benefit perception. *Source:* Adapted from Rodes-Sanchez et al. (2024).

Some of the papers reviewed by Rodes-Sanchez et al. discuss whether risks and benefits are perceived or assessed independently or dependently of each other. Four papers (Bearth et al., 2014; Hakim et al., 2020; Labrecque & Charlebois, 2011; Song et al., 2020) argue for dependency between the two processes due to the impact of one or more other factors such as dread (e.g. Song et al., 2020), or trust. Alternatively, five papers (Amin et al., 2014; Hu et al., 2020; Jacobs et al., 2015; Steenis & Fischer, 2016; Wang, 2015) suggest that risk-benefit perceptions are independent. This may be because a third factor affects individual risks and benefits differently, or because high risk perception and high benefit perception can be experienced simultaneously.

G.2 | CHARACTERISTICS OF RISK-BENEFIT TRADE-OFFS

Consumers face a variety of potential trade-offs that have consequences for communication. Additional information may not necessarily help individuals' decision-making as comparing or trying to quantify different benefits and costs can be challenging. Risk benefit communication strategies need to consider these potential trade-offs and how they impact information processing and consumer behaviour.

Individuals consider, both consciously and intuitively, a range of factors when facing risk-benefit trade-offs about food and these tend to vary greatly depending on the characteristics of individuals and on cultural context. In Jaskiewicz et al. (2023), predominantly using studies in European countries, findings show that consumers are more likely to accept new food technologies if they are informed about their potential benefits alongside addressing perceived risks (Bearth et al., 2022; Busch et al., 2020; Hartmann et al., 2018). Some evidence indicates that information on the origin and traceability of food products can increase consumer perceptions both of a product's safety and its healthiness. For example, consumers want information about the origin of dairy, poultry, red meat, fruit and vegetables to understand their safety (Füzesi et al., 2018). According to some studies, organic foods are associated with safety and health, more than being good for the environment (Lamonaca et al., 2022; Mondelaers et al., 2009).

However, the literature disagrees about the relative weight of risks and benefits on individual decision making. In the review by Rodes-Sanchez et al. drawing mainly on studies in non-European countries, several papers suggest risks generally outweigh benefits or that the absence of risk can be a pre-requisite to any consideration of benefits. Examples of the reasons given for this varied, including negativity bias, i.e. negative information (about perceived risks), increased risk perceptions more than positive information (about real benefits), increased benefit perceptions in studies on willingness to purchase (Rodríguez-Entrena et al., 2016), willingness to pay (Valente & Chaves, 2018) and willingness to eat

(de Oliveira et al., 2021; Verbeke & Liu, 2014). In one study the health benefits of functional foods were seen to be irrelevant if the risks (nutritional, process-related or high-cost production) were perceived to be high (Labrecque & Charlebois, 2011). Importantly, in all such studies methodological aspects, specifically the measurement instruments used could explain the mixed results and other variables such as age, gender, education level, and geographical location, can have a telling influence.

In other studies, benefits outweighed risks and were often linked to the use of new technologies including human-derived fertiliser (Segrè Cohen et al., 2020), food truck repurchasing (Loh & Hassan, 2021) and consumption of insects (Orkusz et al., 2020). In these studies, the benefits were largely related to price, hedonistic value, quality and taste rather than health. Kim (2012) found that the perceived benefits of GMOs had a 35% greater impact on concern than risks. However, another study indicated benefits outweighed risks for GM crops, but the opposite was true for GM salmon (Amin et al., 2014), suggesting food type may also influence trade-offs.

G.3 | INFORMATION SEEKING AND PROCESSING

Most EU citizens indicate an interest in food safety (EFSA, 2022b), but do not necessarily actively seek information on a topic if it is negative (Ito et al., 1998) or does not conform to their prior beliefs (Poortinga & Pidgeon, 2004). Assimilation of food safety knowledge tends to be passive unless circumstances are exceptional such as during a food safety incident, but providing more information on the severity of a hazard may provoke greater information seeking and willingness to change behaviour (Neuwirth et al., 2000). In the review carried out by Jaskiewicz et al. (2023) some studies indicated that some consumers actively seek food safety information, want to be informed and value food safety and food traceability (Kiliç et al., 2020; Tessitore et al., 2020; Tiozzo et al., 2019). The studies also indicated that consumer knowledge of food safety can be improved. The reasons for this may differ. In the above-mentioned 2022 Eurobarometer several reasons are given by respondents why they may not pay attention to food safety information. While a majority explain that they 'take food safety in the EU for granted' (41%) or 'know enough to avoid or mitigate food risks' (30%), for over 1 in 4 (27%) complexity and the technical nature of food safety information is a barrier, or simply a lack of time (15%) (EFSA, 2022b).

Again, the 2022 Eurobarometer provides extensive information about EU consumers' most frequently used and trusted sources of food safety information, across all EU countries. At the EU level approximately 3 in 5 (61%) indicate television (TV set or online) first followed by family members, friends, neighbours or colleagues (44%). While television is the most selected source both within the oldest age group (72%) and the youngest age group (43%), there is greater uptake of social media and blogs within the youngest age group (43%) than within the eldest (10%) (EFSA, 2022b). However, there are major differences between countries in consumers' preferences for seeking food safety information (Bolek, 2020; DunnGalvin et al., 2019; Kiliç et al., 2020; Tiozzo et al., 2019; Zorell, 2022). The 2022 Eurobarometer provides several examples: use of television ranges from 82% in Portugal to 49% in Finland and Latvia, and 44% in Malta; in Greece (66%) and Bulgaria (62%) family, friends, neighbours or colleagues are an important source, but only 30% in Malta, 32% in Finland and 34% in Lithuania.

Consumers tend to prioritise risks over benefits in their trade-offs when their knowledge is incomplete/lacking (Galati et al., 2019), or information is conflicting (Fontalba-Navas et al., 2020). In addition to knowledge, consumers require information that aligns with their values and attitudes in order to shape their opinions about food-related risks and benefits (e.g. Hansen et al., 2003; Ho et al., 2019; Morgan et al., 2002). One example concerns the benefits of fruit and vegetable consumption alongside the risk of exposure to pesticide residues, where although scientific assessments tell us that the benefits outweigh the risks, consumers may perceive the opposite to be true, resulting in reduced fruit and vegetable consumption (Hartmann et al., 2018). A study by Minnens et al. (2020) evaluated consumer acceptance in five European countries (Belgium, Norway, Spain, Portugal and Ireland) of an online tool called FishChoice to access information about the health benefits of fish/seafood consumption and the potential risks from environmental contaminants of these foods. Some two-thirds of respondents, especially high consumers of seafood, declared they would use the tool to find out about the seafood species, portion size or frequency of consumption. As such, consumers may weigh benefits and risks differently if they have more detailed and accurate information. However, even when they have information, they consider useful, such as traceability information on their food, this does not necessarily affect their food purchasing and consumption behaviour (Kumpulainen et al., 2018).

G.4 | CONCLUSIONS

The following advice on risk-benefit communication is based on the main findings from the literature explored above. It mainly intended to support communication of risk-benefit assessment outcomes. The primary communication objectives of assessors and managers differ in important ways: in line with the definition provided above, assessors must 'explain risk-benefit assessment findings' and managers 'the basis of risk-benefit management decisions'. However, both assessors and managers must enable the exchange of information and opinions about hazards, risks and benefits in an interactive way among all interested parties in EU food safety. Critically, many studies indicate that risk communication and, to some extent, benefit communication are more effective when assessment outcomes and management measures form part of a single, coherent narrative. Therefore, although assessors' and managers' competences vary, they share many communication objectives and should adopt coherent strategies to address them.

G.4.1 | Factors influencing risk and benefit perceptions

- Perceptions of risks and benefits can be both dependent and independent of one another, whether health and/or non-health related, and they can be experienced separately or simultaneously. Both internal and external factors can influence these perceptions.
- Mapping these factors (see G.1 Characteristics of target audiences, above) for each risk-benefit analysis problem is essential for developing effective risk-benefit communication strategies to support the evaluation of consumer risk-benefit trade-offs (see G.4.3 Information and behaviour).
- Communication should seek to address a limited number of these factors at a time to be effective.
- Since trust in science can both decrease risk perception and increase benefit perception, risk-benefit communication should underline the role of science and its commitment to public health goals both in assessments and as a basis for management decisions. However, to be effective this must be done in accessible and non-technical language.

G.4.2 | Information needs

- While some consumers want to be informed about food safety and food traceability, others, for example who do not want to receive information they do not believe, require specially targeted strategies, particularly if they are among vulnerable populations.
- Information about benefits and risks needs to be clear, concise and consistent. This can help individuals align their perceptions with available knowledge about human health-related and other risks and benefits.
- Not all information needs concern knowledge, values and attitudes also shape how people form opinions on specific issues. For example, messaging that recognises personal beliefs and culture alongside factual information may be more effective in supporting knowledge uptake, changing perceptions and driving potential behaviour change (if considered needed by managers).
- Conflicting information should be avoided or where necessary explained within a given context. For example, differing scientific views about the evolving nature of science and/or the roles of the sources of those views can be carefully explained.

G.4.3 | Information and behaviour

- Consumers make trade-offs around health, environmental, economic and social factors based on food information even when the perceived risks, the probability of negative consequences and the values placed upon them, are low. Increased knowledge of risks and benefits related to health does not necessarily motivate individuals to purchase or consume differently.
- To address these challenges, communication planning needs to characterise the trade-offs that consumers will face. For instance, it could be a trade-off between personal health and hedonism (e.g. health vs. taste), or between personal economic interest and food characteristics (e.g. price vs. quality/ease of preparation/availability), or between personal preference and societal considerations (e.g. hedonic value vs. animal welfare, ethics, environment).
- The decisions made often consider many factors at once, rather than being a simple balance between two consequences (e.g. health versus cost). Trade-offs may result in decisions that negatively impact consumer health and can be based on minimal information. Therefore, it could be argued that ensuring the public has access to full, accurate and understandable information can help consumers to make healthier decisions about consumption.

G.5 | TOOLS TO SUPPORT RISK-BENEFIT COMMUNICATION

EFSA's approach to risk communication planning and strategy development (Vrbos et al., 2023), follow the structure of the International Risk Governance Center (IRGC) conceptual framework for understanding risk governance (Florin & Bürkler, 2017; Florin & Parker, 2020). The IRGC framework covers the entire risk analysis process and includes various steps and cross-sectional aspects:

1. Pre-assessment covers the identification and framing of the problem.
2. Appraisal concerns the assessment of the technical and perceived causes and consequences of the risk-benefit.
3. Characterisation and evaluation refer to making a judgement about the risk-benefit and the need to manage it.
4. Management indicates the process of deciding on and implementing risk management options.

Given EFSA's remit as food safety risk assessor, the available tools cover the first two steps only.

G.5.1 | Pre-assessment

This first phase aims at identifying the diverse views and interest in relation to a risk-benefit question and the issues that need to be covered. It serves as a frame for how to assess, manage and communicate.

Within this crucial step of problem framing, three areas should be taken into account for communication planning: (i) the nature of the topic; (ii) knowledge and perceptions; and (iii) institutional and stakeholder interest. EFSA developed a checklist of yes/no questions linked to a decision tree for the evaluation of risk assessment questions (Vrbos et al., 2023). This has been adapted for risk-benefit analysis, in particular, to understand if the risks and benefits are related to similar/unrelated health effects, who is affected and what is known about the perceptions of the potential risks and benefits.

The revised checklist tool is available publicly³⁵ for testing in preparation for future requests for risk-benefit assessments that EFSA may receive.

G.5.2 | Appraisal – concern assessment

According to the IRGC framework, the concern assessment should examine (i) stakeholders' opinions, values and concerns about the risk; (ii) cognitive heuristics and biases that play a role; (iii) potential constraints; (iv) social reaction to the risk; (v) role of institutions and media in tackling public concern; (vi) possible controversies and conflicts (Florin & Bürkler, 2017).

Using social research data, complemented by media and social media listening, allows one to map the volume and sentiment of public discourse on a topic (Vrbos et al., 2023). These methods support the identification of the perceived characteristics of the information source, as they provide data on, e.g. What are the most used and most trusted information sources about the topic? Once all these data are gathered, a value of concern is calculated based on the public's knowledge and perception of the topic. While the original model explained in Vrbos et al. (2023) considers only risk perception, a modified version of the concern assessment that considers benefit perception is proposed. This includes the factors that can influence risk and benefit perceptions, indicated above, and the characterisation of the trade-offs faced by consumers.

The revised concern assessment framework is available publicly³⁶ for testing in preparation for future requests for risk-benefit assessments that EFSA may receive.

G.6 | RECOMMENDATIONS

Several research gaps have been identified in the preparation of this Section:

- Studies involving European populations that support the characterisation of individual and cultural factors influencing food-related risk-benefit perceptions.
- Studies that explore and map the variety of underlying (personal, social, environmental, situational and product-related) factors of consumer decision-making in European populations, the most common combinations of these factors in shaping consumers' risk-benefit perceptions and food-related risk-benefit trade-offs, disentangle perceptions (e.g. personal vs. societal) and decision-making variables (e.g. active/passive acceptance), and the associated information needs and practices.
- Studies on the inter-relationships between perceptions and/or knowledge of human health risks and benefits vis-à-vis non-human health-related effectors of food purchasing and consumption decision-making in European populations.
- Since much of the literature in this area focuses on food-related technologies and innovations, studies should seek to broaden the range of food types covered so that risk-benefit trade-offs involving everyday food categories and types can be better understood.

The Scientific Committee notes that EFSA identified some of these research gaps in 2021 (EFSA, 2021) and set social research objectives on consumer risk-benefit trade-offs integrating them into a research programme on 'Evidence-based risk communication in the EU Food Safety System' (EFSA, 2022a). Therefore, under this programme EFSA is expected to initiate research projects to fill some of these research gaps from 2024 onwards.

³⁵Available on the EFSA Knowledge Junction – <https://zenodo.org/records/10517998>.

³⁶www.fishchoice.eu.

ANNEX A

Public consultation on the draft guidance on risk–benefit assessment of foods

The outcome of the public consultation which was open from 19 February 2024 until 2 April 2024 is presented in Annex A. Annex A is available under the Supporting Information section on the online version of the scientific output.