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Public Health Risk-benefit Assessment Associated with Food Consumption–A Review

Géraldine Boué[1,2], Sandrine Guillou[2,1], Jean-Philippe Antignac[3,4], Bruno Le Bizec[3] and Jeanne-Marie Membré[1,2*]

[1]INRA, Secalim UMR 1014, F-44026 Nantes, France.
[2]LUNAM University, Oniris, Nantes, France.
[3]LUNAM University, Oniris, Laboratory Study of Residues and Contaminants in Food (LABERCA), F-44307 Nantes, France.
[4]INRA, F-44307 Nantes, France.

Author's contribution

This work was carried out in collaboration between all authors. Authors GB, SG and JMM designed the structure of review. Author GB managed the literature search, synthesized the information and wrote the first draft of the manuscript. Authors SG, JPA, BLB and JMM revised the manuscript and contributed ideas throughout the review. All authors read and approved the final manuscript.

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ABSTRACT

Background: In the food safety field, risk assessment, including microbial and chemical components, has been applied for many years. However, a whole and integrated public health assessment also depends on the nutritional composition of food. While the fact that foods and diets can be a source of both risks and benefits now appears undisputed, carrying out a risk-benefit assessment (RBA) is still an emerging and challenging scientific subject.
Aims: The purpose of the present review was to synthesize RBA studies associated with food consumption and to summarize the current methodological options and/or tendencies carried out in this field.
Methods: The different data sources explored included around 20 accessible databases using the main terms "risk", "benefit" and "food" as keyword enquiries in article title and full-text. The initial research process led to 3293 screened papers, 160 of which were examined in detail.
Results: There were 126 articles dealing with RBA studies and 34 with the RBA methodological framework. Most of the available papers dealt with the comparison of nutritional beneficial effects and chemical adverse effects related to fish consumption. The majority of studies undertook a comparison of consumer exposure to risks and benefits with regard to reference safety values. However, more varied studies have emerged during the last 15 years, contributing to the

**Corresponding author: Email: Jeanne-marie.membre@oniris-nantes.fr;*

diversification and the development of this issue.
Conclusion: RBA appears to be a promising scientific discipline and should be the next step in assessing the overall impact of food on health.

Keywords: Risk-benefit assessment; food; chemistry; microbiology; nutrition.

1. INTRODUCTION

Food safety management has adopted a risk-based approach in both the microbiological and chemical fields. In this context, the impact of more and more hazards associated with food consumption is evaluated by a risk assessment framework. In the nutritional field, food is recognized as having beneficial effects on health but also adverse effects. As a result, the concept of an integrated risk-benefit assessment has emerged in the last decade.

The risk can be defined as the probability that an adverse health effect affecting an organism, a system, or a sub-population will occur, as a consequence of an exposure to a hazard in food [1]. In contrast, the benefit is defined as the probability that a positive health effect will occur. Risk and benefit can be simultaneously related to the consumption of most foods that are commonly associated with various types of microbial (e.g. pathogens), chemical (e.g. acute toxic or endocrine-disrupting substances), and/or nutritional (e.g. saturated fatty acids) hazards, together with beneficial nutritional components (e.g. unsaturated fatty acids).

Risk-benefit assessment (RBA) falls with in the concept of risk-benefit analysis, which is an integrative approach associating three interconnected and complementary parts: risk-benefit management, risk-benefit assessment, and risk-benefit communication. The EFSA agency [2] advises mirroring the traditional risk analysis process to undertake a risk-benefit analysis, while considering some differences like the addition of a benefit assessment and a risk-benefit comparison as illustrated in Fig. 1.

The objective of RBA is to assess risk and benefit scientifically and objectively in the same integrative methodology. Then, risk-benefit management sets up two kinds of public health action: modification of food standards, reconsidering legislation to improve the quality of food available, and establishing recommendations for consumers to change their food habits into a healthier diet and lifestyle (food choice, consumption habits and cooking practices).

Several studies of RBA have already been undertaken and methodological developments in this field were first carried out by the European Food Safety Authority (EFSA) [2,4] and the Netherlands National Institute for Public Health and the Environment (RIVM) [5]. Then, some European collaborative research projects have worked on the RBA framework through these programs: “Benefit Risk Assessment For Food” (BRAFO)[6], “Best PRActices of Risk-BEnefit Analysis” (BEPRARIBEAN)[7], “Quality of Life – Integrated Benefit and Risk Analysis” (QALIBRA) [8] and “Benefit-Risk Assessment for Food: an Iterative Value-of-Information Approach”(BENERIS) [9].

In this context, RBA is becoming an established discipline. The aim of our work was to synthesize RBA studies associated with food consumption and to summarize the methodologies in a common framework.

2. METHODS

The research of articles aimed to collect RBA studies associated with food consumption and information on the RBA methodology. We followed the PRISMA data search process advised by Moher et al. [10] to organize the research of articles.

Databases explored included Web of Science, PubMed, MEDLINE, CABI, FSTA, ScieLO, Science Direct, EBSCO HOST, ACS Publications, Annual Reviews, edp Sciences, Endocrine Society, Cambridge Journals, NRC, High wire Press, World Cat, Science.gov and Google Scholar. Other sources were explored like Google, citation tracking, key journal search etc.

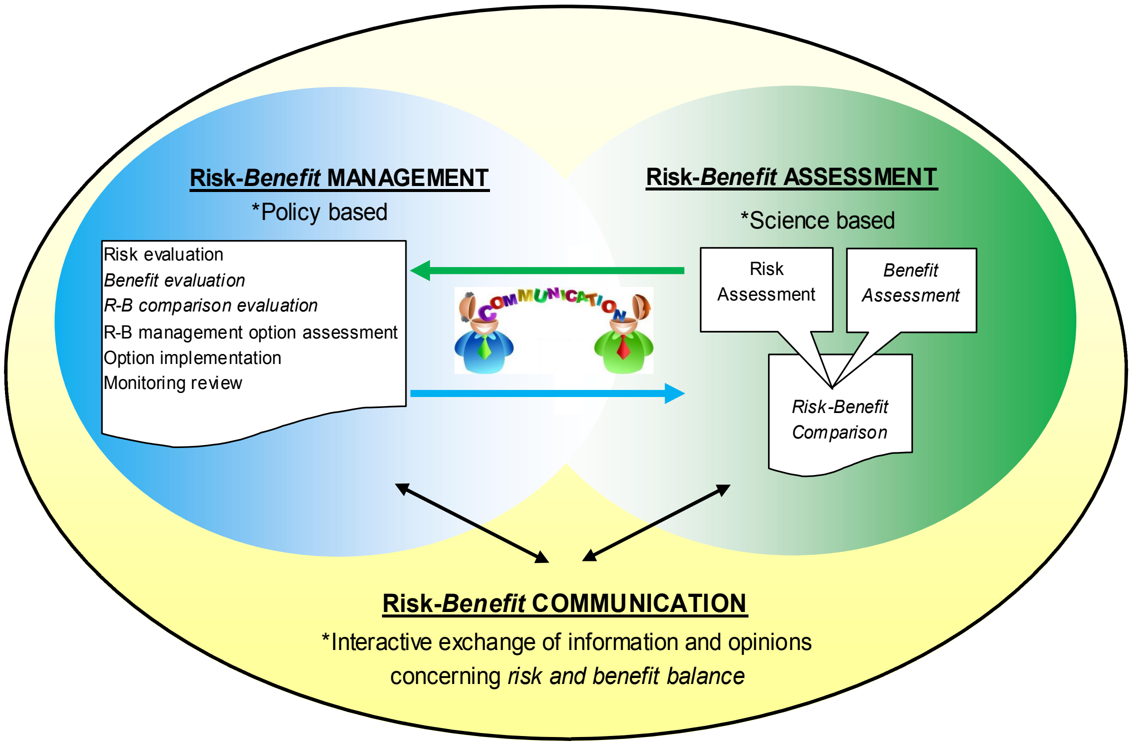

Fig. 1. Evolution of the conventional risk assessment conceptual framework toward an integrated risk-benefit paradigm, adapted from WHO [3]. The new elements are indicated in italics

These data searches were restricted to articles introducing RBA in terms of public health associated with food consumption in the fields of nutrition, chemistry, and microbiology. Only studies written in English or French without a publication date restriction were considered. The latest research was undertaken on 20th May 2014.

The same research was done on all the databases mentioned above. First, the search was based on the keywords "Food", "Risk* AND (Benefit* OR Beneficial*)" in the title but this did not provide all the relevant articles. Therefore, the search criteria were extended to the topic. Unfortunately, some databases did not have the option to search by topic. In this case, the nearest available option was used or, if there was none, we looked for the word "food" in the whole article. Below are the keywords used when the topic option was available, and when it was not.
When the topic option was available (e.g. for Web of Science):

- TITLE: (risk* AND (benefit* OR beneficial*)) AND TOPIC: (food)
- TITLE: ((chemi* OR toxicolo* OR microbi* OR nutrition) AND (risk* AND (benefit* OR beneficial*))) and TOPIC: (food)
- TITLE: ((risk* AND (benefit* OR beneficial*)) AND (health)) and TOPIC: (food)
- TITLE: ((risk* AND (benefit* OR beneficial*)) AND (public health)) and TOPIC: (food)
- TITLE: ((risk* AND (Benefit* OR Beneficial*) AND (review)) and TOPIC: (food)
- TITLE: ((risk* AND (benefit* OR beneficial*)) AND (state of the art)) and TOPIC: (food)

When the topic option was not available (e.g. for Science Direct):

- TITLE(risk* AND (benefit* OR beneficial*)) and FULL-TEXT(food)
- TITLE((chemi* OR toxicolo* OR microbi* OR nutrition) AND (risk* AND (benefit* OR beneficial*))) and FULL-TEXT(food)
- TITLE((risk* AND (benefit* OR beneficial*)) AND (health)) and FULL-TEXT(food)

- TITLE((risk* AND (benefit* OR beneficial*)) AND (public health)) and FULL-TEXT(food)
- TITLE((risk* AND (Benefit* OR Beneficial*) AND (review)) and FULL-TEXT(food)
- TITLE((risk* AND (benefit* OR beneficial*)) AND (state of the art)) and FULL-TEXT(food)

The article screening was carried out in three consecutive steps. The first selection of articles was based on the title accordance with the terms searched, then the abstract was explored, and finally the full article was screened. Articles that met the following criteria were selected for inclusion:

- The full article was written in English or French.
- The article was specific to the food sector.
- The main subject was a study of RBA introducing a comparison of risk and benefit or was about the methodology of RBA.
- The RBA assessment was specific to the field(s) of nutrition and/or microbiology and/or chemistry. Other subjects, like economy and sociology, were excluded.
- Reviews dealing with risks and benefits of food, like a review of the positive and adverse health effects due to the consumption of a specific food, were also selected to identify potential RBA studies.

Regarding articles dealing with the RBA methodology, the different steps recommended to undertake an RBA and the terminologies used were identified in order to summarize a common framework, which is presented in the Results section. The RBA studies identified were classified into two groups: performed and potential studies. For each study undertaken, the topic, the scientific field (microbiology, nutrition and chemistry), the type of comparison and the main results are presented in Table S1 (Appendix). Potential studies were investigated to compile a non-exhaustive list of future research needed in RBA.

3. RESULTS

Based on the research process, 3293 papers were identified comprising 2896 peer-reviewed articles found through databases and 397 from other sources corresponding to the grey literature (mainly scientific reports and theses) or from on-line documents (website pages, electronic articles, web-seminars). The results and process are summarized in Fig. 2. The screening step excluded 1819 papers by title checking and 182 by abstract reading. The screening was extensive because RBA is also an important topic in medicine, with the aim of balancing the beneficial effects of drugs against their potential adverse effects.

At the end of the query process, 160 articles were included in the review, 126 dealing with RBA studies (70 applications with recommendations and 56 studies on positive and negative health effects), and 34 with the RBA methodological framework.

3.1 Studies of Risk-benefit Assessment

There were 70 articles reporting RBA applied to food. In this section, these are presented chronologically, by scientific discipline (microbiology, chemistry, and/or nutrition), by comparison criteria and by category of applications. Beside RBA studies in the strictest sense, there were also 56 studies on positive and negative health effects, which could potentially be used in RBA.

3.1.1 History of RBA studies

The first RBA study appeared in 1999. Since then, the number has increased gradually Fig. 3. The first case study undertaken concerned the assessment of fish consumption, which is still by far the most studied topic (70% of RBAs). Fish consumption is a well-known source of both health benefits provided by omega-3 and risks due to environmental pollutants (dioxins, PCBs and methyl mercury). These RBAs have often been conducted at the level of a specific country by food safety agencies or various scientific groups.

Beside RBA on fish, many other case studies have emerged: supplementation or fortification of foods, assessment of nitrates and nitrites in fruits and vegetables, food-specific molecules such as acrylamide created during the manufacturing process, water and milk treatment, replacement of sugar by intense sweeteners, consumption of trans-unsaturated fatty acids, fish cooking practices, etc. Fig. 3.

3.1.2 Scientific fields of RBA studies

All these studies fall within the fields of nutrition and/or microbiology and/or chemistry. However, only a few studies have performed an integrated approach including these three disciplines Fig. 4.

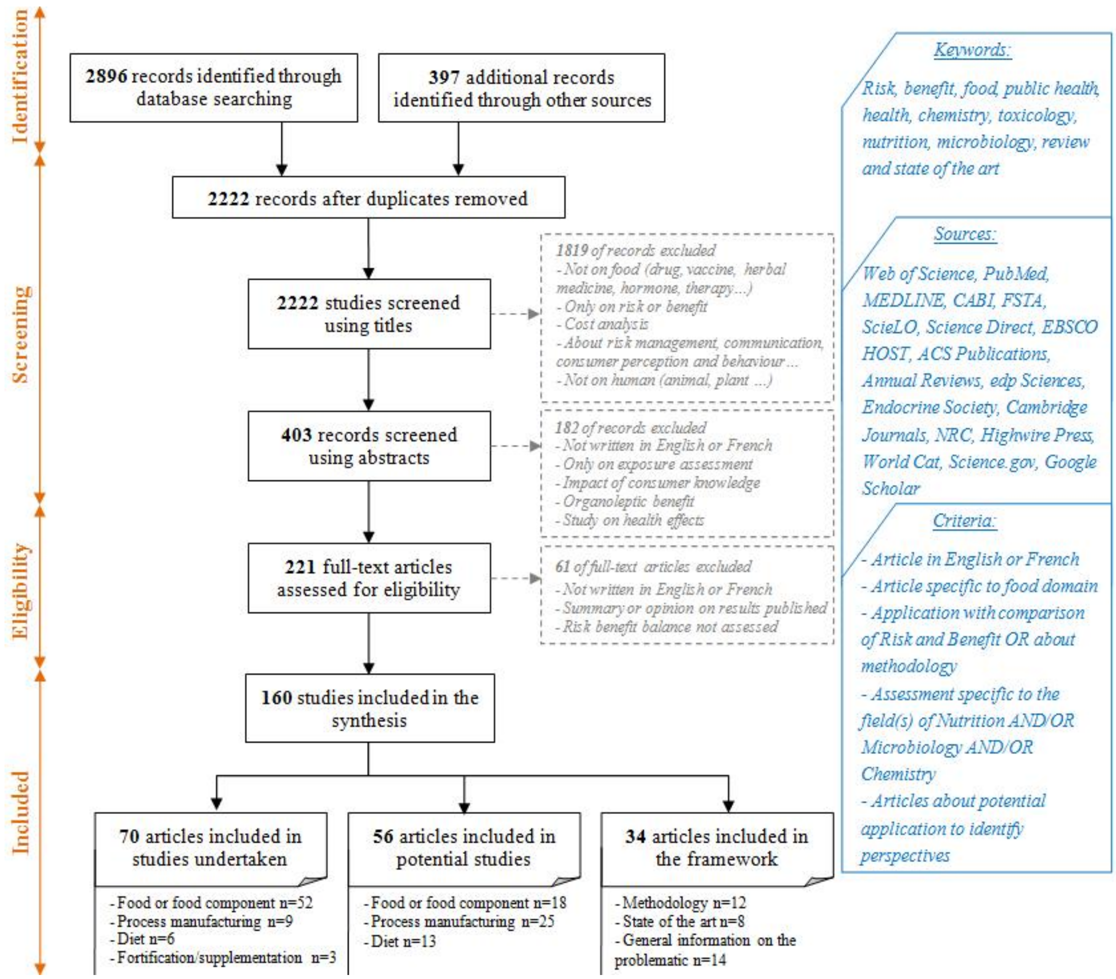

Fig. 2. Over view of the applied data search process and the results based on PRISMA's four-phase diagram [10]

Moreover, the three available studies [11-13] that integrated these three disciplines compared chemical and nutritional risks-benefits using safety reference values and gave recommendations on hygiene practices, which cannot be assimilated into a proper quantitative nutrition-chemical-microbial RBA. More generally, microbial risk is not often assessed in RBA and rarely in a quantitative way. Recently, Berjia et al. [14] carried out a comparison of nutritional benefits and microbiological risks associated with fish consumption.

3.1.3 Comparison criteria used in RBA

Different criteria are used to compare risks and benefits:

1 *Comparison of risks and benefits under constraints, based upon safety reference values.* This is a comparison of scenarios of consumer exposure. For each scenario of consumption, consumers are exposed to different risks and benefits related to the field of chemistry and/or nutrition and/or microbiology. The aim of this comparison is to set a threshold in accordance with safety levels set by food safety agencies. Regarding the risks identified, this threshold is set below the maximum levels of tolerable exposure (i.e. Acceptable Daily Intake, Tolerable Daily Intake, Upper Limit) and in agreement with nutritional intake recommendations (Recommended Daily Allowance, Estimated Average Requirement). Above this threshold, consumers could be exposed to a risk. Then, benefits are maximized, if possible, with respect to this threshold. This comparison can be considered semi-

quantitative because the RBA output is not expressed in a quantitative way (even if the assessment in chemical, microbiological or nutritional field might be quantitative). In addition, the process is likely to be iterative: RBA conclusions will be revised as often as the safety levels are reviewed. A comparison under constraints has been performed 46 times among the 70 studies Fig. 5.

2 *Comparison of risks and benefits based upon health endpoint*. For example, risk can be expressed as the probability of increasing the prevalence of coronary heart disease and benefit as the probability of decreasing this prevalence. It might also be expressed using the intellectual quotient (IQ) endpoint. A comparison based upon health endpoint has been performed 15 times among the 70 studies Fig. 5. Only articles that compared health endpoints one by one were included in this group.

3 *Comparison of risks and benefits based upon a composite metric* like the Disability Adjusted Life Years (DALY). This aims to compare quantitatively the impact of different diseases all together, contrary to the last group. It provides a comprehensive assessment of the consequences of a disease by integrating the quality of life lost(w) after the disease onset, the duration of the disease (Years of Life with Disability, YLD) and Years of Life Lost (YLL) [15]. At an individual scale, the DALY metric is calculated as indicated in Eq. 1, and is illustrated in Fig. 6 by the case of a person who has fallen sick and died after a period of life with a disability.

$$DALY = w. \ YLD + YLL \qquad (1)$$

The use of the DALY metric as a comparison criterion requires many data, which are unfortunately not always available. However, to avoid this problem, epidemiological data can be used to inform the probabilities of falling ill, dying and recovering, as was done by Hoekstra et al. [16] and Berjia et al. [14]. A comparison using a composite metric has been performed 9 times among the 70 studies Fig. 5.

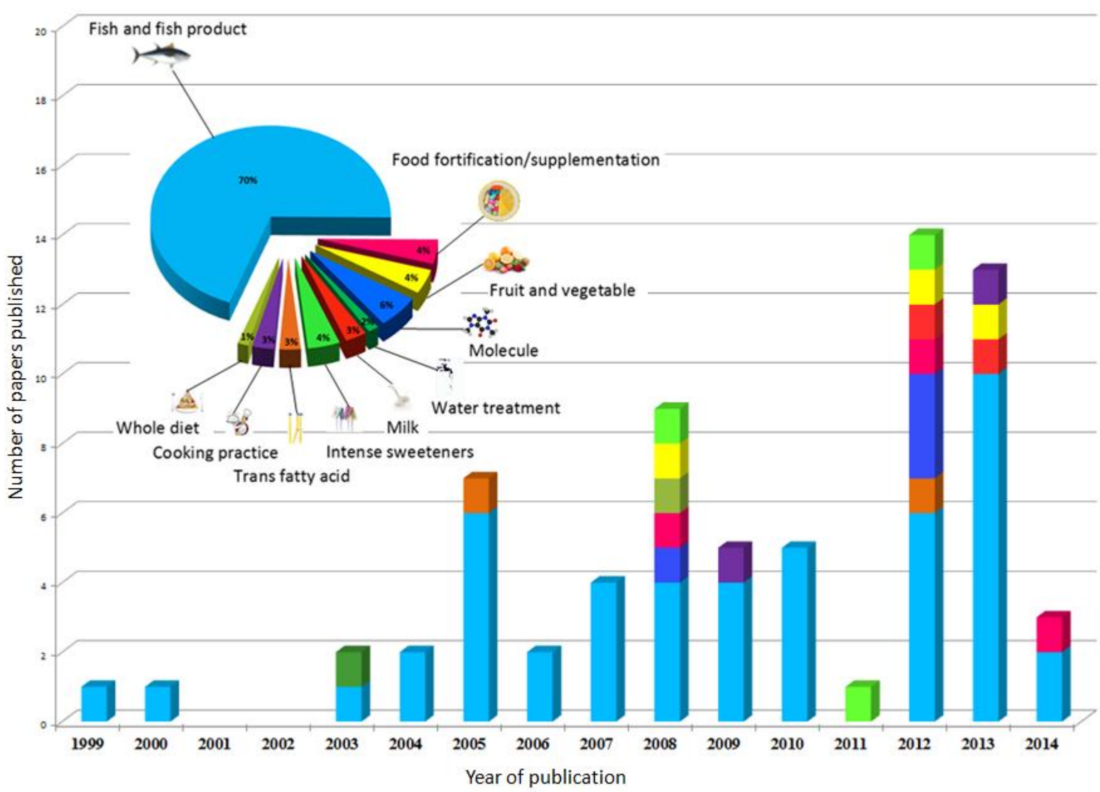

Fig. 3. Classification of the 70 studies performed by year and food category

3.1.4 Main RBA applications

Studies undertaken in recent years have resulted in progress in scientific knowledge in RBA. They have also enabled the food authorities to make recommendations on food consumption, such as the EFSA on fish consumption [18]. More generally, RBA research has led to promising applications, which can be schematically split into two categories: those leading to recommendations by food safety authorities and those leading to process and formulation design by manufacturers.

The applications are listed below. However, it is important to keep in mind that the conclusions presented here are extremely summarized, and can by no means be considered definitive statements concerning recommendations. More information on each study is provided in Table S1 (Appendix). However, for a comprehensive view of the study, please refer to the original paper.

- ***Applications leading potentially to recommendations***
  - ***Impact of a specific food on health***

The most investigated case study is fish. Fish contains docosahexaenoic (DHA) and eicosapentaenoic fatty acids (EPA) recognized for their health benefits but it is also contaminated by pollutants such as methyl mercury and dioxins, sources of adverse effects now clearly demonstrated. Fish composition is also dependent on fish species, fish feeding and place of production, which considerably influence its chemical contamination and fatty acid content. In addition, health effects vary greatly according to the subpopulation affected, which is a major issue in RBA. This topic has been investigated for 15 years and is still in progress because of its complexity. Overall, each study tackles the same subject (fish consumption) but brings new information by studying particular conditions (assimilated into co-variables in the analysis) affecting the risk-benefit assessment.

The overall recommendation is to consume two fish dishes per week, including one with fatty fish [11,18-20], while alternating fish species, production type (farmed or wild) and production location. The recommendation varies from strictly two portions per week of fatty fish, including ¼ of lean fish [21,22], to two to three servings per week [12,23]. Some studies also give specific recommendations according to the subpopulation at risk, such as women of childbearing age and children [24].

Other studies have compared the impact of risks and benefits on specific health endpoints and have given ranges of recommendations to minimize the risk of stroke [25], coronary heart disease (CHD) [26,27], and IQ change in the newborn [28,29] or stroke and fetal development disturbance [30].

In addition, as highlighted by Cardoso et al. [31], the risk-benefit balance of fish consumption varies between countries. RBAs have been carried out at a country level in Norway [32], the Netherlands [14,16], Poland [33,34], France [35], China [36-40], the USA [41,42] and Bermuda [43]. In addition, the type of fish species could change the risk-benefit balance [44-48]. Likewise, the type of farming may have an impact [49,50]. As a result of these two factors (population and fish species), some specific populations could be negatively impacted by fish consumption. For instance, the Portuguese population, which consumes about 57kg of fish per year, should favor certain fish species to limit the potential risk due to high intake [51-53]. Likewise, the Inuit population should limit its fish consumption [54]. Conversely, the Kahnawake community south of the St Laurence river, also high fish consumers, is not exposed to risk [55].

The complexity of the assessment of fish intake is increased by the fact that fish consumption by pregnantor lactating women or women of childbearing age could impact the newborns' neurodevelopment and thus increase or decrease their IQ [56-58].

Finally, a few quantitative RBAs regarding fish consumption have been performed, providing figures that enable RBA recommendations to be deciphered. For example, in the US adult population, the current fish consumption enables to gain 5000 healthy years per year per 100000 people, calculation based on the Washington state [59]; also in US, a 50% increase in fish consumption could save 120000 years annually of perfect health for people [60]. More specifically, based on a French study on 1011 people, it was concluded that a weekly consumption of 1104 g of fish could save between 97 and 285 healthy years annually [35]. This example demonstrates that a quantitative comparison of risks and benefits is more transparent and objective than a comparison under constraints.

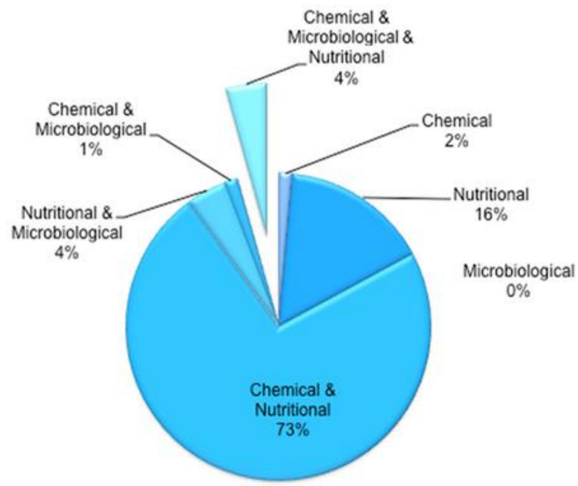

Fig. 4. RBA studies performed classified by scientific fields, based on 70 studies

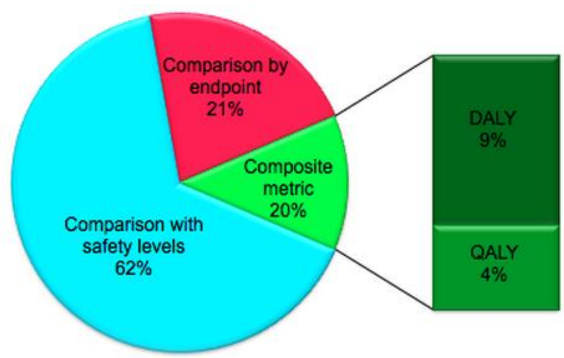

Fig. 5. RBA studies performed classified by type of comparison, based on 70 studies

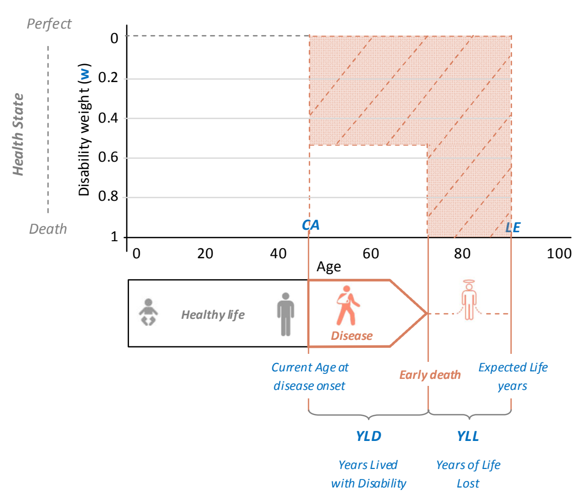

Fig. 6. Illustration of DALY adapted from Tijhuis et al. [17] with the case of a person who falls sick and dies after a period of disability

Recommendations concerning other food categories have also been given. Although not based upon a quantitative comparison, it has been pointed out that the intake of fruits and vegetables [61,62] and soy proteins [48] should be increased since these food categories do not expose consumers to risk. In contrast, the intake of trans fatty acids should be limited [63,64].

- ***Impact of a particular type of diet on health***

The type of diet has also been studied through RBA to assess its overall impact on health.

Replacement of sugar by intense sweeteners has been judged healthy because it prevents over weight and caries [64,65] although risks can outweigh benefits for children who are high consumers of soft drinks with a potential risk of exceeding the acceptable limit of intense sweetener intake [66].

Software has been developed to assess individually risk-benefit related to diet. Some programs are specific to a product, e.g. fish consumption [67,68], while others include a wide range of foods [69,70].

- ***Applications leading potentially to process and formulation design***

- ***Impact of manufacturing process on health***

The manufacturing process is identified as a source of risks and benefits because it could introduce risk and/or benefit or modify the risk-benefit balance.

Water treatment decreases microbial contamination but introduces chemical risk at the same time. The balance has been quantitatively assessed by Havelaar et al. [71]who demonstrated that the benefit outweighed the risk. Milk treatment is also beneficial because it decreases microbial risk in spite of biochemical reactions [72].

RBA may be used as a tool to optimize the process line by assessing the impact of different production parameters on the risk-benefit balance. Rigaux et al. [73] has optimized the thermal sterilization of vegetables to maximize vitamin concentration without exposing consumers to microbial risk. Likewise, the thermal process of cookies might be optimized to enhance their antioxidant activity while limiting the formation of harmful compounds [74]. The type of thermal process also has an influence on food composition and thus on the risk-benefit balance. For instance, a comparison of fish cooking processes demonstrated that grilling is healthier than boiling or roasting [75]. More generally, to optimize the thermal process, it is necessary to analyze altogether the potential loss of nutritional properties, the possible formation of hazardous molecules such as acrylamide [72,76] and benzo(a) pyrene [64], and the efficiency of microbial inactivation.

- ***Impact of food formulation on health***

The positive impact of bread supplementation with folic acid on public health has been quantitatively assessed. In the Netherlands, a small supplementation of 70 µg per 100 g of bread could save 7000 healthy years annually [64] and a higher supplementation (i.e. 140 µg per 100 g of bread) could save 11812 healthy years annually [77].

It has been reported that margarine supplemented with plant sterol could save eight healthy years per 1000 people [78].

3.1.5 Studies on the positive and negative health effects associated with food consumption

Besides RBA studies, there were also 56 studies on the positive and negative health effects, which could potentially be used in RBA. A list of the main subjects of interest is provided below.

First, some foods or food components have been identified as ambivalent, i.e. food for which it is not straight forward to assess whether the risk is higher than the benefit or *vice versa.* Among them, it is worth mentioning: coffee [79-84], tea [85,86], alcohol [87-90], broccoli [91], meat [92,93], chocolate [94], phytoestrogen [95,96], is oflavone [97] and nitrite/nitrate [98,99].

Other issues related to food agricultural practices and food manufacturing practices have been pointed out [100]: organic food production [101], use of pesticides [102,103], use of genetically modified organisms [104-108], the thermal process [109], irradiation of food [110-112], use of artificial sweeteners [113-115], use of antimicrobials [116], red meat cooking practices [117], food fortification[118], the occurrence of the Maillard reaction [119], milk treatment [120,121], etc.

Finally, RBA related to diets, such as the Mediterranean diet [122,123], a raw diet [124], vegetarianism [125,126], and baby food infant formulae or breastfeeding [127-133], could be of interest.

3.2 Methodology of Risk-benefit Assessment

Risk-benefit assessment (RBA) is an emerging discipline and its framework is still in progress. However, important works have been carried out by European scientists to develop the RBA approach.

The search identified 34 documents related to the RBA framework. Twelve of them dealt with the methodology step by step. Among them, four papers were published by safety agencies, the EFSA [2,4] and RIVM [5,77], four others by the European projects BRAFO [6,134] and QALIBRA [8,135] and four by scientific researchers [136-139]. The European BEPRARIBEAN project [7] also contributed to developing this framework through six' states of the art' in risk-benefit analysis [17,140-144], concluded in Tijhuis et al. [145]. Fourteen other papers added information about the framework. The International Life Sciences Institute organized a session about the risk-benefit balance of food at the North America Annual Meeting in 2013; a presentation was made about the risk-benefit analysis of food [146], another about risk and benefit for chemical contaminants [147] and a third dealt with the risk-benefit assessment of nutrient intake[148]. Two other European projects, BENERIS [9,149] and Plantlibra [150], addressed this issue, two theses [56,151] were published, and other scientific researchers published articles [15,152-156] on more specific points of the framework.

The first work on RBA methodology was carried out by the EFSA in 2006 [4] followed in 2010 by their recommendations on risk-benefit analysis methodology [2]. In parallel, the RIVM published a decision tree [5]. Then the BRAFO working group suggested an integrative approach [6], applied its methodology to case studies [48,64,72] and published a consensus document [134].

Other works have contributed to the RBA framework development. For example, the QALIBRA project has provided online software [8] which enables a quantitative comparison of risk and benefit to be made based on DALY (Eq. 1) and Quality Adjusted Life Years (QALY). Within the BENERIS project, an information and exchange web-platform has been created [9]. The BEPRARIBEAN project has enabled good practices to be established in risk-benefit analysis [7,145] within various scientific fields: Medicine [140], Environmental Health [141], Food Microbiology [142], Economics and Marketing-Finance [143], Consumer Perception [144], and Food and Nutrition [17].

The RBA methodology is based on the risk assessment framework [3] universally applied in the fields of microbiology and chemistry, but a risk-benefit comparison step is added. The RBA framework is described below in detail and summarized in Fig. 7.

First, according to the papers investigated, there is a consensus to start the RBA by a preliminary step consisting of "0. Problem definition" [2,5,6,8], in order to define the case study (a food, a food compound or a diet), the (sub) population targeted, and different scenarios of consumer exposure to be assessed (reference and alternative scenarios).

Then, RBA mirrors a traditional risk assessment [2,4], which includes four steps: hazard identification, exposure assessment, hazard characterization and risk characterization [3]. However, the terminologies used need to be adapted to integrate the benefit assessment. In fact, in a risk assessment, the term "hazard" is used to define a biological, chemical or physical agent able to cause an adverse health effect [157]. The risk is thus "a function of the probability of an adverse health effect and the severity of that effect, consequential to a hazard(s) in food" [1]. The term "benefit" is unanimously used to mirror the risk but we found different terms used to mirror the term "hazard": "positive effect" [6,64,72,134], "benefit" [4,77,78], "positive health effect" [2,158], "beneficial effect" [17], etc. Nevertheless, in the field of nutrition, the same agent could be a source of risk and benefit depending on the consumer exposure [136]. In this context, we propose to use a more general term to encompass the term hazard and its counterpart on the benefit side. We have named this term "Health Effect Contributing Factor" (HECF) and we define it as an agent able to cause an adverse or a positive health effect in the case of exposure. We chose this term because an HECF could be positive and negative, thus applicable in the nutrition field. In addition, as a positive or beneficial (health) effect is the consequence of a benefit and not its source, as a hazard is for a risk, the use of the term HECF can skirt this problem. In the same way, we have grouped together the terms risk and benefit under the expression "Health Impact" (HI), which we define as a function of the probability of an adverse or positive health effect and the severity of that effect, resulting from exposure to an HECF. A positive HI is a benefit and a negative HI is a risk. In this conceptual framework, a decrease in risk is considered a benefit and a decrease in benefit is considered a risk Fig. 7.

After defining the problem (step 0), risk and benefit are assessed in parallel in each field (nutrition, chemistry and microbiology) following the risk assessment steps. If we introduce the terminologies proposed above, we can name the next four steps as follows:

"1. Identification of HECF",
"2. Exposure assessment",
"3. Characterization of HECF" and
"4. Health impact characterization".

At any step, even if the assessment is qualitative or semi-quantitative, EFSA and BRAFO [2,6] advise stopping the assessment if risk outweighs benefit or *vice versa*. Yet, Berjia et al. [14] illustrated in a cold-smoked salmon study that a quantitative comparison of risk and benefit could reverse the risk-benefit balance. However, due to a lack of data, a quantitative comparison is often not feasible. For these reasons, we suggest an alternative after step 4 Fig. 7. If the consumer is not exposed to both risk and benefit, there is no interest in performing a risk-benefit comparison, and the assessment is only performed from the risk side or from the benefit side. If the data available are too scarce to carry out a quantitative comparison, a comparison with a composite metric is not feasible but a comparison under constraints could be undertaken.

When the appropriate data are available and the risk-benefit comparison is of interest, a quantitative RBA can be performed. The assessment is extended to step"5. Harmonization of HI in the same metric" and then to step "6. Assessment of different scenarios of consumer exposure".

To move harmonization forward (step 5), there are still scientific bottlenecks. Indeed, risk assessment differs in each field because each has its own characteristics while the risk-benefit comparison aims to integrate all the results in the same metric. Performing a quantitative RBA is thus difficult due to the lack of a common unit to express the risk. Chemical risk assessment often expresses the risk as the probability of exceeding a threshold, or a safety reference value; microbiological risk assessment output is the probability of getting sick or dying from a disease; nutritional health assessment integrates two elements: deficiency or excess of a food component, and homeostasis (internal regulation to maintain a compound ata relatively constant concentration).

Finally, assessors report their conclusions to the decision-making managers who select the best scenario. At this stage, it is important to keep in mind that the best scenario is not necessarily the one corresponding to the best benefit-risk balance as the managers have to take other considerations into account, such as economic factors or food availability.

Two recent studies clearly illustrate how a quantitative RBA in the fields of microbiology/nutrition and chemistry/nutrition could be applied from step 0 to step 6 Fig. 7. They both carried out a full quantitative comparison of risks and benefits using DALY as a comparison criterion.

Berjia et al. [14] were the first scientists to perform a quantitative RBA in the fields of microbiology and nutrition. They balanced the risk of listeriosis due to cold-smoked salmon consumption with the health benefit due to omega-3 intake. They concluded that a change in the consumption of smoked salmon from the reference scenario (women 23 g/day and men 20 g/day) to the alternative scenario (40 g/day for adults) could save 9343 DALYs in the Danish population (5.57 million inhabitants), if the product was consumed before four weeks of storage. The sensitivity analysis highlighted that the net impact on health depends on the storage time of the product before consumption: from five weeks onwards, the net health impact is reversed and the overall effect is negative because of the increasing risk of listeriosis.

The second example of RBA was performed in the disciplines of chemistry and nutrition, which are currently those most explored. Hoekstra et al. [16] balanced the risk and benefit of fish consumption in Denmark. The net public health impact resulting from a change in the consumption of fish from 100 g/day to 200g/day could save 2.7 DALYs per 1000 people.

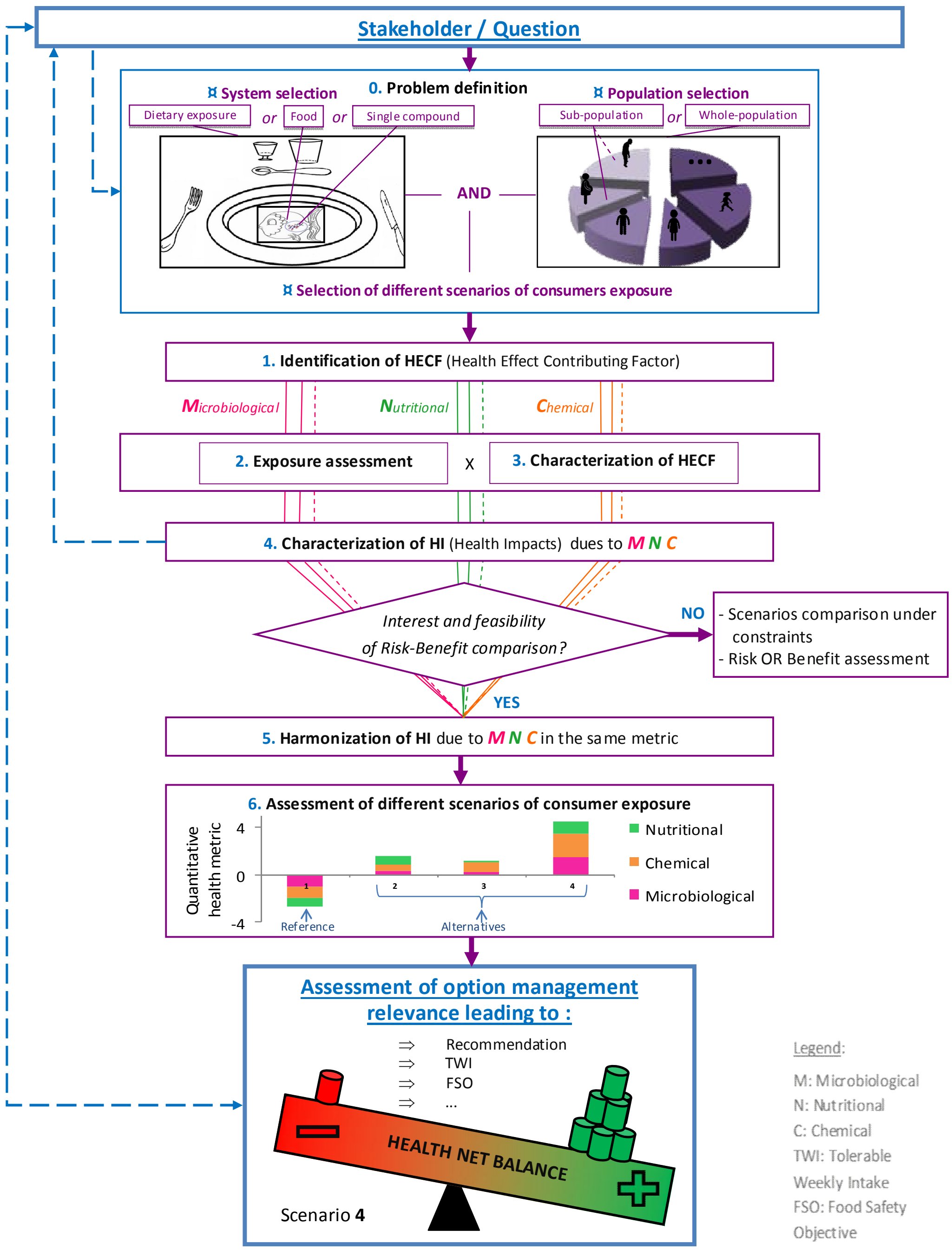

Fig. 7. Summary of risk-benefit assessment methodological framework based on different literature sources

4. CONCLUSION

The risk-benefit assessment discipline emerged at the beginning of the 21st century. RBA studies are intended to address various issues concerning the food supply-chain "from farm to fork". Although the first and most popular studies were related to fish consumption (48 of the 70 studies analyzed in this review), research has now diversified into a wider range of food categories such as fruits, vegetables and soy protein. The majority of RBA studies aimed to compare chemical risk with nutritional benefit (51 out of 70). The number of RBAs integrating components of nutrition, chemistry and microbiology was relatively low (3 out of 70); moreover, they were not fully quantitative but limited to a comparison under constraints (i.e. comparison of consumer exposure to reference safety levels).

Although the methodology is still in progress, these studies followed the same overall methodology based on the universal risk assessment framework [3] as advised by the EFSA [2]. Risks and benefits are first assessed independently and then compared with each other. This comparison can be made under constraints (46 out of 70 studies), based on health endpoints (15 out of 70) or using a composite metric such as DALY (9 out of 70). This lattermetric is a practical tool to compare the effect of different diseases on health, integrating their severity and duration. To generalize further the use of a composite metric as a comparison criterion, the harmonization of scientific approaches needs to be enhanced; in particular, output risk (or benefit) assessment has to be expressed in a common unit.

To conclude, RBA is currently recognized as a scientific discipline with a wide range of applications. It is becoming a tool used in public health management, for instance in food recommendations on fish consumption [11,18,28,32]. It might be used in the future by food manufacturers as an aid in process and formulation design [72,77].

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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APPENDIX

Table S1. Summary of the main results of risk-benefit assessment studies

Comparison based on*	Scientific domain**	Main results	Reference (first author, year)
• ***Food component(s) is/are a source of risk(s) and benefit(s)***			
		Fish	
- Safety levels	N/C	Fish consumption is high in Portugal (≈57kg/year). Assessment of the three most consumed species demonstrated that its consumption should be limited to one serving/week of silver scabbard fish or three servings/week of hake or ray.	Afonso, 2013 [52]
	N/C	A daily consumption of 160 g of fish muscle (6 species studied) does not expose consumers to risk and contributes to nutritional benefit. Consumption of liver should be avoided and a weekly consumption of *L. whiffiagonis* is recommended.	Afonso, 2013 [51]
	N/C	Consumption of two portions of fish per week is recommended including one portion with a high content of EPA and DHA, but with changes in species and points of production (subgroup specifications are given).	AFSSA, 2008 [19]
	N/C/M	The ANSES agency recommends that the general population consume 200 g/week of fish (including 100 g of fish with a high content of EPA and DHA). Specific recommendations are given for the sensitive subpopulation. It also advises specific hygiene measures.	ANSES, 2013 [11]
	N/C	A list of intake recommendations is given for different subpopulations (infants, healthy adults, CHD patients and hyperglyceridemia patients) depending on fish and fish species to achieve the recommended weekly intake (RWI) without exceeding the tolerable weekly intake (TWI).	Balshaw, 2012 [24]
	N/C	Consuming fish two to three times a week decreases cardiovascular diseases, the risk of osteoporosis and fractures. Fish with up to 1 mg/kg methyl mercury should be limited to one serving per month. Pregnant or lactating women may consume one of the three weekly portions with a high omega 3 content.	Becker, 2007 [23]
	N/C	The assessment of fish consumption ineight European countries highlighted that the probability of being exposed to risk and benefit depends on the fish species. Countries with a low fish intake could be subject to small risk and benefit (Italy and the United Kingdom) or low risk but high benefit (Germany and the Netherlands) while high consumers are exposed to both (France, Spain, Portugal and Iceland).	Cardoso, 2010 [31]
	N/C	The Portuguese population exceeds the provisional tolerable weekly intake (PTWI) of methyl mercury regarding the consumption of hake, ray and silver scabbardfish without achieving the relative daily allowance (RDA) and the relative daily intake	Cardoso, 2013 [44]

		(RDI) of Selenium, EPA and DHA. They advise limiting the consumption of these three fish species to less than one meal/week.	
	N/C	The Kahnawake community of south of the St Laurence river is not exposed to chemical risk due to fish consumption and fishing.	Chan, 1999 [55]
	N/C	Salmon and trout sold in Quebec can be regularly eaten to take advantage of nutritional benefit without exposing consumers to chemical risk (e.g. farmed Atlantic salmon can be consumed in one serving/day).	Dewailly, 2007 [45]
	N/C	43 fish species from Bermuda were analyzed and recommendations are given by subgroup. For example, women of childbearing age should not consume predatory fish while other subgroups should limit their consumption to one portion per week or month.	Dewailly, 2008 [43]
	N/C	In China, a consumption of 80 to 100 g/day of marine oily fish from the Chinese market is associated with potential nutritional benefit without exposing consumers to chemical risk.	Du, 2012 [37]
	N/C	No difference between wild and farmed fish has been identified. The advantage of farmed fish is that the contaminant level can be controlled and decreased by modification of fish feeding. A consumption of one to two portions/week is advised with restrictions for sensitive groups.	EFSA, 2005 [18]
	N/C	A daily consumption of Siberian grayling from Yenisei River provides the RDI of EPA but could exceed reference doses (RfD) of chromium. Concentration may vary according to month.	Gladyshev, 2009 [46]
	N	A curve of the balance of net benefit-harm is created with estimated thresholds. However, more data are required to estimate thresholds and asymptotes using this curve.	Gochfeld, 2005 [42]
	N/C	Wild salmon have significantly fewer chemical contaminants than farmed salmon and a higher EPA content. Farmed salmon from Europe contains a higher level of chemical contaminants than those from South and North America and a similar EPA content.	Hites, 2004 [50]
	N/C	In Canada, 35% of the Inuit population is exposed to chemical risk due to consuming fish contaminated by methyl mercury. To decrease this risk and keep the benefit, the consumption of ringed seal liver could be replaced by ringed seal meat, ringed seal blubber, beluga mukluk or Arctic char, for example.	Laird, 2013 [54]
	N/C	The Portuguese adult consumption of black scabbardfish should be limited to 90 g grilled meat and 120 g of fried meat. Edible crab brown meat should not exceed 27 g boiled meat per week and its consumption should be avoided by children and lactating or pregnant women.	Maulvault, 2013 [53]
	N/C/M	A consumption of 270 g to 340 g/week of fish is advised. Children under 12 years	Nesheim, 2007 [12]

		old and pregnant and lactating women should limit tuna consumption to150 g/week and avoid predatory fish. Other subgroups can consume more fish but they should change fish (and seafood) species. There is additional benefit by including seafood high in EPA and DHA. Microbial risk could be limited by hygiene practices during handling and cooking.	
	N/C	Consumption of two portions/week, including one oily fish, decreases CVD risk and improves fetal development. Pregnant and lactating women should select certain fish.	SACN/COT, 2004 [20]
	N/C	Fish consumption has been assessed as safe in the State of Michigan. A list of the top 11 fish was established to increase benefits.	Sidhu, 2003 [41]
	N/C	Consumption of 181-213 g/week of certain fatty fish species and 26-72 g/week of lean fish or shellfish provides a good risk-benefit balance.	Sirot, 2010 [21]
	N/C	A consumption of 200 g/week of selected fatty fish and 50 g/week of lean fish maximizes benefit and minimizes risk.	Sirot, 2012 [22]
	N/C	Consumption of canned fish from the Polish market presents higher benefit than risk. Limitation depends on fish species.	Usydus, 2008 [33]
	N/C	Fish products from the Polish market vary greatly in terms of potential beneficial and adverse health effects; recommendation of quantity depends on species.	Usydus, 2009 [34]
	N/C	Consuming fish from Taihu Lake to achieve RDA of EPA and DHA does not expose consumers to chemical risk (PCBs and PBDEs).	Zhang, 2012 [40]
	N/C	The risk-benefit ratio has been assessed for four fish species from Taihu Lake in China and for three muscles (dorsal, ventral and tail) and three viscera (heart, liver and kidney). The current Chinese fish consumption does not present a risk, except for ventral and tail consumption of top mouth cutler that should be avoided.	Zhang, 2012 [39]
	N/C	It is recommended that the Norwegian population increase their fish consumption to achieve two meals of fatty fish per week.	VKM, 2006 [32]
	N/C	Consumption of 200 g/week of farmed salmon decreases CHD incidence and increases contaminant intake but still below the PTWI.	Watzl, 2012 [48]
- Endpoint	N/C	Fish consumption (from one to twelve servings per week) decreases the relative risk (RR) of stroke compared with the scenario of no consumption.	Bouzan, 2005 [25]
	N/C	In HongKong, moderate fish consumption by pregnant women is a source of benefit for the IQ of their children with a gain of 0.79 to 5.7 points if they vary the species.	Chen, 2014 [36]
	N/C	A consumption by pregnant women of one to seven servings/week of fish (depending on fish species) decreases CHD and increases the future newborn IQ. Details are given for each subgroup and as a function of fish species.	FAO/WHO, 2010 [28]
	N/C	CurrentUS fish consumption prevents 30000 deaths per year from CHD and 20000 deaths per year from stroke. Women of childbearing age should increase their fish	FDA, 2009 [30]

		consumption to 340 g/week to improve fetal neurodevelopment.	
	N/C	RDI of EPA and DHA could not be achieved through farmed or wild salmon consumption without exposing consumers to carcinogenic risk. Intake recommendations are given depending on fish market location.	Foran, 2005 [49]
	N/C	The IQ gained by children during their mother's pregnancy is positive with a consumption of 175 g/week and 450 g/week of 30 fish species from Zhoushan in China; optimal weekly consumption is given for every species. Consumption of *Scoliodon sorrakowah* is not recommended.	Gao,2014 [38]
	N/C	Risk and benefit due to fish consumption are assessed to optimize newborn visual recognition memory (VRM) and limit CHD. A table of intake recommendations depending on species is provided.	Ginsberg, 2009 [29]
	N/C	To ensure their child's IQ is more than 100 points, Finnish pregnant women should reduce their consumption of vendace by 13%, white fish by 18%, perch by 31%, and pike by 90% and increase their intake of Atlantic salmon by 2% and Baltic herring by 4%.	Gradowska, 2013 [56]
	N/C	A small increase in fish consumption decreases CHD mortality risk by 17% and non-fatal heart disease risk by 27%.	König, 2005 [26]
	N/C	Current fish consumption by Finnish pregnant women generates compensation in effects on infant's IQ. Fatty fish consumption creates a gain in IQ and lean fish consumption an adverse IQ effect.	Leino, 2013 [57]
	N/C	Salmon consumption presents more health benefit than risk. However, the risk-benefit balance of Arctic grayling, pike, sablefish and halibut cannot be assessed because data depend on regions and studies.	Loring, 2010 [47]
	N/C	Consumption of one to two servings/week reduces CHD risk by 36% and total mortality rate by 17%. Women of childbearing age, pregnant or lactating should consume two servings/week with species restrictions.	Mozaffarian, 2006 [27]
	N/C	Women's fish intake during pregnancy causes a decrease in newborn IQ for most species consumed. Risk clearly outweighs benefit (until 11 IQ points lost with swordfish), and only a few species slightly improve the IQ (+1 point for mackerel).	Zeilmaker, 2013 [58]
- DALY/QALY	N/M	Consumption of 40 g/day of cold-smoked salmon by the Danish population could improve population health with a potential gain of 10000 healthy years annually if the product is consumed before 4 weeks of storage.	Berjia, 2012 [14]
	N/C	In US, an increase of 50% in fish consumption by the adult population, except women of childbearing age, could save 120000 healthy years annually.	Cohen, 2005 [60]
	N/C	In France, a higher fish intake (1104 g/week) than the current consumption (334 g/week) could save between 97 and 285 healthy years based on the French study CALIPSO on 1011 people.	Guevel, 2008 [35]

	N/C	The Dutch population could improve their health with a consumption of 200 g of fish/week. Onaverage, 2.7 healthy years per 1000 people could be gained every year compared to the current consumption.	Hoekstra, 2013 [16]
	N/C	In Washington state, adult consumption of fish has net beneficial effects on health with a gain of approximately 5000 healthy years saved per year per 100000 people but the net health balance is negative for women of childbearing age.	Ponce, 2000 [59]
		Fruits and vegetables	
- Safety levels	N	Overall, consumption of 400 g of vegetable per day is a source of beneficial effects and does not expose consumers to a relevant risk due to nitrate intake.	EFSA, 2008 [61]
- **Endpoint**	N/C	An increase of one serving of vegetable and one of fruit per day could prevent 20000 cancer cases and create 10 cases due to pesticide consumption.	Reiss, 2012 [62]
		Soy protein	
- Safety levels	N	With a consumption of 25 g/day of soy protein, beneficial effects clearly outweigh the potential risk: reduction of CVD, breast and prostate cancer risk.	Watzl, 2012 [48]
		Trans fatty acids	
- Safety levels	N	The substitution of 5% of the energy intake from saturated fatty acids by 5% from carbohydrates brings beneficial and adverse health effects related to the same disease (CVD).	Verhagen, 2012 [64]
	N	A consumption of more than 2% of trans fatty acids within the total energy food intake improves CHD risk. A suggestion of an UL of 1% of trans fatty acids within the total energy food intake and a mention of %trans fatty acids of total fatty acids on food labeling is made.	AFSSA, 2005 [63]
• The manufacturing process is a source of risk(s) and benefit(s)			
		Milk treatment	
- Safety levels	N/M	Microbial benefit (reduction of microorganisms) from heat treatment outweighs potential risk due to the reduction of lysine and the inactivation of bioactive molecules.	Schütte, 2012 [72]
		Water treatment	
- DALY/QALY	C/M	Water treatment by ozonation decreases Cryptosporidium parvum infection but introduces chemical risk due to bromate. The overall health effect is a gain of one healthy year per million people annually.	Havelaar, 2003 [71]
		Vegetable transformation	
- Safety levels	N/M	The green bean process could be optimized to achieve the RDA without exceeding a microbial threshold of *G. stearothermophilus* by reducing waiting times and blanching duration and by increasing the sterilizing value or by decreasing the pH of the end product.	Rigaux, 2013 [73]
		Cookie process	

- Safety levels	N/C	Heat processing of cookies produces harmful compounds and modifies antioxidant activity depending on time, temperature, sugar and leavening agents. The risk-benefit ratio on compound quantity is lower at low temperature and small duration but the impact on health is not quantified.	Morales, 2009 [74]
		Fish culinary treatment	
- Safety levels	N/C	The comparison of three fish cooking practices (boiling, grilling and roasting) has demonstrated that grilling fish is the best fish treatment tooptimize nutritional benefit and limit chemical risk with a limitation of two meals/week.	Costa, 2013 [75]
		Acrylamide formation	
- Safety levels	N/C	The use of sodium bicarbonate to bake products should reduce acrylamide concentration but it could cause a nutritional loss and generate other unknown molecules.	Seal, 2008 [76]
	N/C	Reduction of acrylamide in potato and cereal-based products through measures applied in production is desirable.	Schütte, 2012 [72]
		Benzo(a)pyrene formation	
- Safety levels	C	The use of artificial smoked flavor or industrial smoking control is beneficial to reduce the risk of benzo(a)pyrene.	Schütte, 2012 [72]
• Diet is a source of risk(s) and benefit(s)			
		Breastfeeding	
- Safety levels	N/C/M	Benefit associated with breastfeeding outweighs risks due to contaminants and contributes to an efficient neurodevelopment, the creation of defense against infection and the reduction of obesity risk.	VKM, 2013 [13]
		Replacement of sugar by intense sweetener	
- Safety levels	N	Substitution of sugar by intense sweeteners in beverages decreases sugar consumption (too high for adolescents) but acesulfame K intake becomes close to the acceptable daily intake (ADI) and benzoic acid ADI could be exceeded.	Husoy, 2008 [66]
	N	The substitution of sugars by low calorie sweeteners in beverages is associated with benefit: it limits caries risk, prevents overweight and chronic disease risk.	Verhagen, 2012 [64]
	N	For young adults in the Netherlands, the substitution of 100% sugar by intense sweeteners in beverages is beneficial in caries prevention and body mass reduction and does not expose this population to potential risk.	Hendriksen, 2011 [65]
		Individual assessment of risk and benefit exposure	
- Safety levels	N/C	RIBEPEIX is software to assess risk-benefit associated with individual fish consumption according to chemical and nutritional safety reference values.	Domingo, 2007 [67,68]
	N/C	RIBEFOOD is an application available online to assess individual overall diet according to safety reference values. The software guides consumers to find food substitution to improve their risk-benefit balance.	Marti-Cid, 2008 [69]

• RBA is used in food formulation			
		Margarine fortification	
- DALY/QALY	N	Margarine fortification with plant sterol in the Netherlands should save 8 healthy years annually per 1000 people.	Hoekstra, 2013 [78]
		Bread supplementation	
- DALY/QALY	N	In the Netherlands, bread fortified with 140 µg/100 g folic acid should result in 11812 healthy years saved annually.	Hoekstra, 2008 [77]
	N	In the Netherlands, a small bread fortification of 70 µg/100 g folic acid should result in 7000 healthy years saved every year with a loss of 53 healthy years.	Verhagen, 2012 [64]

** Risk-benefit comparisons are sorted into three groups, 'safety levels', 'endpoint' and 'DALY/QALY' which are explained in section 3.1.3; ** N: Nutrition, C: Chemistry, M: Microbiology*

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