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Abstract

Background: Risk-benefit assessment (RBA) of foods aims to assess the combined negative and positive health effects associated with food intake. RBAs integrate chemical and microbiological risk assessment with risk and benefit assessment in nutrition.

Scope and Approach: Based on the past experiences and the methodological differences between the underlying research disciplines, this paper aims to describe the recent progress in RBAs, identifying the key challenges that need to be addressed for further development, and making suggestions for meeting these challenges.

Key Findings and Conclusions: Ten specific challenges are identified and discussed. They include the variety of different definitions and terminologies used in the underlying research disciplines, the differences between the “bottom-up” and the “top-down” approaches and the need for clear risk-benefit questions. The frequent lack of data and knowledge with their consequential uncertainties is considered, as well as the imbalance in the level of scientific evidence associated with health risks and benefits. The challenges that are consequential to the need of considering substitution issues are discussed, as are those related to the inclusion of microbiological hazards. Further challenges include the choice of the integrative health metrics and the potential scope of RBAs, which may go beyond the health effect. Finally, the need for more practical applications of RBA is stressed. Suggestions for meeting the identified challenges include an increased interdisciplinary consensus, reconsideration of methodological approaches and health metrics based on a categorisation of risk-benefit questions, and the performance of case studies to experience the feasibility of the proposed approaches.

1 Meeting the challenges in the development of risk-benefit
2 assessment of foods

3

4 *Review*

5

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ACCEPTED MANUSCRIPT

14 1. Introduction

15 Food is a basic requirement for life, providing the essential nutrients and energy required for optimal health.
16 However, food may also be associated with adverse health effects, because it may contain natural toxins,
17 hazardous chemical substances or pathogenic microorganisms that can affect health negatively.
18 Additionally, it is possible that the dietary intake of specific nutrients in foods is either too low or too high,
19 resulting in potential deficiencies or toxicity symptoms.

20 The diverse causes of these health effects associated with food consumption and the demand for advice on
21 safe and healthy diets have led to the development of different research disciplines in food safety and
22 nutrition. The negative health impact of human exposure to chemical substances and pathogenic
23 microorganisms through food is evaluated in two separate disciplines, chemical and microbiological risk
24 assessment. Apart from that, both health risks and health benefits associated with foods and diets have
25 been studied through the discipline of nutrition. However, in the past decade, the joint assessment of risks
26 and benefits associated to hazardous agents, food compounds, nutrients, single foods and whole diets has
27 been taken up, resulting in the establishment of "risk-benefit assessment" (RBA) as a new multidisciplinary
28 and integrated scientific discipline (Boué et al., 2015; Tijhuis et al., 2012; Verhagen et al., 2012a).

29 With the overall aim of exploring how RBA can be further developed, this paper aims to describe the recent
30 progress in RBAs and to identify and discuss key challenges in RBA research. To clarify the fundamentals of
31 RBA and to provide a basic understanding of the background of many of the challenges, the main concepts
32 of the underlying disciplines chemical risk assessment, microbiological risk assessment and nutritional risk
33 and benefit assessment are explained. Following that, the developments in RBA thus far are addressed. The
34 major part of the paper is devoted to a discussion of ten challenges, as well as to suggestions for how they
35 can be met. The conclusion summarizes the authors' vision on the future developments of the research area.

36 1.1. Risk and benefit assessment in food safety and nutrition

37 The use of risk assessments has traditionally been an integrated part of a common risk analysis framework
38 (Figure 1), where risk assessment is done by risk assessors who provide scientific advice to support decision
39 making by risk managers, such as food authorities or food producers, on the potential risks associated with
40 food consumption. Risk communication is an essential part of the risk analysis, both between risk assessors
41 and risk managers, and between assessors, managers and other stakeholders (FAO/WHO 2006a).

42 Risk assessment was first formalised for chemicals by the establishment in 1980 of the International
43 Programme on Chemical Safety (IPCS), which proposed a scientifically based process including four
44 elements: hazard identification, hazard characterization, exposure assessment and risk characterization
45 (Figure 2). The first step, hazard identification, involves the identification of the inherent toxicological
46 properties of a chemical substance in the food that may affect human health adversely. Depending on the
47 nature of the chemical substance, the information on hazards may stem from *in vitro* studies (for example on
48 genotoxicity), experimental animal studies, and human data. The next step, hazard characterization, involves
49 dose-response evaluations of the toxicological effects of the chemical substance that are identified in the

50 previous step, including identification of critical effect levels such as no observed adversary effect level
51 (NOAEL), lowest observed adversary effect level (LOAEL), or a benchmark dose (BMD) (IPCS, 2010).
52 These critical effect levels are based on either acute or chronic effects and are usually determined on the
53 basis of results obtained from animal experiments. After applying uncertainty factors to account for
54 differences in sensitivity between species (e.g., animal to man) and within the human population, the critical
55 effect levels are translated to health-based guidance values such as acceptable daily intake (ADI), tolerable
56 daily intake (TDI) or acute reference dose (ARfD) (IPCS, 2010). In exposure assessment of the chemical
57 substance, the exposure from food is estimated by use of accurate and representative data of relevant food
58 consumption and occurrence of chemical substances in the foods. The last step, risk characterisation,
59 integrates the outcomes of the hazard characterisation and the exposure assessment, and the output is
60 given to the risk managers.

61 Microbiological risk assessment has mainly been used for bacterial pathogens, but it has also been applied
62 to viruses and parasites. It was developed after chemical risk assessment was established and adopted
63 much of the terminology. However, the nature of microorganisms has led to specific challenges, which
64 resulted in some essential differences in the definitions (see Section 2.1), as well as in the risk assessment
65 methodology (Lammerding, 2013).

66 First, the definition and identification of the microbiological hazard are complicated by the fact that
67 microorganisms adapt and evolve over time, so new strains can emerge with different characteristics than
68 those that were originally described. Next, the dose-response relation typically describes acute health
69 effects, with the probability of acute illness being described as a function of the ingested dose in a single
70 meal. Due to the differences in responses between humans and animals, data for microbiological dose-
71 response models can usually not be derived from animal experiments. As an alternative, human data are
72 required, but these are not easily obtained. The use of biologically plausible “single hit” models that assume
73 that, with low probability, a single bacterial cell can lead to illness, is a general practice in microbiological
74 dose-response modelling (Haas et al., 2014; FAO/WHO, 2003). Exposure assessment is complicated by the
75 fact that living organisms can multiply, and consequently, the occurrence of microbial growth and inactivation
76 imply that concentrations can change during food processing and storage. Therefore, concentration data
77 alone are insufficient and the ingested doses have to be estimated by means of mathematical modelling in
78 so called “process risk models” that apply predictive models for growth and inactivation (FAO/WHO, 2008;
79 Zwietering & Nauta, 2007). Note that this implies that, in contrast to chemicals, exposure depends on the
80 growth and inactivation characteristics of the microorganism of concern (Figure 2). Critical limits for the
81 presence of microorganisms are generally not determined on the basis of the hazard characterization only,
82 so equivalents of NOAEL and BMD as used in toxicology are not applied. Instead, risk-based microbiological
83 targets such as food safety objective (FSO) are used, which are derived from risk characterization, i.e., a
84 combination of hazard characterisation and exposure assessment (FAO/WHO, 2006b).

85 Risk assessment of essential nutrients follows the same principles as chemical risk assessment, with the
86 notion that essential nutrients have a dual risk relationship with risks occurring at both the upper end
87 (‘excess’) and lower end (‘deficiency’) of the intake range (NCM, 2014). Another distinct feature is that data

88 on adverse effects in relation to excessive or deficient amounts of nutrients are often available from human
89 studies, which compared with chemical risk assessments overall, may reduce the size of uncertainty factors
90 applied. The tolerable upper intake level (UL) is the maximum level of chronic daily nutrient intake from all
91 sources judged to be unlikely to pose a risk of adverse health effects to humans (EFSA, 2006) and thus
92 includes an uncertainty factor as in the case of chemicals. The lower threshold intake (LTI) is the level of
93 intake below which, on the basis of current knowledge, almost all individuals will be unable to maintain
94 “metabolic integrity”, according to the criterion chosen for each nutrient (EFSA, 2010b).

95 Consideration of specific nutrient intakes associated with adverse health effects above or below specific
96 intake levels has received less attention in the nutrition area compared with non-nutrients, such as drugs,
97 food additives, and pesticides (IOM, 2007). The concept of the risk assessment of nutrients was stimulated
98 by the IPCS in 2002 (IPCS, 2004), and by the Codex Alimentarius, FAO/WHO, EFSA and others
99 (FAO/WHO, 2006c; Aggett, 2010; Taylor & Yetley, 2008). In addition, the implementation of an organized
100 nutritional risk assessment approach for scientific reviews has been stimulated by the increased use of food
101 supplements, fortified- and functional foods and subsequent requests by regulatory agencies to identify
102 upper levels of nutrient intake (Taylor & Yetley, 2008; Taylor, 2007). In 2010, EFSA published a scientific
103 opinion on the general principles for development and application of dietary reference values (DRVs) (EFSA,
104 2010b), and other DRV processes have followed the same risk assessment approach, including the update
105 of the Nordic Nutrition Recommendations (NCM, 2014).

106 Current approaches thus predict a threshold above which the nutrient intake is excessive, and another
107 threshold below which the intake is inadequate, while an intake range between these two boundaries can be
108 considered an ‘optimal’ intake range within which the recommended intake and the benefit assessment is set
109 (NCM, 2014). Nutritional benefit assessment may thus be considered as the intake range beyond which
110 there is a risk. Nutritional RBA can be broadened to not only consider nutrients, but also to include any
111 excess or deficient intake of foods, diets or energy.

112 One example of the application of benefit analyses is the European health claim regulation, which states that
113 health claims should be “substantiated by generally accepted scientific evidence and by taking into account
114 the totality of the available scientific data, and by weighing the evidence” (EU Commission, 2006). The steps
115 involved in the assessment of health claims include identification and characterization of the food or the food
116 compound, definition of the effect and assessment of whether such an effect can be considered beneficial to
117 human health. Finally, the scientific substantiation for a beneficial effect is assessed based on the totality of
118 the current evidence between the consumption of the food or the food compound and the claimed effect
119 studied in the appropriate target group (EU Commission, 2006).

120 A comparison of the application of risk and benefit assessment for chemical substances, microorganisms
121 and nutrients shows that, traditionally, risks are considered for all, but benefits only in nutrition. An essential
122 difference between different types of risk and benefit assessment is illustrated in Figure 3. Typically, looking
123 at both acute and chronic adverse effects, chemical and microbiological risk assessments investigate
124 situations where exposure is to be considered “too high”. This implies that the risk increases with higher

125 doses, and threshold doses may be derived as cut-off points below which the intake is considered safe, or
126 the associated risk is considered acceptable (Barlow et al., 2015). In contrast, within nutrition, both the
127 situation where there is a risk of nutritional deficiency and the situation where there is a risk of nutrient
128 intoxication are relevant, creating a “window of benefit” (Palou et al., 2009; Tijhuis et al., 2012)). Interestingly,
129 research in situations where the intake is too high (above the upper intake level (UL)) is commonly referred
130 to as toxicology, whereas research considering beneficial intake or too low intake, is part of nutrition.

131 1.2 The development of risk-benefit assessment

132 Although independent risk and benefit assessments have proven to be useful for decision support in food
133 safety and nutrition, their results may be too much focused on one hazard, one food compound or one health
134 effect. When establishing guidelines and advice on food consumption, nutrient intake and diet choices, there
135 is a need for an overarching approach, in which all of the relevant health risks and benefits are included and
136 compared. This need for RBAs has been identified earlier in several publications (EFSA, 2007; EFSA,
137 2010a; Renwick et al., 2004) and led to the development of RBA of foods as a new research discipline. An
138 RBA is multidisciplinary by nature, and may require expertise from not only toxicologists, microbiologists, and
139 nutritionists, but also from epidemiologists, chemists, librarians, statisticians, and medical scientists. As
140 proposed in the EU-funded project BRAFO (Benefit-Risk Analysis of FOods) (Boobis et al., 2013), it is
141 common to use the risk analysis and risk assessment frameworks (Figures 1 and 2) as the basis for the RBA
142 methodology by applying the established concepts to both risks and benefits. A recent extensive review of
143 studies related to the combined RBA of foods, nutrients and compounds shows that the majority of published
144 studies have been related to fish consumption where the nutritional beneficial effects are compared with the
145 adverse effects from chemicals (Boué et al., 2015). This RBA of fish (e.g. (Hoekstra, Hart, et al., 2013)) is an
146 example of an RBA case where the content of polyunsaturated fatty acids, and in particular
147 docosahexaenoic (DHA), and eicosapentaenoic fatty acids (EPA), recognized for their health benefits, is
148 counterbalanced by the content of pollutants such as methylmercury and dioxins, known to potentially induce
149 adverse health effects. There is also an example of microbiological aspects being added to an RBA of fish
150 (Berjia et al., 2012).

151 Several European projects have been conducted in which methods and modelling frameworks were
152 developed, leading to considerable progress in the risk-benefit area (Boobis et al., 2013; Hart et al., 2013;
153 Hoekstra et al., 2012; Verhagen et al., 2012a). Among others, the BRAFO project and EFSA developed the
154 “tiered approach” to be used as a general framework for RBA¹ (Fransen et al., 2010; Hoekstra et al., 2012).
155 The basis is that a number of tiers have to be evaluated before making a decision on the required steps to
156 be taken in the RBA. This approach proposes that a qualitative assessment is sufficient if data are scarce or
157 there is clear evidence that risks outweigh the benefits (or vice versa). If the balance between benefits and
158 risks is unclear, the assessment has to be performed at a higher tier, including quantitative assessment. As
159 part of the BRAFO project, a number of relevant risk-benefit studies that illustrate the usefulness of a tiered

¹ Within the BRAFO project, the term benefit-risk assessment was preferred over risk-benefit. For consistency we consequently use risk-benefit assessment (RBA) throughout this paper.

160 approach for RBAs have been performed (Hoekstra et al., 2008; Schütte et al., 2012; Verhagen et al.,
161 2012b; Watzl et al., 2012). A specific software tool, QALIBRA, has been developed to facilitate the
162 performance of quantitative assessments in the final tier (Hart et al., 2013; Hoekstra, Franssen, et al., 2013).

163 2. Challenges in risk-benefit assessment

164 Although significant progress has been made in the development of methods and terminology in RBA,
165 several challenges remain. Some of these challenges relate to the differences between the underlying
166 research disciplines, which have different use of terminology and different approaches for the assessment of
167 health effects related to the consumption of food. Other challenges relate to the specific objective of RBAs,
168 the scarcity of the required data, or the complexity of the characterization of health effects. Below, we
169 provide a description of ten major challenges that were identified during the course of working with RBAs,
170 with explanations of the challenges and discussion on the way forward for meeting them in the future.

171 2.1 Definitions

172 The different approaches used in the disciplines contributing to RBA (Section 1.1) apply different terminology
173 or may apply the same terminology in a different way. Dissimilar definitions can lead to confusion and lack of
174 understanding of the risk-benefit question (Section 2.3). As an example, the central concept of "hazard" is
175 defined differently in various contexts. Published definitions of hazard include "inherent property of an agent
176 or situation having the potential to cause adverse effects when an organism, system, or (sub)population is
177 exposed to that agent" (IPCS, 2004), "the potential of a risk source to cause an adverse effect(s)/event(s)"
178 (Renwick et al., 2003) and "a biological, chemical or physical agent in, or condition of, food with the potential
179 to cause an adverse health effect" (CAC, 2011). In the latter definition, the hazard is the agent (or risk
180 source, that is the pathogen, chemical substance or food compound) and in the others it is an *inherent*
181 *property or the potential* of this agent. Due to this difference in definitions, the hazard is usually synonymous
182 to the pathogen(s) of concern in microbiological risk assessment, whereas it usually is the potential health
183 effect caused by the chemical substance or food compound in chemical risk assessment and nutrition
184 (Barlow et al., 2015).

185 Similarly, there are different definitions of "risk", for example "the probability of an adverse effect in an
186 organism, system, or (sub)population in reaction to exposure to an agent" (IPCS, 2004; EFSA, 2010a), or "a
187 function of the probability of an adverse health effect and the severity of that effect, consequential to a
188 hazard(s) in food" (CAC, 2011). So in one definition the risk is a probability, in the other, it is a combination of
189 probability and severity.

190 When mirroring risk assessment to benefit assessment, the benefit is defined at a level comparable to both
191 the hazard and the risk (EFSA, 2006; Boobis et al., 2013), so "benefit" is both the counterpart of "hazard"
192 and the counterpart of "risk". Hence, the term "benefit" can be used for anything between the agent causing
193 the health effect and the probability and magnitude of that effect. Moreover, when used as equivalent of
194 "risk", the benefit is not necessarily interpreted as the probability of a positive effect, but commonly as the

195 decrease in the probability of an adverse health effect. This wide interpretation of the one of the central
196 concepts in RBA can be considered confusing.

197 The present definitions can be well understood in a historical perspective, given that RBA has evolved from a
198 variety of disciplines. However, for further development, the discipline "risk-benefit assessment of foods"
199 needs a clearer set of definitions and harmonized terminology that is comprehensible for all those involved.
200 To accommodate the fact that some agents or food compounds (i.e. "hazards" of "benefits") can be both a
201 source of positive and negative health effect depending on the exposure (Figure 3), Boué et al. (2015)
202 propose to use the term "health effect contributing factor" (HECF) for "the agent able to cause an adverse or
203 positive health effect in the case of exposure". This is a useful first step in the reconsideration of the
204 terminology used in RBA. Consensus within the international research community is required for clarification
205 and harmonization purposes and definitely when it would be used for regulatory purposes. Obtaining such a
206 consensus is a process that should be led by international authorities, and should include representatives of
207 all relevant disciplines involved in RBA.

208 2.2 Bottom-up versus top-down approach

209 In this paper, we distinguish between two overall approaches to assess health effects in RBA and refer to
210 them as "bottom-up" and "top-down". This terminology is derived from studies in microbiological food safety
211 aimed at ranking microbiological food risks (EFSA, 2015; Cassini et al., 2016). The two approaches are
212 characterised by their different starting point. The typical risk assessment approach, which starts with the
213 hazard identification for the food product or its ingredients and finishes with the human health outcome
214 obtained after combining the exposure assessment with a dose-response model (Figure 2), is referred to as
215 the bottom-up approach. The alternative top-down approach starts with the adverse (or beneficial) health
216 outcomes as obtained from human observational studies, i.e., incidence data and identified risk factors.
217 These are then traced back to the food sources that caused the disease of concern (or benefit of desire),
218 thus linking the health effect to the food product.

219 A similar distinction in approaches can be made in nutritional and chemical risk assessment. The usual risk
220 assessment approach (i.e., bottom-up) is targeted at intake of specific nutrients or food compounds, and
221 the dose-response relation is typically derived from animal experimental data. The alternative top-down
222 approach is an approach where relative risk estimates from human observational studies are used and
223 linked to foods or food compounds that are identified as risk factors. In the review of the BRAFO project,
224 Boobis et al. (2013) identify these two approaches as one based on experimental animal data (bottom-up)
225 and one based on human observational studies (top-down). We prefer the bottom-up and top-down
226 terminology as it is more generic and can also be applied for microbiological risk assessment, which does
227 not apply animal data.

228 Hence, with the bottom-up approach, the assessment starts with the food product, food compound or
229 contaminant, followed by an exposure assessment and a dose-response model used for the risk-benefit
230 characterization. An advantage of this approach is a direct causal link between intake of the food product or

231 food compound (or contaminant) of concern and the associated health effect. A disadvantage is that there
232 may be a large uncertainty attending the exposure assessment and (especially) the dose-response.

233 With a top-down approach, the starting point of the analysis is the incidence of a health outcome in the
234 consumer. Typically, data from epidemiological studies (case-control studies, cohort studies, randomized
235 controlled trials) are used to associate human health outcomes with risk factors that are defined in terms of
236 food consumption, allowing for the estimation of metrics such as the odds ratio or the relative risk. These
237 measures of association are then combined with population statistics and incidence data to estimate the
238 actual health risks in the population. The relative risks may also be used to construct a dose-response
239 relation, where the relative risk is a function of the intake as specified in the underlying study. The strength of
240 human observational studies is that they are based on actual health effects, measured in specified
241 populations. Weaknesses are that the observed associations are not a proof of causation, that the studied
242 population may not be representative for the population group of interest and that many data are required if
243 the health effect of interest is small. For microbial pathogens, a top-down approach can be used to estimate
244 the number of cases of disease caused by a pathogen due to its presence in a specific food, a method
245 referred to as "source attribution" (Pires et al., 2009). Here incidence data on a specific health outcome (e.g.,
246 gastroenteritis caused by salmonellosis) is traced back to a specific food source (e.g., chicken meat) by the
247 use of subtyping information of isolates of the pathogen in human cases and food sources.

248 Generally, within RBA, it is necessary to use different approaches for different health effects of food
249 compounds or contaminants. For example, in the studies on fish of (Berjia et al., 2012; Hoekstra, Hart, et al.,
250 2013) (Figure 4), the effects on coronary heart disease, stroke and neurological development of children (IQ)
251 are derived from top-down approaches, but those related to exposure to dioxins and *Listeria monocytogenes*
252 are derived from bottom-up approaches. The reason for the application of these different approaches is
253 obviously the availability of data, which in turn is related to the feasibility of acquiring the requested data and
254 also the quality of the studies providing the data. Still, if different approaches are used to obtain different
255 health effect estimates in the same RBA, it may be hard to compare them. Not only can there be a difference
256 in the known bias associated with the approach (such as a potential to overestimate the risk obtained from
257 dose-response models derived from animal experiments), but also the nature of the uncertainties associated
258 with the assumptions of the approaches will be different (Section 2.5).

259 Studies that combined and compared bottom-up and top-down approaches may help clarify how the two
260 methods can be integrated in RBA. For example, Bouwknegt et al. (2014) compared the approaches in a
261 case study on *Campylobacter* in the Netherlands and identified the differences in the underlying
262 uncertainties. They found that the difference in the point estimates of the risks as found by the different
263 approaches can be large, but they still have overlapping uncertainty intervals. This implies that one cannot a
264 priori conclude that one approach is better than the other. It is advisable to aim for evidence synthesis by
265 using an approach that takes advantage of all available data and combines bottom-up and top-down
266 approaches. One option for evaluating such a combined approach is the performance of simulation studies
267 where the expected results of a hypothetical epidemiological study are investigated on the basis of a risk
268 assessment.

269 2.3 The risk-benefit question

270 The crucial initial step of an RBA is the definition of the risk-benefit question (Hoekstra et al., 2008) or
271 problem definition (Boobis et al., 2013; Boué et al., 2015; EFSA, 2010a). The risk-benefit question is
272 generally a comparison between two, or a series of, choices, alternative policies or courses of action,
273 described in the form of scenarios (Boobis et al., 2013). In these scenarios, both positive and negative health
274 effects have to be taken into consideration. When a series of scenarios is compared, the risk-benefit
275 question can be used to identify the optimum intake (Berjia et al., 2014). An aim of the risk-benefit question
276 is to specify the RBA-task in such a way that it is feasible and will provide useful results. For example, an
277 RBA of fish should indicate what sort of fish (e.g., lean/fatty, farmed/wild), target population group, and in
278 general any other constraint that could narrow the risk-benefit question. In the end, the level of specification
279 of the question will also depend on the data available.

280 As a variety of risk-benefit questions can be asked, it can be helpful to categorise them and to identify
281 specific approaches that can be used to answer these different categories of questions. Here, one type of
282 categorisation is the level of aggregation: the risk-benefit question can be targeted at a food compound level
283 (a nutrient, a chemical or microbiological contaminant), a food product level (e.g., fish) or a diet level
284 (Hoekstra et al., 2008).

285 When the risk-benefit question is targeted at the food compound level, it should be a compound that is
286 associated with both positive and negative health effects, e.g., a (micro-) nutrient. Examples for RBAs
287 directed at the food compound are those for folic acid (Hoekstra et al., 2008) and vitamin D (Berjia et al.,
288 2014) (Figure 4). The choice between a bottom-up or top-down approach will depend on whether the health
289 effects associated with food compounds are obtained from animal experiments or human observational
290 studies. To assess the total intake of the food compound, it will be necessary to consider the intake of all
291 relevant foods and food products in the diet that contain it, and the concentrations of the compound in these
292 foods and food products have to be known. As this can be rather complicated, one can choose a risk- benefit
293 question that only considers a difference in intake or concentration in one or a few food products, making
294 some assumptions for the background diet.

295 When the risk-benefit question considers a food product, the positive and negative health effects can be
296 associated with different food compounds or contaminants that it contains. Typical examples of RBAs
297 directed at this level of aggregation are those performed for fish (Berjia et al., 2012; Hoekstra, Hart, et al.,
298 2013; Figure 4.) The health effects of the intake of the food product may be directly available from
299 epidemiological data or a human trial study, allowing the use of a top-down approach. Relative risk estimates
300 can inform about the health impact of one intake scenario compared with another. Alternatively, a bottom-up
301 approach may be used where all relevant food compounds (and contaminants) in the food product have to
302 be identified and comprised in the RBA to assure that the health effects of interest are included. In that case,
303 a selection of relevant food compounds and contaminants needs to be made based on the associated levels
304 of evidence and the precise risk-benefit question. However, because in some cases only exposure through

305 the selected food product is considered, and not the total exposure from all food products containing the
306 compounds, it is difficult to use a bottom-up approach with a dose-response relation for each compound.

307 When considering a whole diet, the bottom-up RBA approach will usually not be feasible, unless the risk-
308 benefit question is clearly delimited: the number of food compounds (and contaminants) and their combined
309 intakes easily get too large for a complete exposure assessment and hazard characterisation. However, a
310 top-down approach using studies on human consumption may be possible if the appropriate data are
311 available, for example from a dietary intervention study. Van Kreyl et al., 2006, performed a study to analyse
312 the health effects of the current diet in the Netherlands that may be regarded as an RBA of diets, but
313 otherwise, to our knowledge, no formal RBAs of whole diets have been performed so far.

314 In each of these three categories of risk-benefit questions, the options for inclusion and exclusion of food
315 compounds and contaminants, food products and health effects are large. To clarify the selected elements in
316 the risk-benefit question, we propose the use of schematic framing of the risk-benefit question, as
317 exemplified in Figure 4 for four published risk-benefit studies for food compounds or food products. A
318 scheme like this is broadly applicable and may offer a transparent way to identify different types of risk-
319 benefit questions and clarify how the risk-benefit question is addressed. In the case of an RBA of a whole
320 diet, the scheme would be pretty complex, which stresses the difficulty of doing an RBA of a whole diet.

321 2.4 Lack of data and knowledge and the consequential uncertainties

322 The data needs for an RBA are large and diverse. RBAs frequently face data gaps and lack of knowledge,
323 such as lack of human data, information on dose-response and intake levels for specific population groups.
324 These challenges are also faced in other modelling exercises (such as many risk assessments), and need to
325 be addressed by documentation and discussion of the assumptions made. A consequence of limited data
326 and lack of knowledge is that the uncertainty related to the assessment may be large. Yet, characterising
327 this uncertainty is crucial in the risk-benefit characterisation.

328 As part of the QALIBRA project, Hart et al., 2013, provided an overview and discussion on the importance
329 and challenges related to uncertainty in RBA and described strategies to deal with uncertainty. The
330 QALIBRA software tool developed in the project allows the user to perform stochastic RBA and, as part of
331 that, analyse uncertainty, either by quantitative methods or by qualitative scenario analyses. This has been
332 an important step forward for the analysis of uncertainty within RBAs.

333 Still, as previously identified by Boobis et al., 2013, and others, there are different areas within RBAs where
334 lacking data creates a major challenge. An important area is dose-response modelling. For chemical
335 substances, the dose-response relations are usually derived from animal experimental data, where a set of
336 assumptions is needed to establish a threshold that can be applied for human consumers. As the objective
337 of these dose-response relations in animals is often to identify potentially dangerous doses and to set safe
338 health-based guidance values such as the ADI or TDI, the assumptions may tend to overestimate the true
339 human health risks. Yet, for RBAs, it is important to derive the magnitude of the positive and negative health
340 effects in the same way and therefore one needs the best possible estimate of the likelihood of the health

341 effect from a dose-response relationship, not the “worst case” value. For chemical dose-response
342 relationships, this means that the use of BMD models may be preferred over NOAELs and LOAELs, and that
343 the uncertainty factors used to translate animal data to human guidance values may not be appropriate if the
344 dose-response relationship is to be applied in RBAs.

345 The uncertainty attending the dose-response relations for microbial pathogens is also large. These dose-
346 response relations are usually based on human volunteer studies or outbreak data, which means they are
347 based on limited data sets, for specific strains and specific population groups, and generalised thereafter.
348 Dose-response relations based on studies with healthy young volunteers may be expected to underestimate
349 the risk, whereas those derived from outbreaks (with more virulent strains) may overestimate the risk.
350 Further, it is known that immunity plays an important role and may lead to overestimation of the risk, but it is
351 difficult to include this in the modelling (Havelaar & Swart, 2014).

352 Another uncertain element of the dose-response modelling is the long-term effect of exposure, which is
353 specifically relevant for chemical substances. An acute effect is the direct consequence of an individual
354 ingested dose and therefore relatively easy to describe in dose-response model. For long-term effects,
355 however, it is much harder to identify how different doses accumulate into health effects. The use of
356 physiologically-based pharmacokinetic (PBPK) models (Boobis et al., 2013; Zeilmaker et al., 2013) can be
357 useful, but these models still need further development.

358 If the dose-response modelling is based on relative risk estimates obtained from human observational
359 studies, uncertainties may be large as well. Some important issues are, for example, the uncertainty
360 regarding the causality of observed associations between risk factor and effect and the representativeness of
361 the data. To account for the uncertainties, top-down approaches (using this type of effect modelling) and
362 bottom-up approaches (using the other dose-response relations) may be combined in a comparative
363 analysis (Section 2.2).

364 Uncertainties are an inevitable intrinsic element of science, risk assessment and RBAs, and it is of utmost
365 importance that they are not ignored. A challenge here is that, as in risk assessment, it is not primarily the
366 objective of an RBA to assure that the uncertainty is small enough (as aiming for a p-value smaller than
367 0.05), but to indicate how large the uncertainty actually is (Nauta, 2007). One should deal with the identified
368 uncertainties by explicitly addressing and characterizing them in the assessment and by clearly
369 communicating them to all stakeholders. By framing the risk-benefit question (Figure 4) and addressing the
370 required data, RBA models can be important in identifying the most important data gaps and the crucial lack
371 of knowledge. Thus, they can guide future data generation and research. Setting the future research agenda
372 based on the most important sources of uncertainty can therefore be one of the key outputs of an RBA.

373 2.5 The imbalance in level of scientific evidence

374 The level of scientific evidence needed for identifying negative and/or positive health effects of a food
375 compound, food or diet is not consistent (Boobis et al., 2013), because the presence of benefits and the
376 absence of risks need to be guaranteed (Hoekstra, Hart, et al., 2013; Tjihuis et al., 2012). In the case of

377 health claims, a nutritional benefit needs to be scientifically substantiated with convincing evidence of the
378 cause and effect relationship, before it can be accepted according to the current EU regulation (Section 1.1).
379 At the other hand, in the case of setting dietary guidelines, a nutritional benefit of a food or food group may
380 only need to be scientifically substantiated at the level of probable likelihood of an association (Kromhout et
381 al., 2016; Tetens et al., 2013; WHO, 2003). Finally, the level of scientific evidence needed for identifying
382 risks or negative health effects may be small, as only an indication of a risk is sufficient for the scientific
383 substantiation.

384 Due to this discrepancy in the level of scientific evidence needed for considering a food compound or
385 contaminant as a “hazard” or a “benefit”, risks are more likely to be included in an RBA than benefits, thus
386 leading to a potential bias in the RBA (Boobis et al., 2013; Hoekstra, Hart, et al., 2013; Tijhuis et al., 2012).
387 Another consequence of this discrepancy is that different types and levels of uncertainty will be associated to
388 the risk assessment on the one hand and the benefit assessments on the other, which complicates the
389 characterization of the combined RBA even further (Section 2.4).

390 The imbalance in the required level of scientific evidence for risks and benefits demands a paradigm shift
391 from the RBA as a sum of risk and benefit assessment to the RBA as a well-integrated risk-benefit
392 assessment. Such a well-integrated RBA deals not so much with studying a hypothesis about the presence
393 or absence of a health effect associated with the intake of a (certain amount of) food product or food
394 compound or contaminant, but predominantly with the size of the health effects. Even though the strength of
395 evidence for the presence of a health effect is strongly correlated to the size of the effect, these are not the
396 same thing. Stochastic modelling techniques, which include quantification of uncertainty and variability, allow
397 an evaluation of potential health effects, even if the effects themselves are not statistically significant. In
398 doing so, it may be possible to study how the estimated size of the effect, and some alternative scenarios
399 about these effects, may impact public health. From this, one might conclude that the risk or benefit is not
400 very large, even if the evidence would be convincing, or the opposite, that a risk or benefit may be large,
401 even if the level of evidence is low. Findings like this can indicate crucial data gaps (Section 2.4) and may, in
402 an objective way, help identify where further research is needed.

403 2.6 Substitution

404 In general, an RBA compares the health effects of two or more intake scenarios, defined as specified
405 changes in the amount or type of food consumed. As a side effect, these specified changes in intake may
406 also imply a change in the intake of other food products to compensate for the part of the diet that is deleted
407 or added. So far, however, such “substitution” is rarely included in an RBA. The risks and benefits of
408 increasing fish intake are for example frequently studied, but the related decrease in the intake of one or
409 more other foods and the consequential health effects of that decrease are not included in the assessment
410 (Berjia et al., 2012; Hoekstra, Hart, et al., 2013). Ideally, the risks and benefits of the change in intake in
411 these other foods are included in the comparison of intake scenarios, but this severely complicates the RBA
412 because it extends the list of risks and benefits to be included in the assessment. A complicating factor in

413 this context is also that this substitution in terms of alternative amounts and types of food eaten may vary
414 among individuals, adding even more to the complexity of the RBA.

415 Alternatively, it can be that substitution is the specific purpose of the RBA, as for example in the case of food
416 fortification, when a non-fortified food is replaced by a fortified food, and substitution is an inevitable part of
417 the scenarios investigated (Hoekstra et al., 2008). Likewise, substitution has been investigated in an RBA
418 when added sugar is substituted by artificial sweeteners (Hendriksen et al., 2011; Husøy et al., 2008;
419 Verhagen et al., 2012b). In the first case, no additional precautions need to be taken, as the fortified and
420 non-fortified diets are similar except for the content of the specific nutrient. In the sugar-artificial sweetener
421 case, the substitution leads to non-isocaloric diets and this may need to be addressed because it implies that
422 the diet may change in more aspects than just the intended substitution.

423 To meet this challenge, it is a prerequisite that substitution is acknowledged in the RBA, either by specifically
424 addressing it in the intake scenarios that are analysed, or by referring to it in the discussion of the
425 assumptions and in the uncertainty characterization. As simplified substitution scenarios, one can consider
426 replacements in the same food groups (e.g. meat and fish) and isocaloric alternatives (to make sure the
427 energy intake stays similar). Next, the impact of substitution can be analysed in separate scenarios, where
428 different options for substitution are compared.

429 2.7 The use of quantitative metrics

430 Within the tiered approach for RBA (Fransen et al., 2010; Hoekstra et al., 2012), a qualitative approach can
431 be sufficient if it is clear that the risks dominate the benefits or vice versa. If, alternatively, a quantitative
432 approach is applied, the use of one common integrated health metric is needed to combine different positive
433 and negative health effects in an RBA and to compare different health effects within and between
434 assessments. The quantitative metric that is used most in published RBAs of foods is the disability adjusted
435 life years (DALY). The DALY is a measure that indicates how many healthy years of life are lost due to
436 premature death or due to decreased quality of life associated with a disease or hazard (Devleeschauwer et
437 al., 2014; Havelaar et al., 2000; Hoekstra et al., 2008; Murray, 1994). The quality of life is determined by the
438 duration of illness and a weighing factor that indicates the severity of the specific disease considered
439 (Salomon et al., 2015). The DALY is increasingly used for risk ranking (Van der Fels et al., 2018) and in
440 burden of disease studies (Havelaar et al., 2015), which aim to compare and prioritise health risks, it is used
441 as an aid to policy makers when they have to decide where to spend their available resources. Methods
442 used and results obtained in these studies are also useful for RBAs because the health effects considered
443 can be the same and a large part of the underlying calculations is similar.

444 The DALY is commonly applied at a population level. Burden of disease, for example, is defined as the sum
445 of individual DALY across the population, and applied as a measurement of the gap between current health
446 status and an ideal health situation where the entire population lives to an advanced age, free of disease and
447 disability (WHO, 2013). As risk-benefit questions are usually targeted at a change of intake scenario within
448 the population (Section 2.3), the DALY is also commonly applied as a population metric in an RBA. However,
449 populations consist of a large variety of individuals with varying food preparation habits, consumption

450 patterns and sensitivity to food hazards. When the RBA is done and the risk-benefit balance for the
451 population is interpreted as the risk-benefit balance for the average consumer, this does not mean that this
452 balance is the same for all individual consumers. It can be that the balance goes in different directions for
453 different subpopulations, e.g., the elderly, pregnant women or children, and because there are differences in
454 intake and sensitivity between individuals. Therefore, the variability between consumers has to be taken into
455 consideration, for example by using a stochastic approach (Hart et al., 2013).

456 Apart from the DALY, other metrics can be used, such as monetary integrated metrics like the cost-of-illness,
457 which aims to calculate the direct and indirect monetary costs to society related to disease and death, or
458 willingness-to-pay, a stated preference method which elicits the resources an individual is willing to give up
459 for a reduction in a specific health risk. We refer to Mangen et al., 2014, for a comprehensive overview of
460 these different metrics.

461 Even though the use of the DALY seems to be an established choice in RBAs, one should consider
462 alternatives and remain critical on the choice of the preferred metric. Because this choice guides part of the
463 data needs of the RBA and may have an impact on the interpretation of the final result, this choice should be
464 made when the risk-benefit question is defined. As different metrics may convey different messages, the use
465 of more than one metric could be considered as well. When metrics are used beyond the level of the general
466 population, it is important to consider the impact of variability between consumers. Both the risk-benefit
467 assessors and the decision makers should be aware of the strengths and weaknesses of the health metric
468 chosen, as well as the underlying ethical dimensions (Arnesen & Kapiriri, 2004; Arnesen & Nord, 1999; Van
469 der Fels et al., 2018).

470 2.8 Including Microbiology

471 As RBAs have predominantly been developed within the research areas of nutrition and toxicology, the
472 concepts and definitions used are largely based on these two research areas (Section 1.1) and microbiology
473 is not often included (Magnússon et al., 2012). Even though one of the first RBA publications relates to the
474 risks and benefits of drinking water disinfection (Havelaar et al., 2000), only 7 of the 70 references indicated
475 in the RBA review of Boué et al. (2015) include microbiology. Among those, there is only one from the
476 BRAFO project, which, among topics not related to microbiology, discusses heat treatment of milk (Schütte
477 et al., 2012). Microbiological benefits, e.g., the use of probiotic bacteria, have to our knowledge not yet been
478 included in an RBA.

479 Reasons for this underrepresentation of microbiology in RBA are probably the intrinsic differences in the
480 underlying research disciplines and the different nature of the associated health effects. Microbiological risks
481 are often linked with mild health effects such as short episodes of gastro enteritis. They can also lead to
482 long-term sequelae and severe chronic effects, but these are typically not registered and less often
483 measured (Havelaar et al., 2012). In principle, microorganisms can rather easily be eliminated from foods by
484 application of a heating process, which might suggest that microbiological risks from food can quite easily be
485 prevented. However, microbial contamination of food products and exposure are common, and, to some
486 extent, more easily accepted by consumers (Kher et al., 2013).

487 Burden of disease studies (Section 2.7) show an opposite trend compared with published RBA studies:
488 because the availability of the relevant data is larger, the recent World Health Organization (WHO) study on
489 the global burden of foodborne disease (Havelaar et al., 2015) is primarily focused on microbiological
490 hazards, and only four chemical substances have been considered in the WHO report. The results suggest
491 that the disease burden related to the exposure to microorganisms may be larger than that for chemicals, but
492 more comparable disease burden estimates for chemical substances are required before an overall
493 comparison between the burden of chemical substances and microbiological pathogens can be made.
494 However, the results confirm that risk associated with microbiological hazards can be quantified and that it is
495 important to include microbiological risks in RBAs as well.

496 The inclusion of microbiological risks and benefits in RBAs requires that the specific characteristics of
497 microbiological agents are acknowledged, and that they are included in case studies. As illustrated by Berjia
498 et al. (2012) microbiological risks can specifically be of importance when the effects of food processing are
499 included in the risk-benefit question, as the doses largely depend on the storage and food preparation. It
500 would therefore be advisable that data on food preparation (such as storage times, temperatures and the
501 applied cooking style) are included in dietary surveys.

502 The challenges from differences in approach between chemical and microbiological risk assessment needs
503 further study to allow the development of a more integrated approach towards RBAs (Sections 1.2 and 2.5).
504 Recently developed tools that are increasingly adapted to allow comparisons between chemical and
505 microbiological health risks (e.g. FDA-iRisk; Chen et al., 2013) can help to address these challenges.

506 2.9 The scope of risk-benefit assessments

507 The scope of a risk-benefit question in relation to food may be much wider than direct health impact and can
508 include socio-economic, psychological and/or environmental dimensions (Boobis et al., 2013). When
509 consumers select their food, the health effect is only one of the concerns; others include cost, taste, quality
510 and sustainability of the production. An indicated health risk may be counterbalanced by each of these, for
511 example, if low price and good taste are considered benefits that outbalance the health risk.

512 One may consider widening the scope of RBAs of foods and include some of the aspects mentioned above.
513 Cost is an obvious choice, which is an intrinsic part of the RBA when metrics such as the cost-of-illness or
514 willingness-to-pay are used (Section 2.7). It can also be added to the RBA by means of a cost-utility, cost-
515 benefit or cost-effectiveness analysis, as for example done for the costs of intervention strategies that aim to
516 lower the public health risks of *Campylobacter* from broiler meat (Mangen et al., 2007; Van Wagenberg et
517 al., 2016). Measurements such as the “cost per avoided DALY” can be highly informative for risk-benefit
518 managers because they can indicate the economic consequences of scenarios in RBAs and allow for a
519 comparison of policies.

520 Also, environmental sustainability can be taken into account, for example by the use of life cycle assessment
521 (LCA), a product-oriented environmental assessment tool that provides a systematic way to quantify the
522 environmental effects of individual products or services (Hermansen & Nguyen, 2012). A methodology is

523 being developed to include nutritional health impacts in LCA (Stylianou et al., 2016), which could clearly
524 contribute to the development of RBAs with a scope beyond immediate health effects of food intakes.

525 Ultimately, it can be attractive to address all of the relevant aspects in one overall analysis, for example by
526 the use of multi criteria decision analysis (MCDA). This method has for example been applied to the
527 prioritisation of foodborne pathogens (Ruzante et al., 2010), taking into account public health impact
528 (expressed in DALY and cost-of-illness), market impact, consumer perception and acceptance, and social
529 sensitivity to impacts on vulnerable consumer groups and industries. In MCDA, an integrating scoring
530 method is developed, which weighs the importance of different factors that are considered relevant for the
531 decision making, allowing one to come with a final ranking that includes all of these factors.

532 Defining the scope of the RBA is clearly an issue that should be decided upon when the risk-benefit question
533 is formulated. A broader scope includes more relevant issues, but also implies an increasing demand for
534 resources in terms of research efforts, data and method development. Clearly, challenges that complicate
535 RBAs, such as the lack of data and knowledge, and the consequential uncertainties, the imbalance in level
536 of scientific evidence and the use of quantitative metrics, only get more weight when a broader scope is
537 taken. Yet, the ongoing developments show that progress can be made, and with multidisciplinary scientific
538 collaboration and investment in research supporting RBAs, this progress can be strengthened in the future.

539 2.10 The application of risk-benefit assessments

540 So far, several RBAs have been performed, but mainly within research projects that were directed at the
541 development of RBA frameworks and methodology. The aim of these RBAs was primarily to illustrate the
542 potential of the methodology and the risk-benefit question was not posed by independent risk-benefit
543 managers but by the researchers themselves. There is now a need for more experience with the practical
544 application of RBAs and the proposed methodologies. These practical applications of RBAs can fall into two
545 categories: those leading to recommendations or guidelines to food safety and health authorities, and those
546 leading to process and formulation design by industry (Boué et al., 2015). The first application is the one
547 considered most often and typically the request for such an RBA originates from national or international
548 food and health authorities that have a mandate to advise the public on a particular food or diet and have
549 identified a need to establish a scientific basis for this advice. Examples are an RBA on fish and fish
550 products performed in Norway (Skåre et al., 2015) and an RBA on nuts performed in Denmark (Mejborn et
551 al., 2015). Another reason for the authorities to make requests for an RBA is a need for an evaluation of
552 health effects of proposed fortification of foods, as for example with vitamin D, folic acid (Hoekstra et al.,
553 2008) or iodine (Zimmermann, 2008).

554 Food producers may have an interest in RBAs when they change their production or the formulation of their
555 products. This is especially of interest when this change is based on a wish to decrease one specific health
556 risk that can go at the expense of another. For example, when a heating step is introduced to decrease
557 microbiological health risks, this can go at the expense of the formation of potentially carcinogenic
558 substances (Havelaar et al., 2000) and/or decreased vitamin levels. In such cases, RBA can be an excellent
559 tool to settle a dispute that cannot be solved on the basis of the identification of risks and benefits alone.

560 The challenge from increased application of RBAs can only be met by initiating more specific RBA projects
561 based on current demands of risk-benefit managers and by performing RBAs in practice. Food safety and
562 health authorities and the food industry should be open for multidisciplinary collaboration and should be
563 made aware of the potential of RBAs. When RBAs are performed, they should be published in the
564 international peer-reviewed literature, even if a lack of data or major uncertainties obstruct firm conclusions.
565 This is important to assure the scientific quality, to increase the experience in the research community and to
566 aid the international discussion on the potential and challenges of RBAs.

567 3. Conclusion

568 RBA is an evolving discipline in food safety and nutrition that takes advantage of achievements in a variety of
569 underlying disciplines. As it integrates various health concerns, it is a valuable method to estimate the overall
570 health effects related to food consumption and diet choice, which can be applied both by food and health
571 authorities and the food industry. Recognizing the progress that has been made in the past decade and
572 based on previous work, we have identified a series of challenges that should be met to develop the area
573 further and indicated steps that should be taken for further progress. The challenges and suggested ways
574 forward in meeting them are summarized in Table 1.

575 To meet the challenges of RBA, it is important that researchers in underlying disciplines and stakeholders in
576 food regulation, production, retail and consumption from different regions in the world agree on definitions
577 and concepts that are practical and agreeable for all. Based on relevant risk-benefit questions, a series of
578 risk-benefit studies should be performed, not so much to develop methods, but predominantly to identify the
579 practical challenges that are met when working on RBA case studies. When investigating these practical
580 challenges, steps can be made in categorizing them and in developing and harmonising agreeable methods
581 to address them.

582 For the future development of the RBA area, it is important to perform methodological research into some of
583 the identified challenges because they cannot be met by performing case studies alone. Examples are
584 studies into the differences and similarities in results obtained from top-down compared with bottom-up
585 approaches (by the application of comparative analytical tools and simulation studies), research into
586 uncertainty analysis and comparative studies on integrated health metrics and metrics outside the health
587 domain. Additionally, risk communication is one of the key pillars in risk analysis and should also be an
588 inherent part of RBAs of foods, particularly for the communication of quantitative metrics and their attending
589 uncertainties to all stakeholders.

590 Overall, with an increasing demand from different stakeholders for holistic and objective assessments of the
591 health effect of foods, multidisciplinary RBA is a promising research area for the future. Impressive progress
592 has been made and, despite the remaining challenges, we expect that more progress will be made in the
593 next decade. The steps forward proposed in this paper will be useful in taking the research area further,
594 allowing for transparent and reliable RBAs to be performed on a wider scale in the future.

595

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599

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825 Figure captions

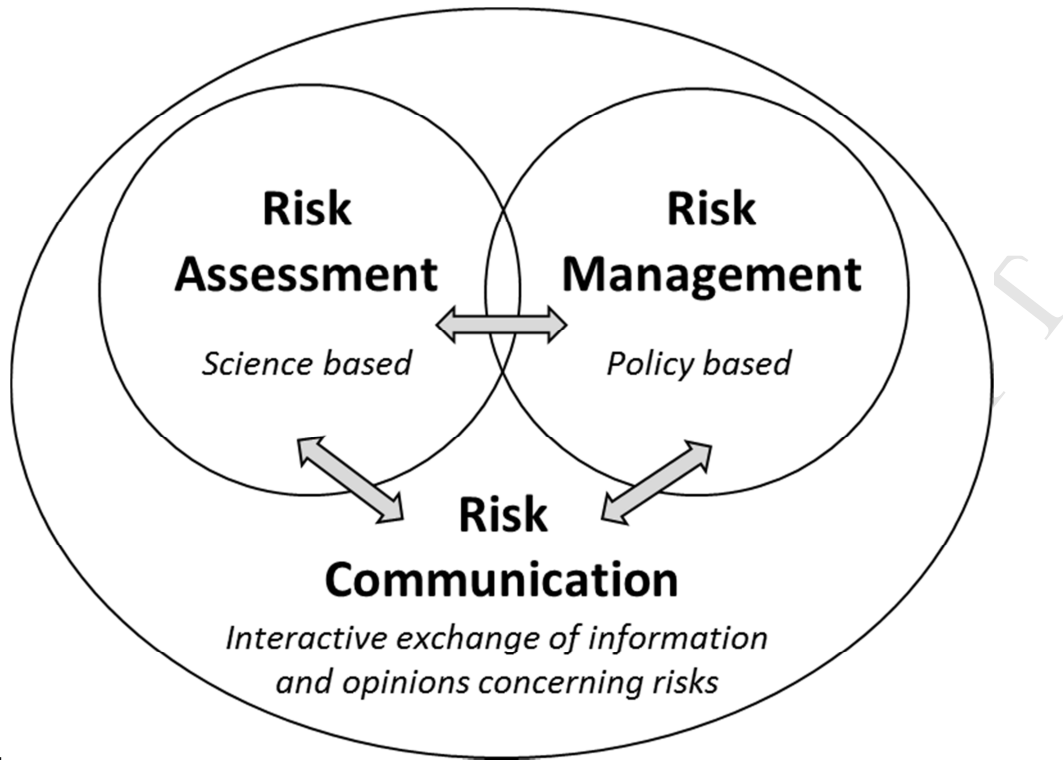
826 Figure 1. The risk analysis framework with the elements risk assessment, risk management and risk
827 communication. Adapted from WHO (2005).

828 Figure 2. The elements of risk assessment as used in toxicology, microbiology and nutrition. Differences in
829 the approach used in the three disciplines are explained in the text. Traditionally, the link between hazard
830 identification and exposure assessment is not indicated in toxicology and nutrition, whereas it is essential in
831 microbiology, where exposure depends on the microorganism of concern.

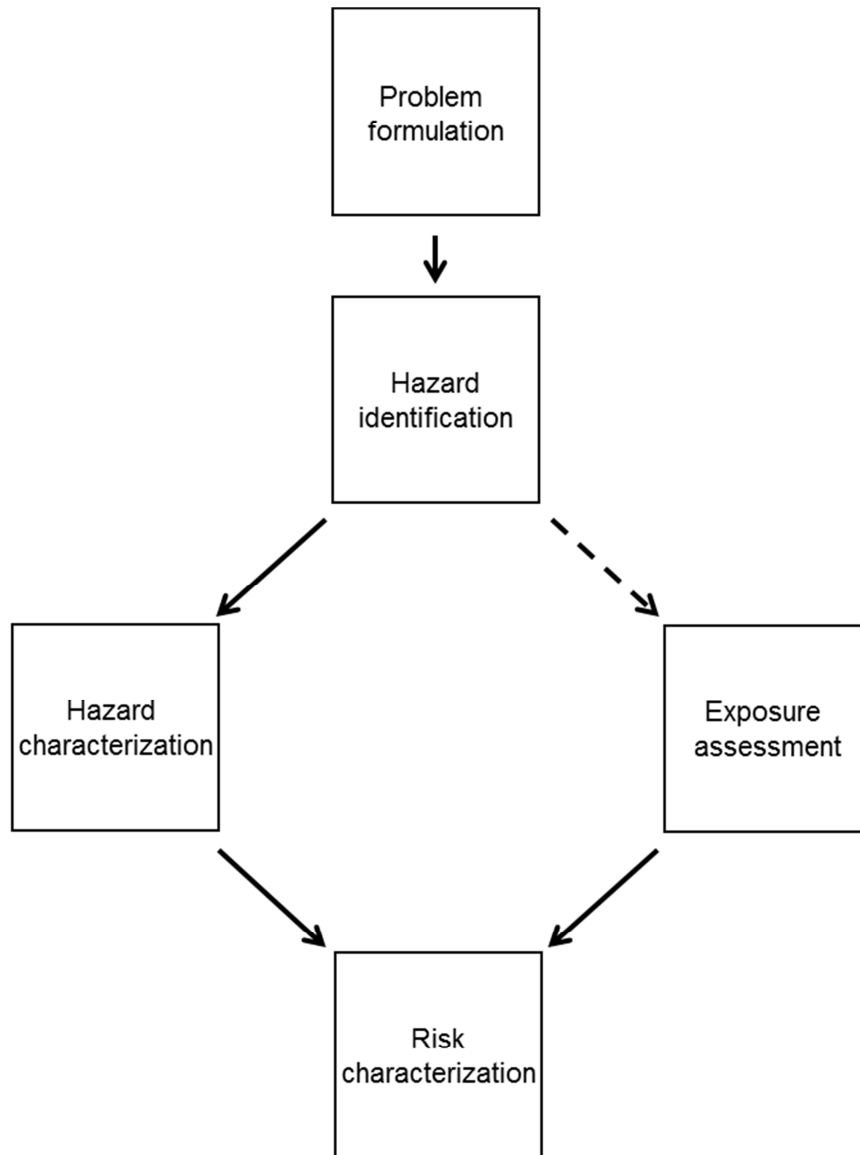
832 Figure 3. A comparison of approaches for hazard characterization used in toxicology and microbiology (left)
833 and nutrition (right). In toxicology and microbiology, the risk increases with the dose; benefits are not defined.
834 In nutrition, intake of a food compound can be too low or too high; intake between these levels ("the window
835 of benefit") is considered beneficial for health. X: Dose with critical response as used in chemical risk
836 assessment (e.g., LOAEL or BMD); no equivalent metric exists in microbiological risk assessment. LTI:
837 Lower threshold intake, intake below this level represents a deficiency; UL: Upper intake level, intake above
838 this level could give a toxic effect.

839 Figure 4: Examples of risk-benefit frames where the level of aggregation is the food product (above) or the
840 food compound (below). The first two examples represent elements of the studies from Hoekstra, Hart, et al.,
841 2013, and Berjia et al., 2012, and illustrate how an RBA of a food product may include several food
842 compounds and contaminants, which each can have several health effects (either negative or positive,
843 indicated by + and -). Alternatively, effects can be directly linked to the intake of the food products (i.e., CHD
844 and stroke). The other two examples are derived from Berjia et al., 2014, and Hoekstra et al., 2008, and
845 illustrate how an RBA of a food compound can include several health effects and several food products, or
846 even other sources of exposure. Note that Berjia et al., 2014, does not specifically study the sources of
847 vitamin D and Hoekstra et al., 2008, only considers scenarios involving fortified bread.

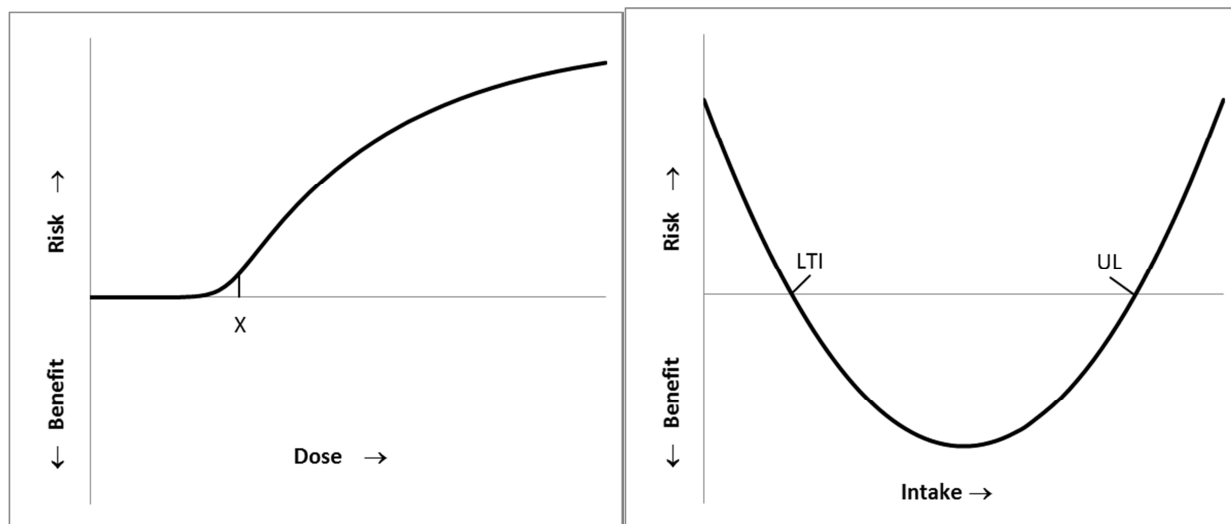
848



849 Figure 1.



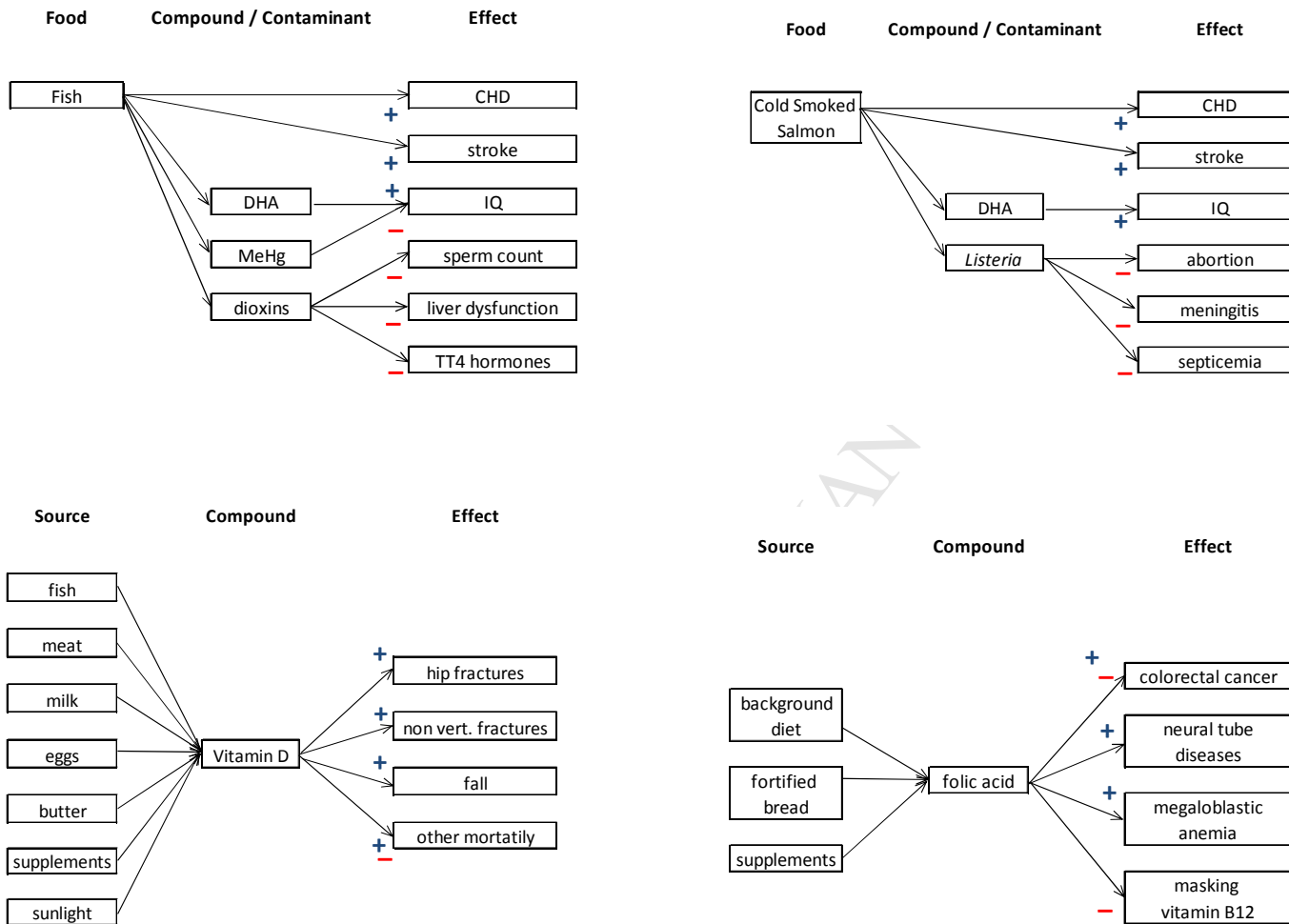
850 Figure 2.



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852 Figure 3.

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Figure 4.

855 Table 1: A summary of the challenges in risk-benefit assessment as discussed in this paper, with a brief
 856 indication of the proposed way forward.

Topic	Challenge	Suggested way forward
Definitions	Definitions of basic concepts differ between disciplines underlying RBA.	Create awareness and reach consensus.
Top-down versus bottom-up	Risk and benefit assessments can be based on top-down human observational evidence or bottom-up risk assessment approaches, which may provide different health effect estimates of food compounds or contaminants.	Perform studies that combine the two approaches to compare potential bias and uncertainties, either by case studies or simulation studies.
Risk-benefit question	A wide and confusing range of questions is possible, which may require different methods.	Define the risk-benefit question in close collaboration with risk-benefit managers. Categorise questions and frame the risk-benefit question schematically.
Lack of data and knowledge; uncertainty	Missing data and knowledge can lead to large uncertainties attending RBA.	Identify, characterise and communicate uncertainties; fill up the crucial identified data gaps.
Imbalance of level of evidence	The level of evidence required for benefits is usually larger than for risks, hence risks are more likely to be included in RBAs.	Put emphasis on the size of the health effect rather than on the presence or absence of the health effect.
Substitution	When an alternative intake scenario implies a change in consumption of one food product, it will have consequences for others. There can be many options for substitution.	Find a comparable food product and include it in the analysis, use isocaloric alternatives, or compare several scenarios.
Quantitative metrics	Qualitative and quantitative approaches can be used and various health metrics can be selected. They can be applied both at population level and individual level.	More than one metric can be useful, quantitative assessments can be preferable even if the risk-benefit balance is clear. Well balanced choices for the metrics applied have to be made when the risk-benefit question is defined.
Including microbiology	Microbiology is not well integrated in current RBA methods, definitions and concepts may	Perform more RBAs that include microbiological hazards, take

	be different. Yet it is an intrinsic part of food safety with significant health implications and therefore it should be included in RBAs.	advantage of experience in disease burden estimation and risk ranking.
Scope	The scope of RBAs can be extended beyond health concerns, for example by including costs and environmental sustainability.	Develop methods and metrics to do this further, integrate methods such as LCA and MCDA into RBAs.
Application	The (Quantitative) RBA methodology has not yet been applied much, it is unclear to what extent the developed methods are practically applicable.	With case studies, show how useful the RBA can be in different areas and discuss experiences.

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858 Nomenclature

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ADI	Acceptable daily intake
ARfD	Acute reference dose
BMD	Benchmark dose
BRAFO	Benefit and Risk Analysis for Foods (EU project)
DRV	Dietary reference value
DHA	Docosahexaenoic acid
EFSA	European Food Safety Authority
EPA	Eicosapentaenoic acid
FAO	Food and Agriculture Organization of the United Nations
FSO	Food safety objective
IPCS	International Programme of International Safety
LCA	Life cycle assessment
LOAEL	Lowest observed adversary effect level
LTI	Lower threshold intake
MCDA	Multi criteria decision analysis
NOAEL	No observed adversary effect level
RBA	Risk-benefit assessment
TDI	Tolerable daily intake
UL	Upper intake level
WHO	World Health Organization

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Highlights

- RBA combines chemical and microbial risk assessment with risk and benefit assessment in nutrition.
- Key challenges in risk-benefit assessment of foods are addressed.
- Challenges relate to interdisciplinarity, methods, data, health metrics and applications.
- Suggestions for meeting the identified challenges are discussed.