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Risk-benefit in food safety and nutrition - outcome of the 2019 Parma Summer School

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Abstract

Risk-benefit assessment is the comparison of the risk of a situation to its related benefits, i.e. a comparison of scenarios estimating the overall health impact. The risk-benefit analysis paradigm mirrors the classical risk analysis one: risk-benefit assessment goes hand-in-hand with risk-benefit management and risk-benefit communication.

The various health effects associated with food consumption, together with the increasing demand for advice on healthy and safe diets, have led to the development of different research disciplines in food safety and nutrition. In this sense, there is a clear need for a holistic approach, including and comparing all of the relevant health risks and benefits. The risk-benefit assessment of foods is a valuable approach to estimate the overall impact of food on health. It aims to assess together the negative and positive health effects associated with food intake by integrating chemical and microbiological risk assessment with risk and benefit assessment in food safety and nutrition.

The 2019 Summer School on risk-benefit in food safety and nutrition had the objective was to provide an opportunity to learn from experts in the field of risk-benefit approach in food safety and nutrition, including theory, case studies, and communication of risk-benefit assessments plus identify challenges for the future. It was evident that whereas tools and approaches have been developed, more and more case studies have been performed which can form an inherent validation of the risk-benefit approach. Executed risk-benefit assessment case studies apply the steps and characteristics developed: a problem formulation (with at least 2 scenarios), a tiered approach until a decision can be made, one common currency to describe both beneficial and adverse effects (DALYs in most instances). It was concluded that risk-benefit assessment in food safety and nutrition is gaining more and more momentum, while also many challenges remain for the future. Risk-benefit is on the verge of really enrolling into the risk assessment and risk analysis paradigm. The interaction between risk-benefit assessors and risk-benefit managers is pivotal in this, as is the interaction with risk-benefit communicators.

Highlights:

- The risk-benefit analysis paradigm mirrors the classical risk analysis one: risk-benefit assessment goes hand-in-hand with risk-benefit management and risk-benefit communication.
- There is a clear need for a holistic approach in food safety and nutrition, including and comparing all of the relevant health risks and benefits.
- The risk-benefit assessment of foods is a valuable approach to estimate the overall impact of food on health.
- Recent risk-benefit assessment case studies apply the characteristics developed: a problem formulation (at least 2 scenarios), a tiered approach until a decision can be made, a common currency to describe both beneficial and adverse effects (e.g. DALYs).

Introduction

Food and nutrition are essential for life. Food contains many components: macronutrients, micronutrients and non-nutrients. The benefit of foods is, first and foremost, to provide nutrition (energy and nutrients). Non-nutrients are either contaminants, natural toxins or other substances, some of which are claimed to have beneficial effects. Potential health benefits are associated with nutrition and health claims, which are currently managed under EU Regulation 1924/2006, and for which EFSA evaluates the scientific substantiation (Verhagen & van Loveren, 2016; Verhagen, Vos, Francl, Heinonen, & van Loveren, 2010). Food placed on the market is assumed to be safe if correctly handled, and many laws are in place to secure the safety of food in the EU (Regulation 178/2002 eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:02002R0178-20190726; Regulation 1381/2019: eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32019R1381; Regulation 2073/2005 https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32005R2073&from=EN; Regulation 396/2005 https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32005R0396&from=EN).

Food safety is fundamental. This applies to chemical food safety, microbiological food safety and physical food safety. Risk assessment (composed by scientific advice and information analysis) is the first and fundamental step of food safety in the European framework (Commission of the European Communities, 2000). The basic steps of risk assessment do apply to all factors relevant to the food production chains: the scientific implementation of such steps obviously depends on the nature of the potential hazards (chemical , biological or physical), their target(s) (human health, health of food-producing organisms, ecosystems) as well as on whether the object of risk assessment has an intended use in food production, e.g. feed and food additives, or is an undesirable factor such as environmental pollutants or food-borne zoonoses (see for the details the work by the EFSA's Scientific Committee and Panels, https://www.efsa.europa.eu/en/science/scientific-committee-and-panels).

As such, on the one hand, food contains necessary and beneficial components, whereas, on the other hand, all components are potentially adverse (Paracelsus, 17th century: “dose makes the poison …”). Indeed, food and food components may be both beneficial and adverse. Even the same food component may have the potential of being both beneficial and adverse. For example, vitamins and minerals are necessary micronutrients of which a certain level of intake is needed for normal biological functioning of the human body. Meanwhile, not only too low intakes but also too high intakes of micronutrients could result in adverse effects. In order to address the “dual risk paradigm” and being able to evaluate both the risk of inadequacy and the risk of toxicity in populations, Dietary Reference Values are set including also Tolerable Upper Intake Levels (EFSA, 2017; EFSA NDA Panel (EFSA Panel on Dietetic Products, 2006; Verkaik-Kloosterman, McCann, Hoekstra, & Verhagen, 2012). Hence, there are many potential cases for which a risk-benefit assessment could be performed, such as a nutrient present in many foods that presents risk and benefit simultaneously, a diet and its alternative with more or less of a food that provide a specific nutrient with benefit and another nutrient with risk, a food that undergoes (or not) a specific process and or treatment and which composition is modified (at the chemical and/or nutritional and/or microbiological level), the partial or total replacement of one food by another and the comparison of the exposure to one specific component (eg chemical). And in addition, risk-benefit assessment also includes considerations of chronic risk versus acute risks, chemical benefit versus microbiological risk, risk-risk ranking and risk-risk comparison, etc. For each case, the way of formulating the problem / terms of reference and the methodology for getting a common metric (eg the DALY) is case specific. An overview of the different cases studies conducted until recently is given in (Boué, Guillou, Antignac, Le Bizec, & Membré, 2015).

Risk-taking is normal in everyday life if there are associated (perceived) benefits such as self-improvement, emotional engagement, and control (Lupton & Tulloch, 2002). Risk-benefit assessment, also for food safety and nutrition, is the comparison of the risk to its related benefit, i.e. a comparison of scenarios estimating the overall health impact. It has decades of history in the area of medicines (Luteijn et al., 2012), but is relatively young in the area of food safety and nutrition (Tijhuis, de Jong, et al., 2012; Tijhuis, Pohjola, et al., 2012; Verhagen, Tijhuis, et al., 2012). As concerns risk-benefit assessment in the area of food safety and nutrition, it is important to realise the opposing starting points (Figure 1). Risk assessment for chemical food safety is typically done by toxicologists and aims at identifying the highest doses not associated with an adverse effect. In addition, safety/uncertainty factors are applied to achieve safe levels for human exposure, resulting in intake levels that are essentially *without effect*. In contrast, risk and benefit assessment for nutrition is typically done by nutritionists/epidemiologists, who work with dose levels with clear (beneficial) effects (e.g. minimal effective doses, scientific substantiation of health claims), i.e. they focus on intake levels that are essentially *with effect*. A genuine risk-benefit assessment therefore envisages to express risks and benefits of foods and food ingredients into one currency, thereby allowing for a qualitative and especially quantitative comparison of public health impacts of adverse and beneficial effects (Boobis et al., 2013; Boué, Guillou, Antignac, Le Bizec, & Membré, 2015; Vidry et al., 2013) (Hoekstra et al., 2008) (Hoekstra, Hart, et al., 2012); (Tijhuis, de Jong, et al., 2012; Tijhuis, Pohjola, et al., 2012; Verhagen, Andersen, et al., 2012)).

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Figure 1.

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A risk-benefit assessment should help policymakers to make informed and balanced management decisions. The risk-benefit manager can weigh the calculated and assessed benefits versus the risks in a balanced way. This can be illustrated by Figure 2, in which a hypothetical micronutrient deficiency in the population leads to a small percentage of the population being at risk of too low intake with inherent public health losses. When increasing the micronutrient intake, e.g. by fortification or supplementation, the micronutrient deficiency may be resolved, but causing a small percentage of the population being at risk of because of too high intakes. In either case, a small portion of the population is at risk of adverse health effects. This theoretical example illustrates the interplay in risk-benefit analysis: risk assessors can calculate/assess the public health effects, whereas risk-benefit managers (policy makers) need to decide for one or another scenario. The one decision is not necessarily better than the other. Any choice is a choice; even not taking a decision is a decision in itself. This is not a pure theoretical case as it has already been explored a decade ago at the hand of fortification of flour/bread with folic acid, in which the public health burden was found to be decreased overall but not for everybody in the population (Table 1)(Hoekstra et al., 2008; Verhagen, Andersen, et al., 2012; Vidry et al., 2013). Despite the clear net benefits, in the Netherlands, the risk managers decided not to fortify flour because of concerns for risks of the non-target population. Health authorities decided to encourage (again) pregnant women and women who want to become pregnant to take folic acid supplements.

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Figure 2.

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Table 1.

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In Europe, in the last decade several major projects were concluded to explore the area of risk-benefit analysis for food and nutrition: BRAFO (Boobis et al., 2013; Hoekstra, Hart, et al., 2012; Verhagen, Andersen, et al., 2012; Vidry et al., 2013), Qalibra (Hart et al., 2013), Beneris (Karjalainen et al., 2013), Bepraribean (Kalogeras et al., 2012; Luteijn et al., 2012; Magnusson et al., 2012; Pohjola et al., 2012; Tijhuis, de Jong, et al., 2012; Tijhuis, Pohjola, et al., 2012; Ueland et al., 2012; Verhagen, Tijhuis, et al., 2012), and more recently the RiskBenefit4EU project (Alvito et al., 2019; Assunção, Alvito, et al., 2019).

All these projects were developing methodology and approaches to qualitatively and quantitatively compare risks and benefits, including the opinion of the European Food Safety Authority (EFSA Scientific Committee, 2010); an overview of these projects is provided in (Verhagen, Tijhuis, et al., 2012). In general, a risk-benefit assessment consists of the comparison of alternative scenarios with a reference (Assunção, Alvito, et al., 2019; Assunção, Pires, & Nauta, 2019; Boobis et al., 2013; Boué et al., 2015; Hoekstra, Hart, et al., 2012; Souza, Assuncao, Oliveira, Neill, & Meira, 2019; Vidry et al., 2013). So, at least two scenarios need to be identified. Then, it is advisable to perform a risk-benefit in a tiered approach and stop the assessment once enough information is available to weigh the one scenario versus the other. The approaches developed have been validated in a series of test cases reported as part of or alongside those projects.

The Parma Summer School was born in 2016 in a collaboration between University of Parma and European Food Safety Authority and is organized in the EFSA premises, in Parma. It is organised every year. The aim of the no-fee Summer Schools is to promote the meetings between young researchers, post-docs and Ph.D. students with the best expertise in food science field.

The Summer School is organised by the University of Parma, EFSA and other Universities and scientific institutions. The 2019 edition has been co-organised with the collaboration of the School of Advanced Studies in Food and Nutrition (Parma University), the University of Piacenza, University of Barcelona, Swedish Food Agency, Technical University of Denmark and Italian National Institute of Health. The topic was "Risk-Benefit in Food Safety and Nutrition" (http://www.parmasummerschool.unipr.it/). Over two days, the speakers covered a mix of theory and practical aspects and illustrated those with some case studies; the programme is available at: www.parmasummerschool.unipr.it/program/. While more than 300 applications have been received to attend the 2019 Parma Summer School, the maximum number of participants was limited to 150. The participants have been filtered by the scientific committee by a careful evaluation of a short CV.

The event evaluation showed high satisfaction among the participants of the course, both in general terms as well as concerning the content of the sessions. This paper summarises the main outcomes of the individual presentations as well as the overall event. The aim of the event and this paper is to provide an opportunity to learn from experts in the field of risk-benefit approach in food safety and nutrition, including theory, case studies, and communication of risk-benefit assessments and identify challenges for the future.

This paper first gives a general introduction into food safety, nutrition, and risk assessment, then into nutrition, benefits and health claims, and finally risk-benefit assessment of medicinal products. Then the execution of risk-benefit assessment is presented, followed by several case studies and other issues on risk-benefit assessment. Finally the paper addresses developments in risk-benefit assessment for food and nutrition and gives final reflections and conclusions.

1 General introduction into food safety, nutrition, and risk assessment

1.1 Introduction into food safety and risk assessment

Risk assessment, together with risk management and risk communication are the three elements in the classical risk analysis paradigm (World Health Organization, 2009). They are clearly separated while also connected one to another. Whereas this originally applies to food safety risk assessment, it is also fully valid to risk-benefit assessment (Boobis et al., 2013; EFSA Scientific Committee, 2010; Pohjola et al., 2012; Tijhuis, de Jong, et al., 2012; Tijhuis, Pohjola, et al., 2012; Vidry et al., 2013).

Risk assessment is a specialised field of applied science that involves reviewing scientific evidence through a four step-process: hazard identification and hazard characterisation, exposure assessment and risk characterisation (World Health Organization, 2009). These steps are applicable to both chemical, physical as well as microbiological risk assessment. Also microbiological food safety and physical food safety follows these lines, with the connotation that microorganisms can multiply along the farm to fork chain. These steps can be illustrated by means of an example, such as Methylmercury (MeHg) (EFSA CONTAM Panel (Panel on Contaminants in the Food Chain), 2012).

i) Hazard identification: the identification of an agent that is capable of causing adverse health effects. Methylmercury forms in aquatic environments, mostly sediments, as a product of mercury released into the environment by human activities or geochemically. It is neurotoxic and capable to bioaccumulate.

ii) Hazard characterisation: the nature of the adverse effects and their doses-response relationships. MeHg is extensively absorbed in the gut and crosses placenta and blood-brain barriers. Developmental neurotoxicity is the leading effect (i.e., occurring at lowest exposure levels), whereas developmental immunotoxicity and cardiovascular effects also deserve attention. For this contaminant, robust human data (epidemiology as well as toxicokinetics) allow to derive a Tolerable Weekly Intake (TWI: 1.3 µg/kg b.w). Biomonitoring data support the assessment of the dietary intake: the Hg concentration in maternal hair (biomarker of maternal burden in pregnancy) translates into the corresponding dietary exposure. For the derivation of the TWI, uncertainty factors are used in order to account for interindividual variations and remaining gaps of knowledge.

iii) Exposure assessment: identification of exposure to a hazard and quantification of the amounts involved. Fish, and to a lesser extent other seafood, is the source of exposure for MeHg. Large predatory fishes (e.g., tuna, swordfish) are more contaminated because they bioaccumulate more than smaller species with a lower place in the feeding chain. Interestingly, MeHg levels are comparable between wild and farmed fish, when this is fed with meals from small marine organisms. Intake by consumers varies with geographical areas and dietary habits. However, data are burdened by a number of uncertainties (see below). In general, exposure assessment must consider high consumers (e.g., the 95th percentile of consumers) and age-related variations in dietary habits: there are significant differences between adults and small children (up to three years).

(iv) Risk Characterisation: the likelihood that an agent will cause harm calculated in the light of the nature of the hazard and the extent to which people, animals, plants and/or the environment are exposed to it. For MeHg, the mean dietary exposure across age groups and countries does not exceed the TWI, but high consumers may exceed it significantly. These conclusions are consistent with the findings of Hg biomonitoring in the EU.

The examination of the opinion on MeHg hints to several general issues in food safety risk assessment. First, the biology of living organisms that produce our foods does influence contaminant

accumulation. This can be indicated by the higher MeHg levels in large predatory fishes as compared to other seafood, as well as by other contaminants that bioaccumulate in food-producing animals. Examples include: arsenic, which bioaccumulates in seafood, and is metabolised into organic forms of low toxicity, (EFSA CONTAM Panel (Panel on Contaminants in the Food Chain), 2009), and dioxins that show a significantly higher accumulation in sheep liver as compared to bovine liver (EFSA CONTAM Panel (Panel on Contaminants in the Food Chain), 2011). Then, the human factor: the risk assessment of MeHg depends on national or regional habits of seafood consumption (EFSA Scientific Committee, 2015) including fatty fishes (EFSA CONTAM Panel (Panel on Contaminants in the Food Chain), 2012). Communities with a high consumption of large fatty fish are less susceptible to MeHg effects due to the concurrent intake of n-3 long-chain polyunsaturated fatty acids, which protect the neuro-development (EFSA CONTAM Panel (Panel on Contaminants in the Food Chain), 2012). This is already a risk-benefit issue: eating fish because of the beneficial n-3 long-chain polyunsaturated fatty acids or not eating fish because of the adverse MeHg content. Third, the need to cope in a consistent way with uncertainties, also by evaluating their impact on the conservativeness of the assessment (EFSA Scientific Committee et al., 2018). Exposure assessment of contaminants is particularly "vulnerable" to uncertainties, e.g.: uneven geographical distribution of data collection, non-standardised (thus, inadequately comparable) methods for sampling and/or analysis of food commodities, high percentage of samples below the limit of detection ("left-censored"), which might simply reflect the use of analytical methods of insufficient sensitivity (Mantovani, 2018).

Last but not least, the type of question addressed to the risk assessor ("Terms of Reference", ToRs) is not the same for all potential hazards. The formulation of ToRs is usually flexible, depending on specific needs. For substances, products or processes intentionally added to the food chain (pesticides, feed and food additives, food contact materials, novel foods, etc.) in most cases an "applicant" must provide data (a dossier) in accordance with sectorial legislation (including a standardised set of toxicity and other safety tests), thus, ToRs need to refer to the relevant legislation. Hazards occurring in the food chain unintentionally (chemical and biological contaminants), typically are not supported by a dossier and, consequently, the assessment relies on other available data. For contaminants, the assessment outcome is an estimate of risk (probability and magnitude of an adverse event), whereas for intentionally added items the outcome concludes on the safety under defined conditions of use. One example is the supplementation of animal feeds with selenium from selenium-enriched yeasts which should not exceed 0.2 mg/kg because higher levels could lead to an excessive selenium intake particularly in children (EFSA FEED Panel (Panel on Additives Products or Substances used in Animal Feed), 2011).

1.2 Introduction into nutrition, benefits and health claims

According to the World Health Organisation (WHO), a healthy diet is sufficient and balanced in terms of quantity, quality and safety. Without going into the details of the definition (Development Initiatives, 2018), it is evident that a large proportion of the world population still consumes "unhealthy" diets, whose detrimental impact is responsible for about 11 million preventable deaths globally per year, more even than smoking tobacco (G. B. D. Risk Factor Collaborators, 2018; GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). Nutrition research has the potential to make a profound positive impact on human health globally and can play an important role in informing public health programmes and policies.

Actually, the potential beneficial effects of foods and specific bioactive compounds of foods may be evaluated through epidemiological observations, human interventions and mechanistic studies of cells or animals. When evidence from different types of nutrition studies are systematically searched for, evaluated and combined with well-established methodology, it provides a sound basis for

inclusion into risk benefit assessment. A number of methodological issues in nutrition research will be discussed below.

Because randomised controlled trials are not practically or ethically possible for many research topics in nutrition, observational epidemiological studies are the main contributors to the evidence base to support food and nutrition policy recommendations. However, it has been questioned whether epidemiologic associations of nutritional factors with health outcomes could represent causal effects that can inform public health policy and guidelines. In nutritional epidemiology, assessment of exposure poses particular problems because dietary intakes are complex and in-depth knowledge on methodology is required to gain reliable results from dietary assessment. It is problematic that, authors often use causal language when reporting the findings from observational studies (Ioannidis, 2018)(eg, "optimal consumption of risk decreasing foods results in a 56% reduction of all-cause mortality"), when study design would only allow interpretation of association. Burden-of-disease studies and guidelines often endorse these estimates. Even when authors add caveats, results are still presented by the media as causal, generating unrealistic expectations in the lay public struggling to understand the sometimes conflicting messages about what constitutes a healthy diet. It is necessary to systematically review the evidence as the number of new publications on food and nutrition is overwhelming. However, meta-analyses could also be performed with methodologic flaws and arrive at erroneous or misleading conclusions, reigniting controversy over apparently settled debates (Barnard, Willett, & Ding, 2017). All of this has raised questions regarding the ability of nutritional epidemiologic studies to inform policy. On the other hand, as recently pointed out by (Giovannucci, 2019), the main results obtained from nutritional epidemiology are coherent and, taking into account all the possible inaccuracies, valuable insights on diet and health outcomes can be obtained from studies on free-living populations. For instance, a robust body of evidence suggests that the reduction in dietary sodium intake and the concomitant increase in dietary potassium intake should lower blood pressure, which in turn could reduce cardiovascular risk (Gay, Rao, Vaccarino, & Ali, 2016). Also looking at complex dietary patterns instead of food/nutrients, there is consistent evidence that the Mediterranean diet positively affects risk factors for metabolic and cardiovascular diseases (Dinu, Pagliai, Casini, & Sofi, 2018), ultimately reducing total and cardiovascular mortality (Trichopoulou, Costacou, Bamia, & Trichopoulos, 2003). A solid approach to assess and take into account of uncertainties of the available scientific evidence will increase the transparency of the resulting scientific advice and make it more robust for decision-making (Satija, Yu, Willett, & Hu, 2015).

In this scenario, the "Hill criteria", published in 1965 by Sir Austin Bradford Hill, are very useful in inferring causality from observational data, and making timely policy decisions that could avert preventable morbidity and mortality in the population (Hill, 1965). In his classic paper, Hill outlined a checklist of several key conditions for establishing causality: strength, consistency, temporality, dose-response, plausibility, coherence, and experimental evidence. Accordingly, public health decisions should be made on the weight of the available evidence, acknowledging its limitations, and seeking to obtain further, better evidence when possible. This has also been recognised by EFSA in formulating some recent guidances (EFSA Scientific Committee et al., 2018; EFSA Scientific Committee, Hardy, Benford, Halldorsson, Jeger, Knutsen, More, Naegeli, Noteborn, Ockleford, Ricci, Rychen, Schlatter, Silano, Solecki, Turck, Benfenati, et al., 2017; EFSA Scientific Committee, Hardy, Benford, Halldorsson, Jeger, Knutsen, More, Naegeli, Noteborn, Ockleford, Ricci, Rychen, Schlatter, Silano, Solecki, Turck, Younes, et al., 2017; Hardy et al., 2015). Equally important is to acknowledge when evidence is insufficient to formulate any guidance. In this case, the communication to the public should clearly outline all the relevant options to enable informed choice.

In addition to epidemiological considerations underlying the science of nutrition and setting of dietary reference values, EFSA has worked very intensely on the scientific substantiation of health claims of food and food ingredients under EU Regulation 1924/2006 (eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02006R1924-20141213) . When evaluating a health claim dossier,

EFSA evaluates the extent to which: 1. the food/constituent is defined/characterised, 2. the claimed effect is 'beneficial to human health', and 3. a cause and effect relationship is established. Unless all these three questions can be answered positively, a health claim cannot be considered scientifically substantiated. The final conclusions of an EFSA scientific evaluation can be along three grades of evidence: a cause and effect has been established, there is insufficient evidence to establish a cause and effect relationship, or a cause and effect has not been established. To date, >3000 health claims have been evaluated (Verhagen & van Loveren, 2016; Verhagen et al., 2010), the result of which was that the claims have been concluded as either scientifically substantiated (ca 250), insufficient evidence for the health claim (a few), and scientifically not substantiated (the large majority). The European Commission with the EU Member States subsequently took decisions to allow health claims for most, albeit not all, health claims that have been judged by EFSA as being scientifically sufficiently substantiated. All decisions by the European Commission have been included in a register of (allowed, not allowed) health claims under Regulation (EU) No 432/2012 (eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32012R0432&from=EN): ec.europa.eu/food/safety/labelling_nutrition/claims/register/public/?event=register.home . Full information on health claims in EU can be retrieved from the website of the European Commission (ec.europa.eu/food/safety/labelling_nutrition/claims_en) and EFSA (www.efsa.europa.eu/en/topics/topic/health-claims).

1.3 Risk-Benefit assessment of medicinal products

Increased interest in the decision-making process behind drug approvals have led to significant changes by which drug regulatory authorities conduct their assessments and communicate their decisions. For medicinal products, risk-benefit assessments are already common practice for decades (Luteijn et al., 2012).

A new medicinal product is granted a Marketing Authorisation in the European Union only once regulators have determined that the benefits of the product outweigh the risks associated with its use. There are several challenges in this process. Available data are not always complete and fraught with uncertainties. Any attempt to maximise the benefits of a medicine, e.g. through an increase in the administered dose, will most likely compromise the equally important goal of minimising its risks. The task is further complicated by the often-differing preferences between patients and regulators on the valuation criteria that need to be applied in benefit-risk assessment.

The European Medicines Agency (EMA) has adopted PrOACT-URL, as the framework for its benefit-risk evaluations of new medicinal products (Pignatti et al., 2015). This is generic framework that can be used in any decision-making problem and was initially developed by (Hammond, Keeney, & Raiffa, 1998). It consists of eight discreet steps all of which are included in the benefit-risk assessment process of medicinal products:

1. PROBLEM, defines the therapeutic context of the applied indication including key aspects such as severity of the condition, life-threatening or not and characteristics of affected population;
2. OBJECTIVES, describes the aims of therapy, e.g. survival prolongation or disease modification and the key endpoints to ascertain this;
3. ALTERNATIVES, are the alternative treatment options to the proposed investigational product (no treatment or placebo, different dose, pre-existing available treatments);
4. CONSEQUENCES, refers to the clinical effects, both positive (favourable) and negative (unfavourable) of the medicinal product. These are also displayed in a tabular format

("Effects Table") as a means to improve the transparency of the benefit-risk assessment and support the communication among the EMA's scientific committees and the public;

5. TRADE-OFFS, after the presentation of the data, the relative importance of the observed effects in terms of clinical relevance needs to be determined;
6. UNCERTAINTY, the impact of the inherent uncertainties in the available data in the decision is described;
7. RISK, the decision is also impacted by one's risk attitude, the level of risk one is willing to accept in order to obtain some level of benefit and is to a large extent informed by the therapeutic context;
8. LINKED DECISIONS, is used to consider the consistency of this decision with similar past decisions, and assess whether taking this decision could impact future decisions.

Adoption of this structured framework by the EMA is in line with a world-wide trend towards a more explicit benefit-risk analysis as illustrated in the current Guideline on Enhancing the Format and Structure of Benefit-Risk Information of the International Council for Harmonisation of Technical Requirements for pharmaceuticals for Human Use (ICH; database.ich.org/sites/default/files/M4E_R2__Guideline.pdf).

2 Execution of risk-benefit assessment

When executing a risk-benefit assessment, several concepts and tools need to be discussed first in order to understand and appreciate the science behind it. These are the subject of the next paragraphs: assessment of burden of disease, the different steps in a risk-benefit assessment, computational tools and methods in risk-benefit assessment, and ranking of dietary risks.

2.1 Burden of Disease

Burden of disease (BoD) estimates describes death and loss of health due to diseases, injuries and risk factors, and allow for the establishment of public health priorities. The one-dimensional nature of measures such as incidence, prevalence, and mortality does not provide the full picture of the health impact of diseases and do not allow a valid comparison across diseases and health states. The lack of harmonized health metrics has led to the development of summary measures of population health such as the Disability-Adjusted Life Year (DALY) (Devleesschauwer et al., 2015; Devleesschauwer et al., 2014; Murray, 1994).

The DALY measures the gap between a given health state and an ideal state of health and wellbeing (Figure 3). One DALY equals one healthy year of life lost. It is the sum of Years Lived with Disability (YLD), which combines information on disease incidence or prevalence, duration and severity (as measured by disease-specific disability weights), and the Years of Life Lost (YLL) due to premature death (Devleesschauwer et al., 2015; Devleesschauwer et al., 2014; Murray, 1994). The DALY concept can be used to describe risks equally well as benefits (benefits constituting negative, i.e. beneficial, DALYs).

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Figure 3.

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In the context of food safety and nutrition, disease burden estimates are useful to estimate the impact of foods on population health. For instance, disease burden can be attributed to a dietary risk factor (e.g. low consumption of fruits) or a hazard in foods (e.g. a heavy metal in food) to rank human health risks and support policy makers in setting priorities (World Health Organization, 2015). Poor dietary habits were ranked the leading risk factor for global mortality and second leading for global disease burden by the Global Burden of Disease (GBD) 2017 Study, covering 15 dietary risk factors globally (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018)). In addition, the WHO foodborne disease burden epidemiology reference group (FERG) published in 2015 estimates for global and regional illnesses, deaths and DALYs for 31 foodborne hazards in 2010, including 17 enteric pathogens, 11 parasites, and 3 chemicals (Havelaar et al., 2015; World Health Organization, 2015). In 2018, estimates for four food-associated heavy metals were added (Gibb et al., 2019).

However, acting on one food-associated risk factor alone may affect exposure to other risk factors, potentially causing reduced exposure to beneficial compounds or increased exposure to food hazards. Risk-Benefit Assessment (RBA) addresses the challenge to this issue by accounting for the potential health impact of public health strategies, balancing both the adverse and beneficial health impacts of food in an integrated and overall assessment.

2.2 The different steps in a risk-benefit assessment

Since its inception in 2002, EFSA has over the years produced ample guidance for doing risk assessment, both cross-cutting ones as well as sector-specific (vertical) ones. An overview is on the EFSA website: www.efsa.europa.eu/en/methodology/guidance. Among these, EFSA provides guidance on the depth of a risk-benefit assessment (EFSA Scientific Committee, 2010). This three step approach includes 1) an initial assessment to check whether the risks or benefits clearly outweigh the other 2) a refined assessment that may include comparisons of different scenarios, dose response modelling and/or consideration of different populations and 3) a comparison of risks and benefits using a composite metric, for example DALYs. Each step should be followed by a report to the risk-benefit manager and advice on whether to stop the assessment or perform the next step.

The process of RBA is similar to that of a risk assessment and characterizes risks and benefits throughout the process: health effect identification, health effect characterization, exposure assessment and risk- and benefit characterization (for illustrations see for example (S. M. Pires et al., 2019)).

A tiered approach has been suggested for conducting a risk-benefit assessment (Assunção, Pires, et al., 2019; Boobis et al., 2013; Boué et al., 2015; EFSA Scientific Committee, 2010; Hoekstra, Hart, et al., 2012; S. M. Pires et al., 2019; Vidry et al., 2013)

The approach consists of an initial step 0 followed by four tiers:

0. Prologue, pre-assessment and problem formulation
1. Characterization and screening, which is a risk and a benefit assessment.
2. Qualitative evaluation
3. Deterministic computation of a common health metric, e.g. a DALY
4. Probabilistic computation of a common health metric.

The method of the RBA has to be tailored to the particular RBA-question after careful problem formulation. This is done in dialog between risk managers and risk-benefit-assessors. The risk-benefit question should include the target population, the comparison scenarios and the level of aggregation (the whole diet, a particular food or a substance in a food); for examples see (Nauta et al., 2018). The identified literature about risk is likely to differ from the literature about the benefits. Interpretations of data also depends on tradition within disciplines. Thus, for a fair grading of the quality of the evidence, a multidisciplinary team is necessary. The method for health effect characterization will vary depending on whether the data at hand is continuous, categorical or quantal. To estimate how much of the food or food compound is consumed, national data or the EFSA Comprehensive European Food Consumption Database may be used. If the exposure is acute, probabilistic methods are used, and for chronic exposure it is necessary to transfer the available intake data to habitual intakes. The risk and benefit characterization will depend on the assessment

level according to EFSA 2010: at step 1 (the initial assessment) comparing exposure to health based guidance values is adequate, while at step 3, by definition a common metric such as DALYs, QALYs or Cost of Illness should be applied.

2.3 Computational tools and methods in risk-benefit assessment

The idea of the RBA approach is that two scenarios, a reference and an alternative, each with a different exposure of the substance or food of interest are compared on the bases of the occurring risks and benefits. In some cases, it is necessary to express the impact of all health effects, risks and benefits in a common health metric to be able to weigh all aspects of the difference between the reference and the alternative scenario(s). In risk benefit assessments very often the DALY (Disability Adjusted Life Years) is used as the common health metric.

This approach (Figure 4) is clearly captured in a scheme developed by (Boué et al., 2015) and based on the BRAFO scheme (Boobis et al., 2013; Hoekstra, Hart, et al., 2012; Vidry et al., 2013), with some modifications (Assunção, Alvito, et al., 2019).

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Figure 4.

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Hart et al. (Hart et al., 2013) thoroughly describe a calculation method for the DALY as a health metric in the third and fourth tier and Hoekstra et al. (Hoekstra et al., 2013) compute DALYs resulting from the incidence of several diseases for a population with different intakes of fish.

Figure 3 above, illustrates how the difference in health impact between two exposure scenarios is calculated for one person. Sometimes one typical person is sufficient but mostly many individuals have to be computed to take account of the variability in exposure between individuals. The figure shows the schematic life course of a single individual for two different intakes (reference, red and alternative, green). In the reference scenario the individual develops a heart disease at a young age and dies at age 60. In the alternative the individual does not develop the heart disease and lives until age 90. Although in the extra time he does develop some other diseases. The yellow area depicts the difference in life course i.e. scenarios, expressed in DALYs. The calculation of the DALY difference can be complicated because it depends on when, which disease is developed and age of death for each individual in the population of interest. When epidemiological studies with good quality and incidence data are available, age of onset and age of death can be estimated using the PAF (Population Attributed Fraction) methodology. For effects that are based on animal experiments *ad hoc* solutions need to be found. For both possibilities see e.g. Hoekstra et al. (Hoekstra et al., 2013) and Nauta et al. (Nauta et al., 2018).

To perform a quantitative risk-benefit assessment, a well-formulated problem is needed in which the exposure in all relevant subpopulations of the food or substance of interest is clear in a reference and alternative scenario. Furthermore, data, expertise and scientific creativity in fields such as toxicology, epidemiology, nutrition and modelling is necessary to develop the dose-response models to calculate the health impact (DALYs).

2.4 Risk ranking of dietary risks

Whereas risk-benefit becomes a more and more accepted term, risk-benefit assessments sometimes also come in disguise. Exchanging risk-benefit for benefit-risk, such as in the BRAFO project (Boobis et al., 2013; Hoekstra, Hart, et al., 2012; Vidry et al., 2013) is a matter of preference. Moreover, risk-risk comparisons and risk-ranking approaches are also quite similar to risk-benefit assessments and they use the same concepts (e.g. expressing effects in a common currency such as the DALY).

Ranking of dietary risks is something we more or less inevitably do in our daily life, when we are buying, preparing and eating foods. This ranking is often not scientific based but is a result of previous knowledge, cultural and social background, personal preferences etc. On the other hand, risk ranking is also an established scientific discipline including a large variety of qualitative and quantitative ranking methods (Lindqvist, Langerholc, Ranta, Hirvonen, & Sand, 2019; Van der Fels-Klerx et al., 2018). A proper ranking of dietary risk is useful not only for the individual consumer but also for national and international food authorities and other regulatory organisations, which can use the outcome of risk ranking to prioritise allocation of resources to mitigate food related hazards (Devleesschauwer et al., 2017). Quite often, consumers are faced with a distorted media debate causing unnecessary fears about dietary items that are of negligible risk. In such case, a simple and transparent adaptive system like risk ranking, which can provide information based on health measurements is useful.

The Swedish Food Agency developed the "Risk Thermometer" as a tool for comparison of chemical risks associated with chronic exposure via food (Sand et al., 2015). By choice the Risk Thermometer is based on both scientific considerations (risk assessment) and value-based considerations (risk management) with the aim to communicate levels of risks to consumers, the media, and other stakeholders. The tool may be used to assess and compare exposures to environmental contaminants, pesticides, food additives, chemicals used in food contact materials, as well as minerals/nutrients.

In Denmark a national research project was performed with the aim to rank foodborne hazards based on their population-level health impact, i.e. the burden of disease they cause. The foodborne hazards and food-associated diseases addressed were selected based on available evidence of their public health impact (i.e. reported incidence), and on recent scientific studies published in peer-reviewed literature. This health impact was measured in terms of incidence and mortality of disease due to exposure to a hazard in the population, as well as of a health metric to take into account duration and severity of disease; the DALY was selected as the health metric to apply for burden of disease estimation (Lea S Jakobsen et al., 2019; Lea Sletting Jakobsen et al., 2016; Pires, Jakobsen, Ellis-Iversen, Pessoa, & Ethelberg, 2019).

Estimating the burden of disease caused by microbial and chemical hazards turned out to have different requirements and challenges. For chemicals, there was a long lag time between exposure and development of disease/symptoms making it more difficult to establish cause and effect relationship. For microbial hazards, challenges can be underdiagnosed and underreporting of each disease.

In this project ranking was solely based on health outcomes but it should be considered whether risk ranking rather should be a complex integration of various indicators like health burden (incidence, mortality and severity), economic impact and potential for and type of interventions. A solution could be to apply a multi-criteria decision analysis (MCDA)(Ruzante et al., 2010; Ruzante, Grieger, Woodward, Lambertini, & Kowalcyk, 2017).

The EFSA-commissioned paper (Van der Fels-Klerx et al., 2018) on risk ranking gives an overview of available risk ranking methods. In the paper, each identified ranking method was critically reviewed to extract the potentials and limitations for the ranking of human health risks related to feed or food. The paper covered toxicological, biological and nutritional health risks of well-known chemical substances, biological agents and nutritional components in food and feed. The risk ranking method to choose is very much dependent on the available data, the question asked, the resources available, and how accurate the answer should be.

Recently, and not available at the time of the Summer School, the FAO published its new guideline for risk ranking: at http://www.fao.org/documents/card/fr/c/cb0887en/.

3. Case studies and other issues on risk-benefit assessment

The Summer School also contained several case studies as well as presentations on other issues that are of relevance in risk-benefit assessment (parmasummerschool.unipr.it/program/). Those topics and presentations are illustrated below. The case studies illustrate the paradigm in risk-benefit assessment, including problem formulation, scenario development, comparisons of risk and benefits on the basis of one currency etc. Alongside, the below case studies on pesticides and BPA are illustrative to shaping the scientific area of risk-benefit assessment in food safety and nutrition.

3.1 Case study: Risk-benefit assessment of raw milk

Milk is a highly nutritious food and a debate has been occurring on the potential risks and benefits associated to the human consumption of raw milk when compared to pasteurized milk. Raw milk promoters claim that this food product presents a higher nutritional value, especially in terms of vitamin contents and a beneficial microflora through probiotic bacteria, and that it could contribute to allergy prevention (Claeys et al., 2013; Melini, Melini, Luziatelli, & Ruzzi, 2017). However, pasteurization is performed because several human pathogens can be present in raw milk, which has been identified as the cause of several foodborne outbreaks in the EU (EFSA BIOHAZ Panel (Panel on Biological Hazards), 2015). Despite these concerns, there is a trend to consume more raw milk, for example in some EU countries such as Italy (Giacometti et al., 2013) and Estonia (Kalmus, Kramarenko, Roasto, Meremae, & Viltrop, 2015), where the sale of raw milk occurs through self-service vending machines. Previous studies comparing the human health risks and benefits of raw milk consumption found that the risks are larger than the benefits (Claeys et al., 2013; MacDonald et al., 2011; Melini et al., 2017). However, the overall health impact of drinking raw milk instead of pasteurized milk has never been quantified.

The objective of this risk-benefit assessment was to quantify the health impact of raw milk consumption compared to pasteurized milk consumption in terms of DALYs (Assunção, Pires, et al., 2019a; Assunção, Pires, et al., 2019 b). As a preliminary approach, *Listeria monocytogenes* was considered next to the beneficial component vitamin B2, focusing the general adult population, not specifying specific vulnerable groups. Mathematical modelling, including predictive modelling of bacterial inactivation and growth and modelling of dose-response using epidemiological data, was used to quantify the DALYs associated to the consumption of raw milk directly from vending machines, comparing the consumption of one glass of milk (240 mL). Two approaches were applied: i) the bottom-up approach, estimating the incidence of disease due to the exposure via dose-response models (used for *L. monocytogenes*); and ii) the top-down approach, that starts from the epidemiological and incidence data and estimates the number of attributable cases of a certain disease due to an exposure (used for the vitamin B2) (Nauta et al., 2018). Published data were considered to perform the exposure assessment. The BCoDE software was used to estimate the associated DALYs (ECDC BCoDE toolkit [software application]: Version 1.7.0. Solna: European Centre for Disease Prevention and Control; 2019. Available from: ecdc.europa.eu/en/healthtopics/burden_of_communicable_diseases/Pages/Tool.aspx). The Dutch food composition database was utilized to estimate the vitamin B2 intake through milk consumption (RIVM, 2016: www.rivm.nl/en/dutch-food-composition-database). Modelling resources and the GBD Results Tool were used to estimate the associated DALYs for the different considered scenarios (ghdx.healthdata.org/gbd-results-tool). The differences in terms of DALYs regarding the health impact of consuming one cup of raw milk per day when compared to pasteurized milk were performed, quantified and expressed as the difference in DALYs (per 100,000 European citizens).

Main results revealed that overall the consumption of raw milk compared to pasteurized milk presents higher risk than benefit, when considering *L. monocytogenes* and vitamin B2. Additionally, it was verified that storage of raw milk in vending machines is of particular importance for the magnitude of the risk associated to *L. monocytogenes*. For example, in extreme conditions (3 days at 8°C), an increase in disease burden of 7.6 DALYs/100.000/year was estimated due to listeriosis. In contrast, preventable DALYs/100.000/year associated to vitamin B2 would not exceed 1 DALY/year. Integrating the results obtained in the different scenarios, including those considering extreme conditions, revealed that raw milk consumption presents higher risk than the consumption of

pasteurized milk. Additionally, the consumption of raw milk requires special efforts to control the storage conditions of milk and to ensure its safety.
In addition to these results, some remarks should be added. The present case study was an exploratory approach to the risks and the benefits associated to the consumption of raw milk when compared to pasteurized milk. In addition, additional risks and benefits should be considered to have a comprehensive overview of this situation. Health effects associated to the consumption of raw milk, such as the reduction of auto-immune diseases (Perdijk et al., 2018), or potential effects on the microbiota (Melini et al., 2017) should be considered in further refined assessments. Additionally, different populations are potentially affected by different benefits and risks, e.g. pregnant women and young children and specific scenarios could be considered in the future. Despite all these important considerations, the present case-study shows that risk-benefit assessment could be applied to cases when food components other than nutritional and chemical should be considered, namely microbiological food components.

3.2 Case study: The health impact of substituting red and processed meat by fish

Sufficient intake of fish and limited intake of red and processed meat is commonly encouraged by national dietary guidelines to prevent various lifestyle diseases. One way to fulfill these guidelines would be to substitute red and processed meat by fish. However, quantitative evidence of the public health gain of such substitution is lacking. Furthermore, while fatty acids in fish have been suggested to reduce risk of fatal coronary heart disease (CHD) and exert beneficial effects on neurodevelopment in fetuses of exposed pregnant women, fish also contain contaminants including methylmercury (MeHg) and dioxin and dioxin-like polychlorinated biphenyls (dl-PCBs), which may compromise the nutritional benefits (EFSA NDA Panel (EFSA Panel on Dietetic Products, 2014b; FAO/WHO, 2011). Thus, the overall health impact of substituting red and processed meat by fish may be highly dependent on the types of fish substituting for red and processed meat.

Thomsen *et al.* estimated the health impact of substituting red and processed meat by fish in the Danish diet (Thomsen et al., 2018). The RBA was based on Danish national food-based dietary guidelines, recommending a minimum weekly intake of 350 g of fish and a maximum weekly intake of 500 g of red and processed meat. The health impact of consuming a minimum of 350 g of i) a mix of lean and fatty fish, ii) fatty fish, iii) lean fish and iv) tuna, respectively, was estimated and compared to the current fish consumption in the Danish population (reference scenario), as reported by the Danish National Survey of Diet and Physical Activity (DANSDA) 2011-2013 (Pedersen et al., 2015). An individual-level and meal-based substitution of red and processed meat was modelled for all individuals with fish consumption levels below 350 g/week in the dietary survey (reference scenario) to compensate for the increased fish consumption in the alternative scenarios. The substitution distinguished between fish and meat types (red and processed meat, respectively) generally consumed as part of hot meals and cold meals by using meal-specific substitution factors to account for differences in portion sizes.

The RBA considered the following health effects associated with consumption of fish and exposure to nutrients and contaminants in fish; protection against fatal CHD (docosahexaenoic acid and eicosapentaenoic acid), enhanced neurodevelopment (fish), compromised neurodevelopment (MeHg), thyroid toxicity (dioxin and dl-PCBs), and male infertility toxicity (dioxin and dl-PCBs). The considered health effects associated with consumption of red and processed meat were: colorectal cancer (red and processed meat), stomach cancer (processed meat), thyroid toxicity (dioxin and dl-

PCBs), and male infertility toxicity (dioxin and dl-PCBs). The change in incidence and mortality of disease was estimated by combining information on food intake and exposure to nutrients and contaminant with dose-response data from epidemiological studies and from animal study extrapolations. DALYs were estimated by combining this information with disease severity and duration, and national and standard expected life expectancy data. The health impact of substituting red and processed meat by fish among Danish adults was estimated in terms of the difference in DALYs between each of the alternative scenarios and the reference scenario. The health impact of the substitution varied largely by the type of fish consumed. The highest benefit was estimated when all 350 g of fish was either a mix of lean and fatty fish or only fatty fish. A smaller health gain was estimated when all 350 g of fish was lean fish and a marked health loss was estimated when all 350 g of fish was tuna. The main drivers of the health impact were the beneficial effects of fatty acids in fish on fatal CHD and the effect of fish consumption (beneficial and adverse) on neurodevelopment in unborn children.

In another study, (Thomsen et al., 2019) used probabilistic methods to model the variability in individual substitution behaviors and health impact distributions of substituting part of the red and processed meat by a mix of lean and fatty fish in the Danish adult population. The highest benefit was estimated for women in the childbearing age and for men above 50 years of age. However, a small fraction of women was assigned an overall health loss due to MeHg exposure during pregnancy and the associated adverse effects in unborn children. The study also compared exposures to micronutrients and contaminants to established dietary reference values and health-based guidance values, respectively. The substitution decreased the proportion of Danish adults with inadequate intake of vitamin D by 25 % while no changes in the proportion with inadequate intake of iron was estimated. Meanwhile, the proportion of the population exceeding the tolerable weekly intake (TWI) for MeHg would increase from 0.3 % to 6 %. The estimated health impact of dioxin and dl-PCBs was negligible compared to the overall health impact of the substitution in terms of DALYs. The European Food Safety Authority (EFSA) CONTAM Panel recently set a new TWI for dioxin and dl-PCBs based on new epidemiological evidence on adverse effects on male fertility (EFSA CONTAM Panel (Panel on Contaminants in the Food Chain) et al., 2018). The health impact estimations for dioxin and dl-PCBs were not based on this new evidence and Danish exposures to dioxin and dl-PCBs were not compared to the new TWI in the studies by Thomsen et al. (Thomsen et al., 2019; Thomsen et al., 2018). Meanwhile, the EFSA CONTAM panel estimated a considerable exceedance of the TWI across European countries. Thus, the implications of the new evidence on the adverse effects of dioxin and dl-PCBs on the risk-benefit balance of fish consumption should be assessed in future RBAs.

3.3. Case study: Risk-benefit of pesticides

There is an increase of the world population as well as less arable land and less irrigation water. The total area of agricultural land decreases both in quantity due to urbanisation and erosion, as well as in quality due to contamination, salinization, loss of fertility and biodiversity. A solution to this problem, has two main underlying drivers: eat less and increase crop yield. Whereas, crop yield could be further increased by modern technologies, there is also a consistent loss of crop yields due to weed competition, pests and diseases (more than 65%). As concerns loss of crop yields, the use of plant protection products (PPP) could avoid losses by 28% (Savary, Teng, Willocquet, & Nutter, 2006). A PPP or “pesticide” is something that prevents, destroys or controls a harmful organism (pest) or disease, or protects plants or plant products during production, storage and transport. Pesticides can be acaricides, insecticides, fungicides, herbicides, etc. These are applied as PPP after formulation with a variety of compounds.

As such, pesticides confer a benefit to society by controlling pests and upholding crop yields. Yet, pesticides also are associated with potential risks to man, animal, plant and environment. This validates the consideration of pesticide use in a qualitative risk-benefit comparison. However, a full-fledged quantitative risk-benefit comparison for pesticides has not been performed to date.

The environmental fate of a pesticide after application is a complex system which is linked to different environmental compartments, such as atmosphere, biosphere, soil and water. The conditions for the authorization, in EU, of a plant protection product are stringent. PPP must be sufficiently effective, have no immediate or delayed harmful effect on human health, not have any unacceptable effects on plants or plant products, not cause unnecessary suffering and pain to vertebrates, and have no unacceptable effects on the environment. In Europe, various regulations and directives regulate the use of pesticides: Regulation 1107/2009/EC (eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32009R1107) considers their placing on the market and Directive 2009/128/EC (eur-lex.europa.eu/legal-content/EN/ALL/?uri=celex%3A32009L0128) drives their sustainable use. The risk evaluation of PPP is related to knowledge about efficacy after application following a good agricultural practice, maximum residue level in commodities, human toxicology, environmental fate and ecotoxicological effect on non-target organisms (bird, fish, aquatic invertebrates, algae, aquatic plant, mammals, bees, other arthropods, earthworms, soil micro-organisms, etc).

PPP's are only allowed on the market if there is prove of efficacy against a pest. For that, it must be demonstrated that there is a benefit, in term of pest control and consequently yield improvement, linked to the application of the pesticide. Also, information must be provided on the (possible) occurrence of the development of resistance of the pest as well as absence of unacceptable effects to succeeding and adjacent crops, food, and pollinators and natural enemies. Good Agricultural Practice (GAP) must be applied, including information on application rate, maximum number of applications, days between one application and the next, water volume to dilute PPP, growth stage at least treatment, minimum number of days that must pass between the time of the last application of a pesticide and the harvest (to ensure residue levels below the statutory legal limits).

Risk assessment is done using exposure assessment and hazard characterisation using a tiered approach with increasing complexity. For human health risk assessment, different routes of exposition (dermal, inhalation, food consumption) are considered in workers, operators, bystanders, residents and consumers. Both active ingredients and PPP are studied to define toxicological endpoint and different route of exposition as occupational during application or during re-entry in field/greenhouse after application, non-occupational during or after the application and with diet.

For environmental risk assessment, several routes of contamination are evaluated such as leaching into groundwater, run-off, spray drift and point contamination during farming activities, mixture loading, disposal of remaining of mixtures and spray equipment washing after application. One drop of PPP with 20% of active ingredient must be diluted in 100 cubic meters of water (a pond 100 square meter, 1 meter deep). As the different ways of contamination could affect several non-target organisms, PPP can only be used if risk assessment for human and environment demonstrate that the PPP do not pose a risk to humans and the environment.

To check if the assessment done during the authorisation processes, several monitoring plans are carried out in EU and in each Member State, for different target, as food, groundwater and surface water quality. For example, the 2017 EU report on pesticide residues in food (EFSA, 2019) shows that 96% of samples analysed did not exceed the maximum residue level permitted in EU legislation. EFSA concluded that according to the current scientific knowledge, the long-term dietary exposure

to pesticides was unlikely to pose a health risk to consumers, informing that risks are under control and so benefits can prevail.

3.4 Case study: Risk-benefit of alternatives to bisphenol A

Food Contact Materials (FCMs) are chemicals of emerging concerns due to the risk they pose to human health and the environment as well. Among them, bisphenol A (BPA or 4,4'-isopropylidenediphenol, CAS no. 80-05-7) and, to a very minor extent, several of its BPA-like derivatives and alternatives (bisphenols/BPs), are used in polycarbonate-based plastics [*e.g.*, returnable beverage bottles, infant feeding (baby) bottles, tableware, mugs], in epoxy resin-coated cans and vats, but also as dye developers in thermal paper for printers of small devices (*i.e.*, adding machines, cash registers and credit card terminals) (Cavaliere, Lorenzetti, & Cozzini, 2020; EFSA CEP Panel (Panel on Food Contact Materials, 2015). Considering dietary exposure as the main route, EFSA established in 2015 a temporary Tolerable Daily Intake (t-TDI) of 4 μg/kg bw *per* day, relying mostly on the adverse effects on mammary gland and reproductive, neuro-behavioral, immune and metabolic systems (EFSA CEP Panel (Panel on Food Contact Materials, 2015; Fowler, Penninks, & Wölfle, 2015).

The European Chemicals Agency (ECHA) included BPA among the Substances of Very High Concern (SVHC; REACH regulation EC/1907/2006, Annex XIV) (European Commission, 2006) for both its toxicological effects (toxic for reproduction; REACH art.57c) and endocrine disrupting properties (REACH art.57f). The European Union (EU), moreover, allows BPA use in FCMs with a specific migration limit (0.05 mg/kg), whereas it exists a lower one in toys (0.04 mg/kg). Furthermore, since 2011, EU banned BPA to manufacture polycarbonate infant feeding bottles, a ban extended in 2018 to plastic bottles and packaging containing food for babies and children under 3 years old. Lastly, an EU ban on BPA to manufacture thermal paper will apply from 2020.

Hence, an increasing effort by companies to replace BPA with a series of newly produced BPs having similar physico-chemical properties but less toxicological concerns in terms of reproductive and hormone-like adversity on human health. Although acting on a multitude of molecular, cellular and tissue targets, regulatory agencies have a strong BPA toxicological profile, whereas a paucity of data is existing on most BPs. Indeed, data availability on BPs is mostly restricted to no animal testing, either *in silico* (by read-across and Quantitative Structure-Activity Relationship/QSAR) or *in vitro* (by gene reporter assays), and the common target usually investigated is the estrogenic-like Mode-of-Action (MoA) of BPA. One replacement being widely considered by thermal paper industry is the chemical bisphenol S (BPS or 4'-sulphonyldiphenol, CAS no. 80-09-1). However, concerns have been expressed that it may cause similar health problems as BPA. To make sure that another hazardous chemical is not replacing the existing one, BPS is currently under substance evaluation and the European Commission enquired ECHA to investigate it further as a BPA substitute in thermal paper. This positions the work on BPA and related bisphenols under risk-ranking (of the one bisphenol *versus* the others); risk-ranking is one of the risk-benefit methods in disguise (see above).

As mentioned above, toxicological comparisons among bisphenols have been performed so far by no animal testing as strongly recommended by EU regulations at least as a prioritizing screening. In particular, the *in silico* approach used has been mostly QSAR, a ligand-based approach broadly used to predict the physico-chemical properties of chemicals that, in any case, needs a SAR database. As an alternative, different *in silico* method, the molecular docking, a non-statistical computational approach able to determine the binding strength between the active site residues and specific molecule(s), may be an expedient tool as a faster and reliable prioritizing screening to study the binding compatibility of BPs to a molecular target [*e.g.*, a nuclear receptor (NR) as the estrogen receptor-α (ERα)] in comparison to BPA. Such a molecular docking analyses (Cavaliere et al., 2020)

have been recently exploited to investigate the interaction between twenty-six BPs (including 7 BPA metabolites) and six different NRs, namely ERα, ERβ, estrogen-related receptor-γ (ERRγ), androgen receptor (AR) and two AR mutants (AR^{T877A} and AR^{W741L}) usually occurring in prostate cancer (PCa) patients. Shortly, the overall obtained data, based on four different docking score systems, showed that BPS appeared as a safer chemical in comparison to BPA considering its lower strength of binding to ERα and ERβ and the absence of binding to ERRγ. On the other hand, BPS and many other tested BPs appeared less safe in terms of a potential androgenic-like MoA since they bound to the AR mutants with similar strengths of the anti-androgenic pharmacological drugs used to treat PCa.

3.5 Economic sustainability of healthy diets

The sustainability of food systems must be considered in the context of global environmental and socio-economic challenges. Growth in world population and urbanization, greenhouse gases emissions and climate change, ecosystem degradation, slowing global agricultural productivity growth, food losses and wastes, are all factors involving huge socio-economic and environmental impacts. Moreover, the triple burden of malnutrition (undernutrition, overnutrition, and micronutrient deficiency) is still widespread in several countries (FAO, 2018). In this context, the transition towards more healthy and sustainable diets, involving sustainable food production systems, is necessary for global sustainable development (Willett, Rockstrom, & Loken, 2019; Walter Willett et al., 2019).

Diets should meet energy needs, provide a diversity of foods of high nutritional quality and be safe to consume. FAO indicates sustainable diets as those diets "with low environmental impacts which contribute to food and nutrition security and to healthy life for present and future generations". Sustainable diets are also "respectful of biodiversity and ecosystems, culturally acceptable, accessible, economically fair and affordable" (Burlingame & Dernini, 2012). This definition has major implications: sustainable diets imply nutrition and health outcomes (e.g. prevent malnutrition), environmental outcomes (e.g. water and land use, biodiversity, climate change), economic outcomes (e.g. income, employment, affordability) and social equity outcomes (e.g. availability). Several studies have shown synergies of diets achieving environmental and health objectives; in general, moving from ruminant meat to plant-based food rich diets confers both improved health and environmental benefits (Aleksandrowicz, Green, Joy, Smith, & Haines, 2016; Walter Willett et al., 2019). At the same time, trade-offs between unbalanced outcomes are also possible; for instance, increasing fish consumption may improve the intake of omega 3 fatty acids, iodine and vitamins A and D in order to meet dietary guidelines, but at the same time might further deplete marine resources.

According to a recent study of the EAT Lancet Commission on Healthy Diets From Sustainable Food Systems, global consumption of fruits, vegetables, nuts and legumes will have to double, and consumption of foods such as red meat and sugar will have to be reduced by more than 50% in order to achieve the UN Sustainable Development Goals and meet the dietary shifts required by 2050 (W. Willett et al., 2019; Walter Willett et al., 2019). Other studies have identified dietary patterns, such as Mediterranean diet, involving health and environmental benefits, with no significant differences in the total budget (Germani et al., 2014). A mathematical programming model was applied to identify a sustainable diet involving three dimensions: nutrition/health (macronutrients), environmental impact (carbon, water, ecological footprint), and affordability (cost of the diet). Dietary information was collected from students attending the last year of high schools and modelled to identify dietary shift towards sustainable diet. The sustainable diet, according to the mathematical model, may lead to a 51% cut in CO_2 emissions, 9% reduction in water consumption and 26% less land needed to regenerate the resources compared to the current diet.

The modelled sustainable diet is not more expensive than the current diet, therefore fully affordable for the population under study (Donati et al., 2016).

In any case, significant changes are needed, involving a different allocation of the budget to the different food groups, and more sustainable production systems, while providing healthy diets for the global population. Several policy interventions can be considered to promote healthy and affordable diets from sustainable food systems (W. Willett et al., 2019; Walter Willett et al., 2019). Softer interventions should provide information or educate the public with campaigns to increase population awareness or intensify marketing efforts on only healthy and sustainably produced foods. Other more intense interventions may involve fiscal incentives and disincentives to guide choices. Taxing unhealthy targeted ingredients (e.g. sugar) and subsiding healthy food products (e.g. fruit and vegetables) have been demonstrated to affect consumers' behavior (Afshin et al., 2017). Harder interventions could restrict or eliminate choices, e.g. removing inappropriate choice options.

In conclusion, the scientific evidence has already shown the need for a substantial global shift toward sustainable dietary patterns, for large reductions in food losses and wastes, and for major improvements in food production practices. More and better scientific research is essential to identify the drivers able to trigger these dietary behavioral changes.

3.6 Mechanism of biological activity in food compounds; balance between positive and negative effects

Dietary patterns, or the food we eat, are the sum of a multitude of small molecules partly even foreign to the body, which after being ingested and digested, may be altered by the trillions of microorganisms that inhabit our gastrointestinal tract. They may alter the chemical structures of such compounds and thus modifying the lifespan, bioavailability and biological effects (Marchesi et al., 2016). In this context, dietary patterns modulate the gut microbiome and alter its functions by modulating the production of microbial metabolites (Koutsos et al., 2017; O'Keefe, 2016; Trošt et al., 2018; Yang & Yu, 2018; Zhang & Davies, 2016). Lastly, these gut microbial metabolites have been shown to be capable of regulating homeostasis and the risk of disease (Guijas, Montenegro-Burke, Warth, Spilker, & Siuzdak, 2018; Marchesi et al., 2016).

Over the last decades, scientists have developed sophisticated methods that have radically broadened our knowledge of the function of native phytochemicals (Brasili & Filho, 2017; Little, Combet, McMillan, Horgan, & Roxburgh, 2017). To date, the most common approach for studying the potential beneficial effects of native phytochemicals against pathologies, such as cancer has involved the use of several *in vitro* assays based on a variety of human 2D cell lines (Brasili & Filho, 2017; Choy et al., 2016). Although multiple hints on the possible anticancer effects have been already published, these results cannot be applied to *in vivo* human situations. It is increasingly accepted that the biological effects cannot be directly linked to native compounds (D'Angelo et al., 2014; Earl et al., 2018; Neis, Dejong, & Rensen, 2015; Ravindranathan et al., 2018; Sharon et al., 2014; Toden et al., 2018; Trošt et al., 2018; Ulaszewska et al., 2016), particularly polyphenols, which are biologically transformed once they enter human body (Langhans, 2018; Little et al., 2017; Marchesi et al., 2016; Shankar, Kanwal, Candamo, & Gupta, 2016; Trošt et al., 2018). In addition, immortalised cell lines kept in 2D growth conditions differ metabolically from *in vivo* cells and have a limited ability to teach us about the function of organs and intra/inter-organ signalling (Dutta, Heo, & Clevers, 2017).

To partially overcome this problem, some researchers have proposed the use of different animal models (Gasperotti et al., 2015; Smith et al., 2013). However, although animal models have been shown to be useful for many goals (e.g. they are vital for discovering the gut-brain axis (Dinan & Cryan, 2017a, 2017b; Golubeva et al., 2017; Kelly et al., 2016; O'Mahony et al., 2009), their metabolism is not the same as humans', including their microbiome, which differs drastically. Recently, organoids have proved to be a better model system for cancer studies (Drost & Clevers, 2018; Fujii et al., 2016; Mebarki, Bennaceur, & Bonhomme-Faivre, 2018; Sato & Clevers, 2015; Sato et al., 2011; Schweiger & Jensen, 2016). Definition of an organoid includes the three characteristics of organisation, multicellularity and function. (Drost & Clevers, 2018; Fujii et al., 2016; Mebarki et al., 2018; Sato & Clevers, 2015; Sato et al., 2011; Schweiger & Jensen, 2016). During *in vitro* culture, organoids mimic physiological organogenesis due to their ability to grow in 3D and self-organise into structures, mirroring the original tissue and real-life scenarios much more closely than any other model used to date (Drost & Clevers, 2018; Fujii et al., 2016; Mebarki et al., 2018; Sato & Clevers, 2015; Sato et al., 2011; Schweiger & Jensen, 2016). Therefore, futures studies combining intestinal organoids and dietary components can reveal gut epithelium responses and explain the mechanism by which certain gut microbial metabolites may prevent or trigger gastrointestinal diseases associated with the food we eat.

3.7 Risk-benefit approach in food and nutrition as basis for public health policy

According to the World Health Organization (WHO), health policy refers to "decisions, plans, and actions that are undertaken to achieve specific health care goals within a society". In the framework of food and nutrition, food-based dietary guidelines (FBDG) provide evidence-based guidance that aims at reducing nutritional risk while promoting population health. If the nutritional risks are generally defined as the risks of not complying with the population reference intakes or exceeding upper safety limits, the chemical or biological risks have been for a long while considered separately from benefits of food consumption when defining FBDG as public health recommendations. Fish is one of the first foods for which risks and benefits have been taken into account simultaneously to derive consumption recommendations (FAO/WHO, 2011).

There are many FBDG across the world, with communalities as well as differences (Bechthold, Boeing, Tetens, Schwingshackl, & Nöthlings, 2018; Erve van 't et al., 2017; Herforth et al., 2019). In Europe, only the French FBDG considered in a mathematical model both risks linked to the presence of contaminants in foods and benefits of food consumption, in the context of their 2016 update (Bechthold et al., 2018)(ANSES, 2016). ANSES developed a mathematical model with the aim to determine food consumption levels that would not only cover the nutritional needs and reduce the risk of chronic non-communicable diseases (diabetes, obesity, cancer…), but also limit the risk related to food contaminants, while taking into account the eating habits of the population. Optimized consumption levels for the population were calculated using the so-called "simplex" method (Dantzig, 1963). These calculations were based on a linear programing with constraints, as a generalization of a model developed for the consumption of fish and other seafood (Sirot, Leblanc, & Margaritis, 2012).

This new model included 41 nutritional constraints aiming to reach the dietary reference values for macronutrients, vitamins, minerals and energy, while remaining under the existing upper safety limits. The model also contained thirty-nine additional toxicological constraints, in order to remain under the health-based guidance values defined for contaminants such as trace elements, mycotoxins or persistent organic pollutants. Three constraints were defined to limit consumption of red meat, processed meats, and sugar-sweetened beverages, for which a strong association was found in the literature between a quantifiable maximum consumption and an increase in the risk of

disease. Lastly, in order to increase the adherence of the general population to the recommendations, which is known to be relatively low (Ball, Mishra, Thane, & Hodge, 2004; Kearney & McElhone, 1999) the model also comprised 61 additional constraints to find solutions within the range of consumptions currently observed in the population.

The model was applied to French data on food consumption (Dubuisson et al., 2010; Lioret et al., 2010), nutritional composition of foods (ANSES, 2013) and contamination (ANSES, 2011a, 2011b). For men and women datasets, solutions were found to the mathematical problem, corresponding to vectors of intakes. Except for vitamin D and for iron in women with high requirements, the nutrient needs of the population were covered, notably for magnesium and vitamin C, for which the prevalence of inadequacy was high in France (ANSES, 2015). This result underlined that the population reference intakes are generally compatible altogether, and that they are compatible with the situation of contamination of foods in France. The exceptions of vitamin D and iron had already been identified elsewhere, e.g. in Australia, following a similar approach for defining FBDG (NHMRC, 2013: https://www.nhmrc.gov.au/about-us/publications/australian-dietary-guidelines). For example, the population reference intake for vitamin D is not possible to reach in France taking into account the concentration of this nutrient in the main foods contributing to vitamin D intake (such as fish and dairy products) but also their contamination levels as well as the eating habits of the population. This result underlines the need for specific management measures for vitamin D such as supplementation under medical supervision, exposure to sunlight while respecting recommendation for skin cancer prevention, or food fortification as public health policy.

This approach was developed as a tool to help stakeholders in defining public health policies and allowed to integrate both the benefits and risks linked to food consumption. The consideration of toxicological constraints in the model led to a reduction in exposure to contaminants while ensuring the coverage of the nutritional requirements. The use of a mathematical algorithm makes it possible to integrate many parameters and not to limit to observed dietary patterns, in a search of objectivity. However, public health policies need an integrative approach combining not only scientific data on food consumption and nutrition, but also social, environmental or economical aspects (Bechthold et al., 2018; Herforth et al., 2019). In the future, this modelling tool could evolve and incorporate other criteria such as availability and affordability of foods, or environmental sustainability.

4. Developments in risk-benefit assessment for food and nutrition

4.1 Challenges of Risk-Benefit

Risk-benefit assessment of foods is a powerful tool that can provide the public or authorities with information on the health impact of current or future dietary choices, and has during the last decades expanded from assessing single specific foods or nutrients to also including assessment of whole dietary patterns and food safety interventions. In the last years, RBA has gained increased interest and several case studies has been carried out (Berjia, Andersen, Hoekstra, Poulsen, & Nauta, 2012; Berjia et al., 2014; Boue et al., 2017; Eneroth, Wallin, Leander, Nilsson Sommar, & Akesson, 2017; Hoekstra et al., 2013) which together with an expanding international network has led to further development of existing methods and new updated models (Berjia et al., 2014; Persson et al., 2018; Thomsen et al., 2019; Thomsen et al., 2018). Performance of risk-benefit case studies provide new interesting results but also reveals short-comes and inherent challenges in the performance of the risk-benefit assessment (Nauta et al., 2018). Many of these challenges were discussed at an EFSA sponsored expert workshop in Copenhagen in May 2017 (S. M. Pires et al., 2019). One of the challenges are the lack of data/knowledge and uncertainty. The need for data in RBA is large and diverse and often the assessor is faced with data gaps and lack of knowledge like lack of data from human study, no information on dose-response and missing intake levels for specific population groups. Due to limited data and lack of knowledge, the uncertainty may be large and characterising this uncertainty is therefore crucial in the risk-benefit assessment. Ideally, the identified uncertainties should be explicitly addressed and characterized in the assessment, as well as clearly communicated (Hart et al., 2013; Nauta et al., 2018). However, RBA models can identify the most important data gaps and crucial lack of knowledge and thus guide future data generation and research. Another challenge is the imbalance of level of evidence. The level of scientific evidence needed for identifying negative and/or positive health effects of a food compound, food or diet is not consistent. For health claims, a nutritional benefit needs to be scientifically substantiated with convincing evidence of the cause and effect relationship, before it can be accepted (Verhagen & van Loveren, 2016; Verhagen et al., 2010). On the other hand, the scientific evidence needed for identifying risks or negative health effects may usually be less, as often only an indication of a risk is sufficient for the scientific substantiation. If these practices are transferred to the RBA, risks are more likely to be included in an RBA than benefits, thus leading to a potential bias in the RBA. It is therefore essential to make a paradigm shift from considering the RBA as a sum of risk and benefit assessment to consider the RBA as a well-integrated risk-benefit assessment.

Another overall challenge is the resources and time load used for the risk-benefit assessment. Some steps like literature search and identification and selection of health effects are very time consuming and these processes need to be more streamlined in order to turn RBA into a more useful tool.

In RBA, the endpoint is the human health impact of food intake scenarios (Boobis et al., 2013; Tijhuis, de Jong, et al., 2012; Tijhuis, Pohjola, et al., 2012), but RBA based only on health will often not be sufficient to address risk management and societal questions. Therefore, there should be a possibility to consider and balance the health impact with effects on other factors such as sustainability, economy, and societal values. Recently, the first attempts to include sustainability in risk-benefit assessments have been published (Hollander, De Jonge, Biesbroek, Hoekstra, & Zijp, 2019; Seves et al., 2016). The question whether other disciplines should be included in the RBA must be included in the risk benefit question in communication with risk-benefit managers.

An integrated approach requires an interdisciplinary procedure as well as exchange of data from the different disciplines involved. However, adding such factors makes the analysis more complex, potentially less transparent and more difficult to update. It also increases the number of stakeholders involved and requires a methodology in which those effects can be transparently weighted and compared. Multi-Criteria Decision Analysis (MCDA) has been designed to address such complex decision problems, while making the analysis transparent and systematic. MCDA is a robust decision analysis tool that integrates different factors (i.e. criteria), while considering the preference and values of policy makers as well as stakeholders (Ruzante et al., 2010; Ruzante et al., 2017) . The challenges associated with incorporating other factors relevant to policy decision besides the outcome on health will not be the application of MCDA, but rather the data available and the different magnitudes of uncertainty.

4.2 General reflections on risk-benefit

Before and beyond science, risk and the assessment of risks, is a social construct. Therefore, it is composed by facts (scientific data) but also, and unavoidably, by values, expectations and perceptions. These factors influence the Terms of Reference, which depend on the values making-up the regulatory framework, and even the availability and quality of evidence, as this depends on the interest and resources devoted to a specific problem. In the European Union food and nutrition are perceived as something that has to be safe; thus, food safety is a key social value (European Commission, 2000; op.europa.eu/en/publication-detail/-/publication/6d4b523b-dad8-4449-b2b4-9fa9b0d6e2be). This is the current picture that will hold its ground while new (and even contradictory) issues emerge: besides being safe, food should support and improve health; food production must be sufficient for a growing population. Meanwhile, food production must be sustainable in terms of resources consumption, greenhouse emissions and preserving biodiversity.

RBA is a multi-step process that mirrors the steps of risk assessment and applies to specific instances (Boobis et al., 2013; Boué et al., 2015; Hoekstra, Hart, et al., 2012; S. M. Pires et al., 2019; Tijhuis, de Jong, et al., 2012; Tijhuis, Pohjola, et al., 2012; Vidry et al., 2013). Such instances arise whenever scientific evidence may support two or more options that go into different directions. Cases for RBA span from food and dietary choices (eat more or less seafood during pregnancy? (EFSA NDA Panel (EFSA Panel on Dietetic Products, 2014a) through food products and processes (fortify flour with folic acid?) (Bruins et al., 2015; Hoekstra et al., 2008; Verhagen, Andersen, et al., 2012; Verkaik-Kloosterman et al., 2012). Noticeably some EFSA opinions are definitely relevant to RBA, although not following a formal RBA approach: examples include the safety and efficacy of feed additives to improve the nutritional values of foods of animal origin (improved human nutrition vs. risks of exceeding the tolerable intakes for animals and/or humans of nutrients with recognized toxicity, (EFSA FEED Panel (Panel on Additives Products or Substances used in Animal Feed) et al., 2017) or of biocides to reduce microbial contamination of meats at the abattoir (reduction of microbiological hazards vs. possible toxicological and environmental hazards (EFSA CONTAM Panel (Panel on Contaminants in the Food Chain) et al., 2018).

RBA obviously needs interdisciplinary expertise; however, these different items (e.g., nutritional benefit vs toxicological risks as for fish consumption (EFSA NDA Panel (EFSA Panel on Dietetic Products, 2014b; EFSA Scientific Committee, 2015) should be compared on a qualitative and, when required, on a quantitative basis. Indeed, the basis for RBA relies on a common, consistent, robust and transparent (i.e., trustworthy) metrics for benefits and risks. The first tier is the qualitative comparison; the screen may quickly indicate a clear predominance of either risks of benefits (as in the case described of raw milk, where risks predominate (Claeys et al., 2013; MacDonald et al., 2011; Melini et al., 2017). Otherwise, the use of quantitative comparison should be envisaged.

Of the burden of disease estimates, DALYs appear as the most robust metrics. It is comprehensive as it takes into account the number, onset and severity of cases of adverse effects, either induced or prevented (Devleesschauwer et al., 2015; Hoekstra, Seijo, et al., 2012; Hoekstra et al., 2008). It may be unfeasible to estimate DALY for all possible endpoints. When multiple potential endpoints are present (e.g., in the case of folic acid), it is possible to concentrate on a few based on sound and transparent selection criteria such as weight of the evidence and magnitude (a-priori assessment, expert judgement).

RBA is a well-described process (Boobis et al., 2013; Boué et al., 2015; Hoekstra, Hart, et al., 2012; S. M. Pires et al., 2019; Tijhuis, de Jong, et al., 2012; Tijhuis, Pohjola, et al., 2012; Vidry et al., 2013), which should be implemented further through more case studies. Ideally these case studies could include multiple options, (e.g., different levels of addition of folic acid to flour or of seafood consumption) and/or different target populations for risks and benefits (as for folic acid fortification: neural tube defects in new-borns vs. masking vitamin B12 deficiency in the elderly): in this way the risk assessors would provide a transparent scientific support to the decisions by risk managers (Hoekstra et al., 2008).

RBA, as a science-driven process, develops as the relevant scientific fields develop. For instance, the new and lower TWI for dioxins derived by the EFSA based on human studies and toxicokinetics modelling (EFSA CONTAM Panel (Panel on Contaminants in the Food Chain) et al., 2018), might impact on existing and future RBA for such foods as dairy products or fatty fishes. The increasing knowledge on toxicity modes of action (endocrine disruption, epigenetics) allows a better characterization of hazards, including those from mixtures (EFSA Scientific Committee et al., 2019). Also, the development of methods for linking toxicity mechanisms to health outcomes, such as Adverse Outcome Pathways (EFSA PPR Panel (Panel on Plant Protection Products) et al., 2017), may improve the use of epidemiological data for risk assessment of chemicals.

Also looking at the benefit side, to evaluate the evidence from nutritional epidemiology and to integrate it into health assessment is challenging. In addition, also in the field of food safety, epidemiological data is becoming more available and epidemiological considerations can further progress the science in that field. EFSA is already exploring this approach such as for pesticides (Ntzani, Ntritsos G, Evangelou, & Tzoulaki, 2013). This stresses the importance of interdisciplinary research teams, for quality assessment and interpretation of studies from different scientific traditions.

When assessing the pros-and cons of whole diets, these have to be sufficiently characterized. For example, scores used to classify adherence to the Mediterranean diet are not always adequately evaluated (Zaragoza-Martí, Cabañero-Martínez, Hurtado-Sánchez, Laguna-Pérez, & Ferrer-Cascales, 2018). Dietary habits of individuals are likely to change with time, so timing of dietary assessment is also crucial in the interpretation. Moreover, dietary habits of the EU population evolve, and should be monitored as changes may significantly influence the RBA scenarios and outcomes.

Meta-analysis, which has the strengths of numbers and of standardization, is increasingly used to assess human studies on health promotion and/or disease prevention, but the interpretation of findings may be discrepant. A conservative approach considers only substantial (3-4 and more) Relative Risks (RR), whereas others accept the “accumulation” of low-level RRs that go in the same direction. Another way of looking at meta-analyses puts more emphasis on focused hypothesis testing and biological plausibility: for instance, in order to get consistent results, meta-analyses assessing the impact of a dietary style “X” on cardiovascular health should consider all main risk

factors, based on physiological knowledge, such as lipids, blood pressure (salt), oxidative stress (micronutrients) and glucose (sugars).

Some ways forward were identified during the discussion. Concerning exposure, Total Diet Studies (TDS) look very promising: the intakes of nutrients and contaminants are measured together in the foods cooked in the way they are consumed. TDS also allow for stratification according to age groups and regional differences. It is a standardized methodology (European Food Safety Authority & Food and Agriculture Organization of the United Nations, 2011) with the possible problem of its requirements in terms of time and human resources. Also, exposure assessment studies increasingly make human biomonitoring data available from cohorts and biobanks. However, biomonitoring still presents important uncertainties due to the insufficient knowledge on the factors influencing variability within and among populations.

The straightforward approach in RBA assessment is the quantification of risks and benefits for health which can be measured through a common metric. Another approach can be the assessment of the safety of use for a given purpose at a given dose in comparison with its efficacy or usefulness and possible substitutes. In this second approach, which is implemented for chemical substances by the European Chemical Agency, the health risk assessors contribute to the outcome together with other inputs by risk managers, which can include health benefits. For instance, as already mentioned, the favourable impact of a biocidal agent on the microbial contamination of foods may need being weighed against the risks at the intended conditions of use (EFSA CEP Panel (Panel on Food Contact Materials et al., 2018).

Yet, a third conceptual approach is raising. The issue of environmental sustainability calls for a framework where risks and benefits for health of a given food technology or food chain are integrated with evidence on the ability to support food security in a sustainable way. Potential synergies as well as unintended outcomes should be carefully evaluated when defining strategies aiming at achieving nutritional, environmental and socio-economic goals. Introducing a new comparative metrics to be assessed together with health effects looks ambitious, but it might be difficult to put into practice. Elaborating a parallel RBA to be integrated with the health/safety RBA might be more feasible, robust as well as more readily usable by risk managers.

Whatever approach is adopted, this is a challenge that risk assessors in food safety and nutritionists have to face in this overcrowded world unduly pursuing a high rate of resource consumption.

4.3 Concluding remarks

When taking risk-benefit further, there are ample scientific and other opportunities and challenges. Alongside, the development of approaches and entering new case studies, also the developments in science in the area of food safety risk assessment merit attention. To this end, EFSA recently started exploring topics such as Uncertainty, Weight-of-Evidence, and Biological Relevance, all contributing to refinement of scientific risk assessment (EFSA Scientific Committee et al., 2018; EFSA Scientific Committee, Hardy, Benford, Halldorsson, Jeger, Knutsen, More, Naegeli, Noteborn, Ockleford, Ricci, Rychen, Schlatter, Silano, Solecki, Turck, Benfenati, et al., 2017; EFSA Scientific Committee, Hardy, Benford, Halldorsson, Jeger, Knutsen, More, Naegeli, Noteborn, Ockleford, Ricci, Rychen, Schlatter, Silano, Solecki, Turck, Younes, et al., 2017; Hardy et al., 2015) and most certainly also applicable in the area of risk-benefit assessment. In addition, the EFSA's Prometheus framework (Promoting MetTHods for Evidence Use in Scientific assessments), aims at further defining the process and

guiding principles for evidence use in scientific assessments and critically evaluating the available methods to fulfil these principles (European Food Safety Authority et al., 2018).

In the debates around risk-benefit assessment of food safety and nutrition several considerations are important. From a theoretical point of view, risk-benefit assessments may in fact also be considered as comparing one risk with another risk rather than with a benefit (risk-risk comparisons). Basically, in many cases the benefit is a decrease in risk. This is widely illustrated by the 2006-RIVM report 'Our Food Our Health' (van Kreijl, Knaap, & Van Raaij, 2006) (translated into English with support from EFSA) and it recent update (https://www.rivm.nl/publicaties/what-is-on-our-plate-safe-healthy-and-sustainable-diets-in-netherlands). That was in essence a huge comparison of public health burden estimates of food safety issues versus (un)healthy nutrition, indicating that the public health burden of unhealthy dietary behaviour (eating too much and eating wrong) outweighs by far the public health burden by food safety topics. More recently, the WHO published another estimate of the ranking global burden of foodborne diseases (Havelaar et al., 2015; World Health Organization, 2015). And also EFSA recently published on the development of a risk-ranking toolbox (EFSA BIOHAZ Panel (Panel on Biological Hazards), 2015; Magnusson et al., 2012) and procured an overview of methodology and application of risk-ranking for prioritisation of food and feed related issues on the basis of the size of anticipated health impact (Van der Fels-Klerx et al., 2018). Furthermore, the concept of sustainable diets has grown in importance recently. Although the food system is able to provide safe, nutritious and adequate food supply, it may also place significant threats on climate, air, water, land, and other natural resources. Therefore, a wider approach is needed to understand and evaluate the overall effects of dietary behaviours, combining health with socio-economic and environmental goals, defining the road for a widespread, multi-sectorial, multi-level action to change (W. Willett et al., 2019; Walter Willett et al., 2019).

RBA should be on the agenda for food safety and nutrition agencies all over Europe because it supports the decision-making on issues such as cases of contamination of otherwise healthy foods, different level of risk in different strata of the population and on how to advise the population when research on food and health is inconclusive. Unfortunately, few RBAs are available for policy making on food and health. Identifying the relevant positive (benefits) and negative (risks) factors in the documentation of a policy decision, is a good starting point, even when a full RBA cannot be performed, e.g. because of lack of data.

Risk-benefit is on the verge of really enrolling into the risk assessment and risk analysis paradigm. The interaction between risk-benefit assessors and risk-benefit managers is pivotal in this, as is the interaction with risk-benefit communicators. When this has been sufficiently matured, overall risk-benefit assessment in food safety and nutrition can progress and become an integral part of the teaching programs of food experts around the world. Initiatives like the Parma Summer School here described are important steps. In addition, in a few years, the concept needs to be consolidated in the programs of all the relevant MSc courses, making the Parma Summer School some sort of advanced level specialisation on the topic. Indeed, risk-benefit assessment (in food safety and nutrition) is contemporary and challenging.

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