P.O. Box 253
6928 Manno
Switzerland

1828 L Street, NW, Suite 510
Washington, DC 20036-5114
USA

+41/(0)91/610 94 70

+1 202 204 7665

www.crn-i.ch

Background provided by EFSA

Lines 120-155: EFSA is to be applauded for trying to systematize a process that to date has not been attempted by any other government health body. CRN-I generally agrees with the assessment that RCTs have had limited success in identifying benefits for nutrients and that EFSA and the world nutrition community would be able to better conduct benefit risk evaluations if more emphasis were placed on models that can be better used to measure nutrient based health benefits.

Lines 121-6: This paragraph should acknowledge that most regulatory authorities, including the European Commission, separately regulate benefits and risks for foods. Policies and regulations for benefits are specified through Population Reference Intakes (PPI) or similar concepts and Health Claims (including disease risk reduction, and functions).

Terms of Reference

(no comments)

Section 1.1

Lines 232-238: Insert a sentence (or two) to acknowledge that Risk Analysis Principles by the Codex Committee on Nutrition and Foods for Special Dietary Uses describes the possibility that benefit could be described as a reduction in the risk of an adverse effect resulting from an inadequate intake of a nutrient. At minimum, this reference should be included with the current text.

Section 1.2

Lines 252-258: In 2006, CRN commented to the Risk Analysis Working Group of the CCNFSDU that a Lower Level (LL) for benefits, and thus for the lowest recommended nutrient intake, could be defined and identified in a manner exactly analogous to the UL procedure for identifying the highest intake to be considered safe. Also, CRN concluded that acceptance and implementation of such a concept was unlikely because the PRI/RDA concept is so well entrenched.

Section 1.3

Line 267: Here and in several other sections the document needs to clearly state that persistence of the adverse effect is either added or included in the concept of severity.

Section 2.1

Line 316: Specify that the concern with nitrosamine formation is the carcinogenicity of most members of this chemical class.

Section 2.2

Lines 342-343: Add a sentence to acknowledge that use of risk benefit analysis to control entry of new products into the marketplace would require new legislation or regulation because most jurisdictions now regulate citation of benefit and safety under separate reviews and decisions.

Lines 349-354: If EFSA believes there is a legitimate reason to keep stakeholders out of the assessment, it should be stated here. Otherwise this paragraph should indicate that procedures will be established to permit the participation.

Section 2.3

Lines 362-364: This is a false comparison. Stepwise procedure and quantitative analysis are not mutually exclusive.

Lines 367: It is not clear how Step 1 can be validated without Step 2. This also applies to other locations in the document.

Lines 373-375: This double standard is not justified. It allows for, or facilitates, pernicious neglect of benefits.

Section 2.3.1

Lines 27-29: The intent of this sentence is not clear.

Line 38: Probabilistic is very general. What exactly is meant.

Lines 40-41: Dose response modeling has many forms. What exactly is meant?

Section 2.3.2

Lines 15-16: The meaning is vague. When is quantification "full?"

Lines 20-24: A major need for good data and detailed analysis is the need to support risk communication. This should be included in the paragraph.

Section 2.4

Line 61 and 65: Persistence should be mentioned here, or severity defined to include it.

Line 89: "for discussion" would be more accurately replaced by "to dispute."

Lines 83-94: The degree to which DALY and QALY values are arbitrary is not adequately described.

Lines 105-109:   This is a good example of an unjustified double standard. ADI or TDI values do not require the data to demonstrate causality, but the RDI and related values require demonstration of causality through RCTs. This structure guards against false claims but does nothing to prevent pernicious neglect to provide benefits. Oppositely, the structure provides excessive caution against adverse effects—even non-existent ones.

Lines 121-123: Another approach is that in the recent R-B analysis for vitamin D (Bischoff-Ferrari et al., Osteoperosis International). That analysis does not try to equate the health or societal value of the risk and the benefit, but instead examines the intake and serum 25OH vitamin D levels at which the risk and the benefit occur. Thus it can identify a safe and beneficial range of intakes without assigning somewhat arbitrary HALY or DALY values.

Section 3.1

Lines 128-136: This discussion does not adequately convey the concept that specificity and causality are issues for health benefit and risk effects.

Lines 137-141: See comment for lines 121-123, above.

Line 142: Risk benefit likelihood values may be estimated, but the assessment cannot be determined directly for the individual—except after an occurrence.

Section 3.1.1

Lines 174-176: Many cardiac drugs have biomarkers that have been only loosely validated to indicate morbidity or mortality risk.

Lines 180-181: Progress toward this goal should be indicated here.

Section 3.1.2

Lines 187-192: Folic acid could be mentioned as an example.

Section 3.2.2

Lines 222-239: A major limitation of RCTs is not mentioned here but should be. Although RCTs are necessary to show causality in humans, a failure to identify a specific beneficial effect in a specific RCT should not be overly generalized. The failure to find benefit may reflect a choice of an inappropriate endpoint, or it may reflect the status of the test cohort but not a majority of the population or a significant subpopulation.

Section 3.3

Line 268: Give at least one example of such nutrients.

270-277: The usual example of the 100x factor for extrapolation from animal data to humans, and the separation of the 100 into 10 x 10 has much more history than justification. The assignment of 10x for inter-individual variation may be appropriate in this context but often leads to unworkable answer when applied to human data. For example, a 10x factor for calcium, iron or zinc would lead to UL values well below the PRI values.

Section 4

Line 304: Imperfect knowledge is not a useful term—do we ever have "perfect knowledge?

Section 4.1:

Line 317: See line 304 in Section 4, above.

Lines 328-338: See comment above for Section 3.3 lines 270-277.

Section 4.2

Lines 344-347: The limitations of RCTs mentioned in the comment for lines 222-239 should be acknowledged here.

Section 5

Line 381: Again the double standard: Benefits must be "likely" but risks need to be only "potential." This standard can produce pernicious neglect of providing benefits, while overreacting to possible risks.

Section 5.1.3.1

Line 432: For Scenario 1, the heading is misleading. "Maximising the risks" reads as though this is an objective. Would it be better to say "Conditions of maximum risk?"

Line 449: For Scenario 2, the heading would better read "Conditions of minimum risk."

Section 5.1.3.3

Lines 486-489: This is easy to say and difficult to achieve. What composite matrix could be used?

1 **SCIENTIFIC OPINION**

2 **Guidance on human health risk benefit assessment of foods**[1]

3 **EFSA Scientific Committee**[2, 3]

4 European Food Safety Authority (EFSA), Parma, Italy

5 **ABSTRACT**

6 (Max. 300 words, no paragraph breaks)

7 *[The abstract will be drafted when the opinion is finalised, i.e. after the comments received during the public*
8 *consultation have been reviewed by the working group in charge of preparing the draft opinion.]*

9 **KEY WORDS**

10 Risk, benefit, assessment, problem formulation, risk benefit assessment paradigm, stepwise approach, metrics

11

12 SUMMARY

13 The European Food Safety Authority (EFSA) asked its Scientific Committee to prepare a guidance
14 document for performing risk benefit assessments of food related to human health risks and human
15 health benefits.

16 Risk benefit assessments are performed in different disciplines, under various perspectives and use a
17 wide range of quantitative or semi-quantitative tools. In this opinion, guidance for performing risk
18 benefit assessments of food focuses on human health risks and human health benefits and does not
19 address social, economic and other considerations such as "cost-effectiveness" considerations.

20 The Scientific Committee notes that there is less experience with benefit assessment than with risk
21 assessment and therefore proposes to mirror the risk assessment paradigm by introducing four steps
22 for the benefit assessment, i.e. positive health effect identification, positive health effect
23 characterisation (dose response assessment), exposure assessment and benefit characterisation.
24 Following this approach will facilitate a transparent comparison of risks and benefits in the risk
25 benefit assessment.

26 Problem formulation should precede the risk benefit assessment. Agreement on the terms of reference
27 between the risk benefit assessor and the risk benefit manager is critical for ensuring a useful and
28 relevant outcome for the risk benefit manager goals.

29 After problem formulation, a stepwise approach is recommended using three steps: i) initial
30 assessment, addressing the question whether the health risks far outweigh the health benefits or vice
31 versa, ii) refined assessment, aiming at providing semi-quantitative or quantitative estimates of risks
32 and benefits at relevant exposure by using common metrics, and iii) comparison of risks and benefits
33 using a composite metric such as DALYs or QALYs to express the outcome of the risk benefit
34 assessment as a single net health impact value. At each of the three steps, both risk assessment and
35 benefit assessment are usually performed at the population level. Where differences in the sensitivity
36 to the agent under consideration exist or are assumed to exist in specific subpopulations, separate
37 consideration of these subpopulations is needed.

38 After each step of the risk benefit assessment, discussion should take place between the risk benefit
39 assessor and the risk benefit manager on whether sufficient information has been provided or whether
40 the terms of reference should be refined in order to proceed with the next step of the assessment. The
41 outcome of each step of the assessment should also include a narrative of the strengths and
42 weaknesses of the evidence base and its associated uncertainties. The overall magnitude of
43 uncertainty associated with a risk benefit assessment may often be large. This should not be regarded
44 as implying a failure of the assessment; on the contrary, it provides essential information for decision-
45 making and helps in identification of data needs.

46 A number of metrics which can be used in the risk benefit assessment are described in the document.
47 It should be noted that more than one metric will be needed to capture all dimensions of health for a
48 risk benefit assessment. It is important that the risk benefit manager is aware of the limitations of the
49 metrics used for measuring risks and benefits.

50 The Scientific Committee recommends that metrics for the characterisation of positive health effects
51 are further developed. Weight factors of the impact of the most common diseases should, wherever
52 possible, be agreed upon internationally and justified if adapted to regional conditions, in order to
53 ensure harmonisation and recognition of the assessment.

54

55 The Scientific Committee recommends that, when designing a survey for generating data, a closer
56 collaboration between risk assessors and benefit assessors aims at ensuring that data generated by one
57 or the other can be used in a broader risk benefit assessment context. Further more, there is a need for
58 hard biomarkers of effect for both risks and benefits.

59 Two examples of the approach for risk benefit assessment are given. The first one (selenium, an
60 indispensable nutrient) illustrates the case where the risk and the benefit are associated with one
61 single agent, while in the second example (fish), the risk is due to one selected contaminant in food
62 (methylmercury), whilst the benefit is due to other food components. The examples highlight the
63 complexity of risk benefit assessment, already when entering the first steps of the assessment.

64

65

66   **TABLE OF CONTENTS**

119

120 **BACKGROUND AS PROVIDED BY EFSA**

121 Where a food or food substance is recognised to have the potential to exert both health benefits and
122 health risks it is important for risk benefit managers to be able to weigh the risks against the benefits
123 on the basis of a qualitative or quantitative risk benefit assessment. However, there is currently no
124 agreement on general principles or approaches for conducting a risk benefit analysis for food and the
125 assessment of risk to human health of food substances or nutrients is usually conducted independently
126 of possible health benefits.

127 EFSA organised a scientific colloquium on risk benefit analysis of foods in July 2006 to have an open
128 scientific debate on the methods and approaches for risk benefit analysis of foods[4]. There was a
129 general consensus that a risk benefit analysis should mirror the approach already agreed upon in the
130 risk analysis, namely consist of a risk benefit assessment part, a risk benefit management part, and a
131 risk benefit communication part. The risk benefit assessment should be comprised of 3 elements, i.e.
132 risk assessment, benefit assessment and risk benefit comparison. As for the risk assessment paradigm
133 which is well established, the benefit assessment should also include the following steps: positive
134 health effect identification, positive health effect characterisation (dose-response assessment),
135 exposure assessment, and benefit characterisation. Finally the risk benefit comparison should contain
136 a means, quantitative if possible, to compare/weigh the potential human health risks against the
137 potential human health benefits. For this a common scale of measurement ("composite metric") for
138 the risk and the benefit would facilitate the communication of the results.

139 It is considered that the decision to initiate a risk benefit analysis would best be made on a case-by-
140 case basis and, given the resources required to carry out such an analysis, should only be undertaken
141 when clearly needed. Therefore the formulation of the problem ("why is the risk benefit analysis
142 being done, why do we need it?") is pivotal; furthermore, it is emphasised that the question asked by
143 the risk benefit manager to the risk benefit assessor should be clearly understandable.

144 Regarding tools/data available or needed to quantify the human health risks and health benefits it is
145 considered that tools for classification of risks and of benefits would need to be developed, together
146 with tools for comparison and prioritisation of risks and benefits. Both tools and data should be
147 available, together with a common scale of measurement for risk and benefit. In order to provide
148 confidence in the outcome of a risk benefit assessment, the assumptions made for the assessment as
149 well as the uncertainties embedded in the outcome should be stated explicitly.

150 It has been proposed at the EFSA Scientific Colloquium[4] that the "state-of-the-art" of risk benefit
151 assessment had advanced beyond the brainstorming stage and that it was now time to advance to the
152 "learning by doing" stage. Although it may be premature at present to develop a prescriptive
153 framework for risk benefit assessment, it is suggested that a guidance document should be developed
154 with respect to methodology, approaches, tools and potential limitations in the risk benefit
155 assessment.

156

---

[4] See http://www.efsa.europa.eu/en/science/colloquium_series/risk_benefit_analys.html

157

TERMS OF REFERENCE AS PROVIDED BY EFSA

159 EFSA requests the Scientific Committee to prepare a guidance document for performing risk benefit
160 assessments of food related to human health risks and human health benefits. To this end the
161 document should give considerations to the following issues:

162   • Scope and objective of risk benefit assessment;

163   • Identification of situations for which a risk benefit assessment might be appropriate;

164   • Guidance on problem formulation particularly considering the type of risk benefit analysis
165   needed;

166   • Development of a harmonised language to express risk and benefits;

167   • Usefulness of currently available toxicological, epidemiological and nutritional data to assess
168   risk benefit;

169   • Consideration of methods and approaches needed to assess the risks and benefits and to
170   compare them, e.g. common scale of measurement for the comparison of human health risks
171   and health benefits;

172   • Considerations on how animal and other data can be extrapolated to the human situation in
173   order to facilitate human risk benefit comparison;

174   • Identification of potential limitations of any risk benefit assessment;

175   • Ongoing research activities, such as DG RTD projects and activities undertaken by other
176   organisations in order to join efforts and aim at harmonised approaches for risk benefit
177   assessment;

178   • Recommendations on future initiatives to overcome current limitations.

179

180

181 **ASSESSMENT**

182 **1.   Introduction**

183 In July 2006, EFSA organised a scientific colloquium on risk benefit analysis of foods[4,] during which
184 it was proposed that the "state-of-the-art" of risk benefit assessment had advanced beyond the
185 brainstorming stage and that it was now time to advance to the "learning by doing" stage. Although it
186 may be premature to develop a prescriptive framework for risk benefit assessment, it was suggested
187 that a guidance document should be developed with respect to methodology, approaches, tools and
188 potential limitations in the risk benefit assessment. Since then, several activities such as the Beneris[5],
189 Qalibra[6] and Brafo[7] projects, which EFSA has been following closely, have been commenced to
190 address the issue of risk benefit assessment.

191 Risk benefit assessments are performed in different disciplines, under various perspectives
192 (government, industry, patients) and using a wide range of quantitative and semi-quantitative tools.
193 Examples are human medicine (e.g. assessment of the benefits and risks in the context of a new drug
194 application) and engineering. Many of such assessments include socioeconomic considerations or
195 aspects beyond human health that are not directly comparable and require value judgments to be
196 compared.

197 The classic case where value judgments are needed is when the risk or benefit assessment is used as
198 the basis of a benefit cost analysis. In this case risks and benefits are given monetary values reflecting
199 market prices directly or indirectly. The use of economic methods such as willingness to pay studies
200 or co-joint analyses could be helpful in eliciting information on the consumer or citizen preferences
201 and valuing the benefits and risks. The direct and indirect monetary costs of years of life lost through,
202 and years of life spent with diet-related diseases, like cardiovascular diseases or cancer can be
203 calculated based on morbidity and mortality statistics. With regard to food safety, Havelaar et al.,
204 (2007) suggested to integrate microbiology, epidemiology, risk assessment and economics to support
205 risk benefit managers in formulating strategy and taking decisions.

206 In this opinion, guidance for performing risk benefit assessments of food related to human health risks
207 and human health benefits is provided to enable risk benefit managers to weigh the risks against the
208 benefits. Similar to the general principles of risk benefit assessment used by the European Medicines
209 Agency (EMEA)[8], the EFSA's Scientific Committee decided to exclude social, economic and other
210 considerations such as "cost-effectiveness" from its considerations.

211

---

[5] See http://www.beneris.eu/
[6] See http://www.qalibra.eu/
[7] See http://www.brafo.org
[8] Reflection paper on benefit-risk assessment methods in the context of the evaluation of marketing authorization applications of medicinal products for human use; page 5: Under Community law (Regulation 726/2004), in the interest of public health, authorisation decisions under the centralised procedure should be taken on the basis of the objective scientific criteria of quality, safety and efficacy of the medicinal product concerned, to the exclusion of economic and other considerations such as "cost-effectiveness". http://www.emea.europa.eu/pdfs/human/brmethods/1540407enfin.pdf

212

1.1. Risk assessment - Definition

213

Risk assessment is the first of three components of risk analysis. It is "*a process intended to calculate or estimate the risk to a given (sub)population, including the identification of attendant uncertainties, relating to 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*" (IPCS, 2004). For the purpose of this opinion the agent will be a food itself or a constituent of a food (incl. contaminants, microbes), and the target system is the human body.

Different organisations use different definitions of risk, depending on the focus of their activities. In the context of this opinion, the following definition of risk will be used:

Risk: The probability of an adverse effect in an organism, system[9], or (sub)population in reaction to exposure to an agent (IPCS, 2004).

The terms *hazard* and *adverse health effect* have been defined for the use in risk assessment:

Hazard: Inherent property of an agent or situation having the potential to cause adverse effects on health when an organism, system, or (sub)population is exposed to that agent (slightly modified from IPCS, 2004).

Adverse (health) effect: a change in morphology, physiology, growth, development, reproduction or life span of an organism, system[9] or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences (IPCS, 2004; FAO/WHO, 2006).

Notably hazard describes the exposure dependent potential of an agent to cause harm which in this context consists of an adverse effect on health. Therefore, adverse health effects caused by an insufficient intake, e.g. of an indispensable (essential) nutrient are not attributable to a hazardous property of that nutrient; while adverse health effects caused by excessive intake are. Accordingly, the evaluation of a nutrient could be done as a risk-risk comparison, by comparing the risk of inadequacy (deficiency or absence of a beneficial effect) to the risk of excessive intake (toxicity) (Renwick et al., 2004, EFSA, 2006a).

1.2. Benefit assessment - Definition

240

In common language a *benefit* provides an advantage, a help or an aid and *beneficial* is something which is helpful or good for something or someone. This means that risk and the term benefit in its conventional sense would not be a pair of corresponding opposite terms, while adverse health effect and positive effect on health are. There is also no term for the inherent potential of an agent (food) to cause beneficial effects on health which would correspond to the term hazard as applied in risk assessment.

In the context of this opinion and in line with the definition of risk, benefit is considered to consist of the probability of a positive effect on health (see box on "Benefit"). The reduction of a risk will also be considered as a benefit. Consequently, the following definition of benefit is used:

---

[9] The Scientific Committee interprets "system" to include future generations (see IUPAC definition of a harmful substance: http://sis.nlm.nih.gov/enviro/glossaryh.html)

250 **Benefit:** The probability of a positive health effect and/or the probability of a reduction of an adverse
251 health effect in an organism, system[9], or (sub)population, in reaction to exposure to an agent.

252 In contrast to risk assessment there is not much guidance published on how to perform benefit
253 assessment of foods and food constituents. The evaluation of health claims according to Regulation
254 1924/2006 by EFSA can be considered as an example of benefit assessment (EFSA, 2009). It is
255 proposed in this opinion that positive health effects of nutrients, foods or constituents of food are
256 assessed in a similar way to hazards, that is potential benefits should be identified, described, weighed
257 and arranged according to their magnitude, and their dose-response relationship should be
258 characterised (see right side of Figure 1)

259

1.3.   Risk benefit assessment - Definition

261 The EFSA scientific colloquium on Risk Benefit Analysis of Food (EFSA, 2006b) concluded that a
262 risk benefit analysis should mirror the approach agreed upon for risk analysis (IPCS, 2004; Codex
263 Alimentarius Commission, 2005; WHO/FAO, 2006), and therefore should include a risk benefit
264 assessment, a risk benefit management and a risk benefit communication part. This opinion focuses
265 on the risk benefit assessment.

266 In the risk benefit assessment, the probability of an adverse health effect or harm (both incidence and
267 severity) as a consequence of exposure can be weighed against the probability of benefit, if both are
268 known to be possible.

269 The Scientific Committee proposes the following terms and their counterparts for the assessment of
270 the probability of harm (= risk) and of the assessment of the probability of the positive health effects
271 (= benefit).

Risk Assessment	Benefit Assessment
Hazard identification	Positive health effect identification
Hazard characterisation (dose response assessment)	Positive health effect characterisation (dose response assessment)
Exposure assessment	Exposure assessment
Risk characterisation	Benefit characterisation

272

273 Figure 1 illustrates the proposed procedure for a risk benefit assessment which consists of two
274 separate and independent arms of assessing the risk and the benefit, respectively. The individual steps
275 on both sides are comparable: identification of the possible hazards and positive / reduced adverse
276 health effects together with their biological mechanisms if possible; characterisation of the identified
277 hazards and positive / reduced adverse health effects with respect to severity, reversibility and dose-
278 response relationship; and characterisation of the risk and the benefit, that is the probability of each
279 identified hazard or positive health effect to occur in a population or population group. The exposure
280 assessment is positioned as a central part of the risk benefit assessment and should take into account
281 all relevant dietary and non-dietary sources. Finally, the risk benefit comparison will weigh the risks
282 against the benefits.

283
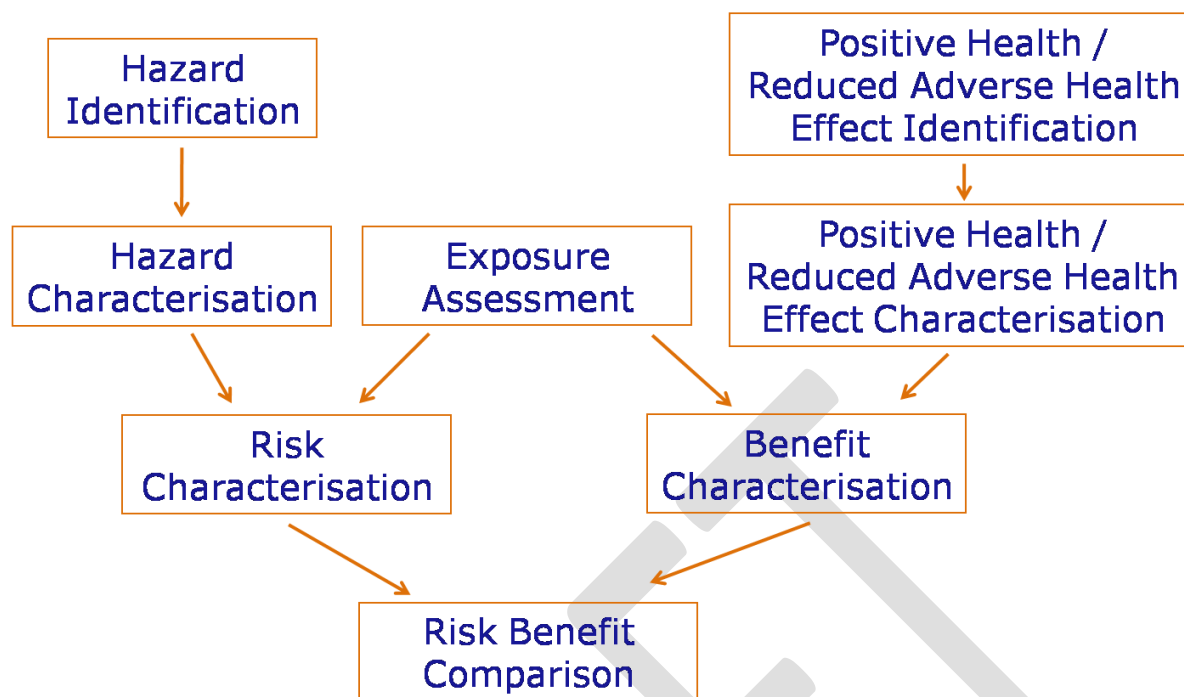
284
285   Risk assessment and benefit assessment each include four steps: identification of hazard or positive / reduced adverse health
286   effect, characterisation of hazard or positive / reduced adverse health effect (which includes dose-response assessment),
287   exposure assessment, and characterisation of risk or benefit which are weighed or compared to each other as the final step.

288   **Figure 1:**   The risk benefit assessment paradigm, as recommended by the EFSA Scientific
289   Committee and based on the discussions of the EFSA scientific colloquium on risk benefit analysis of
290   foods[4].

291

292   Different scenarios for the risk benefit assessment can be foreseen due to the nature of the benefits
293   and risks. The different scenarios for different risks and benefits connected with one food and
294   concerning the same or different populations are outlined in Section 2.1.

295

296   **2.   Proposed approach for risk benefit assessment**

297   **2.1.   Examples of situations for which a risk benefit assessment might be appropriate**

298   Where a food or food constituent has the potential to exert both beneficial and adverse health effects,
299   it is important for risk benefit managers to be able to weigh the risks against the benefits. Particularly
300   in a situation when dietary exposures associated with risk and benefit are close there is a need to
301   determine if there is a dietary exposure range within which there is a balance between risks and
302   benefits.

303   Risk benefit assessment would be appropriate in situations, such as, but not restricted to:

304   •   Where a single compound or food constituent has both positive and negative health effects.
305   These effects may occur: i) in the same population, e.g. for zinc, vitamin A, phytosterols,
306   iron; ii) in different populations e.g. for folic acid enriched food, where the prevention of
307   neural tube defects in the unborn child should be compared with potential hazards, such as
308   masking of vitamin B_{12} deficiency in the elderly, dementia or colon cancer.

309   • Where positive and negative health effects, either in the same or different populations result
310   from different components in the same food e.g.: i) fatty fish, where the main potential
311   beneficial effects related to prevention of cardiovascular diseases by n3 fatty acids need to be
312   compared with the potential negative health effects of environmental pollutants such as
313   dioxins or PCBs, or ii) consumption of vegetables, where the positive effects such as
314   supplying of micronutrients and prevention of certain types of cancer should be weighed
315   against the potential hazards of the presence of nitrates, such as methaemoglobinaemia in
316   infants and nitrosamine formation.

317   • Before the start of an intervention, such as folic acid fortification, or fluoridation of drinking
318   water.

319   • Where a significant change of dietary consumption patterns has occurred or may occur in the
320   future, e.g. substituting sugar by low-calorie sweeteners.

321   • Where chemicals are used to prevent microbial contamination, e.g. use of biocides.

322   • Where the beneficial effect, such as enhanced retention of nutritional value resulting from
323   improved processing procedures, requires to be assessed against the negative effects
324   associated with a greater survival of foodborne pathogens.

325   • Where new knowledge emerges with major implications for either the risk(s) or the benefit(s)
326   in a previous risk benefit assessment. For example the possible association between folic acid
327   consumption and colon cancer.

328

2.2.   Problem formulation

330 Problem formulation should precede the risk benefit assessment because a clear formulation of the
331 problem is critical for ensuring a useful and relevant outcome of the risk benefit assessment. Problem
332 formulation in risk assessment was addressed among others by US EPA (1998) and by the FOSIE
333 project (Food Safety in Europe: Risk assessment of chemicals in food and diet (Renwick et al.,
334 2003)). In contrast, problem formulation in benefit assessment or risk benefit assessment has received
335 very little attention to date.

336 Problem formulation is the responsibility of the risk benefit manager and preferably should be
337 conducted in dialogue with the risk benefit assessor to ensure that the outcome, i.e. the formulated
338 Terms of Reference, is appropriate for the risk benefit management goals. The Terms of Reference
339 should define the risk benefit question to be addressed. Risk benefit questions are of two main types:

340   • What is the balance of risks and benefits caused by a particular diet (often the current diet) or
341   dietary component (e.g. fish)?

342   • What would be the net health impact of a specified change in the diet, e.g. a public health
343   intervention, a new product, or a change in consumer preferences?

344 The Terms of Reference should specify which type of risk benefit question is asked and the diet,
345 dietary element or dietary change to be assessed. It will generally be helpful also to specify the
346 population to be considered, e.g. the whole European population, one or more national populations, or
347 a particular subpopulation (e.g. children, immunocompromised, etc.), as this may be important for the
348 risk benefit manager and can have significant time and/or data implications for the assessment.

349 The Terms of Reference should also specify the timetable for completing the assessment, and
350 optionally it may specify whether and which stakeholders should be involved in the process. In some

351 cases the Terms of Reference may identify some types of health effects that should be included in the
352 assessment, if they are of particular interest to the risk benefit manager or to stakeholders. However,
353 this is not essential, because identifying relevant potential effects is an intrinsic part of the risk benefit
354 assessment.

355

2.3.   Proposed approach for risk benefit assessment

357 As mentioned in Chapter 1 the risk benefit assessment should comprise three elements: risk
358 characterisation, benefit characterisation and a comparison of risks and benefits. As shown in figure
359 1, this implies that both hazards and positive health effects need to be characterised, and that by
360 taking the results of the exposure assessment into consideration, risks and benefits are characterised.
361 The final part of the risk benefit assessment comprises a direct comparison of potential health risks
362 and potential health benefits. One of the conclusions of the EFSA scientific colloquium on Risk
363 Benefit Analysis of Food (EFSA, 2006b) was that, although a quantitative assessment is to be
364 preferred, it was generally advised to follow a stepwise approach.

365 After problem formulation a stepwise approach for the risk benefit assessment is recommended using
366 the following steps:

367 • Step 1, Initial assessment

368 • Step 2, Refined assessment

369 • Step 3, Assessment using a composite metric (see section 2.4)

370 The Scientific Committee underlines that after each step, discussion should take place with the risk
371 benefit manager on whether sufficient information has been provided or if the terms of reference
372 should be refined in order to proceed with the next step.

373 It is to be noted that a different level of evidence is commonly required for benefit and risk; for
374 benefit the evidence frequently needs to be convincing whereas for risk it may be more appropriate to
375 take a conservative approach on the basis of a lower weight of evidence.

376 For all the steps in the risk benefit assessment, the rationale for following a certain approach and for
377 selecting specific parameters should be clearly described. The risk benefit assessment should include
378 a description of the assumptions and uncertainties, and explain the outcome. This will help the risk
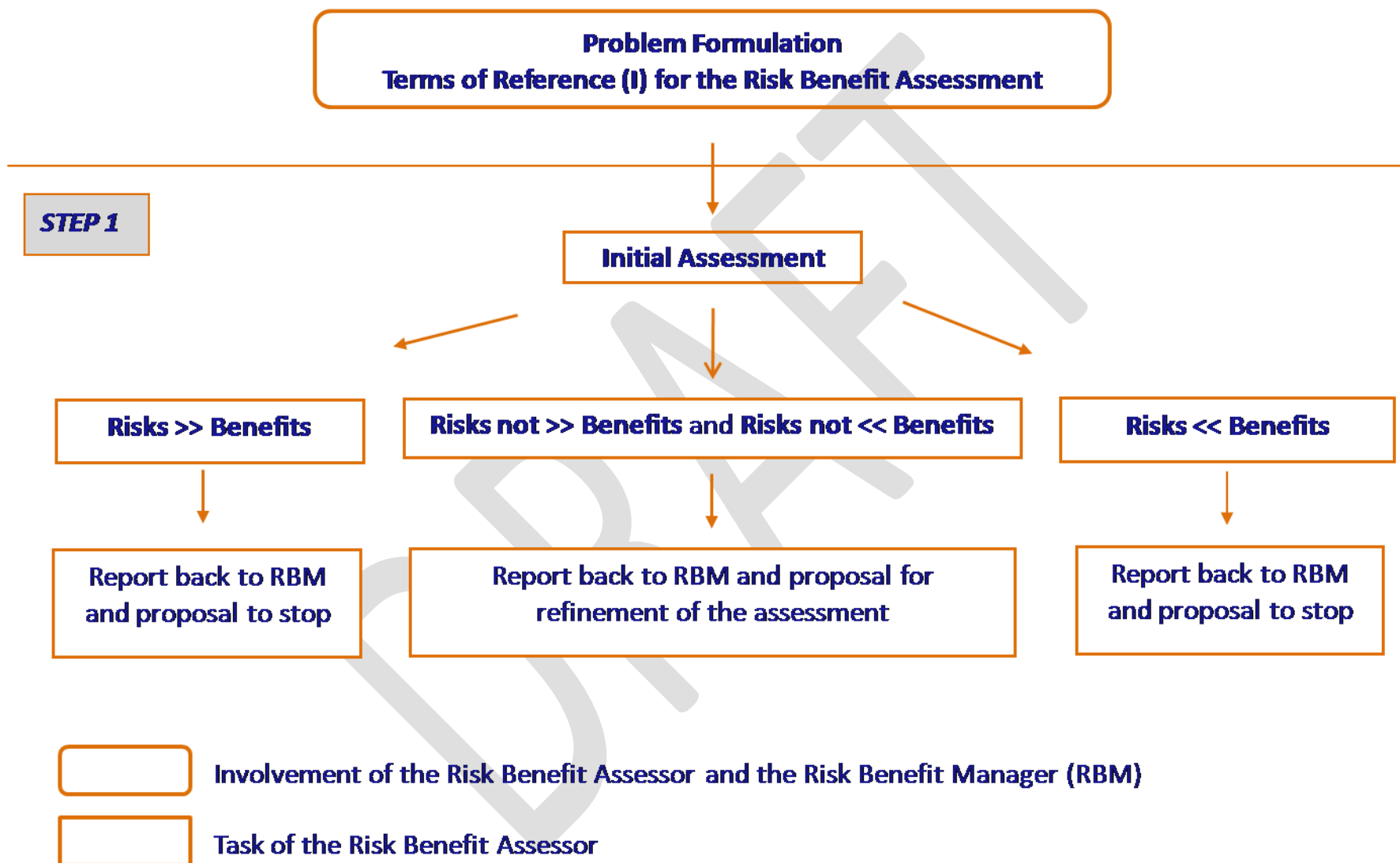379 benefit manager to understand its relevance in relation to the management decisions to be taken.

Figure 2: First step of the EFSA approach for risk benefit assessment – Initial assessment

1 **2.3.1.   Step 1 – Initial assessment**

2 This step addresses the question of whether the health risks far outweigh the health benefits or *vice*
3 *versa*. In order to do so, risks and benefits are considered separately and their health impacts are
4 compared to conclude whether the risks clearly outweigh the benefits or the benefits clearly outweigh
5 the risks. To make such a comparison, all relevant factors related either to a potential health risk or to
6 a potential health benefit need to be considered.

7 Due to the inherent uncertainties in this assessment, this step can best be performed by addressing two
8 different scenarios:

9 • Scenario 1: Estimate the risks at a high dietary exposure to the relevant agent(s) in food,
10 together with the benefits at a low dietary exposure to the relevant agent(s) in food, i.e. upper
11 bound for risks and lower bound for benefits. If by doing so, risks are still much smaller than
12 benefits (risks << benefits), this ends the risk benefits assessment, as the assessment will have
13 to focus on benefits. In all other cases, a proposal will be made to the risk benefit manager to
14 refine the assessment by proceeding to step 2.

15 For example, if with this scenario, it appears that the exposure of the population is clearly
16 below an existing health based guidance value (such as ARfD, ADI, TDI, UL) for the
17 hazardous compound(s) that needs to be considered, then there is no appreciable health risk.
18 In that case, the question that needs to be answered is whether the available evidence is strong
19 enough to conclude on whether there is a potential beneficial effect for the situation being
20 evaluated. In the case of indispensable nutrients, if exposure is at or above dietary reference
21 values or nutrient status parameters are within the normal range, there is no appreciable risk
22 of nutrient insufficiency and the assessment can stop.

23 • Scenario 2: Estimate the risks at a low dietary exposure to the relevant agent(s) in food,
24 together with the benefits at a high dietary exposure to the relevant agent(s) in food, i.e. lower
25 bound for risks and upper bound for benefits. If by doing so, risks are still much greater than
26 benefits (risks >> benefits), this ends the risk benefit assessment, as the assessment will have
27 to focus on risks. For example, when there is no evidence for a health benefit for a
28 dispensable or indispensable nutrient (e.g. exposure below effective dose) the remaining
29 question is whether there is a possible health concern.

30 When there is either no appreciable health risk (based on scenario 1) or no appreciable health benefit
31 (based on scenario 2), this is reported back to the risk benefit manager with the proposal to stop the
32 assessment.

33 In all other cases, a proposal will be made to the risk benefit manager that the assessment of the risks
34 and the benefits should be refined by proceeding to step 2. A dialogue should follow to agree on new
35 Terms of Reference (II), taking into account:

36 • Endpoints and population(s) to be considered to adequately reflect the objectives of the risk
37 benefit assessment (see section 3.1).

38 • Possible refinement of the exposure assessment, e.g. by incorporating probabilistic exposure
39 assessment or specific exposure scenarios as indicated by the risk benefit manager.

40 • Potential for quantification of hazards and positive heath effects, e.g. by dose response
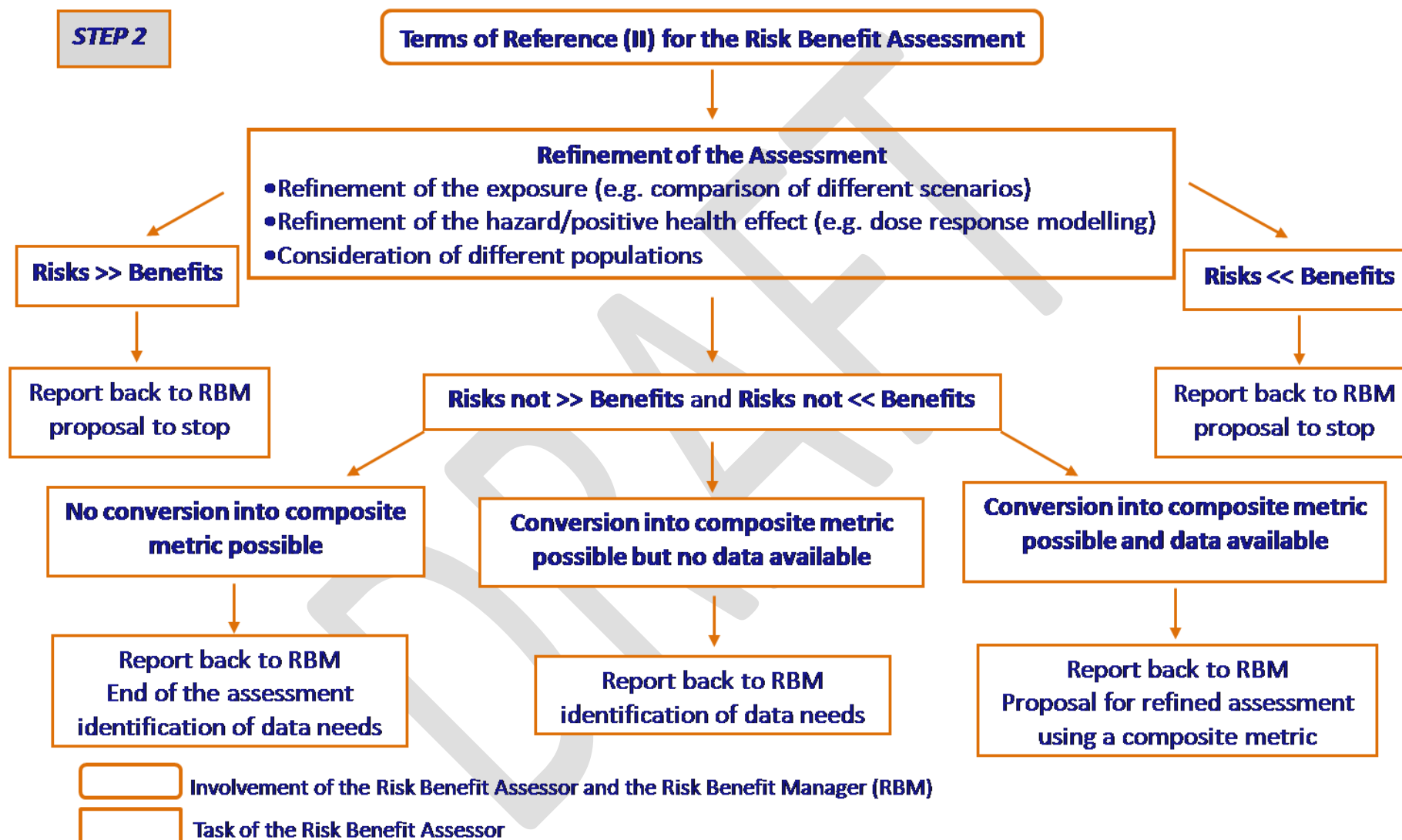41 modelling

Figure 3: Second step of the EFSA approach for risk benefit assessment – Refinement of the assessment

2.3.2.   Step 2 – Refinement of the assessment

The approach taken in step 2 will be determined by the Terms of Reference (II). The aim is to provide, depending on the available data, semi-quantitative or quantitative estimates of risks and benefits at relevant exposures, using common metrics, i.e. a measurement expressed in the same unit, for example, incidence or mortality, where possible (see section 2.4). However, in many circumstances quantification may not be possible.

Possible outcomes might be:

- Estimates of the proportion of the population, or a relevant subgroup with exposure that is above a health-based guidance value or below a dietary reference value or a minimum dose level for a positive health effect[10]

- Estimates of disease incidence or mortality occurring at a particular exposure level, and the impact of changing the exposure, e.g. by dietary intervention such as fortification or advice

- Estimates of the proportion of the population (or subgroup) that could become ill based on a probabilistic approach to both exposure and susceptibility

- Probabilistic distribution of the health benefit and health risk in combination with a full quantification of their inherent uncertainties.

In all cases the uncertainties in the estimations should be described, and quantified to the extent possible (see section 4).

Where risks do not markedly outweigh benefits (risks not << benefits), or *vice versa* (risks not >> benefits), there may still be evidence on the basis of one or more common metrics for a net risk or a net benefit. However, it is the decision of the risk benefit manager as to whether this will suffice to support policy or whether additional refinement will be necessary. This could either be via step 3, or by acquiring new data.

Hence, the outcome of the risk benefit assessment is reported back to the risk benefit manager and a dialogue between the risk benefit assessor and the risk benefit manager should follow to agree whether or not to proceed to step 3 with composite metrics, i.e. a single measure that reflects a number of dimensions of health, including morbidity and mortality (see section 2.4). To assist in this decision, the outcome of step 2 should include an assessment of whether it would be possible to derive composite metrics, on the basis of available information. This will help the risk benefit manager in deciding on whether conversion into a composite metric would be necessary and, if so, feasible. If necessary and feasible, this will require the formulation of new Terms of Reference (III).

---

[10] Where such a value has been recommended by health authorities. However, it is recognised that there is no agreed basis for deriving reference values for beneficial effects other than to avoid deficiency of essential nutrients

STEP 3

Terms of Reference (III) for the Risk Benefit Assessment

↓

Comparing risk(s) and benefit(s) using a composite metric

↓

**Report back to RBM
End of the assessment
identification of data needs**

Involvement of the Risk Benefit Assessor and the Risk Benefit Manager (RBM)

Task of the Risk Benefit Assessor

35

36 **Figure 4:** Third step of the EFSA approach for risk benefit assessment – Comparison of risks and
37 benefits using a composite metric

38

39 **2.3.3.   Step 3 – Comparison of risks and benefits using a composite metric**

40 The Scientific Committee recommends that the Terms of Reference (III) should indicate whether
41 there is a preference on which composite metric should be used to compare and/or aggregate the risks
42 and benefits. In step 3, composite metrics are used to combine two or more of the following elements:
43 increases or decreases in morbidity, mortality, disease burden, and quality of life**.**

44 The choice of composite metrics should be made on a case by case basis, based on the specific risk
45 benefit question, identified hazards and positive health effects. The choice of a composite metric
46 should be justified.

47 The outcome of the risk benefit assessment can be expressed as a single net health impact value. The
48 Scientific Committee recommends however, when reporting to the risk benefit manager on the
49 outcome of the risk benefit assessment, to provide as well the respective health impact values
50 expressed in the selected composite metric for each relevant health effect and each relevant sub
51 population with their respective uncertainties. The net outcome of the risk benefit assessment should
52 therefore not be considered in isolation. When reporting to the risk benefit manager the risk benefit
53 assessor needs to consider that the result "is more than a number" and should be considered together
54 with the outcome of the Step 2 assessment.

55 In some cases the outcome of the assessment might not lead to a clear conclusion because the inherent
56 uncertainties are too large. In reporting back to the risk benefit manager, recommendations on data
57 needs to reduce uncertainty should be made.

58

59 **2.4.   Metrics used in risk benefit assessment**

60 Health effects can be assessed in a number of different dimensions, such as incidence of effect,
61 severity of effect, mortality rate, and in the case of positive health effects, quality of life. More than
62 one metric will be needed to capture all dimensions of health for a risk benefit assessment.

63 A common metric is a measurement expressing risks and benefits in the same unit, for example,
64 incidence or mortality.

65 A composite metric for risks and benefits reflects a number of dimensions of health, such as severity
66 of the disease, morbidity and mortality, expressed in the same unit.

67 The terminology that is used for the metrics of morbidity, mortality and disease burden varies.
68 Therefore the Scientific Committee recommends that the definitions in the dictionary of epidemiology
69 (latest edition, International Epidemiological Associations, Dictionary of Epidemiology, Editor
70 Miquel Porta) be used. Alternatively, the terms used should be explicitly defined in each risk benefit
71 assessment.

72 Effects expressed in a common metric can be compared, but care must be exercised in the
73 interpretation of the comparison. Comparing the incidence of a minor ailment with that of a major
74 disability is obviously of limited value. Even comparison of the incidence of the same effect may be
75 problematical due, for example, to differences in severity or age group affected. Whilst mortality
76 metrics are more directly comparable, these also have limitations; they do not capture the total
77 number of people affected such as when risks and benefits occur in different sub-populations varying
78 in size. Similarly, mortality rate does not take into account the severity of the cases. Death may occur
79 suddenly, or it may occur only after a prolonged period of ill health. Moreover, this metric, when
80 expressed as mortality rate standardised for a given number of the population does not indicate
81 whether the deaths are occurring in particular age groups, which may be an important consideration
82 for risk benefit managers.

83 Whilst composite metrics, such as disability or quality adjusted life years (DALYs or QALYs), can be
84 used for direct comparison of effects, it is important to recognise that not all relevant dimensions are
85 captured in these metrics, for example, whether the effect is in children or adults, This is because
86 these metrics combine incidence with life years to obtain an estimate of years saved or lost
87 respectively, so that a few young people with many years of potential life can give an equivalent value
88 as a larger number of elderly people with far fewer years of potential life. In addition some of the
89 DALY or QALY weightings are open for discussion.

90 There are some aspects of positive health effects that are difficult to quantify for inclusion in the
91 DALYs or QALYs. Currently, generally agreed metrics for positive health effects and well being are
92 lacking, in part because there are no agreed weighting factors for positive health effects. It is
93 recommended that further work be undertaken to define metrics to measure positive health effects and
94 well being.

95 It is important that the risk benefit manager is aware of the limitations of the different metrics used for
96 measuring risks and benefits. Metrics for assessing the risks and benefits are presented in Appendix
97 A.

98

99 The reader is referred to section 2.3 for a description of the stepwise approach proposed for the risk
100 benefit assessment.

101

102 *Step 1 Initial assessment*

103 In this case the question is whether the risks by far ($>>$) outweigh the benefits or *vice versa*. The risks
104 and benefits should therefore be analysed separately.

105 No specific health metrics are used in this step. Rather, exposure is compared with agreed health
106 based guidance values, such as ADI or TDI for risk and RDI or minimum dose levels for a positive
107 health effect.

108

109 *Step 2 Refinement of the assessment*

110 In contrast to step 1 where risks and benefits were assessed at upper and lower bounds of exposure, in
111 step 2, the risks and benefits are assessed semi- quantitatively or quantitatively at relevant exposures.
112 For example, the number of people in whom dietary intake exceeds a health based guidance value
113 could be estimated.

114 The metrics to be used for this step should include estimates of morbidity (prevalence and/or
115 incidence), and mortality, some of which will be common metrics. Metrics for disease burden can be
116 particularly useful for capturing benefits, where these are a consequence of a reduction in disease
117 risks. Where positive health effects are to be assessed, suitable metrics, when available, should be
118 used for measuring the benefits.

119

120 *Step 3 Comparison of risks and benefits using a composite metric*

121 In this step, risks and benefits are compared using composite metrics such as DALYs or QALYs. The
122 outcome of this step can be expressed as a single net health impact value, but must be interpreted with
123 caution.

124

125 **3.   Specific aspects in risk benefit assessment**

126 **3.1.   Importance of the selected endpoint(s) and the subpopulation(s) considered in the**
127 **assessment**

128 The endpoint(s) proposed for assessment of risk or assessment of benefit should have biological
129 relevance to the outcome of concern. Hence, for risk, the endpoint should represent an adverse effect.
130 Likewise, for benefit, the endpoint should represent a desirable change in health status or a likely
131 positive consequence for health or well being, for example resistance to infection. This requirement
132 carries with it the implication that the endpoints selected for use in the assessments will ideally have
133 consequences for, or reflect, morbidity or mortality. Often, however, there will be uncertainty about
134 this relationship and hence use of this criterion for the selection of endpoints will not always be
135 possible. The assessment should therefore include a narrative of the strengths and weaknesses of the
136 evidence base, and the associated uncertainties.

137 For indispensable nutrients, the obvious benefit endpoint will be the absence of risk for nutrient
138 deficiency. It is conceivable that there may be additional endpoints for benefit associated with the
139 substance, e.g. a reduced risk of some forms of cancer with vitamin D intake in excess of recognised
140 nutritional requirements. However, there may also be an increased risk of adverse effects. Each of
141 these endpoints will need to be characterised separately.

142 At each of the three steps, the risk benefit assessment can be performed at the individual or the
143 population level. In a public health context, both risk assessment and benefit assessment are usually
144 performed at the population level. Where differences in the sensitivity to the agent under
145 consideration exist or are assumed to exist in specific subpopulations, separate consideration of these
146 subpopulations is needed. An assessment of all endpoints in all subpopulations will not always be
147 necessary; the assessment should focus on the situation where the endpoints have the greatest impact
148 or where there is the greatest uncertainty.

149

3.1.1. Types of data

151 The confidence in the relationship between the exposure to an agent and consequences for human
152 health will depend on the type of data. For example, for benefit data obtained in intervention studies
153 in human volunteers, the relationship for human health can be very strong, whereas for data from
154 studies in vitro the relationship is likely to be much weaker. Sources of information may be *in silico*,
155 i.e. simulation and modelling, *in vitro*, *in vivo* in experimental animals, observational and
156 interventional human studies. For several of these study types, guidance is available on study design
157 and reporting, e.g. OECD test guidelines. Adherence to such guidance reduces uncertainty as to the
158 reliability of the data, for example through external quality assurance and adherence to good
159 laboratory practice, but does not necessarily ensure relevance. Hence, expert judgment will always be
160 necessary in interpreting the significance of the results of a particular study with respect to either risk
161 or benefit to human health.

162 The type of data for endpoints may be categorical, ordinal or continuous. Examples are, respectively,
163 number of fatal myocardial infarctions, mild – moderate – severe liver damage, serum potassium
164 concentration. Appropriate descriptive statistical methods should be used in summarising such data
165 sets. Information should be provided on study design (e.g. species and strain, sex, route of exposure,
166 vehicle, duration, age of animals), analytical methodology, performance characteristics, number of
167 replicate determinations, historical control data. For data obtained in humans, the characteristics of
168 the study population, matching of any control group, power to detect an effect size of a given
169 magnitude or incidence should be provided.

170 A number of endpoints have been proposed for the assessment of positive health effects, e.g. number
171 of healthy life years and life expectancy, motor, cognitive, neurologic and metabolic function,
172 wellbeing, satiety and hunger (Asp et al., 2003). As mentioned before, the methodology for
173 quantifying such endpoints is less well developed than that for assessing adverse health effects.

174 There is increasing interest in the use of biomarkers in assessing biological responses. As in other
175 areas of science, the use of any biomarker should be accompanied by a full appreciation of its
176 limitations, as well as its advantages. As indicated above, assessments should ideally be performed on
177 endpoints of known adverse or beneficial effects on health, the so called hard biomarkers. Only rarely
178 will a biomarker be sufficiently robust for this to be the case. In such instances, the biomarker would
179 be considered a surrogate endpoint. It is anticipated that there will be considerable advances in this
180 area in the coming years. A clear strategy for biomarker qualification will need to be established
181 before such surrogate endpoints can be used to replace frank endpoints in risk or benefit assessment.
182 On the other hand, biomarkers reflecting intermediate changes, which although necessary are not
183 sufficient by themselves for a biological outcome, may still be of value in providing supportive
184 information for the assessment.

185

3.1.2.   Subpopulation selection

Risks and benefits may occur in the population at large. However, the benefit(s) may be greater in one subpopulation, whilst the risk(s) may be greater in a different subpopulation. Information on both subpopulations, those at risk and those at benefit, will be required to enable risk benefit management decisions to be made on the basis of the most relevant information. If these subpopulations are not identifiable by pre-defined criteria, then specific assessments cannot be performed, e.g. in the case of a genetic polymorphism that is not routinely screened.

193

3.2.   Use of human data for exposure and effect

3.2.1.   Exposure

The nature and quality of the dietary intake measurement is an important determinant of the adequacy of the exposure data for both risk and benefit assessment. Different methods are available, which are intended to measure the habitual food and/or supplement intake over a defined period of time. These methods are in various degrees susceptible to confounding and different biases and need to be carefully interpreted.

In many cases, food consumption surveys are conducted primarily for nutritional purposes. Although there are some limitations which have to be taken into account, these surveys can be used in risk benefit assessment. Repeated 24-hour recall dietary surveys, food-frequency questionnaires, one- to seven-days diaries and duplicate diet studies provide increasingly more robust data on dietary intake but are also increasingly complex and resource intensive, whilst the subject compliance decreases with study complexity. The assessor should be aware of the differing reliability of the exposure data and of their origin.

Moreover, the quality of dietary intake data depends both on the reliability and on the natural variability of the composition data for foods. Not all (computerised) food composition databases provide information on the number of samples analysed, analytical methodology and distribution of analysed values. Levels of nutrients, residues and contaminants in foods are rarely measured parallel to the assessment of food consumption; mostly results from market basket investigations or regular monitoring activities are combined with available food consumption data.

In epidemiological studies, biomarkers may be used as a measure of exposure to an agent (e.g. blood levels, toenail concentrations, DNA adduct). Such biomarkers of exposure reflect the internal dose and exposure from all sources. When such biomarkers are used, back-calculation to dietary exposure is often needed, using kinetic modelling. In addition to model uncertainty, there can be uncertainty in identifying the contribution of a specific route of exposure (i.e. food) against other sources (e.g. inhalation).

220

3.2.2.   Effects

Human data related to both adverse and positive health effects of substances in food reflect real-life exposures. Human studies can have either an experimental (e.g. clinical trials or intervention studies) or an observational (e.g. case control studies and cohort studies) design.

225 Intervention studies, ideally performed as randomised-controlled-trials (RCT) have the advantage of
226 good control for confounders and biases when studying a cause-and-effect relationship between
227 diets/dietary constituents and both adverse and positive health effects. Therefore they provide the
228 highest strength of evidence. Due to ethical, financial and practical reasons, it is unlikely to be
229 possible to conduct an experimental study in humans looking for adverse effects as the primary
230 endpoint. Adverse health effects may be incidentally observed in studies conducted in the expectation
231 for beneficial effect and should be systematically recorded and analysed. It should be noted that
232 health outcomes with a long latency (e.g. cancer or heart disease) can not be adequately investigated
233 in studies of short duration. Intervention studies can only be carried out once toxicological screening
234 has given reasonable evidence that harm will not occur. Randomised, placebo-controlled intervention
235 studies are best used to study beneficial outcomes of minor components of the diet such as trace
236 elements or vitamins, as there will be no significant perturbation of the diet and compliance can be
237 expected to be high. Because of the high costs of large-scale intervention studies, exposure is usually
238 limited to a few or even one exposure level, thus limiting information regarding the exposure–
239 response relationship, which is a major limitation.

240 Observational epidemiologic studies are based on dietary exposure that is more relevant to the general
241 population. Observational studies cannot establish causality of a relationship based only on a
242 statistical association. High-quality observational epidemiologic studies can, however provide strong
243 arguments for causal associations for both risks and benefits and have less practical limitations if
244 performed and evaluated according to strict quality criteria.

245 In summary, intervention trials (Randomised Controlled Trials) provide the strongest evidence for a
246 causal relationship between risk/benefit and dietary exposure and have the lowest chance for potential
247 bias to occur, whilst the influence of confounding on the results of observational studies can be
248 reduced by appropriate design and data analysis.

249

**3.3.   Considerations on how animal and other data can be extrapolated to the human
situation in order to facilitate human risk benefit comparison**

252 Risk benefit assessments may deal with microorganisms and/ or chemicals including nutrients. For
253 each of these categories the assessment of risks and benefits is carried out independently and the type
254 of data underlying the assessments may differ. Therefore, an important consideration to be taken into
255 account when making risk benefit assessments for the human situation is the nature of the data on
256 which these assessments can be based.

257 For chemicals other than nutrients, data for the risk assessment mostly result from animal studies. It is
258 generally assumed, in the absence of evidence to the contrary, that the effects occurring at lowest
259 doses in animal studies will also be the most sensitive effects in humans. The extrapolation requires
260 conversion of the dose-response data into a human equivalent by scaling, using for instance
261 bodyweight or surface area or a more sophisticated method like physiologically based biokinetic
262 (PBBK) or biodynamic (PBBD) modelling. It is important to stress however that such models and the
263 data required to define them are generally not readily available. For chemicals other than nutrients, for
264 which information on benefits exists, such information often comes from human epidemiology and/or
265 intervention studies.

266 For nutrients and microorganisms, although dose-response data are often limited, data for risk and
267 benefit assessment are mainly derived from human studies. Therefore, extrapolations from animal
268 data to the human situation will not be necessary. In some cases of nutrients, only animal data are
269 available and in such cases extrapolation from animals to humans will be required.

270 In the process of risk assessment these extrapolations from animals to humans are frequently made
271 using uncertainty factors. This method applies to non-genotoxic compounds for which health-based
272 guidance values like Acceptable Daily Intake (ADI), Tolerable Daily Intake (TDI), or Acute
273 Reference Dose (ARfD) are derived by dividing the no-observed-adverse-effect level (NOAEL) or the
274 Benchmark Dose Lower confidence limit (BMDL), identified in an animal toxicity experiment, by
275 uncertainty factors, usually including a factor of 10 for inter-individual differences, and a factor of 10
276 for interspecies differences. The health-based guidance values, thus established, define exposure
277 values at or below which no adverse effects in humans are expected.

278 If the health based guidance values are exceeded, the risk level should be estimated. For that, the
279 dose-response curve from the animal studies has to be converted to a human equivalent, by assuming
280 that the dose response curves in animals and humans are parallel.

281 For compounds that are both genotoxic and carcinogenic, a quantitative risk assessment for the human
282 situation requires the development of biologically relevant models for extrapolation of animal cancer
283 data determined at high levels of exposure to cancer risks at realistic and much lower human levels of
284 exposure. Currently, this low dose cancer risk extrapolation is known to be dependent on the
285 statistical models applied, which are not biologically-based. The low dose risk estimates are known to
286 vary by orders of magnitude with the extrapolation model applied (COC, 2004, EFSA 2005).
287 Therefore, for assessing the risk of this type of substances, the margin of exposure (MOE) approach
288 was introduced by EFSA (2005) as a harmonised approach for the assessment of substances that are
289 both genotoxic and carcinogenic. The MOE approach is applicable in step 1 and 2 of the risk benefit
290 assessment. However the MOE is not a quantitative cancer risk estimate and therefore cannot be
291 translated into a composite metric in step 3. Therefore, at present and until biologically-based
292 methods for extrapolation from animal data are developed, the quantitative assessment of cancer risks
293 within the framework of risk benefit assessment has to be based on human epidemiological data. Even
294 when using epidemiological data, if this is based on occupational exposure, it may not be possible to
295 obtain reliable estimates of risk at the much lower levels of dietary exposure.

296 In the field of nutrition, extrapolation of animal data related to positive health effects to humans is
297 unusual and no standard procedure has been defined to assess if benefits observed in animals can be
298 reproduced in or are relevant for humans. Established dietary reference values for indispensable
299 nutrients on the benefit assessment side may be considered as broadly equivalent to the health-based
300 guidance values derived from the risk assessment.

301

4. Uncertainties in the risk benefit assessment approach

303 Uncertainty has been defined in the EFSA guidance document on uncertainties in dietary exposure
304 assessment (EFSA 2006c) as imperfect knowledge which could be reduced by further investigation.
305 Although aimed at exposure assessment, the guidance has also been used for uncertainties in toxicity
306 (e.g. EFSA CONTAM Panel, 2009), and the approach is sufficiently general that it can be applied to
307 the assessment of adverse and positive effects, and their net health impact after conversion into a
308 composite metric.

309

310 The overall magnitude of uncertainty associated with a risk benefit assessment may often be large.
311 This should not be regarded as implying a failure of the assessment; on the contrary, it provides
312 essential information for decision-making (Codex 2008) and helps in identification of data needs.
313 Uncertainty should be characterised at each step of the assessment, as described below.

314

4.1. Uncertainty in the hazard and the positive health effect characterisation

Identification of adverse and positive health effects involves a number of qualitative uncertainties with respect to imperfect knowledge on the full range of possible effects. For a substance that has been subject to comprehensive systematic toxicological evaluation, the major effects will be known, although there may be uncertainty about mode of action and human relevance of observations seen in experimental animals or in vitro models. For substances that have been less extensively investigated, it should be possible to identify the key data gaps as uncertainties. However in both these circumstances there may be additional uncertainty related to emerging scientific understanding, for example effects such as intolerance, behavioural changes, combined effects with other substances, positive health effects are not evaluated systematically in the same way as toxicological effects. The positive effect of an indispensable nutrient in correcting deficiency is well established, but only applies to individuals who are deficient. Other purported positive effects, such as improved well-being, may be claimed but not substantiated.

The relevant hazards and positive health effects may differ for different subgroups. In some circumstances it may be possible to identify specific subgroups with greater potential for risk or benefit, such as pregnant women when considering beneficial or adverse developmental effects. For other effects it may not be possible to identify the subgroup with greatest risk or benefit. A 10-fold uncertainty factor to allow for the unknown extent of the individual variability in toxicokinetics and toxicodynamics is commonly incorporated into health-based guidance values. So far, such factors have not been identified for beneficial effects. Nutrients are subject to physiological regulation (absorption, distribution, metabolism, storage) which may limit the range of inter-individual variability, and it will be necessary to describe uncertainty on a case-by-case basis. For microbial risks, it is assumed that the young, old and immuno-compromised are appreciably more susceptible than the healthy adults.

Information on doses with or without an effect will be needed for both the risk and the benefit assessments. In practice dose-response data are likely to be more fully characterised for chemicals subject to approval processes than for contaminants, microbial agents or nutrients. The uncertainties in the hazard and the positive health effect characterisation will differ depending on whether the data are from animal studies, human populations or selected subgroups.

As discussed earlier, randomised controlled trials to investigate benefits generally do not define the dose-response relationship. For observational epidemiological studies, bias, confounding factors and limitations in exposure assessment result in uncertainty in characterising the dose-response relationship (see section 4.2).

4.2. Uncertainty in the exposure assessment

Most exposure assessments require information on food consumption and on the occurrence of the hazardous or beneficial agent in different foods. Often these data are derived from different sources, and specific information relating to relevant subgroups may be lacking. Different approaches are likely to be required for nutrients, non-nutritive chemicals and micro-organisms, because of changes during production, processing and cooking, or whether the risks/benefits relate to acute or chronic exposure. In the step-wise procedure, the first assessments are likely to rely on predictions based on generic exposure scenarios. In subsequent steps, additional data on occurrence and consumption will allow the exposure assessment to be refined.

Microorganisms multiply, survive or die along the food chain from farm, through the processing and retail, to fork. The dynamics of microbial growth and survival can be a source of uncertainty. Hence, the number of microorganisms at the point of consumption is variable and uncertainties will arise as a function of initial contamination and variability in conditions along the food chain (e.g., temperature, pH, salinity, water activity).

4.3. Uncertainty in risk benefit comparison

In step 1 of a risk benefit assessment, a narrative description of risks and benefits at different levels of exposure, with a systematic evaluation of the associated uncertainties may provide an adequate basis for risk benefit managers to make decisions. If step 2 involves modelling of the dose response relationships for health effects and/or a probabilistic exposure assessment, it should be possible to quantify the statistical uncertainty, for example by calculation of confidence intervals. However, it should be made clear that this does not capture all of the uncertainty and there is still a need for a description of the underlying assumptions and different types of uncertainty in the separate assessments, such as the human relevance of data derived from animal experiments and the limitations of epidemiological studies. Further consideration of uncertainty is likely to be required if the risk benefit assessment proceeds to step 3 using a composite metric approach. It will then be important to be transparent about the underlying assumptions used in converting to the composite metric. For example, value judgements are inherent in the weight factors for disease severity used for calculating DALYs and QALYs and assumptions made about survival times for different health endpoints may vary for different countries and regions.

5. Examples of risk benefit assessment

This section provides two examples to illustrate the types of issues that need to be considered in conducting a risk benefit assessment. These include identification of likely benefits, the potential risks and the relevant subpopulation(s). It is important to identify early in problem formulation whether risks and benefits are likely to occur in the same or different subpopulations. Some consideration of the type of assessment that will be feasible is provided, based on the type and extent of information available. For example, data may come from human trials, experimental animals, or epidemiological observations. The extent of data may be such that only information following a single dose level is available (e.g. in many clinical trials), the evidence of benefit may be very equivocal, etc. The examples have been chosen to represent two different scenarios, within the framework of the approach to risk benefit assessment outlined in this opinion. This includes the nature of the agent/food, for example an indispensable nutrient (i.e. selenium) and a situation where the risk is due to one component in a food whilst the benefit is due to another (i.e. fish).

5.1. Risk benefit assessment of an indispensable nutrient: Selenium

Disclaimer: This example is not designed to provide conclusions as to risk benefit of the specific food, but rather to highlight problem formulation and scoping of the risk benefit assessment. The Scientific Committee has not reviewed the evidence of health benefits or risks mentioned below.

5.1.1. Problem formulation

Selenium is an indispensable nutrient and is incorporated as selenocysteine into specific selenoproteins in both a dose- and tissue-dependent pattern, within a certain range of intake and under control of homeostatic mechanisms. Unspecific selenium incorporation of other selenised amino acids into body proteins is also possible, particularly when sulphur amino acids are deficient in the diet. Selenium-dependent glutathione peroxidases are part of the body's defense system against oxidative stress. Selenium-dependent iodothyronine deiodinases regulate thyroid hormone metabolism. Chronic toxicity of selenium (selenosis) has been observed in humans with blood selenium concentrations > 100 µg/dL which correspond to a selenium intake above 850 µg/day and manifest as brittle hair and

407 nails and hair loss, associated with gastrointestinal disturbances, skin rashes, garlic breath odour,
408 fatigue, irritability and abnormalities of the nervous system (Yang et al. 1989). There are some
409 indications that selenium intakes beyond amounts necessary to maximise selenoproteins in plasma
410 reduce the risk of prostate, colon and total cancer (Clark et al., 1996; Yoshizawa et al., 1999) in the
411 adult population. Infants of mothers with diets deficient in both iodine and selenium are at increased
412 risk of congenital hypothyroidism (Vanderpas et al., 1992). Selenium deficiency may increase the
413 virulence of certain enteroviruses for humans. In selenium depleted animals an amyocarditic strain of
414 coxsackievirus B3 was converted to a virulent strain accompanied by changes in the genetic structure
415 of the virus so that its genome closely resembled that of other known virulent CVB3 strains (Beck et
416 al., 1995; 2003).

417 Example of problem formulation: "What is the balance between risks and benefits at the current level
418 of selenium intake in the population?"

419

5.1.2. Endpoints of relevance for the risk benefit assessment

421 The risk and benefit relate in all groups of the population to insufficient, adequate or excessive
422 intakes of selenium. Due to the limited evidence associated with the reduced risk of cancer, the focus
423 of this example is on selenosis for the risk, and reduced risk of deficiency for the benefit.

Type of effect	Endpoint	Target Population	Human health relationship
Risk	Selenosis	Whole population	Increased risk of selenosis at intakes above the Upper Level (UL) (EFSA, 2006a)
Benefit	Cancer	Adult population	Reduced risk of cancer (Clark et al, 1996; Yoshizawa et al., 1999)
Benefit	Normal levels of selenoenzymes and other selenoproteins	Whole population	No signs of deficiency, e.g. normal thyroid function at intakes above the Lower Threshold Intake (LTI)

424

5.1.3. Risk benefit assessment

426 5.1.3.1. Step 1 – Initial assessment

427 In the initial assessment, estimated dietary exposure to selenium of the population is compared to the
428 health based guidance value (tolerable upper intake level, UL) and to the lower threshold intake
429 (LTI). The LTI is by definition not a health based guidance value but is the lowest estimate of the
430 requirement from the normal distribution curve (EFSA NDA Panel, 2010).

431

432 *Scenario 1: Maximising the risks.*

433 Identify a high level, e.g. 95th percentile, of current dietary exposure to selenium. Possible outcomes
434 are:

435   a) The high level of dietary exposure to selenium is above the UL (and above the LTI),

436 Conclude that there is an appreciable risk of selenium toxicity and a benefit (i.e. no risk for selenium
437 deficiency). Report to the risk benefit manager that there is a risk for toxicity which could be reduced
438 without affecting the benefit. Discuss Terms of Reference (II) aimed at identifying an appropriate
439 dietary intake.

440   b) The high level of dietary exposure to selenium is below the LTI (and below the UL)

441 Conclude that there is no appreciable risk of selenium toxicity but there is an appreciable risk of
442 selenium deficiency at this level of exposure. Report to the risk benefit manager that the risks
443 outweigh the benefits and make proposal to stop the assessment.

444   c) The high level of dietary exposure to selenium is below the UL and above the LTI

445 Conclude that there is no risk of selenium toxicity and a benefit (i.e. no risk for selenium deficiency)
446 at this level of exposure. Report to the risk benefit manager that the benefits outweigh the risks and
447 make proposal to stop the assessment.

448

449 *Scenario 2: minimising the risks.*

450 Identify a low level, e.g. 5th percentile, of current selenium intake in the population. Possible
451 outcomes are:

452   d) The low level of dietary exposure to selenium is above the UL (and above the LTI)

453 Conclude that there is an appreciable risk of selenium toxicity and a benefit (i.e. no risk for selenium
454 deficiency). Report to the risk benefit manager that there are clear risks and benefits at this level of
455 exposure and discuss Terms of Reference (II) aimed at identifying an appropriate dietary intake.

456   e) The low level of dietary exposure to selenium is below the LTI (and below the UL).

457 Conclude that there is no appreciable risk of selenium toxicity but there is an appreciable risk of
458 selenium deficiency at this level of exposure. Report to the risk benefit manager that there is a risk of
459 deficiency at current levels of exposure and discuss Terms of Reference (II) aimed at identifying an
460 appropriate dietary intake.

461

462   f) The low level of dietary exposure to selenium is below the UL and above the LTI,

463 Conclude that there is no risk of selenium toxicity and there is a benefit (i.e. no risk for selenium
464 deficiency) at this level of exposure. Risks at higher level of exposure will be determined by the
465 outcome of scenario 1 (outcome "a" and "c").

466

467 5.1.3.2. Step 2 – Refinement of the assessment

468 Following the discussion between the risk benefit assessor and the risk benefit manager on the
469 outcome of step 1, refined Terms of Reference (II) are agreed upon, for example focussing on
470 identifying suitable dietary intake levels at which it is possible to have the benefit of sufficiency
471 without the risk of toxicity.

472 If suitable data are available, the exposure assessment could be refined - this could take the form of a
473 probabilistic analysis of the dietary intake of selenium by the population. This would allow estimates
474 of the proportions of the population with dietary exposure above the LTI and below the UL.
475 Depending on the Terms of Reference (II), the analysis could be repeated with different dietary intake
476 scenarios, which will give an indication of the increase or decrease in the risk and the benefit at
477 specified dietary intake levels.

478 Depending on the Terms of Reference (II), if it is found that risks far outweigh the benefits or benefits
479 far outweigh the risks at specified dietary intake levels, the report to the risk benefit manager could
480 conclude that the assessment could stop. If neither risks nor benefits prevail, then the advice to the
481 risk benefit manager could include consideration of whether or not, it is feasible to convert the health
482 risk and benefit into a composite metric. If conversion is not possible, or theoretically possible but
483 lacking in the necessary data, then identification of data needs would be helpful.

484

485 5.1.3.3. Step 3 – Comparison of risks and benefits using a composite metric

486 Following the discussion between the risk benefit assessor and the risk benefit manager on the
487 outcome of step 2, refined Terms of Reference (III) are agreed upon, utilising a composite metric and
488 aiming at identifying a dietary intake level at which there is an agreed balance between the risk and
489 the benefit. All of the data in this case study are based on human observations, which facilitates the
490 application of a composite metric.

491

492 **5.2.   Risk benefit assessment of fish consumption and exposure to methylmercury**

493 **Disclaimer:** This example is not designed to provide conclusions as to risk benefit of the specific
494 food, but rather to highlight problem formulation and scoping of the risk benefit assessment. The
495 Scientific Committee has not reviewed the evidence of health benefits or risks mentioned below.

496

497 **5.2.1.   Problem formulation**

498 Consumption of fish is often recommended based on its nutritional benefits, but there is concern
499 about a number of contaminants that can be present in different types of fish. Therefore formulation
500 of advice to consumers requires definition of the amounts of fish that would be associated with the
501 respective positive health effects and toxicological hazards. There have been a number of reviews of
502 benefits and risks of fish consumption (e.g. SACN/COT, 2004; Becker et al., 2007; IoM, 2007; VKM,
503 2006; FDA, 2009).

504 The beneficial components of fish include long-chain n3-polyunsaturated fatty acids (n3-LCPUFAs),
505 a number of important vitamins and essential elements, and protein that is less associated with
506 saturated animal fat than for example meat. The content of these nutrients varies in different fish
507 species and varying amounts can also be provided by food sources other than fish. In principle a
508 complete assessment would need to take into account the beneficial effects of increasing intake of
509 these components and the adverse effects that could be associated with decreasing intake, taking into
510 account other dietary sources of the nutrients and contaminants. This would make an assessment
511 extremely complex and hence the approach has generally been to focus on the n3-LCPUFAs, for
512 which fish is the major dietary source. Similarly there are many chemical contaminants present in
513 fish. Persistent organic pollutants generally occur at highest levels in oily fish. Methylmercury is

514 found predominantly in large predatory fish. Other types of contaminant may result from specific
515 pollution incidents. It would not be feasible for a risk benefit assessment to consider all potential
516 contaminants in detail.

517 Example of problem formulation: "What is the balance between the benefits associated with the n3-
518 LCPUFAs and the risks associated with methylmercury at current levels of fish consumption in the
519 population?"

520

521 **5.2.2.   Endpoints of relevance for the risk benefit assessment**

522 The risks and benefits relate to different health effects, different types of fish and sometimes different
523 population subgroups (see table below). Whilst a number of beneficial and adverse effects have been
524 investigated, the strongest evidence is for protection by oily fish against a recurrence of myocardial
525 infarction and for the risks of methylmercury, which is not necessarily associated with oily fish, with
526 respect to neurodevelopmental effects.

Type of effect	Endpoint	Target Population	Human health relationship
Risk	Motor and cognitive milestones of offspring	Women up to one year before and during pregnancy	Impaired neurodevelopment due to methylmercury
Risk	Motor and cognitive performance	Children	Impaired neurodevelopment due to post-natal dietary exposure to methylmercury
Risk	Coronary heart disease Stroke	Adults	Increased risk of cardiovascular disease due to methylmercury
Benefit	Coronary heart disease Stroke	Middle-aged and older people, especially those with previous myocardial infarction	Reduced risk of cardiovascular disease due to n3-LCPUFAs (proposed in reviews such as SACN/COT, 2004; Becker et al., 2007; IoM, 2007; VKM, 2007)
Benefit	Birth weight	Pregnant women	Reduced risk of low birth weight in (premature) infants due to n3-LCPUFAs
Benefit	Visual acuity of offspring	Pregnant women	Improved neurodevelopment due to n3-LCPUFAs
Benefit	Motor and cognitive milestones of offspring	Pregnant women	Improved neurodevelopment due to n3-LCPUFAs

527

528   **5.2.3.   Risk benefit assessment**

529   5.2.3.1.   Step 1 – Initial assessment

530   A number of approaches may be taken in the exposure assessment depending on the data that are
531   available. For the purpose of this case study oily fish, which contain high levels of n3-PUFAs, and
532   fish that contain relatively high levels of methylmercury, such as shark, swordfish and tuna, are
533   considered separately. An alternative approach might be to use data for all fish combined, but this
534   would introduce further uncertainty into the assessment.

535   Estimated intakes are compared to existing health-based guidance values, such as the PTWI for
536   methylmercury of 1.6 μg/kg b.w. (FAO/WHO, 2007) and consumption of at least one portion of oily
537   fish per week, in line with the recommendation of some authorities to obtain the positive health
538   effects (SACN/COT, 2004; Becker et al., 2007).

539

540   *Scenario 1: maximising the risks and minimising the benefits.*

541   Identify a high level, e.g. 95th percentile, of dietary exposure to methylmercury from fish and a low
542   level, e.g. 5th percentile, of consumption of oily fish. Possible outcomes are:

543   a) High level dietary exposure to methylmercury is below the PTWI and low level consumption
544   of oily fish is at least one portion per week,

545   Conclude that there are no appreciable risks and there are clear benefits. Report to the risk benefit
546   manager that benefits far outweigh risks, and propose that the assessment can stop.

547   b) High level dietary exposure to methylmercury is below the PTWI and low level consumption
548   is less than one portion of oily fish per week,

549   Conclude that there are no appreciable risks, and consider whether there are benefits under scenario 2
550   (outcome "e" or "f"). In the case of outcome "e", report back to the risk benefit manager that there is
551   no appreciable risk but a possible benefit and propose to stop the risk benefit assessment and continue
552   with a benefit assessment. In the case of outcome "f", report back to the risk benefit manager that
553   there are neither risks nor benefits and discuss Terms of Reference (II) aimed at identifying an
554   appropriate dietary intake to try to optimise the benefits without inducing appreciable risks.

555

556   c) High level dietary exposure to methylmercury is above the PTWI. and low level consumption
557   is at least one portion of oily fish per week,

558   Conclude that there are clear benefits and possible risks. Report to the risk benefit manager and
559   discuss Terms of Reference (II) to refine the risk benefit assessment.

560   d) High level dietary exposure to methylmercury is above the PTWI and low level consumption
561   is less than one portion of oily fish per week,

562   Conclude that there are possible risks and consider whether there are any benefits under scenario 2
563   (outcome "g" and "h"). In the case of outcome "g", report back to the risk benefit manager that there
564   there are both risks and benefits and discuss Terms of Reference (II) aiming refining the risk benefit
565   assessment. In the case of outcome "h", report back to the risk benefit manager that there are clear
566   risks and no discernable benefits. Propose to stop the risk benefit assessment and continue the risk
567   assessment.

568

569 *Scenario 2: minimising the risks and maximising the benefits*

570 Identify a low level, e.g. 5th percentile, of dietary exposure to methylmercury from fish and a high
571 level, e.g. 95th percentile, of consumption of oily fish. Possible outcomes are:

e) Low level dietary exposure to methylmercury is below the PTWI and high level consumption
573 of oily fish is at least one portion per week,

574 Conclude that there are possible benefits and consider whether there are some risks under Scenario 1
575 (outcome "b" or "c"). "). In the case of outcome "b", report back to the risk benefit manager that there
576 are possible benefits and no appreciable risks. Propose to stop the risk benefit assessment and
577 continue the benefit assessment. In the case of outcome "c", report back to the risk benefit manager
578 that there are both risks and benefits and discuss Terms of Reference (II) aiming refining the risk
579 benefit assessment.

f) Low level dietary exposure to methylmercury is below the PTWI. and high level consumption
581 of oily fish is less than one portion per week,

582 Conclude that there are no benefits. Report to the risk benefit manager and propose to stop the risk
583 benefit assessment and continue the risk assessment.

g) Low level dietary exposure to methylmercury is above the PTWI and at high level
585 consumption of oily fish is at least one portion per week,

586 Conclude that there are clear risks and possible benefits. Report to the risk benefit manager and
587 discuss Terms of Reference (II) aiming refining the risk benefit assessment

h) Low level dietary exposure to methylmercury is above the PTWI and high level consumption
589 of oily fish is less than one portion per week,

590 Conclude that there are clear risks and no discernable benefit. Report to the risk benefit manager that
591 risks far outweigh benefits, and propose that the assessment can stop.

592

593 5.2.3.2. Step 2 – Refinement of the assessment

594 Following the discussion between the risk benefit assessor and the risk benefit manager on the
595 outcome of step 1, refined Terms of Reference (II) are agreed upon, for example focussing on
596 particular subgroups or exposure scenarios.

597 If suitable data are available, the exposure assessments could be refined - this could take the form of a
598 probabilistic analysis of the distributions of methylmercury occurrence in, and consumption of,
599 different types of fish by the relevant population and subgroups. This would allow estimates of the
600 proportions of the different subgroups, and of pregnant women, with dietary exposure above the
601 PTWI or consuming less than one portion of oily fish per week. Depending on the Terms of Reference
602 (II), the analysis (probabilistic or deterministic) could be repeated with different scenarios such as
603 advice to consumers relating to amounts or types of fish to be consumed.

604 The available dose-response data can be modelled in order to estimate the likelihood (and in some
605 instances magnitude) of the different hazards and positive effects at specified exposure levels, such as
606 the mean, 5th percentile and 95th percentile of the relevant population groups. Applying this approach

607 to the exposure modelled for different scenarios will give an indication of the increase or decrease in
608 the risk and the benefit at specified dietary intake levels.

609 Finally, the above two approaches could be combined in an integrated probabilistic approach
610 incorporating information on the individual variability in the identified health effects.

611 In the above approaches the statistical uncertainty could be expressed in terms of confidence intervals,
612 but the report to the risk benefit manager should also describe the uncertainty with respect to the
613 underlying data, e.g. if it is assumed that the dietary habits of pregnant women are similar to those of
614 other women.

615 Depending on the Terms of Reference (II), if it is found that risks far outweigh benefits or benefits far
616 outweigh risks for relevant subgroups, the report to the risk benefit manager could conclude that the
617 assessment could stop. If neither risks nor benefits prevail, then the advice to the risk benefit manager
618 could include consideration of whether or not, it is feasible to convert the health risks and benefits
619 into a composite metric. If conversion is not possible, or theoretically possible but lacking in the
620 necessary data, then identification of data needs would be helpful.

621

622 5.2.3.3. Step 3 – Comparison of risks and benefits using a composite metric

623 Following the discussion between the risk benefit assessor and the risk benefit manager on the
624 outcome of step 2, refined Terms of Reference (III) are agreed upon, leading to an assessment of the
625 risks and benefits utilising a composite metric. All of the data in this case study are based on human
626 observations, which facilitates the application of a composite metric.

627

628

629 **CONCLUSIONS AND RECOMMENDATIONS**

630 Human health risk benefit assessment of food is still in its infancy and subject to a number of research
631 projects throughout Europe. Whereas the risk assessment paradigm is internationally well established,
632 there is much less experience regarding benefit assessment. The Scientific Committee proposes to
633 mirror the risk assessment paradigm by introducing four steps for the benefit assessment, i.e. positive
634 health effect identification, positive health effect characterisation (dose response assessment),
635 exposure assessment and benefit characterisation.

636 The stepwise approach for risk benefit assessment is considered by the Scientific Committee to be
637 scientifically sound and efficient with respect to time and resources needed to reach a conclusion. By
638 introducing a stepwise approach, it allows to reach a conclusion already after a qualitative or semi
639 quantitative assessment, without the need to go to a full quantitative assessment, which is very
640 demanding of data that are often not available.

641 A full understanding between the risk benefit assessor and the risk benefit manager of the problem
642 formulation and the resulting terms of reference is critical for ensuring a useful and relevant outcome
643 for the risk benefit management goals. After each step of the assessment, an iterative dialogue is
644 foreseen between the risk benefit assessor and the risk benefit manager to eventually refine the terms
645 of reference in view of the outcome of the previous step and the data available.

646

647 Two examples of the approach for risk benefit assessment are given. The first one (selenium, an
648 indispensable nutrient) illustrates the case where the risk and the benefit are associated with one
649 single agent, while in the second example (fish), the risk is due to one selected contaminant in food
650 (methylmercury) whilst the benefit is due to other food components. The examples highlight the
651 complexity of risk benefit assessment, already when entering the first steps of the assessment.

652

653 The Scientific Committee recommends that metrics for the positive health effect characterisation are
654 further developed. Metrics used in risk benefit assessment and weight factors associated to most
655 common diseases should be internationally agreed upon in order to ensure harmonisation and
656 recognition of the assessments.

657 The Scientific Committee recommends that, when designing a survey for generating data, a closer
658 collaboration between risk assessors and benefit assessors aims at ensuring that data generated by one
659 or the other can be used in a broader risk benefit assessment context. Further more, the development
660 of hard biomarkers of effect for both risk and benefit is also needed.

661

662 **REFERENCES**

663 Asp NG, Cummings JH, Mensink RP, Prentice A, Richardson DP and Saris WHM (Eds), 2003.
664   Passclaim - Process for the assessment of scientific support for claims on foods. Phase one:
665   preparing the way. Eur J Nutr 42, Suppl 1

666 Beck MA, Shi Q, Morris VC and Levander OA, 1995. Rapid genomic evolution of a non-virulent
667   Coxsackievirus B3 in selenium-deficient mice results in selection of identical virulent isolates.
668   Nature Medicine 1: 433 – 436

669 Beck MA, Levander OA and Handy J, 2003. Selenium Deficiency and Viral Infection. J Nutr
670   133:1463S-1467S.

671 Becker W, Darnerud PO, Petersson-Grawé K, 2007. Fiskkonsumtion – risk och nytta. (fish
672   consumtion risks and benefits). Livsmedelsverket, Rapport 12- 2007 (National Food
673   Administration, Report 12-2007), Uppsala, Sweden, 140 pp. (in Swedish)

674 Clark LC, Combs GF, Turnbull BW, Slate EH, Chalker DK, Chow J, Davis LS, Glover RA, Graham
675   GF, Gross EG, Krongrad A, Lesher JL, Park HK, Sanders BB, Smith CL and Taylor JR., 1996.
676   Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin.
677   A randomised controlled trial. JAMA 276: 1957-1963.

678 COC (Committee on Carcinogenicity of chemicals in food, consumer products and the environment),
679   2004. Guidance on a strategy for the risk assessment of chemical carcinogens.
680   http://www.advisorybodies.doh.gov.uk/coc/guideline04.pdf

681 Codex Alimentarius Commission, 2005. Procedural Manual. 15th Edition. ISSN 1020-8070.

682 EFSA, 2005. Opinion of the Scientific Committee on a request from EFSA related to a harmonized
683   approach for risk assessment of substances which are both genotoxic and carcinogenic. The EFSA
684   Journal 2005: 282: 1-30.

685 EFSA, 2006a. Tolerable upper intake levels for vitamins and minerals. Publications Office. ISBN 92-
686   9199-015-9

687 EFSA, 2006b. EFSA Science Colloquium 6. Risk benefit analysis of foods: methods and approaches.
688   Scientific Colloquium Series of the European Food Safety Authority No.6, July 2006.

689 EFSA, 2006c. Guidance of the Scientific Committee on a request from EFSA related to uncertainties
690   in dietary exposure assessment. The EFSA Journal (2006) 438, 1-54

691 EFSA, 2009. Frequently Asked Questions (FAQ) related to the EFSA assessment of Article 14 and
692   13.5 health claims applications.
693   *http://www.efsa.europa.eu/cs/BlobServer/Report/nda_report_ej1339_FAQ_on_Health_Claims_fin*
694   *al_EN.*

695 EFSA Panel on Contaminants in the Food Chain (CONTAM), 2009. Scientific Opinion on Arsenic in
696   Food. EFSA Journal 2009; 7(10):1351. [198 pp.]. doi:10.2903/j.efsa.2009.1351.

697 EFSA Panel on Dietetic products, Nutrition, and Allergies (NDA), 2010. Scientific Opinion on
698   principles for deriving and applying Dietary Reference Values. EFSA Journal 2010; 8(2):1458. [28
699   pp.]. doi:10.2903/j.efsa.2010.NNNN.

700 EPA (U.S. Environmental Protection Agency), 1998. Guidelines for ecological risk assessment. Risk
701   Assessment Forum U.S. Environmental Protection Agency, Washington DC, 1998.

702 FAO/WHO (Food and Agriculture Organization of the United Nations/World Health Organization),
703   2006. A Model for Establishing Upper Levels of Intake for Nutrients and Related Substances:
704   Report of a Joint FAO/WHO Technical Workshop on Nutrient Risk Assessment. WHO, Geneva,
705   Switzerland. http://www.who.int/ipcs/methods/en.

706 FAO/WHO (Food and Agriculture Organization of the United Nations/World Health Organization),
707   2007. Safety evaluation of certain food additives / prepared by the sixty-seventh meeting of the
708   Joint FAO/WHO Expert Committee on Food Additives (JEFCA). (WHO food additives series ;
709   58). ISBN 978 92 4 166058 7

710 FDA (U.S. Food and Drug Administration), 2009. Draft report of quantitative risk and benefit
711   assessment of consumption of commercial fish, focussing on fetal neurodevelopmental effects
712   (measured by verbal development in children) and on coronary heart disease and stroke in the
713   general population.
714   http://www.fda.gov/Food/FoodSafety/Product-
715   SpecificInformation/Seafood/FoodbornePathogensContaminants/Methylmercury/ucm088794.htm

716 Havelaar AH, Bräunig J, Christiansen K, Cornu M, Hald T, Mangen MJ, Mølbak K, Pielaat A, Snary
717   E, Van Pelt W, Velthuis A and Wahlström H, 2007. Towards an integrated approach in supporting
718   microbiological food safety decisions. Zoonoses Public Health. 54(3-4):103-17.

719 Institute of Medicine (IoM), 2007. Sea food choices. Balancing benefits and risks. National Academy
720   Press, Washington, D.C.

721 IPCS (International Programme on Chemical Safety), 2004. Harmonization Project Document No.1 -
722   IPCS risk assessment terminology. WHO, Geneva

723 Lier EA, Havelaar, AH, Nanda, A, 2007. The Burden of diseases in Europe: A pilot study.
724   Europsurveillance, 12(12):pii=751.

725 Renwick AG, Flynn A, Fletcher RJ, Müller DJG, Tuijtelaars S and Verhagen H, 2004. Risk-benefit
726   analysis of micronutrient. Food Chem Toxicol 42: 1903-1922.

727 Renwick AG, Barlow SM, Hertz-Picciotto I, Boobis AR, Dybing E, Edler L, Eisenbrand G, Greig JB,
728   Kleiner J, Lambe J, Müller DJG, Smith MR, Tritscher A, Tuijtelaars S, Van den Brandt PA,
729   Walker R and Kroes R, 2003. Risk characterisation of chemicals in food and diet, Food and
730   Chemical Toxicology 41, 1211-1271.

731 SACN/COT (Scientific Advisory Committee on Nutrition/Committee on Toxicity), 2004. Advice on
732   fish   consumption: benefits   &   risks.   ISBN   011243083X.
733   http://cot.food.gov.uk/cotreports/cotjointreps/sacnfishconsumption

734 Vanderpas JB, DumontJE, Contempre B and Diplock AT, 1992. Iodine and selenium deficiency in
735   Northern Zaire. Am J Clin Nutr 56: 957-958.

736 VKM (Norwegian Scientific Committee for Food Safety), 2006. Fish and seafood consumption in
737   Norway – Benefits and risks. Norwegian scientific committee for food safety.
738   http://www.vkm.no/eway/default.aspx?pid=277&trg=Content_6486&Main_6177=6501:0:31,2298:1:0
739   :0:::0:0&Content_6486=6187:1686794::1:6224:10:::0:0

740 Yang GQ, Yin S, Zhou RH, Gu L, Yan B and Liu Y, 1989. Studies of safe maximal daily dietary Se-
741   intake and the manifestation of clinical signs and certain biochemical alterations in blood and
742   urine. J Trace Elem Electrolytes Health Dis 3: 123-130.

743 Yoshizawa K, Willett WC, Morris SJ, Stampfer MJ, Spiegelman D, Rimm EB and Giovanucci E,
744   1999. Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer. J
745   Natl Cancer Inst 90: 1219-1224.

746

747

748 **APPENDIX - METRICS FOR USE IN RISK BENEFIT ASSESSMENT**

749 **1.   Common metrics for assessing separately risks and benefits**

750 A number of metrics, suitable for use when assessing risks and benefits separately, are described in
751 this appendix. See also IEA's latest edition of Dictionary of Epidemiology, Editor Miquel Porta).

752 There are three elements of health and disease impact, i.e. **morbidity** (frequency of disease),
753 **mortality** (frequency of deaths) **and disease burden (**number of healthy days/years lost due to a
754 disease**).** More than one metric will be needed to capture all three dimensions for use in a risk benefit
755 assessment.

756 A **"quality of life metric",** measuring positive health effects is also needed for some risk benefit
757 assessments; unfortunately, generally agreed metrics for some positive health effects and well being
758 are currently lacking, which may limit the benefit assessment to a qualitative characterisation of the
759 positive health effect. A table presenting possible metrics to be used in risk benefit assessment, with
760 their advantages, disadvantages and data needs, is given below.

761

762 **2.   Composite metrics for comparing risks and benefits**

763 The metrics commonly used for disease burden are disability adjusted life years (DALYs) and quality
764 adjusted life years (QALYs).

765

766 **DALY**

767 WHO has developed the DALY metric as part of the effort to estimate global disease burden. The
768 DALY includes morbidity, sequelae and mortality in one metric. For further information see the
769 homepage http://www.who.int/healthinfo/global_burden_disease/en/index.html

770 DALYs for a disease or injury cause are calculated as the sum of the years of life lost due to
771 premature mortality (YLL) in the population and the years lost due to disability (YLD) for incident
772 cases of the disease or injury.

773 Therefore, DALY = YLL + wYLD.

774 YLL are calculated from the number of deaths at each age multiplied by a global standard life expectancy for each age. Thus:

775 YLL = (number of fatal cases) × (expected life span at the time of death)

776 YLD for a particular cause in a particular time period are estimated as follows:

777 YLD = (number of incident cases in that period) × (average duration of the disease).

778 "w" is the disability weight factor associated to the considered disease. The weight factor reflects the severity of the disease
779 on a scale from 0 (perfect health) to 1 (death). WHO has set a list of different diseases and their respective weights[11]. Weights
780 can vary with population.

781

---

[11] See http://www.who.int/healthinfo/global_burden_disease/GBD2004_DisabilityWeights.pdf

782 **QALY**

783 The QALY provides a composite metric for disease burden adjusted for the quality of life[12]. Hence
784 the metric is a complement to the DALY concept.

785 A QALY takes into account both the quantity and the quality of life generated by a given intervention,
786 which may have a positive or negative effect on health. A QALY is the arithmetic product of life
787 expectancy and the QALY valuation of the health state for the remaining life-years[13].

788 QALY = YLH + (1-w)YLD,

789 YLH is the number of years lived healthy.

790

791 The QALY metric is based on the number of years of life that would be added due to a positive health
792 effect. A year of perfect health is worth 1, while a year of less than perfect health, for example if the
793 patient would be blind or confined to a wheelchair, is worth less than 1. Death is considered to be
794 equivalent to 0, although, some health states may be considered worse than death and have negative
795 scores. Again, weights may vary with the population.

796

---

[12] See http://www.evidence-based-medicine.co.uk/ebmfiles/WhatisaQALY.pdf
[13] See http://www.medicine.ox.ac.uk/bandolier/painres/download/whatis/QALY.pdf

Table 1: Overview of metrics that could be applied in risk benefit assessment

Metric	Description	Data needs
Mortality	Mortality risk, mortality rates, life expectancy (from birth), years of life lost (YLL)	Cause/age specific mortality Risk-factor related mortality
Morbidity	Incidence of disease, morbidity risk	Prevalence and/or incidence data
Quality of life (QoL)	Consequences of morbidity and health impact not captured by disease, e.g. physical and mental health	Quality of Life indicators
DALY (disability-adjusted life years)	Combines information on severity and duration of a disease in terms of premature mortality and morbidity	Standard life-expectancy per age group, sex, country/region Disease specific information on years of life lost due to premature mortality Disease incidence and specific information on years lived with disability Disease weights for severity
QALY (quality-adjusted life years)	Expected number of healthy years (number of years multiplied by the health-related quality of life during those years)	Disease incidence in a population Duration of disease impact Health impact of disease
HALE (healthy-life expectancy or health-adjusted life expectancy)	Healthy life expectancy summarizes total life expectancy into equivalent years of "full health" Taking into account years lived in less than full health due to diseases and injuries	Period life-table (mortality rates by age and sex) Prevalence of various states of health at different ages Time spent in non-optimal health state

Metric	Description	Data needs
ALE (active life expectancy)	Number of years an individual can expect to live without functional limitations. Combines information on functional status and mortality Can assess expected life in a variety of functional states (without limitations, or with moderate or severe limitations)	Expected years of life remaining per age group Prevalence of functional limitations Person years lived in various stages of functioning
HLY (healthy life years, disability free life expectancy)	Number of years a person would be expected to live free of any activity limitation	Mortality statistics Prevalence of diseases Health-related quality of life measures