EXTERNAL SCIENTIFIC REPORT

APPROVED: 11/12/2019

doi:10.2903/sp.efsa.2019.EN-1768

RiskBenefit4EU – Partnering to strengthen Risk-Benefit Assessment within the EU using a holistic approach

Paula Alvito [a,b], Roberto Brazão [a], Paulo Carmona [c], Catarina Carvalho [d,f], Daniela Correia [f,g], Paulo Fernandes [a], Lea S. Jakobsen [e], Carla Lopes [f,g] , Carla Martins [a,b,h], Jeanne-Marie Membré [i], Sarogini Monteiro [c] , Pedro Nabais [c], Sofie T. Thomsen [e], Duarte Torres [d,f], Sara M. Pires [e], Géraldine Boué [i], Ricardo Assunção [a,b]

[a] Food and Nutrition Department, National Institute of Health Dr. Ricardo Jorge (INSA), Portugal; [b] CESAM, Centre for Environmental and Marine Studies, University of Aveiro, Portugal; [c] Economic and Food Safety Authority (ASAE), Portugal; [d] Faculty of Nutrition and Food Sciences, University of Porto, Portugal; [e] Division for Diet, Disease Prevention and Toxicology, The National Food Institute, Technical University of Denmark, Denmark; [f] EPIUnit – Institute of Public Health, University of Porto, Portugal; [g] Department of Public Health and Forensic Sciences, and Medical Education, Epidemiology Unit, Faculty of Medicine, University of Porto, Portugal; [h] National School of Public Health, NOVA University of Lisbon, Portugal; [i] SECALIM, INRA, Oniris, Université Bretagne Loire, France.

Abstract

"RiskBenefit4EU – Partnering to strengthen the risk-benefit assessment within EU using a holistic approach" was a knowledge transfer project funded by the European Food Safety Authority (EFSA) that integrated a multidisciplinary team from Portugal, Denmark and France. This project aimed to strengthen the EU capacity to assess risks and benefits associated with human food consumption, considering the fields of toxicology, microbiology and nutrition. To train the recipient partners from Portugal on Risk-Benefit Assessment (RBA), a capacity-building program was implemented, including three main activities: theoretical training on RBA concepts; hands-on training applying concepts to a case-study using methods and tools displayed; and scientific missions to provide advanced training in specific domains of RBA. The developed RBA strategy was applied to a case study focusing on the RBA of the consumption of cereal-based products by Portuguese young children. Risks due to aflatoxins, *Bacillus cereus*, sodium and free sugars, were evaluated, as well as the benefit of fibre intake. Five different scenarios of infant cereals and/or breakfast cereals consumption were considered, and the assessment showed that moving from the current consumption to the considered alternative scenarios would result in a gain of healthy-life years. The RiskBenefit4EU project applied a collaborative method to train a new team to perform RBAs of foods and face the challenge of cooperation between experts from different disciplines. During the process of capacity building, a movement from conceptual knowledge towards action was an essential step to effectively increase performance. The developed framework facilitated the case-study accomplishment and contributed to build a shared and harmonized RBA approach and culture. The suggested strategy can now be re-used to capacitate other teams in RBA,and can be considered as a basis to build upon.

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Key words: Risk-benefit assessment, food safety, capacity building, microbiology, toxicology, nutrition, cereal-based foods

Question number: EFSA-Q-2019-00756

Correspondence: paula.alvito@insa.min-saude.pt; ricardo.assuncao@insa.min-saude.pt

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Acknowledgements: This work was supported by the "RiskBenefit4EU – Partnering to strengthen the risk-benefit assessment within EU using a holistic approach" funded by EFSA Partnering Grants (Grant Agreement Number – GA/EFSA/AFSCO/2017/01 – GA02). All the consortium acknowledges the fruitful discussions and support from Sérgio Potier Rodeia and Hans Verhagen from EFSA regarding the RiskBenefit4EU project development and implementation. Ricardo Assunção, Paula Alvito and Carla Martins are grateful to the National Institute of Health Dr. Ricardo Jorge and to FCT/MCTES for the financial support to CESAM (UID/AMB/50017/2019), through national funds. Catarina Carvalho, Daniela Correia, Carla Lopes and Duarte Torres are grateful to the Faculty of Nutrition and Food Sciences of the University of Porto, to the EPIUnit – Institute of Public Health of the University of Porto (UID/DTP/04750/2013) and to the EEA Grants Program, Public Health Initiatives (PT06 - 000088SI3) that supported the National Food, Nutrition and Physical Activity Survey (IAN-AF 2015-2016).

Suggested citation: Paula Alvito, Roberto Brazão, Paulo Carmona, Catarina Carvalho, Daniela Correia, Paulo Fernandes, Lea S. Jakobsen, Carla Lopes, Carla Martins, Jeanne-Marie Membré, Sarogini Monteiro, Pedro Nabais, Sofie T. Thomsen, Duarte Torres, Sara M. Pires, Géraldine Boué, Ricardo Assunção. 2019. RiskBenefit4EU – Partnering to strengthen Risk-Benefit Assessment within the EU using a holistic. EFSA supporting publication 2019: EN-1768. 27 pp. doi:10.2903/sp.efsa.2019.EN-1768.

ISSN: 2397-8325

Summary

"RiskBenefit4EU – Partnering to strengthen risk-benefit assessment within EU using a holistic approach" (RiskBenefit4EU) was a project funded under EFSA's Partnering Grants that aimed to strengthen the capacity to assess and integrate food risks and benefits in the areas of microbiology, nutrition and toxicology through the development of a harmonized framework. RiskBenefit4EU was a knowledge transfer project that integrated a multidisciplinary team from Portugal, Denmark and France. The specific objectives of RiskBenefit4EU were 1) to build capacity among recipient partners on RBA of foods; 2) to develop RBA tools that can estimate the overall health effects of foods, food ingredients and diets; 3) to develop a harmonized framework for RBA that can be applied to data from different countries; 4) to validate the generated framework through the application on a case study; and 5) to disseminate and promote the harmonized framework to potential EU users. Project activities of RiskBenefit4EU included three key components: training (transferring and exchanging knowledge between project partners); research (framework development and its application to a case study); and dissemination and promotion (through web-site and flyer dissemination, publications, and international conference and workshop organisation). Results of the capacity building experience included i) the creation of a multidisciplinary team, ii) the harmonization of RBA concepts among the partners, iii) the development of a stepwise approach, and iv) trainings on the key steps of RBA methodology. The development of a stepwise approach, a crucial step to support the analysis of the practical case study, considered four main steps, addressing the following key points: i) definition of a general frame and scope, including the problem definition and the scenario identification; ii) selection of health effects, through identification and prioritization; iii) risk and benefit quantification, including individual assessment of risks and benefits and health impact quantification; and, iv) comparison of scenarios, interpretation of results and their communication. Training activities were organized to follow this stepwise approach, in order to provide all skills and tools required to carry out a RBA. The development of the training activities was a necessary opportunity to work on a common RBA approach between INRA and DTU (as capacity builders), to transmit this shared method to new Portuguese teams, and thus contribute to the harmonization of the RBA method at the international scale. Under the RiskBenefit4EU project, a case study on the RBA of cereal-based foods usually consumed in Portugal by young children was implemented. The case study aimed to assess risks and benefits associated with the consumption of cereal-based products by Portuguese young children, comparing the current situation (reference scenario) to alternative scenarios, including substitution of foods. This case study followed the harmonized framework developed under RiskBenefit4EU and included at least one component of each discipline, i.e. toxicology (aflatoxins), microbiology (*Bacillus cereus*) and nutrition (fibre, sodium and free sugars). Under this project, important learned lessons included: the importance of creating a multidisciplinary team, collaborating and sharing a common language; to define a capacity building strategy; to develop training activities harmonizing the knowledge under RBA; and to establish a stepwise approach guiding the process of RBA.

This report includes a general introduction on RBA of foods, a description of the project, including related-sustainability and dissemination activities, the developed harmonized RBA framework, and its application on a case study on cereal-based foods consumed by Portuguese children. The lessons learned from the RiskBenefit4EU are presented, as are the group's suggestions to follow-up activities to capacitate new teams to conduct RBA of foods.

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Abbreviations

AFB_1	Aflatoxin B_1
aw	Water activity
B. cereus	*Bacillus cereus*
BC	Breakfast Cereals
BENERIS	Benefit-Risk Assessment for Food: an Iterative Value-of-Information Approach
BEPRARIBEAN	Best PRActices of RIsk-BEnefit Analysis
BRAFO	Benefit-Risk Analysis of Foods
CVD	Cardiovascular Diseases
DALYs	Disability-Adjusted Life Years
DON	Deoxynivalenol
DRVs	Dietary Reference Values
EU	European Union
EFSA	European Food Safety Authority
FAO/WHO	Food and Agriculture Organisation of the United Nations / World Health Organisation
GBD	Global Burden of Disease
HCC	Hepatocellular Carcinoma
IARC/WHO	International Agency for Research on Cancer / World Health Organisation
IC	Infant Cereals
LMF	Low Moisture Food
OTA	Ochratoxin A
PIF	Potential Impact Fraction
QALIBRA	Quality of Life – Integrated Benefit and Risk Analysis
RBA	Risk-Benefit Assessment
RI	Recommended Intake
RR	Relative Risk
STSM	Short-Term Scientific Mission
T2D	Type 2 Diabetes
TEI	Total Energy Intake
UL	Upper Limit
WHO	World Health Organisation

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1. Risk-benefit assessment of foods in the EU

Human diet may present both potential risks and benefits to consumers' health. Beneficial and adverse health effects may occur concurrently due to the intake of a single food item or a single food component. Consequently, any policy action directed at the adverse effects may also affect potential beneficial effects, and vice versa. Thus, estimating the overall impact of foods and diets is of interest for food authorities developing food policy and consumer advice, for businesses developing new food products, and for consumers considering dietary changes (Hart et al., 2013). Risk-benefit assessment (RBA), a relatively new discipline, intends to estimate in a structured approach human benefits and risks associated with the exposure (or lack of exposure) to a particular food, food component or diet, and to integrate them in comparable measures (Boué et al., 2017; Tijhuis et al., 2012a).

In the last years, a number of European projects within RBA of foods have been conducted. BEPRARIBEAN (Best Practices for Risk-Benefit Analysis: experience from out of food into food) project was focused on state of arts in benefit–risk analysis of various scientific fields (Verhagen et al., 2012): Medicine (Luteijn et al., 2012), Environmental Health (Pohjola et al., 2012), Food Microbiology (Magnússon et al., 2012), Economics and Marketing-Finance (Kalogeras et al., 2012), Consumer Perception (Ueland et al., 2012), and Food and Nutrition (Tijhuis et al., 2012a). Good practices to be established in risk-benefit analysis were concluded in (Tijhuis et al., 2012b). BRAFO (Benefit-Risk Analysis of Foods), a European Commission funded project, proposed a framework for RBA of foods or changes in diet that present both potential risks and potential benefits to consumers (Hoekstra et al., 2012). QALIBRA (Quality of Life – Integrated Benefit and Risk Analysis), another EU project, provided methods for quantitative assessment that integrate risks and benefits of dietary change into a single measure of net health impact (e.g. Disability-Adjusted Life Years, DALYs), allowing for the quantification of the associated uncertainties (Hart et al., 2013). BENERIS (Benefit-Risk Assessment for Food: an Iterative Value-of-Information Approach) aimed to create a framework for handling complicated benefit–risk situations, and apply it for analysis of the benefits and risks of certain foods (Tuomisto, 2013). These projects involved the development of methods and modelling frameworks and have led to considerable progress in the risk-benefit area.

However, some challenges remained and new became apparent. These include the integration of full-interdisciplinary approaches considering nutritional, microbiological and chemical components, as well as the use of probabilistic approaches (Boué et al., 2017). Indeed, from the developed RBA studies, only a few that included microbiological, chemical and nutritional risk-benefit factors, and generally these have been carried out in a semi-quantitative and deterministic manner. Moreover, within the EU, RBA methodologies are far from being well established, representing a research gap needing attention from academics, researchers and policy makers (Assunção et al., 2019; Eneroth et al., 2017).

2. RiskBenefit4EU – Project Description

2.1. Aims

RiskBenefit4EU aimed to strengthen the EU capacity to assess and integrate food risks and benefits in the areas of microbiology, nutrition and toxicology through the development of a harmonized framework.

The specific objectives of RiskBenefit4EU project were 1) to capacitate recipient partners on food RBA; 2) to develop RBA tools that can estimate the overall health effects of foods, food ingredients and diets; 3) to develop a harmonized framework for RBA that can be applied to data from different countries; 4) to validate the generated framework through the application to a case study; and 5) to disseminate and promote the harmonized framework to potential EU users. RiskBenefit4EU project gathered the full potential of interdisciplinary research in the different domains of RBA.

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2.2. Structure and tasks

RiskBenefit4EU was coordinated by the National Institute of Health Dr. Ricardo Jorge of Portugal (INSA) and involved two other Portuguese institutions (University of Porto (UP), and Economic and Food Safety Authority (ASAE), the Danish National Food Institute, Technical University of Denmark (DTU Food), and the French National Institute for Agricultural Research (France, INRA).

RiskBenefit4EU included three main activities: training (transfer and exchange knowledge); research (capacity building framework development and its application to a case study); and dissemination and promotion (through web-site and flyer dissemination, publications and international conference and workshop organisation). These activities were organized in five different tasks, as summarized in Figure 1.

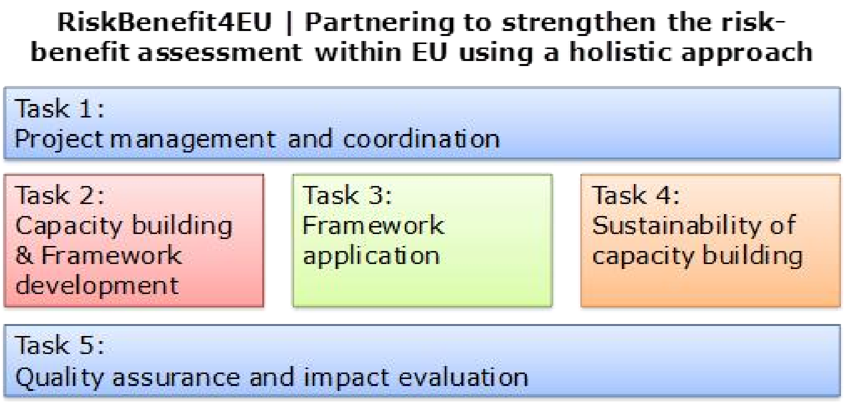

Figure 1. Tasks organisation of RiskBenefit4EU project.

Task 1 focused on management and the associated coordination activities. This task was led by INSA, in close collaboration with all the partners of the consortium and included the organisation of project meetings, training activities, elaboration of mid-term and final report and the financial management.

Task 2 corresponded to the main capacity building activities and framework development and was led by INRA in close collaboration with DTU. This task included knowledge transfer through i) the capacity building of all partners for the methodologies needed for RBA that integrates scientific knowledge on nutrition, toxicology and microbiology, using common health metrics and ii) the development of the harmonized framework for RBA through a holistic approach.

Task 3 was mainly dedicated to the application of the generated framework to a case study. This task was led by DTU in close collaboration with INRA. A case study on consumption of cereal-based foods in children in Portugal, gathering already obtained data, was used to validate the RBA framework, including the three components – microbiological, nutritional and toxicological.

Task 4 was dedicated to the sustainability of the generated capacity building and dissemination activities and was led by INSA. This task was achieved through different activities including i) creation of a project website and flyer; ii) the publication of the main achievements of the project in national and international peer-reviewed journals, in open-access; iii) the organisation of an international conference and workshop, to spread and disseminate the generated framework, to present the main results, and to discuss with different stakeholders future perspectives under RBA; and iv) the planning of future training activities to capacitate other institutions for the RBA using the harmonized framework.

Task 5 dealt with the quality assurance and the impact evaluation of the main activities developed under RiskBenefit4EU. Task 5 was led by UP, in close collaboration with other partners of the consortium. Under this task, questionnaires were created to measure i) the impact of training activities and to

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improve future training activities (under RiskBenefit4EU project and other future initiatives as peer-review articles, engagement of other partners' work and future collaborative projects), ii) short-term scientific missions (STSM) and iii) international conference evaluation.

In addition, during the course of the project six checkpoints were considered (deliverables D1-D6) to ensure the quality and attainment of the specific objectives of the project:

- Action Plan (Annex A, D1)
- Impact evaluation Questionnaires (Annex B, D2),
- Training activities 1 (Annex C, D3) and 2 (Annex D, D4)
- Framework (Figure 3)
- Case-study global evaluation (Annex E, D5)
- International conference (Annex F, D6)

3. RiskBenefit4EU – Main activities: their impact and dissemination

RiskBenefit4EU project promoted a close collaboration among the different institutions involved in the project. At the national level, innovation and research capacities of the Portuguese institutions in the area of risk-benefit assessment were promoted and refined, encouraging the establishment of a collaborative network to develop future projects. At international level, a new framework on RBA on foods was developed and applied to a specific case study, in a close collaboration between recipient partners and capacity builders.

3.1. Activities and outputs

To ensure the capacity building and knowledge transfer under RiskBenefit4EU, the consortium developed several activities (associated links at Appendix A):

1) An action Plan;
2) A flyer (Annex G) presenting the project and a website (https://riskbenefit4eu.wordpress.com/) gathering all outputs generated under the project with documents and materials that could be helpful for teams starting in the area of risk-benefit assessment;
3) The organisation of an international conference (Annex F) and workshop (Annex H), disseminating obtained results, promoting the discussion regarding risk-benefit assessment and gathering critical mass thinking in this area of expertise;
4) The publication of open-access international (Annex I) and national (Annex J) publications, ensuring a free access to main outputs of the project, namely the developed framework and the settled case study;
5) Oral communications (Appendix B) and posters (Appendix C) in national and international symposium, congress, conferences;
6) Two training activities organized by capacity builders for project members (described in detail at topic 4, Annexes C and D), including theoretical and hands-on sessions;
7) Nine short-term scientific missions (STSM) from Portuguese institutions to capacity builders' institutions, for hands-on training on specific domains in RBA;
8) Quality and impact assessment questionnaires for training, STSMs and the international conference (Annex B).

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3.2. Dissemination activities

The RiskBenefit4EU's website included an overview of the project description, the publications produced under RiskBenefit4EU, news related with the project, and contact information.

Two international events were organized under RiskBenefit4EU. The international workshop "Workshop on risk-benefit assessment of foods" was held on 21st and 23rd May 2018, in Lisbon, Portugal (Annex H). It aimed to discuss the importance of risk-benefit assessment in the area of food safety and nutrition, to provide an overview of Portuguese activities in this area of research, and to outline future perspectives on this domain. This event included keynote lectures by national and international scientists presenting different perspectives under RBA. EFSA also participated on the workshop through two presentations, "Risk-benefit assessment in the EU perspective" and "EFSA's guidance on uncertainty in scientific risk assessment", presented by Hans Verhagen. The event gathered more than one hundred participants from Portugal and abroad, interested in the different disciplines that compose RBA, including microbiology, toxicology and nutrition. A book of abstracts was prepared and made available at http://hdl.handle.net/10400.18/5560.

The international Conference "3rd International Conference on Food Contaminants (ICFC 2019)- Challenges on Risk Assessment" was held on 26th and 27th September 2019, in Aveiro (Portugal) (Annex F). This conference presented and discussed new perspectives on risk assessment of foods, human exposure to chemical contaminants, and developments on risk-benefit assessment studies. This multidisciplinary congress provided a forum for both internationally established and young researchers to exchange advanced knowledge on Food Contaminants and Human Health, with a special session dedicated to the risk-benefit assessment of foods. The event gathered 130 participants from 18 different countries. A book of abstracts is available at https://riskbenefit4eu.files.wordpress.com/2019/10/livro-v2_07082019_final.pdf.

3.3. Impact assessment

To evaluate the quality and the impact of the training activities, STSM, and conference organisation, several questionnaires were developed and applied.

Generally, the two training sessions and the STSM were perceived as relevant, appropriate, useful and productive by large majority of participants. Most of them were satisfied or very satisfied with the structure and logistics of the training sessions and the STSM.

Results of the ICFC2019 conference's evaluation based on 42 complete responses to questionnaire showed an average satisfaction of 80 out of 100 on aspects related to the event's organisation and to its scientific content.

4. Capacity building in RBA of foods

The capacity-building approach was developed to answer to the following question: "What are the competences that a team needs to conduct a national RBA project?". It included two main activities: theoretical training, and hands-on training through the implementation of a case-study during STSMs to partner institutions.

As summarized in Figure 2, performing a RBA may require a large range of expertise including: food safety, exposure assessment, risk assessment in toxicology, microbiology and nutrition, epidemiology, dietary assessment, health impact assessment and data analysis (EFSA Scientific Committee, 2010; Tijhuis et al., 2012a). In addition, RBA requires also quantitative skills such as modelling, statistics and

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uncertainty analysis. All these constitute important fields that should be covered in the capacity-building strategy in order to establish the basis to perform a RBA.

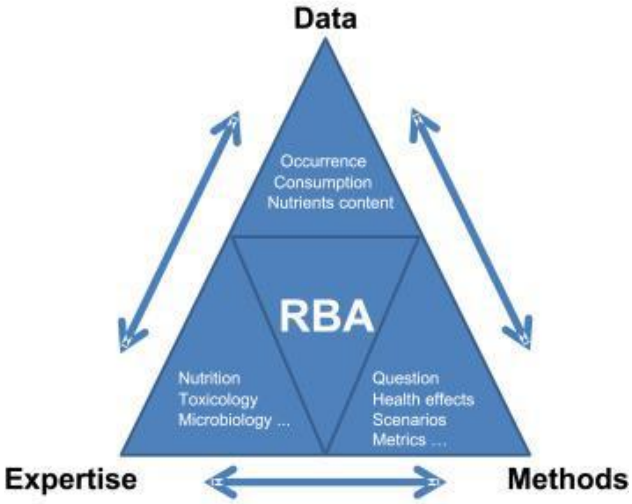

Figure 2. Scientific expertise using data from different domains, using different methods to promote the development of new knowledge on risk-benefit assessment (Assunção et al., 2019).

4.1. Creation of a multidisciplinary team

Expertise in RBA and each individual field of research were joined within the RiskBenefit4EUproject by creating a multidisciplinary and complementary team. The project integrated participants from different National institutions. The list of participants and associated institutions is presented in Appendix D.

INSA brought expertise in risk assessment in toxicology and microbiology, occurrence data collection and food safety; UP in nutrition, epidemiology, dietary assessment, data analysis, food science and technology; and ASAE in data collection of chemicals and pathogens in foods.

4.2. Organisation of RBA trainings

Training on RBA must include theoretical training in the various disciplines, as well as practical training on modelling and data analysis. Detailed programmes of the two one-week training courses conducted for project members can be found in Annex C and D. The first training focused on transfer of knowledge from experienced researchers in RBA (DTU and INRA) to the Portuguese project partners. It integrated topics on nutrition, toxicology and microbiology, as well as on modelling methodologies and estimation of common health metrics. The second training was dedicated to the application of these concepts to the project's case study in order to guide all partners in conducting the RBA of the case study: definition of a protocol (planning phase) and organize the assessment (doing phase).

Learning objectives and main topics covered during the two trainings are summarized on Table 1, and a detailed version available in Annex K.

Table 1: Learning objectives and main topics covered during the RiskBenefit4EU trainings.

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	Learning objectives	Main topics and activities
Training 1 **22nd – 25th** **May 2018**	Be able to perform a qualitative Risk-Benefit Assessment (RBA); To capacitate all partners for the methodologies of RBA, integrating scientific knowledge on nutrition, toxicology and microbiology, using common health metrics (task 2.1.); To develop a harmonized framework for RBA through a holistic approach (task 2.2.).	Brainstorming sessions on concepts: - What is Risk and what is Benefit? - What is Variability? - What is Uncertainty? - What is Health? Individual risk assessment in: - Toxicology - Nutrition - Microbiology RBA Stepwise approach; Connection with the RiskBenefit4EU case study.
Training 2 **8th – 12th** **October, 2018**	Be able to apply main RBA concepts to the project case study and development of a protocol to perform the RBA case study; To guide all partners in conducting the RBA of the case study: definition of a protocol (planning phase) and organize the assessment (doing phase); To refine and validate the generated framework through the application to a case study; To develop RBA tools that can estimate the overall health effects of foods, food ingredients and diets.	Study of RBA examples: - Work on two RBA papers and presentation - Artificial RBA exercise Concepts reminded: - Metric of comparison - Uncertainty in RBA RBA Protocol definition: - Introduction to a stepwise approach - Application to the case study Working groups to progress on the case study.

4.3. Harmonization of concepts between partners

There is no official consensus on the definitions used in RBA. Nevertheless, sharing a common language between team partners and among the multidisciplinary team, and to harmonizing concepts and terminologies is key. RiskBenefit4EU's project partners brainstormed and agreed on the meaning and definition of the following terms: hazard, health effect, adverse health effect, beneficial health effect, risk, benefit, health and health impact (Table 2).

Table 2: Key terms and definitions agreed among team members of the RiskBenefit4EU project.

Terms to be defined	Definition agreed by team members	Source
Hazard	A biological, chemical or physical agent in, or condition of, food with the potential to cause an adverse health effect upon exposure.	Adapted from Codex Alimentarius Commission (Joint FAO/WHO Codex Alimentarius Commission and FAO/WHO, 2015), IPCS (IPCS, 2004), OECD (OECD, 2003)
Health effect	A change in morphology in the human body, or physiology, growth, development, reproduction or life span of humans that results in a change of human health status.	Adapted from FAO/WHO (FAO/WHO, 2006), modified from IPCS (IPCS, 2004)
Adverse health effect	A change in the health, growth, behaviour or development of an organism that impairs its ability to develop or survive. It implies that the	Adapted from EFSA glossary (https://www.efsa.europa.eu/en/glossary-taxonomy-terms)

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	health effect reduces quality of life or causes a loss of life.	
Beneficial health effect	Implies that the health effect increases quality of life, prevents a reduction in quality of life, or prevents loss of life (often equivalent to the prevention of an adverse health effect).	
Risk	A function of the probability of an adverse health effect and the severity of that effect, consequential to exposure to a hazard in food or consumption of a food or diet.	Adapted from IPCS (IPCS, 2004), OECD (OECD, 2003)
Benefit	A function of the probability of a beneficial health effect and the consequences of that effect and/or the probability of a reduction of an adverse health effect, consequential to exposure to a compound in food or consumption of a food or diet.	Adapted from the definition of risk by Codex Alimentarius Commission (Joint FAO/WHO Codex Alimentarius Commission and FAO/WHO, 2015)
Health	A state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.	Adapted from Preamble to the Constitution of WHO (WHO, 1948)
Health impact	The magnitude of the overall difference in health status due to a change in exposure to a food compound or consumption of a food or diet, which may be expressed in a composite health metric, but can also be a combination of metrics.	

4.4. Harmonized Framework on risk-benefit assessment

A harmonized RBA framework was developed by INRA and DTU and used to organize training activities, and to structure the case study performed of the Portuguese team (Figure 3). This approach was based on the main steps already identified by Boué et al. (Boué, 2017; Boué et al., 2017). The approach considers four main steps, addressing the following key points: i) definition of a general frame and scope, including the problem definition and the scenario identification; ii) selection of the health effects, through identification and prioritization; iii) risk and benefit quantification, including individual assessment of risks and benefits and health impact quantification; and, iv) comparison of scenarios and interpretation of results and their communication. Training activities were organized to follow this stepwise approach, in order to provide all skills and tools required to carry out a RBA.

This stepwise approach consists of six steps. First, the problem definition (step 1/6) should state the scope of assessment and the research question to be answered, including the population of interest (general or a sub-group population), the level of aggregation (food component, food or diet) and the type of assessment (qualitative or quantitative) (Boobis et al., 2013; Nauta et al., 2018). The second step is the scenarios definition (step 2/6), which is a narrative description of hypothetical or real situations. The following step in an RBA of foods is the selection of the health effects of interest (step 3/6). In the step of individual assessment of risks and benefits (step 4/6), the chosen approach (qualitative, semi-quantitative or quantitative) is related to the type of questions raised and available data, usually performed in the previous steps of RBA, as schematically presented in Figure 3. If the available data are scarce or if the biological mechanisms are not comprehensively characterized, a qualitative or semi-quantitative approach should be performed. On the contrary, if enough and robust data are available, a quantitative assessment is desirable, through application of mathematical modelling to quantify the risks and benefits. For the quantitative assessment, two major approaches could be applied: i) the bottom-up approach, which is similar to the risk assessment approach, estimating the

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incidence of disease due to an exposure via dose-response models, usually applied for microbiological and chemical hazards, or ii) the top-down approach, that starts from the incidence of a certain disease due to an exposure, usually applied for nutrients and nutritional factors and also for chemical hazards (Nauta et al., 2018). After assessing all risks and benefits selected for the RBA scenario, the next step is the quantification of the health impacts in a common metric (step 5/6), which will enable the comparison. In the final step, results of the RBA are summarized in order to compare scenarios (step 6/6).

This framework was refined during training developments and then validated through with the case study performance.

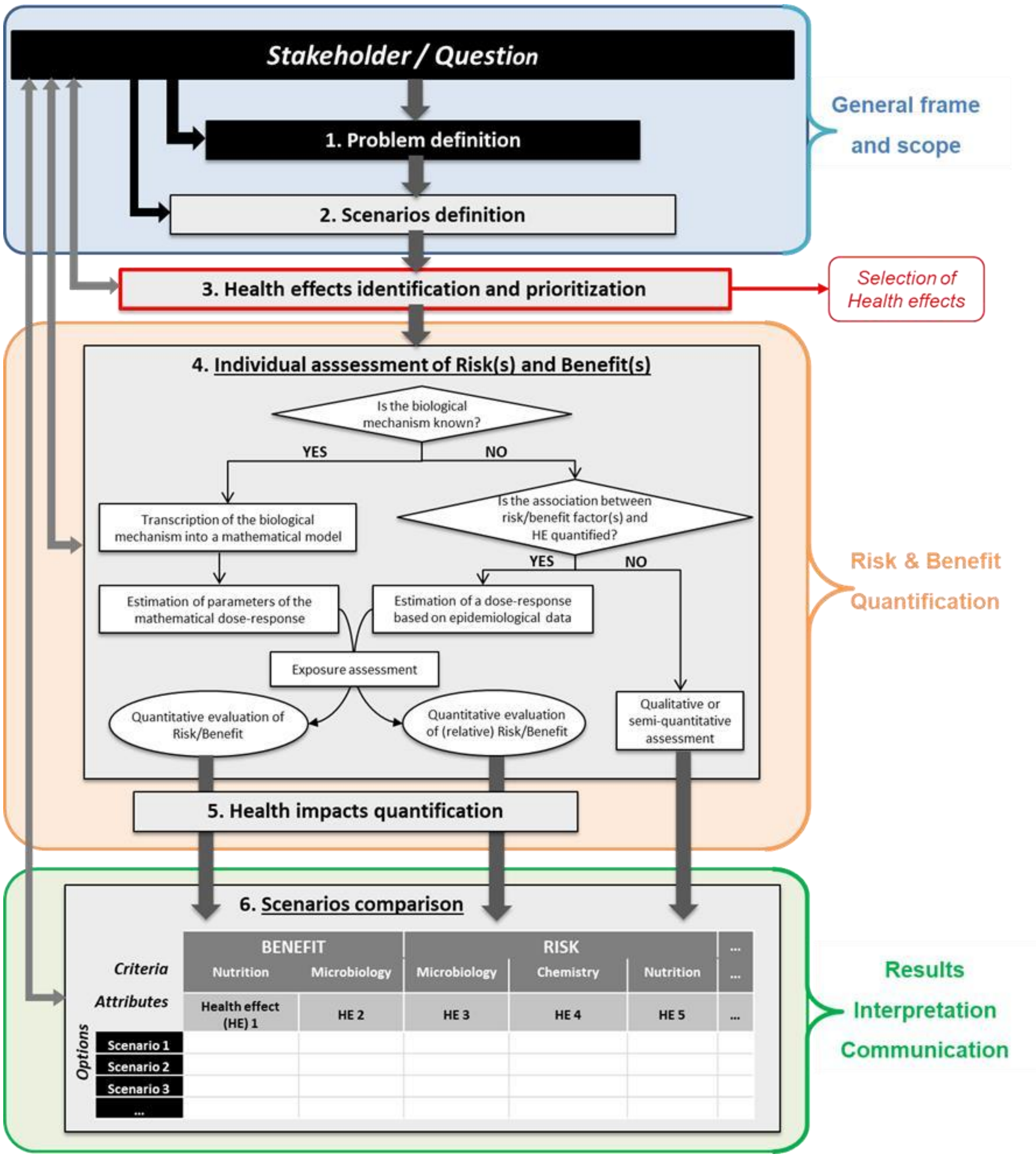

Figure 3. Flowchart of RBA stepwise approach followed under RiskBenefit4EU activities (adapted from (Assunção et al., 2019; Boué, 2017).

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4.5. Main recommendations from the capacity building experience

We summarized the lessons learned from the capacity building experience, so that they can be considered in future initiatives to optimize RBA knowledge transfer. They are a reflection of the success of the activities of the projects, and of the challenges that were faced and surpassed along the way. Key points are summarized in Table 3.

Table 3: Main recommendations from the capacity building experience (Assunção et al, 2019).

Main lessons learned ***from the capacity-building experience***	**Recommendations** ***for future RBA training initiative***
A one-week face-to-face training was valuable to enable active participation and facilitate discussions	Dedicate one face-to-face week with all participants
Training organized by researchers experienced in RBA to: avoid starting from scratch, build on previous work and share and improve a harmonized Risk-Benefit approach at the international scale	Build a team including experienced researchers in RBA and a multidisciplinary team of experts eager to perform the RBA case study was considered as a valuable partnership
Sessions on basics concepts is necessary to create a common scientific culture and understanding of all individual fields of research and methods used in RBA	Allow time for training on basic concepts used in RBA
Organisation of brainstorming sessions on RBA language was worthwhile because it made participants create a common understanding and language which is necessary to when work on a RBA case study	Define a shared language through brainstorming sessions to create a consensus on terminologies on: hazard, health effect, adverse health effect, beneficial health effect, risk, benefit, health impact and health
Introduce and illustrate the RBA stepwise approach with examples of previous RBA performed was an efficient way to become familiar with this complex exercise	Use previous RBA case studies to illustrate and make less abstract the RBA stepwise approach
Particular attention should be dedicated to the consideration of uncertainty and variability in RBA because it is a crucial point that needs to be considered at every stage of the RBA	Introduce concepts of variability and uncertainty early in the week and pay attention to these concepts during following sessions

5. Case study on cereal-based foods consumed by Portuguese children

Under task 3 – "Framework application", a case study on the RBA of consumption cereal-based foods by children in Portugal, gathering already obtained data, was used to validate the RBA framework developed under RiskBenefit4EU and including components of the three main areas: microbiology, nutrition and toxicology.

5.1. Background

Cereal-based foods, including breakfast and infant cereals, are among the first solid foods to be introduced in children's diet (Amezdroz et al., 2015; Rodrigues et al., 2007), constituting an important food group of their diet and contributing for an optimal health (Collins et al., 2010; Schwartz et al., 2008). Cereal-based foods are usually considered a source of essential macronutrients and micronutrients such as vitamins and minerals. Among these, the intake of sodium and free sugars is associated with some deleterious health effects and, in contrast, the intake of fibre is associated with health benefits. High sodium intake is linked with increased blood pressure among adults and children and also with higher risk of cardiovascular diseases in adults (WHO, 2012). Regarding free sugars, moderate quality evidence suggests that reduced intake of free sugars is associated with reduced body weight in children. WHO strongly recommends a reduced intake of free sugars, up to 10% of total

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energy intake, and sets a conditional recommendation to further reduce the consumption to below 5% of total energy intake (WHO, 2015).

Dietary fibre intake is important in childhood and may contribute to significant immediate and future health benefits, including promotion of normal gastrointestinal function, especially laxation; prevention and treatment of childhood obesity; maintenance of normal blood glucose and lipid values, as well as normal blood pressure; and risk reduction for future chronic diseases, such as cancer, cardiovascular disease (CVD), and type 2 diabetes (T2D). Children with higher intakes of dietary fibre also tend to consume diets that are more nutrient dense and they are more likely to meet recommended daily intakes for key nutrients (Anderson et al., 2009).

Besides the nutritional components, some of them beneficial, cereals can also present potential chemical risks, e.g. mycotoxins. Mycotoxins are widely occurring secondary metabolites of plant pathogenic fungi in foods and feeds. Some of the main health toxic effects of mycotoxins include liver cancer (hepatocellular carcinoma; HCC) (aflatoxins), oesophageal cancer and neural tube defects (fumonisins), immunotoxicity and gastroenteritis (DON, deoxynivalenol and other trichothecenes), and renal diseases (OTA, ochratoxin A) (Wu et al., 2014). The most toxic mycotoxins are aflatoxins, which can occur in host crops infected by some species of *Aspergillus* spp. (Wu et al., 2014). Aflatoxins are genotoxic, carcinogenic and immunosuppressive substances, and cause both acute and chronic toxicity. HCC is the third leading cause of cancer deaths worldwide (WHO, 2008) and it was estimated to have been responsible for nearly 746,000 deaths in 2012 (9.1% of all cancer deaths that year) (International Agency for Research on Cancer/World Health Organization (IARC/WHO), 2016). HCC cases were due to different causes, e.g. hepatitis B and C and alcohol use, among other causes.

In Portugal, previous studies have demonstrated the occurrence of aflatoxins in food products consumed by the Portuguese population, including those usually consumed by vulnerable groups as young children (Alvito et al., 2010; Martins et al., 2018; Rodrigues et al., 2012).Previous studies estimated aflatoxins exposure through breakfast cereals (Assunção et al., 2015), infant cereals and biscuits (Assunção et al., 2018) available in the market of the capital region, suggesting exposure levels that may lead to adverse health effects. Cereal-based foods may also be contaminated with microbiological hazards (e.g. *Bacillus cereus*). Breakfast cereals and infant cereals can be considered low moisture foods (LMF), which are mainly characterized by their low water activity (aw). This contributes to a long shelf life, and also to the public perception that these foods were not of concern from a microbiological food safety perspective. Despite the fact that organisms cannot easily grow in LMF, once contamination occurs they can survive for long periods of time and, depending on the organism, can cause illness due to their low infectious dose (e.g. *Salmonella*) or possible subsequent temperature abuse that allows the organism to grow (e.g. *Bacillus cereus*) (Food and Agriculture Organization of the United Nations (FAO/WHO), 2014). *B. cereus* is a well-recognised foodborne microorganism that produces two kinds of illness: a diarrhoeal type and an emetic type (Duc et al., 2005). According to "Ranking of Low Moisture Foods in Support of Microbiological Risk Management" report, *B. cereus* was the most frequently investigated microbial hazard in cereals and grains for burden of illness, prevalence and intervention information (Food and Agriculture Organization of the United Nations (FAO/WHO), 2014). The same report also highlighted that *B. cereus* was the cause of 44/72 outbreaks (31 of them due to rice products) from different regions of the United States, Australia, New Zealand, Asia and Europe. In one of the reported outbreaks, infant cereals were the involved food products (Duc et al., 2005). A FAO/WHO meta-analysis reported a median prevalence of *B. cereus* of 41.7% in dry cereals and cereal products.

Regarding the consumption of cereal-based foods by children in Portugal, some points should be highlighted: 1) young children (6 to 35 months) eat cereals not originally intended to be eaten by that age group; 2) the regulation of these products, as breakfast cereals, was not designed and established considering the specific vulnerability of this population group; and 3) other cereal-based products as infant cereals, in principle, are most adequate and presenting available regulation, developed taking into consideration the age group of the target consumers.

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5.2. Main methodologies

The risk-benefit question defined was: *What would be the health impact of replacing the consumption of breakfast cereals by infant cereals usually consumed by the Portuguese children aged between 6 and 35 months, comparing to the current situation and considering aflatoxins,* Bacillus cereus*, fibre, sodium and free sugars?*

Five different scenarios of infant cereals (IC) and breakfast cereals (BC) consumption were considered (Table 4).

Table 4: Summary of scenarios considered in the risk-benefit assessment of cereal-based products consumed by the Portuguese children.

# Scenario	Description [1]
Reference	Current cereal-based products consumption
1	100% Breakfast cereals consumption (substitution of IC by BC) [2]
2	100% Infant cereals consumption (substitution of BC by IC) [2]
3	Best BC: all cereals consumption was replaced by a specific breakfast cereals product [3]
4	Worst IC: all cereals consumption was replaced by a specific infant cereals product [3]

[1]Amount consumed: substitution preserved the same amount of calories (isocaloric); [2]Randomly selected based on the distribution of the consumption of these products in the population; [3]Products defined using a score, based on three nutritional components [fibre (+), sodium (-) and free sugars (-)]. Best BC → Highest score among BC; Worst IC → Lowest score among IC.

To identify relevant food components, health effects and their prioritization to be considered in the assessment, a two-step literature search was preformed: 1) "Food-compound" literature search, to identify the components of interest for the food products considered; 2) "Compound-health effect" literature search, to identify the health effects associated to a specific food component. Table 5 summarizes the food components and the health effects considered in the RBA.

Table 5: Food components and health effects considered under the risk-benefit assessment.

	Food components	Type of analysis	Health effects
Nutrition	Fibre	Quantitative	Type 2 Diabetes mellitus Cardiovascular diseases
	Sodium	Semi-quantitative	
	Free sugars		
Toxicology	Aflatoxins (AFB_1)	Quantitative	Hepatocellular carcinoma
Microbiology	*Bacillus cereus*	Quantitative	Gastrointestinal disease

Different data sources were used for the RBA, namely: MYCOMIX data for the mycotoxins occurrence, ASAE data for the microbiological contaminants, IAN-AF for the food consumption data, global burden of disease (GBD) results tool and already published data from different sources.

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SPADE software (Dekkers et al., 2014) was used to estimate the intake distribution of total fibre, sodium and free sugars, for each scenario. For risk and benefit characterization, risk ratio (RR) and Potential Impact Fraction (PIF) were calculated. To integrate risks and benefits, and based on PIF, the disability-adjusted life years (DALY) were estimated. DALYs that could be gained or lost by changing from the current situation to alternative scenarios were expressed in terms of change in number of DALY. In addition to the deterministic approach, probabilistic modelling was developed to perform the calculations. Deterministic approach considered a fixed mean value of distributions for all the estimates. In contrast, probabilistic approach used probabilistic distributions to represent different variables. @Risk® software for Microsoft Excel version 6 (Palisade Corporation, USA) was used for this purpose.

For the semi-quantitative analysis, for each scenario, the prevalence of inadequate intake of sodium and free sugars was estimated using SPADE software (Dekkers et al., 2014). The dietary reference values (DRVs) used as cut-off values were: an upper limit (UL) of 1500 mg/day for sodium (Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium, 2011); and a recommended intake (RI) of 5% and 10% of total energy intake (TEI) for free sugars (WHO, 2015).

5.3. Main results

We estimated that levels of exposure to *B. cereus* in all scenarios was lower than the infectious dose. Consequently, *B. cereus* was not further considered in the assessment. Remaining components were included in the assessment. Moving from the current consumption to the "100% BC" and "Best BC" scenarios and due to an increase of the fibre intake and a decrease in the exposure to aflatoxins, a reduction of Type 2 Diabetes Mellitus, Cardiovascular Diseases and Hepatocellular carcinoma cases would be expected, and consequently preventing DALYs, especially in the "Best BC" scenario (Table 6). It is expected a ΔDALY of 0.143 per 100000 individuals in the "100% IC" scenario and 0.877 in the "Worst IC" scenario. On the other hand, scenarios "100% BC" and "Best BC" would present negative ΔDALY, representing a decrease of the expected years living with disability. Hence, the ΔDALY per 100000 individuals obtained for "100% BC" and "Best BC" scenarios are -0.486 and -4.473, respectively. Details on the obtained results will be presented in a scientific paper.

Table 6: Change in DALYs resulting from the integration of risks and benefits considered in the assessment.

	100% BC	**100% IC**	**Best BC**	**Worst IC**
ΔDALY	**-0.486**	0.143	**-4.473**	0.877

BC = Breakfast cereals; IC = infant cereals

Results of the semi-quantitative analysis for sodium and free sugars in the reference scenario indicate that 25% of Portuguese children aged between 6 and 35 months have an inadequate sodium intake. This prevalence was slightly higher for the 100% BC and Worst IC alternative scenarios. On the contrary, the lowest sodium intake would be achieved with the Best BC scenario, with 23% of inadequacy prevalence. Currently, 29% of Portuguese infants and young children have an intake of free sugars higher than 10% of TEI. Once again, the Best BC scenario represents the better alternative, with a prevalence of inadequate intake of 16%. Moreover, the Worst IC scenario presented lower estimated

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prevalence of inadequacy 28% than the Reference scenario. All these results for the prevalence of inadequate intake of free sugars considerably increase if the recommended intake of 5% TEI is considered as cut-off.

5.4. Discussion and main conclusions

The substitution scenarios considered would lead to a gain in healthy-life years, namely the substitution of the current consumption by "100% BC" and "Best BC". The "Best BC" scenario could represent an improvement also in the percentage of the inadequate intake of sodium and free sugars and a slight improvement related with aflatoxins exposure. However, high content in fibre and low in sodium and free sugars, could lead to a low palatability of these cereal-based products and consequently a low adherence by the consumers, especially for the considered age group.

Despite being consumed by this age group in Portugal, breakfast cereals are primarily marketed for children are not recognized as infant foods for legislative purposes (European Commission, 2006). If these products integrated the category "infant foods", stricter maximum limits would be applicable, and consequently extra efforts to produce cereal-based foods presenting lower contamination levels of mycotoxins would be developed. Due to lack of data, the health effects due to intake of free sugars and salt were estimated in a semi-quantitative way, not expressed in the DALYs calculations. Nevertheless, the potential health effects of these two components are recognized as important, and future efforts should be developed to overcome these gaps.

Finally, this case study was successful to validate the harmonized framework of risk-benefit assessment of foods developed under the RiskBenefit4EU project.

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6. Lessons learned from the RiskBenefit4EU and project sustainability

RBA is an area of research in development, and significant progress has been made recently to set general principles for conducting RBA of foods (Boué and Membré, 2018; Vidry et al., 2013). However, building capacity in new teams to conduct RBA studies remains challenging due to the multidisciplinary and specific expertise required (Eneroth et al., 2017; Pires et al., 2019). The RiskBenefit4EU project applied a collaborative method to train a new team to perform a RBA study of foods and face the challenges of cooperation between experts from different disciplines. Important lessons learned under RiskBenefit4EU project could be summarized in four main pillars:

1) *Multidisciplinary team, collaborating and sharing a common language*: collaboration between experienced researchers in RBA and field-specific experts required to perform the RBA case constitutes a valuable partnership, avoiding starting from scratch, enabling building on previous work, and contributing to sharing and improving a harmonized Risk-Benefit approach at the international scale;
2) *Capacity building strategy*: a strategy developed to capacitate the new established team is a fundamental step. The strategy followed under RiskBenefit4EU project, with training activities and scientific missions, the materials and methods used, and the defined learning objectives can be replicated to capacitate other new teams in RBA, and can be considered as a robust basis to build on.
3) *Training activities harmonizing the knowledge under RBA*: training initiatives, covering the main items related with RBA, is a core step in the development of the team's capacity. In addition to building a common language, it can enable a common scientific culture and understanding of all individual fields of research and methods used in RBA. A common culture facilitates the production of fit-for-purpose results for final integration;
4) *Stepwise approach guiding the process of RBA*: the development of a stepwise RBA approach, including the key steps that were explained and illustrated with examples of previous RBA performed, is a facilitator in this process.

Training initiatives developed or under development in the area of risk-benefit assessment of foods profited from the know-how obtained under RiskBenefit4EU, ensuring the sustainability of the project. These include training courses on Risk-Benefit Assessment in Foods at the DTU; and contribution to a series of training activities involving EU Member States and neighbouring countries, organized as part of the Better Training For Safer Food (BTSF) initiative, promoted and funded by the European Commission, by INRA. Future training activities are also being planned involving different partners of the consortium, in order to maintain the knowledge transfer to other institutions at national and international level.

Moreover, another EFSA Partnership Grant project will benefit from lessons learned in this project and will apply the developed framework. The NovRBA project (GP/EFSA/ENCO/2018/03) assesses risks and benefits associated with red meat substitution by other protein sources and involves INRA and DTU as well as the School of Medicine, National and Kapodistrian University of Athens, Greece (coordinator) and the German Federal Institute for Risk Assessment/Bundesinstitut für Risikobewertung, BfR Legal, Berlin, Germany.

Furthermore, efforts are being developed to maintain activities on risk-benefit analysis and to apply them to other set of foods/components/diets in the Portuguese participant institutions. As an example, a risk-benefit assessment on nut consumption in Portugal is being developed, coordinated by INSA (Annex L) in collaboration with ASAE, UP and DTU.

The perspective of evolution of RBA research is promising. On one hand, knowledge on "food" and "health" is ever increasing. On the other hand, there is an increasing interest on all health aspect of foods, which is one determinant of food choices and an important driver of change in human health.

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This has been highlighted through the expansion of the clean label trend, the development of food claims, the creation of food nutritional labelling systems, the research on low processed foods, and the huge number of media communications on food safety crisis (Chen et al., 2016; EFSA, 2015; Hubert et al., 2010). There is now a clear interest to consider other tools such as food dietary recommendations, food (re)formulation and process optimizations. Consequently and more broadly in food safety and nutrition, we need to break borders among areas of research and build on previous experience in RBA to address crosscutting issues (Boué, 2018). This will be possible by developing international collaborations between experts required to address the risk-benefit issue and RBA experts to facilitate the case-study realizations and to build a shared and harmonized RBA approach and culture. RiskBenefit4EU can be used as an example for future collaborative projects in RBA, taking advantage of the gained experience and learned lessons.

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Appendices A-D are available on the online article under "Supporting information".

Appendices A-D

Appendix A - Main activities and associated links

Appendix B - Oral Communications

- Assunção R, 2018. RiskBenefit4EU Project: The Essential Balance of Risks & Benefits of Foods, XVII Congress of Food and Nutrition and I International Congress of Food and Nutrition, Lisbon, 10-11 May 2018
- Alvito P, 2018. Projeto RiskBenefit4EU uma estratégia para a avaliação de risco-beneficio de alimentos em Portugal, Encontros do DAN, INSA, Lisbon, 16th November 2018
- Alvito P, 2018. Seminar: 10 Anos PNCA||10 Anos EFSA Focal Point Ao serviço da Ciência e do Consumidor, ASAE, Lisbon, 12 December 2018
- Jakobsen L, 2019. Risk Benefit Assessment of Foods: Lessons Learned from a Capacity Building Experience Under the RiskBenefit4EU Project, IAFP European Symposium, Nantes, France, 24-26 April 2019
- Carvalho C, 2019. Cereal based products consumption and sodium intake among Portuguese infants and young children, XVIII Congresso de Nutrição e Alimentação, Porto, Portugal, 16-17 May 2019
- Assunção R, 2019. Risk-benefit assessment of cereal-based foods consumed by children a case study under RiskBenefit4EU project, ICFC, 3rd International Conference on Food Contaminants, Aveiro, Portugal, 26-27 September 2019
- Boué G, 2019. Building capacity in risk-benefit assessment of foods: lessons learned from the RiskBenefit4EU Project, ICFC, 3rd International Conference on Food Contaminants, Aveiro, Portugal, 26-27 September 2019

Appendix C - Posters Presentation

- Risk-Benefit Assessment in foods: a case study involving mycotoxins, 10th World Mycotoxin Forum Conference, Amsterdam (The Netherlands), 12-14 March 2018
- Workshop on Risk-Benefit Assessment of Foods, INSA, Lisbon, 21 and 23 May 2018
- Risks & benefits of foods: RiskBenefit4EU project and the case study involving mycotoxins and cereal-based foods, 40th Mycotoxin Workshop, Munich – Germany, 11-13 June 2018
- Risk-Benefit Assessment: A tool for a better food and health policy in Europe, EFSA Conference 2018, Parma – Italy, 18-21 September 2018
- Avaliação de risco-benefício associado à alimentação: um instrumento para uma melhor política alimentar e de saúde na Europa, 11th PortFIR Annual Meeting, Lisbon, 25-26 October 2018
- Partnering to Strengthen the Risk-Benefit Assessment within EU Using a Holistic Approach, IAFP European Symposium, Nantes, France, 24-26 April 2019

Appendix D - RiskBenefit4EU project participants and associated institutions

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Annexes A-L are available on the online article under "Supporting information".

Annexes A-L

Annex A - Action Plan

Annex B - Impact assessment questionnaires

Annex C - Training 1, Program

Annex D - Training 2, Program

Annex E - Case study global evaluation

Annex F - International Conference ICFC 2019, Aveiro, 26th and 27th September

Annex G - Project flyer

Annex H - International Workshop, Lisbon, 21st May 2018

Annex I - Manuscript published in the International Journal

Annex J - Manuscript published in a National Journal

Annex K - Detailed description of risk-benefit assessment topics considered in theoretical training under RiskBenefit4EU project.

Annex L - Poster on application of RiskBenefit4EU framework

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